

2024 ANNUAL CONGRESS

of the Schizophrenia
International Research Society

Responding to Challenges in a Changing World

ABSTRACT BOOK

3-7 April 2024

Florence, Italy

schizophreniaresearchsociety.org



Concurrent Workshops

3:15 p.m. - 5:15 p.m.

1. GLOBAL GUIDELINES FOR THE TREATMENT OF SCHIZOPHRENIA

Dan Siskind, *Metro South Addiction and Mental Health Service*

Overall Abstract: There are numerous treatment guidelines for schizophrenia and related psychotic disorders. However, these guidelines tend to be lengthy, and rarely provide precise recommendations for common clinical scenarios. As such, there is a risk that guidelines are not routinely useful in everyday practice. This is in direct contrast to physical health guidelines, which often distil recommendations into simple stepwise algorithms. Furthermore, the views of people with lived experience are rarely incorporated, meaning that recommendations may not be acceptable to patients. Finally, guidelines often lack global perspective, meaning that recommendations may not be universally feasible.

To address this, we have formed an international consortium to produce 'global guidelines' for the management of schizophrenia, including a treatment algorithm designed for day-to-day use. As part of the process, the consortium is working closely with people with lived experience of schizophrenia and incorporating a global view by engaging with international colleagues. A step-wise process has been followed, including use of umbrella literature reviews, patient focus groups, and a survey/Delphi Consensus of the Treatment Response and Resistance in Psychosis (TRRIP) working group, comprising GREATER THAN 80 clinical and academic experts from 29 countries.

The workshop will present the results of the project to date and involve the audience in the discussion of how to incorporate these into a global guideline. Prof Siskind will chair the workshop, Drs Pillinger and Varvari will present a summary of the umbrella review, Dr Kabir will report results of lived experience focus groups, Drs McCutcheon and Hahn will present the result of the Delphi Survey. Prof Chen will provide a perspective regarding barriers in low and middle income countries.

The workshop will be fully interactive with comment and debate encouraged. Attendees will:

- Gain understanding of the development of clinical guidelines, as per international Appraisal of Guidelines, Research and Evaluation (AGREE) principles.
- Gain insight into the views of patients regarding treatment of schizophrenia, and how these relate to those of clinicians.
- Gain access to the key outcomes of the guidelines, learning about state-of-the-art management approaches through interactive discussion.

1.1. GLOBAL GUIDELINES FOR SCHIZOPHRENIA- RESULTS OF DELPHI SURVEY

Margaret Hahn, *Center for Addiction and Mental Health*

1.2. GOLD-STANDARD MANAGEMENT OF SCHIZOPHRENIA: AN UMBRELLA REVIEW

Toby Pillinger, *Institute of Psychiatry, King's College London*

1.3. DEVELOPING A CONSENSUS FOR THE PHARMACOLOGICAL MANAGEMENT OF SCHIZOPHRENIA

Rob McCutcheon, *University of Oxford*

1.4. PATIENT PERSPECTIVES ON THE PROPOSED 'GLOBAL GUIDELINES' FOR THE MANAGEMENT OF SCHIZOPHRENIA

Thomas Kabir, *University of Oxford*

1.5. A CONCISE OVERVIEW FROM THE UMBRELLA REVIEW IN SCHIZOPHRENIA TREATMENT

Ioana Varvari, *University of Oxford, Oxford Health NHS Foundation Trust*

2. RESEARCH HARMONIZATION AWARD WORKSHOP

Sohee Park, *Vanderbilt University*

Overall Abstract: The past decade has seen rapid development, worldwide, of digital health interventions (DHIs) for people with serious mental health problems, including schizophrenia-spectrum psychosis. When evaluating any health intervention, it is vital to measure and collect empirical data on potential harms as well as potential benefits. Patients, healthcare professionals, policy makers, regulators and funding bodies need this information when deciding whether to use, recommend, certify, prescribe and/or fund a specific health intervention. Despite accumulating evidence of feasibility and acceptability of DHIs for serious mental health problems, and emerging evidence of efficacy, information about their safety is not always systematically collected. Reporting of harms remains generally poor in DHI trials and there is a lack of consistency across trials and countries.

We were awarded the SIRS 2021-2023 Research Harmonisation Award, Digital Health to convene an international network to address the need for greater harmonisation for adverse events reporting in digital psychosis research. A service user researcher in our network emphasised this issue's relevance as follows: "It is important for us to know if technology is safe, and that researchers will value our worldview and actually listen and take note of adverse experiences and formally consider if they should be recorded as an adverse event."

We are a group comprising members from seven countries and include individuals with lived experience of psychosis, early career and senior researchers. To meet our objectives, we drew on existing datasets and members' international expertise, taking particular care to consider lived experience perspectives, cross-cultural issues and international differences. This workshop will consist of the following presentations, delivered by members of our multi-disciplinary iCharts network:

1. iCharts network aims, objectives and methods.
2. Phase 1 findings on the nature and range of adverse events reports.
3. Phase 2 findings from an in-depth analysis of adverse events SOPs.
4. Practical recommendations arising from the programme of work.

2.1. TRANSDIAGNOSTIC AND CROSS-CULTURAL ASSESSMENT OF SOCIAL COGNITION – INITIAL FINDINGS FROM THE SIRS HARMONIZATION AWARD

Amy Pinkham, *The University of Texas at Dallas*

2.2. MINDSET. MINIMUM DATA STANDARDS FOR SCHIZOPHRENIA AND THE ENVIRONMENT

Nicolas Crossley, *Facultad de Medicina, P. Universidad Catolica de Chile*

Sinan Guloksuz, *Maastricht University*

2.3. POOLING AND HARMONIZATION OF PSYCHOSIS COHORT DATA - THE IPEC GUIDE AND VIRTUAL DATABANK

Wim Veling, *University Medical Center Groningen*

3. FINDINGS FROM THE SIRS-FUNDED ICHARTS NETWORK: INTERNATIONAL COLLABORATION FOR HARMONISING ADVERSE EVENTS REPORTING IN TECHNOLOGY FOR SERIOUS MENTAL HEALTH PROBLEMS

Sandra Bucci, *The University of Manchester*

Overall Symposia Abstract: The past decade has seen rapid development, worldwide, of digital health interventions (DHIs) for people with serious mental health problems, including schizophrenia-spectrum psychosis. When evaluating any health intervention, it is vital to measure and collect empirical data on potential harms as well as potential benefits. Patients, healthcare professionals, policy makers, regulators and funding bodies need this information when deciding whether to use, recommend, certify, prescribe and/or fund a specific health intervention. Despite accumulating evidence of feasibility and acceptability of DHIs for serious mental health problems, and emerging evidence of efficacy, information about their safety is not always systematically collected. Reporting of harms remains generally poor in DHI trials and there is a lack of consistency across trials and countries.

We were awarded the SIRS 2021-2023 Research Harmonisation Award, Digital Health. Our objective was to convene an international network to address the need for greater harmonisation for adverse events reporting in digital psychosis research. There is currently no internationally recognised guidance on how to measure, monitor and record adverse events associated with DHIs specifically, with existing guidelines focusing largely on how to monitor and report harms in pharmacological trials. As the field of digital health for psychosis moves beyond feasibility studies into larger trials testing the efficacy and effectiveness of DHIs, and ultimately their implementation, it is an optimum time to harmonise measurement and reporting practices, ensuring future studies systematically monitor and record important safety information. A service user researcher in our network emphasised this issue's relevance as follows: "It is important for us to know if technology is safe, and that researchers will value our worldview and actually listen and take note of adverse experiences and formally consider if they should be recorded as an adverse event."

Convened by Professor Sandra Bucci, our iCharts network (International Collaboration for Harmonising Adverse Event Reporting in Technology for Serious Mental Health Problems) is a group of international experts comprising members from seven countries (UK, Belgium, Germany, Pakistan, Australia, USA, China), including two Low- or Middle-Income Countries (Pakistan, China). Network members include individuals with lived experience of psychosis, and an equal number of early career and senior researchers. To meet our objectives, we drew on existing datasets and members' international expertise, taking particular care to consider

lived experience perspectives, cross-cultural issues and international differences. We carried out the work in two phases to address different aspects of our harmonisation aim. In Phase 1, we collected raw adverse events data from existing digital psychosis studies to catalogue the nature and range of adverse events reported in this context. In Phase 2, we collated and analysed adverse events Standard Operating Procedures (SOPs) to develop best-practice recommendations and a practical resource to support adverse event measurement, monitoring, recording and safety reporting in DHI studies for people with psychosis.

This symposium will consist of the following presentations, delivered by members of our multi-disciplinary iCharts network:

1. iCharts network aims, objectives and methods.
2. Phase 1 findings on the nature and range of adverse events reports.
3. Phase 2 findings from an in-depth analysis of adverse events SOPs.
4. Practical recommendations arising from the programme of work.

3.1. ICHARTS NETWORK AIMS, OBJECTIVES, METHODS AND COMPOSITION

Sandra Bucci^{*1}, Emily Eisner², Stephanie Allan³, Mario Alvarez-Jimenez⁴, Imogen Bell⁵, Matteo Cella⁶, Imran Chaudhry², Joseph Firth², Philippa Garety⁷, John Gleeson⁸, Eric Granholm⁹, Andrew Gumley³, Amy Hardy¹⁰, Thomas Kabir¹¹, Tayyeba Kiran¹², Inez Myin-Germeys¹³, Ulrich Reininghaus¹⁴, Cara Richardson², Mar Rus-Calafell¹⁵, Anita Schick¹⁶, Matthias Schwannauer¹⁷, Suzie Syrett³, Neil Thomas¹⁸, John Torous¹⁹, Evelyne van Aubel²⁰, Thomas Ward²¹, Xiaolong Zhang²²

¹The University of Manchester, ²University of Manchester, ³University of Glasgow, ⁴Orygen, The University of Melbourne, ⁵Orygen, ⁶Institute of Psychiatry, Psychology and Neuroscience King's College London, ⁷Kings College London, ⁸Australian Catholic University, ⁹UCSD, ¹⁰Institute of Psychiatry, Psychology and Neuroscience, King's College London, ¹¹The McPin Foundation, ¹²Pakistan Institute of Living and Learning, ¹³KU Leuven, Center for Contextual Psychiatry, ¹⁴Central Institute of Mental Health, University of Heidelberg, ¹⁵Ruhr University Bochum, ¹⁶Central Institute of Mental Health, ¹⁷University of Edinburgh, ¹⁸Swinburne University of Technology, ¹⁹BIDMC / Harvard Medical School, ²⁰Center for Contextual Psychiatry, KU Leuven, ²¹King's College London, ²²Beijing Anding Hospital

Background: The Good Clinical Practice guidelines of the International Council for Harmonization (GCP-ICH) foreground the importance of monitoring adverse events, defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”. Concerns have been expressed regarding the conceptualization and reporting of adverse events within trials of psychosocial interventions more generally, and in psychosis specifically, because standard definitions were developed for pharmacological trials. While monitoring adverse events is standard practice in clinical trials of DHIs, a recent review highlighted significant issues with respect to transparency of reporting, in particular regarding relatedness of an adverse event to a specific DHI. To address this gap, we convened an international network and, in this symposium, present the findings from our two-year programme of work on this focused topic.

Methods: In this symposium, we present the findings from two key aims of the iCharts network: i) collate and analyse individual level records of adverse events from published international digital health trials for psychosis using content analysis alongside a coding framework approach; and ii) systematic literature search alongside a framework analysis approach to develop a practical, open-source adverse events reporting procedure/tool specific to digital mental health, freely available for the research community.

Results: iCharts comprises international experts working on developing and evaluating DHIs for psychosis and includes experts by experience and clinical/academic researcher from seven countries (UK, Belgium, Germany, Pakistan, Australia, USA, China), including two Low- or Middle-Income Countries (LMIC; Pakistan, China). Carried out across two phases, two 'writing groups' were formed to address different aspects of our harmonization aim. Writing Group 1 collated 593 raw adverse events data from 18 digital psychosis studies to catalogue the nature and range of adverse events reported in digital psychosis trials. Writing Group 2 collated and analyzed 32 adverse events Standard Operating Procedures (SOPs)/guidelines to develop the open-source reporting resource.

Conclusions: Our successful international network of multi-disciplinary researchers has identified putative adverse events researchers can expect to record when conducting digital psychosis studies and has developed best-practice guidelines and a practical resource for adverse event monitoring. The importance of adverse events monitoring, the procedure we followed to establish this successful multi-disciplinary network and to derive our outputs, will be described in this presentation.

3.2. ADVERSE EVENTS REPORTING IN DIGITAL INTERVENTIONS EVALUATIONS FOR PSYCHOSIS: A SYSTEMATIC LITERATURE SEARCH AND INDIVIDUAL LEVEL CONTENT ANALYSIS OF ADVERSE EVENT REPORTS

Stephanie Allan^{*1}, Thomas Ward², Emily Eisner³, John Torous⁴, Ulrich Reininghaus⁵, Imogen Bell⁶, Matteo Cella⁷, Imran Chaudhry³, Thomas Kabir⁸, Matthias Schwannauer⁹, Xiaolong Zhang³, Suzanne Syrett¹, Tayyeba Kiran¹⁰, Aansha Priya³, Cara Richardson³, Anita Schick¹¹, Sandra Bucci¹²

¹University of Glasgow, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK, ³University of Manchester, ⁴BIDMC / Harvard Medical School, ⁵Centre for Epidemiology and Public Health, , Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, ⁶Orygen, The National Centre of Excellence in Youth Mental Health, ⁷Institute of Psychiatry, Psychology and Neuroscience King's College London, ⁸The McPin Foundation, ⁹University of Edinburgh, ¹⁰Pakistan Institute of Living and Learning, ¹¹Central Institute of Mental Health, ¹²The University of Manchester

Background: Many people with psychosis do not get access to evidence-based care. Digital health interventions (DHIs) have significant potential to upscale treatment access to people experiencing psychosis. However, these interventions raise specific concerns around patient safety because many can be used by patients at home without a clinician available to monitor for negative consequences of intervention usage. Adverse Event monitoring and reporting is the gold standard used to identify, record, and manage safety issues in clinical trials. However, little is known about the specific content and context contained within extant Adverse Event reports in trials of DHIs and how these are reported. Additionally, different studies and countries use different reporting standards and may not agree on whether what a participant experiences are an Adverse Event. To address this gap, this study had two aims: 1) to work as

an international team to assess current Adverse Event reporting within DHIs for psychosis by analysing individual-level Adverse Event reports to identify what types of adverse experiences have been reported in DHIs, and 2) To identify areas for improvement in Adverse Event reporting.

Methods: A systematic literature search was conducted to identify evaluations of DHIs in psychosis populations. Study authors were approached via email, by the iCharts network convener and asked to provide anonymised Adverse Events reports. A content analysis was then conducted on the individual level Adverse Event reports shared by DHI trialists working in this field.

Results: Of 169 study authors approached, 20% agreed to share AE reports. A total of 593 anonymized Adverse Event reports were shared from 18 DHI evaluations across six countries. The content analysis identified 19 codes linked to adverse consequences of DHI usage. Psychiatric admission (23%) and psychosis exacerbation (22%) were the two most frequently coded categories. Only 29 Adverse Events (4.9% of total) were reported to be related to the interventions or study procedures. While overall results support the safety of DHIs, in a minority of cases, in a minority of cases DHIs were linked to mood problems and psychosis such as an increase in paranoia. Importantly, 27% of studies did not report information on relatedness for all or at least some Adverse Events. Additionally, 9.6% of Adverse Event reports were unclear because it could not clearly be determined what had happened to the participant.

Conclusions: The results from the studies that shared data support the safety of DHIs, but it is important that Adverse Events are routinely monitored, and intervention evaluated according to best practice. This may be achieved by a change of adverse event reporting culture where adverse events are viewed not as a negative outcome of a research trial, but as a valuable outcome measurement that can enable both clinicians and patients to make informed decisions when offering individual patients a DHI. To help achieve this, the iCharts group have provided recommendations for reporting in future studies including guidance for optimising the collection and sharing of anonymised adverse event reports.

3.3. PHASE 2 FINDINGS FROM AN IN-DEPTH ANALYSIS OF ADVERSE EVENTS SOPS

Xiaolong Zhang^{*1}, Emily Eisner², Cara Richardson², Neil Thomas³, Mar Rus-Calafell⁴, Suzy Syrett⁵, Joseph Firth², Andrew Gumley⁵, Amy Hardy⁶, Stephanie Allan⁵, Thomas Kabir⁷, Aansha Priyam², Sandra Bucci²

¹Beijing Anding Hospital, Capital Medical University, ²University of Manchester, Manchester, ³Swinburne University of Technology, Melbourne, ⁴Ruhr-Universitat Bochum, ⁵University of Glasgow, Glasgow, ⁶King's College London, London, ⁷The McPin Foundation, London

Background: Given the rapid expansion of research into digital health interventions (DHIs) for serious mental health problems, robust and consistent monitoring of their potential harms is crucial. However, reviews suggest that measurement and reporting of adverse events are currently inconsistent across DHI studies. Existing international guidelines focus largely on how to monitor and report harms in pharmacological trials; guidelines specific to DHIs for people with psychosis are lacking. We aimed to examine how existing international guidelines have been operationalised, to date, in the context of DHI studies for psychosis, in order to describe and build on current methods, identify best practice, make recommendations for ideal adverse events monitoring procedures and develop a practical resource to aid future researchers.

Methods: A systematic literature search identified relevant studies testing DHIs in samples with schizophrenia-spectrum psychosis. The iCharts convener approached authors of eligible studies, via email, and asked them to provide a document outlining their Standard Operating Procedure (SOP) for monitoring and reporting adverse events. Additional grey literature searches were used to identify publicly available adverse events SOPs from funders and relevant national regulators, agencies or governmental departments. All retrieved SOPs were analysed using framework analysis. Following an initial round of coding, it was evident that the study SOPs did not fully document the details of all procedures of relevance to adverse events monitoring and recording; additional information was obtained from study authors (n=11).

Results: SOPs were obtained from DHI studies (n=15), funders or regulators (n=12), and health services or universities (n=5). Study SOPs came from studies testing a variety of DHIs and levels of blending, across seven countries and various study designs (full-scale RCT, feasibility RCT, cohort study, pilot study). Framework analysis of SOPs identified commonalities for best practice for certain domains, but also revealed some inconsistencies, challenges and methodological gaps. We found the core adverse event definitions were largely consistent across SOPs and in line with existing pharmacological guidelines, albeit with “investigational medicinal product” replaced by more relevant terms (e.g. “digital health tool”, “investigational psychological therapy”). However, our analysis suggested certain inherent difficulties of applying existing definitions and guidelines from the pharmacological literature to non-pharmacological trials in relation to defining seriousness, relatedness and expectedness of adverse events. Our analysis also revealed substantial gaps in adverse event SOPs regarding how adverse events should be elicited and regarding research staff training/supervision. We found a reliance on implicit knowledge about these processes rather than explicit documentation in SOPs. Our analysis and additional information provided by study authors allowed us to make explicit recommendations for the benefit of future researchers.

Conclusions: Based on this detailed analysis of 32 adverse events SOPs, we developed best-practice guidelines and a practical resource for adverse event monitoring in DHI studies for psychosis, details of which will be discussed in Presentation 4 of the symposium.

3.4. PRACTICAL RECOMMENDATIONS ARISING FROM THE PROGRAMME OF WORK

Emily Eisner^{*1}, Cara Richardson¹, Neil Thomas², Mar Rus-Calafell³, Suzanne Syrett⁴, Joseph Firth¹, Andrew Gumley⁴, Amy Hardy⁵, Stephanie Allan⁴, Thomas Kabir⁶, Aansha Priyam⁷, Sandra Bucci⁸

¹University of Manchester, ²Swinburne University of Technology, ³Ruhr-Universität Bochum, ⁴University of Glasgow, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁶The McPin Foundation, ⁷University of Manchester, Manchester, ⁸The University of Manchester

Background: In undertaking the work described in presentations 1-3, the iCharts network sought to develop best-practice recommendations and practical resources to support adverse event measurement, monitoring, recording and safety reporting in DHI studies for people with psychosis.

Methods: The final presentation of the symposium will pull together core recommendations from across the iCharts programme of work, provide details of a practical resource that will be made publicly available to other researchers in the field, and outline future considerations regarding adverse events monitoring in this area.

Results: Recommendations: We will discuss recommendations regarding: responsibilities of individuals and committees in relation to managing adverse events; definitions of terms; how adverse events may be elicited; avoiding unblinding researchers while managing adverse events; training and supervising research workers in adverse events procedures; meeting adverse events safety reporting requirements; reporting adverse events in publications and reports. Practical resource: We will provide details of a template adverse events SOP, collating our findings from across the framework analysis of SOPs, which will be made publicly available under a Creative Commons Attribution (CC BY). This resource is intended to provide a starting point from which researchers can create an adverse event SOP for use in studies that include a DHI or other digital health tool. Adverse event measurement in this field is likely to evolve over time as DHI studies for psychosis become widespread, and as common adverse events are better documented and known. Our intention is for the publicly available template SOP to be a live document, updated at intervals as needed.

Conclusions: Future considerations: As the empirical evidence supporting the efficacy of DHIs for psychosis accumulates, it will become increasingly important to develop adverse event monitoring procedures in relation to wider implementation of DHIs in health services, outside of a clinical research context. Such procedures will likely depend on local and national governance processes. Nevertheless, stakeholders would benefit from international consistency regarding how adverse event monitoring is managed and reported in the context of implementation, and extended international guidelines would be welcomed. Ultimately, it is essential that data on potential harms of DHIs is collected and made public, whether in a research context or during implementation, so that stakeholders (e.g. patients, health professionals, policy makers, regulators, funding bodies) can access this information when deciding whether to use, recommend, certify, prescribe and/or fund a specific DHI.

Our findings contribute towards international efforts to standardise the measurement and reporting of adverse events in the emerging field of digital mental health to ensure that the safety aspects of DHIs for SMI are well-studied in research and well-understood by those ultimately implementing such interventions.

Keynote: Dr. German Berrios - Psychopathology in a Historical and Cultural Context
6:15 p.m. - 7:15 p.m.

4. PSYCHOPATHOLOGY AND TIME: AN UNEXPLORED RELATIONSHIP

Eric YH Chen, *Nanyang Technical University LKC School of Medicine, Singapore*

4.1. “PSYCHOPATHOLOGY AND TIME: AN UNEXPLORED RELATIONSHIP”

German Berrios, *University of Cambridge*

Individual Abstract: The discipline now called ‘Psychopathology’ was constructed early in the 19th century. An ancillary discipline of Alienism (Psychiatry), it created a set of objects or units of analysis meant to stand alone (diagnosis) and be relatable to the brain (aetiology). Borrowing from medical semiology, ‘mental symptoms’ were configured as existing in the ‘here and now’ (i.e. cross-sectionally, synchronically).

Ab initio, Psychopathology included the Newtonian definition of time as an eternal container. The need to organize serially their objects of interest and create interpretative frames (this is the origin of the theory of evolution) led neighbouring disciplines such as biology and geology to search for a view of time as interactional duration. Psychopathology opted for a compromise: mental diseases became 'temporalized' leading to redefinitions of acuteness and chronicity; but mental symptoms continued being considered as mere atemporal tokens of a prototype. This view remains popular today.

In this lecture it will be hypothesized that a temporalization of at least some mental symptoms should throw additional light onto their structure. It is a common clinical observation that in the acute state of a psychosis some symptoms (e.g. hallucinations and delusions) are oscillatory, that is, come in and out of awareness. This begs the question of whether for each new appearance the symptoms are generated anew or whether they remain extant at some level and their oscillations are caused by masking variables such as distraction, emotional valence, etc.

Equally interesting is the issue of whether chronicity causes a change in symptom structure. It will be further hypothesized that symptoms present in the first episode and in later episodes (although still called by the same name) are in fact different phenomena. In other words, hallucinations seen in a first episode can be considered as prototypical whilst those seen in later episodes are just overlearned behavioural phenocopies.

Lastly, there is the intriguing proposal by Von Monakow and Mourgue suggesting that "chronogenic brain localization" should replace conventional 'geometric localization'. The main implication of this claim concerns the relevance of time to the definition of mental symptoms and psychopathologists need to express a view in this regard.

In summary, it is the purpose of this lecture to show that:

- 1) to remain relevant to psychiatry and neurobiology psychopathology needs to keep reconstructing/updating its conceptual structure; and,
- 2) one of the roles of the epistemological analysis of psychopathology is to generate questions of direct empirical import, relevant to both diagnosis and treatment. This point has been illustrated in this lecture by showing how the addition of time frames illuminates our understanding of mental symptoms.

Plenary Session I: Robin Emsley - Psychopharmacological Developments and the Quest for Optimal Outcomes in Schizophrenia

9:00 a.m. - 10:00 a.m.

5. PSYCHOPHARMACOLOGICAL DEVELOPMENTS AND THE QUEST FOR OPTIMAL OUTCOMES IN SCHIZOPHRENIA

Gemma Modinos, *King's College London*

5.1. PSYCHOPHARMACOLOGICAL DEVELOPMENTS AND THE QUEST FOR OPTIMAL OUTCOMES IN SCHIZOPHRENIA

Robin Emsley, *Faculty of Medicine and Health Sciences, Stellenbosch University*

Individual Abstract: Antipsychotics have been the mainstay of treatment for schizophrenia since the 1950s, and their beneficial effects are extensively documented. Despite their efficacy in alleviating symptoms of acute psychosis, the real-world outcome for afflicted individuals is frequently poor. The course of illness is typically characterised by multiple relapses, accruing morbidity and enduring cognitive and functional deficits. The limitations of currently available antipsychotics have been clearly demarcated and include their relative lack of efficacy against symptoms other than those of psychosis, as well as their very significant side effect burden. Nevertheless, even within the context of these limitations, the judicious and correct use of antipsychotics in clinical practice may provide critical opportunities for clinicians to facilitate a favourable treatment outcome. Masses of data from drug development clinical trials together with real world outcome studies have improved our understanding of the way the illness responds to treatment and have enabled us to focus on those aspects that are malleable to treatment. Key aspects include early effective intervention; using the lowest effective dose to minimise the exquisite sensitivity of individuals to adverse effects in the early stages of treatment; adopting a person-centred approach to promote treatment engagement and focussing psychosocial and pharmacological interventions on medication adherence. While exciting alternatives to dopamine blocking antipsychotics are in an advanced stage of development, the basic treatment principles will remain the same.

Concurrent Symposia

10:00 a.m. - 12:00 p.m.

6. PREDICTING OUTCOME IN UHR: A PERSPECTIVE FROM DATA ANALYSIS AND STUDY COORDINATION

René Kahn, *Icahn School of Medicine at Mount Sinai*

Overall Symposia Abstract: The Accelerated Medicine Partnership- Schizophrenia (AMP-SCZ) was launched in 2020 to “address the critical need for more effective treatments for people with schizophrenia and related mental health conditions” (ampscz.org). AMP-SCZ is a large international longitudinal study of individuals at clinical high risk (CHR) for psychosis who have repeated multimodal assessments, including cognition, MRI, EEG, fluid biomarkers, digital markers, communication behavior and symptoms. It includes multiple languages and spans 42 sites. The project involves collecting data from approximately 2000 CHR individuals and 640 matched healthy controls. This data includes a wide range of longitudinal assessments, such as clinical, environmental, cognitive, biobehavioral, neuroimaging, electrophysiology, and fluid biospecimens markers. Additionally, AMP SCZ collects speech and facial expression samples, as well as measures from novel digital health technologies, passive sensing and actigraphy.

Modern research management assumes a data governance model in which grantees are considered stewards rather than owners of important data sets, and thus there is an expectation that samples are shared with the widest possible community of researchers who can collaborate to gain insights. This presents challenges in the study of complex, heterogeneous conditions involving sensitive health information, which require balancing privacy and autonomy of individuals with the needs of the research community.

This symposium will present data from the 4 cores of the AMP-SCZ, Data Processing, Analysis, and Coordination Center (DPACC) overseeing the data collection, analysis, and dissemination of AMP-SCZ.

The first core will be presented by Cheryl Corcoran from the Icahn School of Medicine at Mount Sinai in New York. The AMP-SCZ DPACC Core 1 has overseen coordination and monitoring for the ongoing AMP-SCZ consortium, with key deliverables including the development and standardization of SOP's across data domains or modalities, to be available to the broader research community, and the use of dashboards and automated programs with high utility for visualization and monitoring of recruitment, data completeness, demographics, and importantly QA/QC that includes ethical, human subjects and safety issues.

The second core will be presented by Sylvain Bouix, from the École de technologie supérieure in Montreal, Canada, reporting on the data operation ecosystem crafted for the AMP SCZ project, a complex, international multisite observational study of young individuals who are at clinical high risk (CHR) for developing a psychotic condition, such as schizophrenia.

The third core, presented by Ofer Pasternak from Harvard University, plays a crucial role in defining and parametrizing the clinical endpoints of the observational study highlighting the significant advantages of intermediate data fusion techniques, like multi-kernel learning (MKL), compared to single modality predictors. He will also present the utility of Dynamic Time Warping approaches, demonstrating the predictive advantage of using longitudinal data as opposed to relying solely on single time point predictors.

The dissemination of program resources developed by the AMP SCZ program is performed by the Dissemination core (Core 4) which will be presented by Tina Kapur from Harvard University which has overseen the dissemination of resources from the AMP SCZ program to the broader community using the program website and has promoted the voices of people with lived experience to enhance the work, resulting in better science and greater community partnership.

6.1. DPACC CORE 1: COORDINATION AND MONITORING ACTIVITIES KEY TO SUCCESSFUL DATA COLLECTION IN THE ACCELERATING MEDICINES PARTNERSHIP IN SCHIZOPHRENIA

Cheryl Corcoran^{*1}, Michael Coleman², Inge Winter-van Rossum³, Owen Borders⁴, Kathryn Lewandowski⁵, Alessia McGowan⁶, Suzanne Garcia⁷, Marek Kubicki⁴, Grace Jacobs⁸, Anastasia Haidar⁴, Nora Penzel⁹, Sylvain Bouix¹⁰, Justin Baker⁵, Rene Kahn¹, Martha Shenton⁴

¹Icahn School of Medicine at Mount Sinai, ²McLean Hospital, ³UMC Utrecht, ⁴Brigham and Women's Hospital, Harvard Medical School, ⁵Harvard Medical School/McLean Hospital, ⁶Icahn School of Medicine At Mount Sinai, ⁷NIMH, ⁸Brigham and Womens Hospital, ⁹Massachusetts General Hospital, Harvard Medical School, ¹⁰École de Technologie Supérieure,

Background: AMP-SCZ was launched in 2020 to “address the critical need for more effective treatments for people with schizophrenia and related mental health conditions” (ampscz.org). AMP-SCZ is a large international longitudinal study of individuals at clinical high risk (CHR) for psychosis who have repeated multimodal assessments, including cognition, MRI, EEG, fluid biomarkers, digital markers, communication behavior and symptoms. It includes multiple languages and spans 42 sites. Together, these features raise challenges for effective coordination, and standardized collection and monitoring of multimodal data over time.

Methods: AMP-SCZ DPACC Core 1 has been tasked with consortium coordination, standardization and monitoring of data collection. For coordination, this has entailed

scheduling, recording and note-taking for meetings, including for the expertise teams for each data modality; the development and monitoring of all Standard Operating Procedures (SOPs), including training, and the building out of complex RedCAP data entry forms and databases for all study measures and variables (data and metadata), including the new PSYCHS (Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS) clinical assessment instrument, key for CHR case ascertainment, measures of symptom severity and occurrence of primary outcomes (e.g., psychosis transition).

For monitoring, AMP-SCZ DPACC Core 1 has overseen measurement fidelity and performance tracking (quality assurance/quality control or QA/QC), ensuring human subject protections and ethical practices (review of IRB documentation, eligibility, informed consent procedures), and oversight and reporting of recruitment and retention rates, demographics, and trends in data collection.

Results: AMP-SCZ Core 1 has created key tools and deliverables, in collaboration with other Cores, that will be available broadly to investigators. In collaboration with Core 2, SOPs were iteratively developed for each data modality (domain), with detailed descriptions of data collection from recruitment to data acquisition, QA/QC, storage and transfer, including training, specific to each domain. In collaboration with Core 4, these SOPs will be disseminated through the ampscz.org website. Further, each Data Domain Team will publish a protocol paper to be included in a special issue of *Nature Schizophrenia* dedicated to AMP-SCZ.

For monitoring, in collaboration with Core 2, automated tools were developed to assess data quality, reliability and other QA/QC metrics for frequent monitoring and rapid feedback to data collection sites and NIMH. A sophisticated dashboard was developed for visualization and to track recruitment/retention, demographics and trends in data collection. The AMPSCZ Data Dashboard has 18 figures that provide information on recruitment, data completeness, demographics, and more.; its purpose is to visualize information that can assist in recruiting the correct demographics for the study, identify unforeseen systemic issues, and make important general information easily accessible. Features include filters for the two networks, individual sites, forms, timepoints, and more. There is also a subject search function that allows information for individual subjects to be viewed.

Specific to QA/QC, manual monitoring by a clinical trialist of 21% of subjects (143 of 686), identifying mostly minor and correctable issues with forms, with immediate feedback provided. In 2023, extensive scripts were set up for automatic checks on most assessments entered into electronic data capture. This extensive data completeness check now allows QA/QC on the full sample, with checks available to data collection networks continuously.

Conclusions: The AMP-SCZ DPACC Core 1 has overseen coordination and monitoring for the ongoing AMP-SCZ consortium, with key deliverables including the development and standardization of SOP's across data domains or modalities, to be available to the broader research community, and the use of dashboards and automated programs with high utility for visualization and monitoring of recruitment, data completeness, demographics, and importantly QA/QC that includes ethical, human subjects and safety issues. These tools will be implemented in the next clinical trial stage of AMP-SCZ.

6.2. DATA OPERATIONS FOR THE AMP SCZ PROJECT

Sylvain Bouix^{*1}, Justin Baker², Tashrif Billah³, Kang-Ik Kevin Cho³, Yoonho Chung², Michaela Ennis², Grace R. Jacobs³, Einat Liebenthal², Daniel Mathalon⁴, Spero Nicholas⁴, Ofer Pasternak³, Habiballah Rahimi-Eichi², Phillip Wolff⁵, René Kahn⁶, Martha E. Shenton³

¹*École de Technologie Supérieure*, ²*McLean Hospital, Harvard Medical School*, ³*Brigham and Women's Hospital, Harvard Medical School*, ⁴*University of California, San Francisco*, ⁵*Emory University*, ⁶*Icahn School of Medicine At Mount Sinai*

Background: Modern research management assumes a data governance model in which grantees are considered stewards rather than owners of important data sets, and thus there is an expectation that samples are shared with the widest possible community of researchers who can collaborate to gain insights. This presents challenges in the study of complex, heterogeneous conditions involving sensitive health information, which require balancing privacy and autonomy of individuals with the needs of the research community. Here, we report on the data operation ecosystem crafted for the AMP SCZ project, a complex, international multisite observational study of young individuals who are at clinical high risk (CHR) for developing a psychotic condition, such as schizophrenia.

Methods: The data flow for this project is unique in that it requires coordination between two research networks each managing different data capture ecosystems, the Data Processing Analysis Coordination Center (DPACC) overseeing data QC, processing, and visualization, and the NIMH Data Archive (NDA) where curated data is disseminated. To handle this heterogeneous federated model, DPACC developed an aggregation tool, Lochness, which can pull data from a wide range of data capture systems, organize the data files on a local data lake, and perform de-identification procedures. This tool has been deployed on two separate servers, one within each research network's IT infrastructure.

De-identified data from both networks are then automatically transferred daily to the DPACC for QC and processing. Key QC and study monitoring metrics are displayed in a custom study dashboard. Data are then further transformed to comply with the NDA data dictionaries and uploaded to the NDA, where data can be explored by AMP SCZ partners in a private collaboration space. Data is also shared with the wider community via traditional NDA data releases.

QC is assessed in near real-time for all data types. Form data are checked for missingness and valid ranges. Automated and manual QC pipelines have been established for all complex data types including EEG, MRI, A/V, fluid and digital biomarker data, monitored by DPACC and AMP SCZ domain experts. All findings are reported back to the research networks management team for follow-up.

Results: The AMP SCZ dataset includes form data from 68 instruments, capturing 14,355 unique variables. In addition to this tabular data, we capture and process MRI (structural, diffusion and resting state), EEG (task and resting state), A/V recordings (20-minute open interview) at two time points, as well as high-frequency data from participant's smartphones and a wearable actigraphy device.

As of October 23rd, 2023, we have QCed data from 763 participants, including 860 EEGs, 841 MRIs, 891 blood and 875 saliva sample collections, 755 open interviews and associated transcripts, as well as smartphone data from 429 participants, totalling over 30TB worth of data.

The first public NDA data release is planned for November 2023, and will have baseline raw data from 430 unique subjects (a total of 39 different measures). The second release is planned for Spring 2024, with a frequency of updates every 6-9 months.

Conclusions: Our process-oriented approach leverages automation to enhance data quality, data flow speed, and collaboration, thereby underscoring the project's contribution to the advancement of research practices involving complex, international multisite studies in sensitive mental health conditions. Near real-time QC allows for problematic measures to be

corrected or re-collected, and deviations in protocols are caught quickly. Finally, our harmonization efforts and tight collaboration with the NDA ensure wide dissemination of the dataset beyond AMP SCZ.

6.3. DATA ANALYSIS FOR THE AMP SCZ INITIATIVE – CHALLENGES AND INNOVATIONS

Ofer Pasternak*¹, Guillermo Cecchi²

¹*Harvard Medical School*, ²*IBM Research*

Background: The Accelerated Medicines Partnership® Schizophrenia (AMP® SCZ) initiative is a large international collaboration with the goal of developing algorithms to predict trajectories and outcomes of individuals at clinical high risk (CHR) for psychosis. The project involves collecting data from approximately 2000 CHR individuals and 640 matched healthy controls. This data includes a wide range of longitudinal assessments, such as clinical, environmental, cognitive, biobehavioral, neuroimaging, electrophysiology, and fluid biospecimens markers. Additionally, AMP SCZ collects speech and facial expression samples, as well as measures from novel digital health technologies, passive sensing and actigraphy. The data analysis for AMP SCZ is conducted by the Analysis and Visualization core (Core 3) of the Data Processing, Analysis, and Coordination Center (DPACC) in collaboration with experts from across AMP SCZ. Core 3 has two primary objectives: 1) developing prediction algorithms for clinical endpoints, and 2) creating algorithms to characterize clinical trajectories, the former to serve as enrichment tools to optimize the logistics of recruitment in future clinical trials, and the latter to optimize early detection of the effect of treatment and provide better mechanistic understanding of CHR trajectories.

Methods: To achieve these objectives, Core 3 is actively engaged in developing and piloting robust, flexible, and clinically-informed predictive algorithms, as well as computational and statistical models. These efforts are aimed at tackling the significant challenges posed by the analysis of a large and complex dataset, including: 1) defining appropriate and well-characterized prediction endpoints, 2) ensuring the generalizability of proposed methods, 3) combining predictive modeling across multiple modalities with a substantial number of features, 4) leveraging longitudinal information and accounting for different time scales across modalities, and 5) addressing issues related to missing data.

Results: Core 3 played a crucial role in defining and parametrizing the clinical endpoints of the observational study. Endpoints include conversion-to-psychosis, remission, and non-remission/non-conversion within assessment periods of 1- and 2-years. Using legacy data, we assessed the expected prevalence of these endpoints to guide our analyses. To ensure the robustness and generalizability of our prediction models, we have set aside 200 CHR individuals for independent validation. This set can validate predictors with an area under the curve of 0.7 or higher, and with a prevalence of 10% or higher. In tackling the challenge of dealing with multiple data modalities, we explored innovative methods for data fusion using legacy datasets that share similarities with the AMP SCZ study. Our findings highlighted the significant advantages of intermediate data fusion techniques, like multi-kernel learning (MKL), compared to single modality predictors. MKL offers interpretability, important for a better mechanistic understanding of CHR, and also identifies correlations across modalities. Applying MKL on legacy data that included clinical, cognitive, MRI and EEG data we found a significant increase of predictive accuracy for MKL (AUC:0.73) relative to the single modality with the highest predictive power (cognitive scores, AUC:0.69). Furthermore, Core 3 developed a novel algorithm inspired by wisdom of crowds. This algorithm combines predictions from 19 previously proposed models, and when applied to legacy data it resulted

with a substantial increase in the conversion rate from originally 10% to 33% in the enriched population (with balanced accuracy of 74.7% and 100% sensitivity). We also investigated the utility of Dynamic Time Warping approaches, demonstrating the predictive advantage of using longitudinal data as opposed to relying solely on single time point predictors. Additionally, we leveraged legacy data to quantify missing data, and tested models for data imputation.

Conclusions: The AMP SCZ initiative, and the innovative yet robust analyses reported above are important to advance the development and use of novel pharmacological interventions for CHR individuals. These analyses place the AMP SCZ project on track to identify important biomarkers for the prediction of clinical outcomes in CHR, and to pave the road for more effective and efficient clinical trials.

6.4. DISSEMINATION FOR THE AMP SCZ INITIATIVE – INFORMED BY LIVED EXPERIENCE

Tina Kapur*¹, Kathryn Lewandowski², Carlos Larrauri³, Ameneh Asgari-Targhi¹, Beier Yao⁴, Lisa Brown⁵, Suzanne Garcia⁶, Michael J. Coleman¹

¹*Brigham and Women's Hospital, Harvard Medical School*, ²*Harvard Medical School/McLean Hospital*, ³*Harvard Kennedy School and The University of Michigan Law School*, ⁴*McLean Hospital*, ⁵*Brigham and Women's Hospital*, ⁶*NIMH*,

Background: The dissemination of program resources developed by the AMP SCZ program is performed by the Dissemination core (Core 4) of the of the Data Processing, Analysis, and Coordination Center (DPACC), in close collaboration with experts from across AMP SCZ.

Methods: Led by investigators at Brigham and Women's Hospital and McLean Hospital, Core 4 works closely with all other cores in AMP SCZ program and with NIMH and FNIH to deliver a consistent message about the AMP SCZ program across participating sites and to the broader community. The mission of this group includes establishing and maintaining an internet presence for dissemination to the research community at large of all tools developed by the program, and for outreach via the website to those affected by CHR. Advocates from NAMI, OneMind, and Mental Health America regularly present their experiences around outreach and communication with an emphasis on considerations from a lived experience perspective to ensure that the voices of lived experience are amplified across the broader AMP-SCZ project. A Fortune 500 company was engaged to coach the Core 4 team on creating a website that is accessible to all, iterating on a Section 508 compliant design.

Results: The AMP SCZ website (<https://www.ampscz.org>) was launched in May 2022 and conveys the aims and activities of the AMP SCZ program in plain language for audiences including researchers, help seeking youth and their families, and clinicians. The website features information regarding (a) study participation including purpose, eligibility, FAQs, and information for clinicians; (b) a map of study sites with contact information, and educational information on schizophrenia and CHR; (c) materials for the research community including study design and protocols, data sharing, and software tools; and (d) study news and events including recruitment updates, published papers, videos, and other resources. The website includes links to advocacy organizations, and regularly features content by people with lived experience including articles, podcasts, and recorded talks. In the 16 months since launch, the site has garnered more than 13,500 sessions and more than 24,500 page views.

As previous literature suggests, we have seen positive effects of our deliberate inclusion of lived experience throughout all phases of AMP SCZ, including through our efforts at dissemination through our website. For example, approximately 18 percent of AMP SCZ website traffic is referral traffic, i.e., visitors clicked a hyperlink on a different website that

took them to the AMP SCZ website. The second highest source of referral traffic is the NAMI website, indicating that those with lived experience have been visiting the AMP SCZ website. This suggests that including people with lived experience and advocacy groups at all stages of the project both enhances the quality of the research and builds a bridge of trust between potential research participants and the scientific community, enhancing recruitment efforts and ensuring that participants are being treated by the research community with respect and proper consideration. The next most popular pages of the website are the “Study Sites” and “Schizophrenia and Clinical High Risk” pages, which display a searchable map of study sites world-wide and information about schizophrenia and clinical high risk, respectively.

Conclusions: DPACC Core 4 has overseen the dissemination of resources from the AMP SCZ program to the broader community using the program website and has promoted the voices of people with lived experience to enhance the work, resulting in better science and greater community partnership.

7. IMMUNE ACTIVATION AND SCHIZOPHRENIA: FOCUS ON RISK AND RESILIENCE TRAJECTORIES

Annamaria Cattaneo, *IRCCS Fatebenefratelli Institute, Brescia; University of Milan; Institute of Psychiatry, King's College*

Overall Symposia Abstract: Immune activation has long been associated with schizophrenia, however the dysregulation of the immune system may be pathologically relevant only in a subgroup of patients. For example, while maternal immune activation (MIA) represents a risk factor for schizophrenia, the majority of exposed offspring will not develop overt pathological sequelae, suggesting a substantial degree of resilience to the effects of MIA. Likewise, non-resolving inflammatory abnormalities are evident only in a subgroup of schizophrenia cases and may predict poorer clinical outcomes. Against this background, our multidisciplinary symposium will bring together key opinion leaders presenting novel data from animal models and clinical cohorts, providing a further understanding of the developmental trajectories and molecular underpinnings that determine risk and resilience to immune activation in schizophrenia. Prof. Urs Meyer (Univ of Zurich) will present data on vulnerability towards MIA in isogenic mouse models and will show how adult offspring can be stratified into resilient and susceptible based on behavioral and molecular signatures. He will also discuss how high social functioning at juvenile age may represent a resilience-promoting factor against long-term behavioral abnormalities and discuss strategies to promote social behaviour in vulnerable animals. Prof Anthony Vernon (King's College London) will present ex vivo structural MRI data obtained in MIA animal model and will discuss the neural correlates associated with risk and resilience. He will also show how multivariate analysis of both neuroanatomical and behavioural data can predict the differing behavioural phenotypes, highlighting the relevance of these data for advancing our understanding of the neurodevelopmental effects induced by MIA and for biomarker-guided approaches. Prof. Annamaria Cattaneo (University of Milan) will show central and peripheral transcriptomic data from a preclinical mouse model, in which immune activation is driven by prenatal stress. She will specifically focus on adolescence as a critical time window for the manifestation of a fully blown phenotype in exposed offspring. In addition, she will present novel transcriptomic analyses in blood samples of patients with schizophrenia and will highlight the presence of shared molecular alterations across species and tissues that could serve as biomarkers of risk prediction. Finally, Fabiana Corsi-Zuelli (Ribeirão Preto, University of São Paulo) will present novel data from two cohorts of individuals with schizophrenia. She will discuss the role of peripheral inflammation in

schizophrenia, spanning from early to chronic stages. She will focus on the association between IL6 and depressive and negative symptoms in individuals with early and chronic schizophrenia. She will also discuss relationships between IL6, brain structures, cognitive performance, and their impact on depressive and negative symptoms. Together with the discussant (Prof. Paola Dazzan, King's College London) this panel of experts will discuss how these findings can advance the understanding of mechanisms involved in vulnerability towards immune-related insults and the potential towards the identification of novel, more targeted strategies for preventive and therapeutic interventions.

7.1. IMPACT OF EARLY IN LIFE INSULTS ON VULNERABILITY AND RESILIENCE TO SCHIZOPHRENIA: HOW CAN WE TARGET IMMUNE RELATED RESPONSES TO PROMOTE PREVENTION AND TREATMENT EFFICACY?

Annamaria Cattaneo*¹, Giulia Petrillo², Ilari D'Aprile², Marco Andrea Riva²

¹*IRCCS Fatebenefratelli Institute, Brescia; University of Milan; Institute of Psychiatry, King's College,* ²*University of Milan*

Background: Exposure to early life adversities represents an important risk factor for the development of psychiatric disorders, including schizophrenia. The enhanced susceptibility to psychopathology may result from changes in gene transcription, which may either transiently affect specific brain structures or produce long-lasting modifications of key player for neuronal function. Animal models are particularly useful to identify the biological systems that are affected in the brain as consequence of such exposures, and peripheral biomarkers that can be translated in the clinical setting. Moreover, they could represent suitable targets for pharmacological interventions.

Methods: Pregnant dams have been exposed to prenatal stress (PNS), which leads to immune activation in pregnant dams, and offspring have been tested at adolescence (n=16 CTRL and n=18 PNS) and adulthood (n=32 CTRL and n=34 PNS per sex) for different behavioural tests (sociability, anhedonia, and cognition) and brain and blood samples have been collected during their neurodevelopment (PND42, PND 62 and PND90). Animals have been stratified into resilient and vulnerable based on the behavioural outcomes and RNAseq analyses have been performed in the brain (hippocampus and prefrontal cortex) and in blood samples. To translate findings into clinical level, RNAseq analyses have been performed also in blood samples of controls and patients with schizophrenia and convergent analyses have been performed. RNA-Sequencing data have been analysed by using DESeq2, whereas pathways analyses were performed by using Ingenuity Pathways Analysis software. At preclinical level, after having identified the most promising candidates from these analyses, we investigated their expression profile of immune related genes (IL-1beta, IL-6, TNF, MIF) and microglia activation (Iba1, CD68, CD45). We also investigated whether sub-chronic treatment with lurasidone (2 weeks), given during the peripubertal period, could modulate the changes originating from prenatal exposure.

Results: PNS exposed animals have been stratified into vulnerable and resilient both at adolescence and at adulthood: PNS adolescent vulnerable animals showed anhedonia and deficits in sociability (p LESS THAN 0.05) and when adult they continued to show reduced social interaction (p LESS THAN 0.05). RNAseq data from hippocampus and prefrontal cortex identified, only in vulnerable animals, a cluster of genes associated with an overactivation of pathways related to immune system, including the Neuroinflammation signaling pathway, Glucocorticoid receptor Signaling and miRNA30a signaling. Interestingly, IL-6 signaling

pathway was observed modulated also in blood samples of vulnerable animals (all p LESS THAN 0.05, FC $\pm$ 1.2, FRD corrected). Microglial activation markers and pro-inflammatory cytokines were differentially expressed in adolescent and adult rats exposed to PNS, with a more pronounced effect in vulnerable animals (+35%, $p=0.0002$; +33%, $p=0.039$ in vulnerable vs resilient animals). Also, in the blood the measured pro inflammatory cytokines (IL-1 β , MIF, and IL-6) are significantly increased in vulnerable animals only and the inflammatory z-score (considering both the blood and the brain) confirmed a pro inflammatory status in association with PNS in vulnerable animals. Importantly, sub-chronic treatment with lurasidone was able to prevent, to a large extent, the up-regulation of miR30a and of IL-6 as well as the changes on genes related to those pathways. In controls and patients with schizophrenia, RNAseq analyses revealed the modulation of 143 genes (p LESS THAN 0.05, FC $\pm$ 1.2, FRD corrected) involved in neurodevelopmental pathways and in immune/inflammatory processes.

Conclusions: In summary, our data suggest that PNS exposure produces a wide range of transcriptional changes in several biological systems, including stress, inflammation, and metabolism. Some of these changes show the peak during adolescence (IL-6 signaling and neuroinflammation), although most of them persist into adulthood. Interestingly, IL-6 pathways came up as the most significant one also in blood samples of patients with schizophrenia. Importantly, chronic lurasidone treatment during peri-puberty is able to counteract or prevent most of these molecular alterations that are known to contribute to stress-related psychiatric disorders, and thus it may be useful in minimizing the individual vulnerability for psychopathology.

7.2. ROLE OF SOCIAL FUNCTIONING IN DETERMINING RISK AND RESILIENCE TO SCHIZOPHRENIA-RELATED PATHOLOGY AFTER MATERNAL IMMUNE ACTIVATION IN ANIMAL MODELS

Ron Schär¹, Flavia Müller¹, Ulrike Weber-Stadlbauer¹, Urs Meyer*¹

¹*University of Zurich*

Background: Infectious or non-infectious maternal immune activation (MIA) during pregnancy is a risk factor for the offspring to develop schizophrenia and related disorders. Despite the increasing evidence for significant health consequences, the majority of MIA-exposed offspring will not develop overt pathological sequelae, suggesting that there is a substantial degree of resilience to the neurodevelopmental effects of MIA. We recently provided experimental evidence for this hypothesis using a mouse model of viral-like MIA, which revealed the existence of subgroups of adult offspring characterized by the presence or absence of behavioral, transcriptional and inflammatory anomalies even under conditions of genetic homogeneity. The present study aimed to investigate the developmental ontogeny and mechanisms underlying dissociable consequences of MIA in an isogenic mouse model of viral-like MIA.

Methods: In a first cohort, pregnant C57BL/6N mice were treated with the viral mimetic, poly(I:C) (5 mg/kg, i.v.) on gestation day 12 ($n = 8$ litters), whereas control dams received vehicle solution on the same gestational stage ($n = 6$ litters). Male and female MIA-exposed offspring ($n = 22$ males and 24 females) and control offspring ($n = 14$ males and 16 females) were subjected to a social interaction test at juvenile age (postnatal day [PND] 25) and were then left to mature into adulthood. At adult age (PND 100 onwards), the same offspring were tested in a number of behavioral tests, including open field exploration, social interaction, prepulse inhibition and working memory. A second cohort of MIA-exposed offspring (8 males and 8 females; from 8 litters) and control offspring (5 males and 5 females; from 5 litters) were

generated for analyses of hypothalamic oxytocin-expressing cells and plasma oxytocin levels after the social interaction test at juvenile age (PND 28). In a third cohort, MIA-exposed offspring (n = 30 males and 30 females, from 12 litters) and control offspring (n = 15 males and 15 females, from 6 litters) were stratified into resilient and susceptible subgroups based on their juvenile sociability index. Susceptible offspring with low juvenile sociability scores received pro-social stimulation (or sham stimulation only) throughout adolescence to early adulthood, after which they were tested at adult age (PND 100 onwards).

Results: Regardless of sex, MIA-exposed offspring could be stratified into two subgroups with low and high sociability scores, respectively, at juvenile age. MIA-exposed offspring with low juvenile sociability scores differed from control offspring with regards to social approach behavior at juvenile age (p LESS THAN .001). As adults, MIA-exposed offspring with low juvenile sociability scores continued to display reduced social interaction compared to control offspring and MIA-exposed offspring with high juvenile sociability scores (p LESS THAN .001) and also displayed significant deficits in prepulse inhibition (p LESS THAN .01) and working memory (p LESS THAN .05). Hypothalamic oxytocin-expressing cells and plasma oxytocin levels were reduced in MIA-exposed offspring with low juvenile sociability scores (oxytocin-expressing cells: p LESS THAN .01, plasma oxytocin: p LESS THAN .05), but not in MIA-exposed offspring with high juvenile sociability scores. Additional investigations are ongoing and will show whether or not pro-social stimulation throughout adolescence is capable of preventing the adult emergence of multiple behavioral and cognitive dysfunctions in susceptible MIA offspring with low juvenile sociability scores. These data will also be presented.

Conclusions: Our findings provide experimental evidence suggesting that the presence of social impairments at juvenile age is predictive of multiple behavioral dysfunctions in adulthood and associated with impaired production of the pro-social hormone, oxytocin. High social functioning at juvenile age may represent a resilience-promoting factor against long-term behavioral abnormalities after MIA.

7.3. STRUCTURAL NEUROIMAGING CORRELATES OF RESILIENCE AND SUSCEPTIBILITY TO MATERNAL IMMUNE ACTIVATION

Anthony Vernon^{*1}, Yi-An Liao¹, Flavia Mueller², Joseph Scarborough², Sina Schalbetter², Eugene Kim¹, Juliet Richetto³, Urs Meyer²

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*University of Zurich*, ³*ETH Zurich*

Background: Infectious or non-infectious maternal immune activation (MIA) is an environmental risk factor for psychiatric and neurological disorders with neurodevelopmental origins. Whilst there is increasing evidence for significant health consequences, the effects of MIA on the offspring appear to be variable. We previously demonstrated that mouse offspring exposed to identical MIA could be stratified into distinct subgroups that were characterized by the presence (susceptible) or absence (resilience) of multiple behavioural dysfunctions. Here, we aim to identify the neuroanatomical correlates of this resilience and susceptibility to MIA using structural MRI.

Methods: MIA was induced in C57BL6/N mice by administration of the viral mimetic, poly(I:C), on gestation day 12 and the offspring clustered into either resilient or susceptible groups using 2-step-recursive clustering (Mueller et al. 2021). A subset of resilient (N=14 [8m, 6f]), susceptible (N=14 [8m, 6f]) and control offspring (N=16 [8m, 8f]) were sacrificed for ex vivo structural MRI. Group differences in neuroanatomy were analysed voxel-wise using tensor-based morphometry with correction for multiple comparisons (5% FDR). To map brain

and behaviour data into single multivariate model, we then applied sparse partial least squares analysis (sPLS).

Results: There were no statistically significant group-wise differences in either regional brain volumes or diffusion imaging parameters (FA, MD) after correction for multiple comparisons. Multivariate sPLS identified a single statistically significant latent variable (LV1) ($p=0.017$). Multivariate maps associated anxiety-like, social, cognitive and sensorimotor gating deficits with volumes of multiple prefrontal and limbic grey matter regions and volumes of major white matter tracts.

Conclusions: In this cross-sectional study, the neural correlates of susceptibility and resilience to MIA induced in identical mouse offspring are best-described using multivariate analysis of both neuroanatomical and behavioural data. These data have relevance for advancing our understanding of the variable neurodevelopmental effects induced by MIA and for biomarker-guided approaches in preclinical psychiatric research.

7.4. PRESSIVE AND NEGATIVE SYMPTOMS ALONG THE EARLY AND CHRONIC STAGES OF SCHIZOPHRENIA: INTEGRATING INTERLEUKIN-6 LEVELS, COGNITIVE PERFORMANCE, AND STRUCTURAL BRAIN ALTERATIONS

Fabiana Corsi-Zuelli^{*1}, Gary Donohoe², Sian Lowri Griffiths³, Cristina Marta Del-Ben¹, Andrew Watson⁴, Tom Burke², Paris Alexandros Lalouis⁵, Declan McKernan⁶, Derek Morris⁶, John Kelly⁷, Colm MacDonald², Jack Rogers³, Nicholas M Barnes³, Carmine Pariante⁵, Golam Khandaker⁸, John Suckling⁹, Bill Deakin¹⁰, Rachel Upthegrove³, Maria Dauvermann³

¹University of São Paulo - Ribeirão Preto Medical School - FMRP USP, ²Cognitive Genetics and Cognitive Therapy Group, The Centre for Neuroimaging, Cognition and Genomics (NICOG), School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, ³University of Birmingham, ⁴UCL Institute of Neurology, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁶National University of Ireland, Galway, ⁷National University of Ireland Galway, ⁸University of Bristol, ⁹University of Cambridge, ¹⁰University of Manchester

Background: Depressive and negative symptoms in schizophrenia (SZ) have been implicated in poor functional outcomes, including treatment resistance. Cognitive deficits, reduced brain structures (cortical thickness and volume), and elevated interleukin (IL)-6 levels may contribute to depressive and negative symptoms in SZ.

Methods: We applied structural equation modelling (SEM) to examine the unique and combined relationships between IL-6 levels, brain structures, cognitive performance, and their impact on depressive and negative symptoms, in two cohorts of participants in the early ($n=102$; 76.5% males, mean age 25.3 ± 4.9 ; BeneMin study) and chronic stages of SZ ($n=42$; 69.0% males, mean age 44.7 ± 10.3 ; iRELATE study). We ran SEM in two groupings of (i) all participants with early and established SZ; (ii) early SZ only. To address the relatively limited sample size in SEM, we also performed a series of exploratory generalised linear models (GLM) to evaluate the influence of IL-6 levels on various independent outcomes of a) depressive symptoms (BeneMin $n=201$; iRELATE $n=94$); b) negative symptoms (BeneMin $n=201$; iRELATE $n=93$); c) brain structure factors (BeneMin $n=102$; iRELATE $n=42$); and d) general cognitive performance factor (BeneMin $n=102$; iRELATE $n=42$). All statistical analyses were adjusted for sex, age, and chlorpromazine equivalent dose.

Results: SEM findings across all participants and in early SZ only showed that higher IL-6 levels were associated with lower brain structures (combined: Beta= -0.247, SE=0.078, p=0.002; early SZ only: Beta= -0.274, SE=0.092, p=0.003). In addition, brain structures were positively related to general cognitive performance (combined: Beta=0.353, SE=0.073, p LESS THAN 0.001; early SZ only: Beta=0.303, SE=0.090, p=0.001). Higher IL-6 levels were not associated with lower general cognitive performance (combined and early SZ only: p GREATER THAN 0.05). In addition, neither IL-6 levels nor brain structures predicted depressive or negative symptoms in SEM analyses (combined and early SZ only: p GREATER THAN 0.05). Exploratory GLM with larger sample size showed that higher IL-6 levels were uniquely associated with more depressive symptoms in early SZ (Beta=1.73, 95% CI=0.48; 2.97, p=0.006) and more negative symptoms in established SZ (Beta=1.02, 95%CI=0.37; 1.68, p=0.002). In addition, higher IL-6 levels were related to lower brain structures in both early (Beta= -0.49, 95%CI= -0.91; -0.07, p=0.021) and established SZ (Beta= -0.26, 95%CI= -0.40; -0.12, p LESS THAN 0.001). Nevertheless, higher IL-6 levels were not associated with general cognitive performance neither in early nor established SZ (p GREATER THAN 0.05). Combining early and established SZ yielded similar results of significant associations between higher IL-6 levels with more depressive (Beta=0.82, 95%CI=0.29; 1.35, p=0.002) and negative symptoms (Beta=0.77, 95%CI=0.14; 1.41, p=0.017), and lower brain structures (Beta= -0.27, 95%CI=-0.44; -0.10, p=0.002), with no association for general cognitive performance (p GREATER THAN 0.05).

Conclusions: We demonstrate that increased IL-6 levels are related to reduced brain structures and more depressive and negative symptoms along the early and chronic stages of SZ. The relationship between IL-6 levels and cognitive performance in SZ deserves further investigation. Our findings suggest that inflammation-related transdiagnostic symptoms may be useful for a better participant selection in anti-inflammatory trials, potentially leading to more effective treatments for individuals with SZ.

8. DISENTANGLING CONTRIBUTIONS TO SOCIAL AND NON-SOCIAL MOTIVATION TRANSDIAGNOSTICALLY

Deanna Barch, *Washington University*

Overall Symposia Abstract: Disruptions in motivation for both social and non-social outcomes and goals are experienced by individuals with psychotic disorders such as schizophrenia (SZ), but also by individuals with other psychosis spectrum illnesses, such as bipolar disorder (BD), as well as individuals with non-psychotic disorders such as major depression (MDD). While we have made some progress in understanding the potential mechanisms of such motivational impairments, there are numerous key open questions, including: a) are the psychological and neural mechanisms that contribute to motivational impairments the same or different across social versus non-social components of motivation? b) are there differential contributions of different types of clinical symptoms to social or non-social motivational impairments, such as depression versus anhedonia versus different forms of cognitive impairment? and c) are the etiological contributions or symptom associations the same or different across diagnostic boundaries? Here we bring together a diverse set of speakers working in both human and animal models to highlight recent innovations and novel data that help address these central questions. Chan and Barch will focus on both the transdiagnostic neural and psychological correlates of social and non-social motivation, including the differential associations with depression versus negative symptoms, a key unexplored topic in the literature. Specifically, Chan will present work showing that individuals with SZ demonstrate disruptions in the ability to adapt their goals and expectations

for financial outcomes relative to individuals with BD and MDD and that clinical measures of depression versus anhedonia/amotivation differentially associate with different aspects of motivation in SZ versus MDD. Barch will present work showing that individuals with SZ and BD demonstrate greater disruptions in effort-based decision-making for valued outcomes compared to individuals with MDD and that both depression and measures of social and non-social amotivation, as well as measures of cognitive control are each uniquely associated with such impairments in SZ and BD. Further, individuals with MDD show reduced activity in the ventral medial prefrontal cortex (putatively associated with subjective value processing) while individuals with SZ and BD show disruptions in activity of the dorsolateral prefrontal cortex (potentially associated with effort computations and goal planning). Catalano and colleagues address the potential key role of attention to social information in understanding disruptions in social motivation among individuals with SZ, using both behavioral and EEG data to show that individuals with SZ show the same level of initial enhanced orienting to social versus non-social stimuli, they show reduced sustained attention to social stimuli as indexed by a reduced late positive potential. Further, individuals with SZ show reduced memory for social and non-social information. Lastly, Powell brings an important pre-clinical perspective to our understanding of the neural mechanisms that drive variation in non-social and social motivation. This work shows that neurodevelopmental models of psychosis (e.g., maternal immune activation, juvenile social isolation) impinge upon social approach motivation. This animal work also illustrates how early social isolation in rodent models informs our understanding of social motivation. Together this set of presentations illustrates important new directions and insights into our understanding of social and non-social motivation impairments transdiagnostically, including both similar and unique pathways across putative diagnostic boundaries.

8.1. DISSOCIABLE NEURAL AND PSYCHOLOGICAL MECHANISMS OF MOTIVATION TRANSDIAGNOSTICALLY

Deanna Barch*¹, Erin Moran¹, Dror Ben-Zeev¹, Adam Culbreth²

¹Washington University School of Medicine, , ²University of Maryland School of Medicine

Background: Disruptions in the drive to achieve positive social, occupational and educational outcomes often reduces the quality of life among individuals with psychotic spectrum disorders, as well as individuals with other illnesses such as major depression. However, we do not know if the same or different neural and psychological mechanisms contribute to these disturbances across diagnostic boundaries. Further, we do not yet understand whether the clinical correlates of such disruptions are the same across diagnoses, including variation in depression symptoms and social and non-social motivation.

Methods: We examined performance on measures of willingness to exert cognitive and physical effort in healthy controls (HC; N=80), schizophrenia/schizoaffective disorder (SZ; N=50), bipolar disorder with psychosis (BD; N=58), current major depression (C-MDD; N=60), and past major depression (P-MDD; N=51). We examined associations to clinician and self-reported social and non-social motivation symptoms, working memory and cognitive control performance, and life function measured by ecological momentary assessment (EMA) and passive sensing. A subset of participants underwent functional neuroimaging during the performance of an effort allocation task. In this version of the EFFRT task, participants make choices between doing an easy task for a low reward, and a harder task (varying percentages of the maximum amount of finger tapping that they could do in a calibration set of trials) for

varying larger amounts of reward. Choices are made in the scanner, and then participants have to complete a random subset of their choices when they exit the scanner.

Results: Compared to HC, the SZ and BD groups, but not the C-MDD or P-MDD groups, showed reduced willingness to exert effort at the higher reward values. In the SZ/BD group, but not MDD, reduced willingness to exert effort for higher rewards was associated with greater clinician-rated motivation impairments, worse working memory and cognitive control performance, and less engagement in social and non-social goal-directed activities measured by EMA. In further EMA analyses, depressive symptoms in psychotic individuals related to both reduced anticipatory and consummatory pleasure in everyday life for both social and non-social activities, while higher negative symptoms related to reduced anticipatory but not consummatory pleasure. In whole brain FDR corrected analyses ($p < .05$), we saw reduced activity in the ventral medial prefrontal cortex (vmPFC) among C-MDD participants on trials where the harder effort task was accepted versus rejected (i.e., at the time of choice), consistent with a disruption in the computation of subjective value among the C-MDD participants. In a priori region of interest (ROI) based analyses, we saw reduced DLFPC activity among SZ and BD individuals at the time when the combined cues of reward and effort are presented. Further, we saw evidence for disrupted activity in the ventral striatum (VS) among the C-MDD individuals. Specifically, the HC, SZ, and BD all show greater VS activity on trials where they accept to do the harder task for more money than when they reject the harder task. In contrast, the C-MDD individuals show overall higher VS activity, but numerically greater VS activity on reject compared to accept trials.

Conclusions: These findings suggest that the neural and psychological mechanisms contributing to motivational impairments differ among individuals with psychosis spectrum disorders versus depression, suggesting dissociable pathways to seemingly similar disruptions. This suggests the need for targeted treatment approaches that are tailored to the particular pattern of disruptions leading to motivational impairments and life function.

8.2. TRANSDIAGNOSTIC RELEVANCE OF RANGE ADAPTATION FOR ANHEDONIA AND AMOTIVATION SYMPTOMS

Raymond Chan^{*1}, Ling-ling Wang², Hui-xin Hu³, Huang Yi-hang⁴, Yi Wang⁵, Jia Huang⁵, Xuan Wang⁴, Zhen-hua Zhu⁶, Hong-yan Sun⁶, Yuan Cai⁶, Wen-long Hou⁶, Gang Ye⁶, Zhao-peng Kang⁶, Simon Lui⁷, Li Hui⁶

¹*Institute of Psychology, Chinese Academy of Sciences*, ²*Shanghai Normal University*,

³*Beijing Forestry University*, ⁴*Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences*, ⁵*The University of Chinese Academy of Sciences*, ⁶*Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; University of Chinese Academy of Sciences*,

⁶*Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University*, ⁷*School of Clinical Medicine, The University of Hong Kong*

Background: Anhedonia and amotivation are transdiagnostic symptoms that shared by different mental disorders including schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder (BD). Range adaptation is the ability to represent stimulus value based on its relative position in the range of prior stimulus values. Range adaptation is important for optimizing value representation, and atypical range adaptation may result in anhedonia and amotivation. In the current study, we explored whether atypical range adaptation is a

transdiagnostic feature found in SCZ, MDD and BD patients. We further investigated whether range adaptation would be associated with anhedonia, amotivation and depressive symptoms.

Methods: We recruited 69 SCZ patients, 37 MDD patients, 45 BD patients and 65 matched controls (HC). Participants complete the Effort-Expenditure for Reward Task-adaptive version which measures range adaptation for both expected value (EV) and outcome value (OV). We also administered clinical rating scales and questionnaires to measure anhedonia and amotivation symptoms.

Results: We found significant group difference in EV adaptation but not OV adaptation among clinical patients and controls. Specifically, SCZ patients showed reduced EV adaptation relative to MDD, BD and HC. Correlation analysis revealed that EV adaptation was positively and significantly correlated with self-reported anhedonia and amotivation, while OV adaptation appeared to be negatively correlated with depression symptom in SCZ patients. In MDD patients, OV adaptation was negatively correlated with interview-based anhedonia and amotivation. However, in BD patients, EV adaptation was positively correlated with self-reported and interview-based anhedonia, amotivation and depression symptoms.

Conclusions: Taken together, our results suggested that reduced EV adaptation is present in SCZ but not in MDD and BD patients. However, all these clinical groups exhibited correlations of OV and EV adaptation with anhedonia and amotivation symptoms. Range adaptation is also correlated with depressive symptoms in SCZ and BD patients. Our work highlights the role of range adaptation in anhedonia and amotivation symptoms across psychiatric disorders.

8.3. COGNITIVE COMPONENTS OF SOCIAL MOTIVATION IN SCHIZOPHRENIA: EXAMINING SOCIAL ATTENTION AND MEMORY

Lauren Catalano*¹, Jonathan Wynn², Michael Green³

¹VA Greater Los Angeles Healthcare System, ²VA Greater Los Angeles Healthcare System/UCLA, ³University of California, Los Angeles

Background: Many people with schizophrenia (SCZ) experience reductions in social approach motivation, or “asociality”, that lead to social isolation and broad functional impairment. Although the prevalence and pervasive negative impact of poor social motivation is well-documented, few studies have examined the causes of social motivation impairments in SCZ. A modern conceptualization of social motivation from the NIMH RDoC expert consensus group includes two cognitive components: (a) attention to social cues, and (b) social learning and memory associated with the formation of relationships. Social attention can be further parsed into separate stages of processing. In SCZ, social stimuli may initially capture attention, but the motivation to sustain attention over time may be impaired. Individuals may also have difficulty with subsequent retrieval of social information. The current study uses electroencephalography (EEG) and event related potentials to systematically evaluate each component and stages of processing to determine where the breakdown in motivation occurs.

Methods: EEG was recorded from a preliminary sample of 20 outpatients with SCZ and 19 healthy controls (HC). We compared SCZ and HC groups using the event related potentials of (a) social attention, and (b) social memory, to examine how these processes unfold over time. Social attention was evaluated using an oddball detection task, which measures initial attention capture (Early Posterior Negativity [EPN]) and sustained attention (Late Positive Potential [LPP]) for social (scenes of persons interacting) versus nonsocial stimuli (scenes with landscapes). Social memory was evaluated using a recognition memory task, which measures neural activity during retrieval (FN400) for social (faces) versus nonsocial stimuli (houses).

Results: Data collection is currently ongoing, with preliminary results presented here. During the oddball detection task, SCZ and HC participants showed similar patterns of initial attention

orienting, such that the EPN was slightly larger for social versus nonsocial stimuli ($F = 2.95$, $p = .09$). In terms of sustained attention, SCZ participants had significantly smaller LPP amplitudes than HC participants to both social and nonsocial stimuli, ($F = 4.658$, $p < .05$); the group by condition interaction was not significant. During the recognition memory task, the SCZ group had poorer recall than the HC group ($F = 5.51$, $p < .05$), and all participants showed better recall of social versus nonsocial images ($F = 33.53$, $p < .001$). The FN400 was larger (i.e., more negative) for new images than for old images during the retrieval phase, showing that individuals successfully remembered which images they had previously seen in the task. There were no significant main effects or interaction effects (group x condition [social, nonsocial]) at this stage of data collection.

Conclusions: While this is an ongoing study, there are some preliminary trends showing impairments in certain cognitive components of social motivation in SCZ. We found that SCZ participants show the same bias as HC to initially orient toward social versus nonsocial images (intact EPN) but have diminished overall sustained attention compared with HC (blunted LPP). Additionally, SCZ participants show better recall of social versus nonsocial information like HC, but they have overall worse memory than HC. Together, these results seem to suggest that there may be deficits at later stages of cognitive processing that may have a downstream influence on decision-making and goal-directed social behaviors. Future analyses will examine correlations between social motivation components (attention and memory), clinician-rated motivation, and social functioning via digital phenotyping.

8.4. NEURODEVELOPMENTAL MODELS: A TOOL TO DISTINGUISH SOCIAL AND NON-SOCIAL MOTIVATION IMPAIRMENTS

Susan Powell^{*1}, Michael Tranter¹, Dionisio Amodeo², Chi-Yu Lai³, Megan Sikkink¹, Mark Geyer¹, Neal Swerdlow¹, Jared Young¹, Samuel Barnes¹, M. Margarita Behrens³

¹University of California San Diego, ²California State University San Bernardino, ³The Salk Institute

Background: Several neuropsychiatric disorders, including psychotic disorders, have developmental origins. Disruption of the maternal environment during prenatal development can significantly contribute to risk for neuropsychiatric disorders such as schizophrenia. There is increasing evidence that prenatal exposure to viruses and other immune-activating factors increases risk for neurodevelopmental psychiatric disorders. Additionally, lack of appropriate social contact early in life alters neurobehavioral development and contributes to neuropsychiatric disorders. Hence, preclinical animal models focusing on prenatal risk factors (e.g. maternal immune activation) and early environmental stressors (e.g. social isolation) have been developed to inform the relationship between social and non-social motivation, their relationship to other cognitive domains, and their neurobiological underpinnings.

Methods: To induce maternal immune activation (MIA), timed pregnant dams are administered PolyI:C (20 mg/kg) or vehicle at E12.5. Offspring are weaned at P24 and tested in a social approach task to measure social motivation and a probabilistic reversal learning task to measure feedback-driven decision-making. For social isolation rearing (SIR) studies, male and female rats are weaned on postnatal day 24 and housed either in isolation (1/cage) or socially in groups of 2/cage. Rats are tested in a social approach task, a probabilistic reversal learning task, and a progressive ratio breakpoint task to measure non-social motivation.

Results: Maternal immune activation, which is associated with decreased social behavior ($t(15) = 3.90$, $p < 0.01$), also produces deficits in probabilistic reversal learning (significant main effect of treatment, $t(15) = -5.18$, $p < 0.001$). Reversal learning deficits in the MIA model were associated with the level of social approach behavior as well

as long-term effects on expression of 24 genes, including genes involved in glutamatergic neurotransmission, mTOR signaling and potassium ion channel activity. SIR rats spent more time exploring the stranger rat compared to the Object ($p < 0.05$); whereas SIR rats did not prefer the stranger rat over the object, i.e. less social approach behavior. Similar to our previous studies, all rats learned the probabilistic reversal learning task as evidenced by increased reversals over test days [main effect of Day; $F(11,286)=16.36$, $p < 0.001$]. SIR rats showed an overall decreased number of reversals across the 12-day training period [Housing, $F(1,26)=34.43$, $p < 0.001$; Housing x Day, $F(11,286)=2.23$, $p < 0.05$] and completed fewer overall trials compared to social rats [$F(1,26)=21.44$, $p < 0.001$]. Conversely, SIR rats do not show impairments in motivation for food reward in a Progressive ratio breakpoint study.

Conclusions: Decreased social motivation is associated with cognitive flexibility deficits across two neurodevelopmental models relevant to psychosis, maternal immune activation and social isolation rearing. Social motivation deficits in MIA mice are associated with deficits in cognitive flexibility and alterations in gene expression in frontal cortex. SIR rats display deficits in social motivation and probabilistic reversal learning, but no deficits in motivation for food reward as measured in a progressive ratio breakpoint task. While experimenter-imposed social isolation provides a viable experimental model for understanding some biological mechanisms linking social dysfunction to clinical and neural pathology in schizophrenia, it bypasses critical antecedents to social isolation in schizophrenia, notably deficits in social reward and social motivation. Recent efforts at modeling social motivation using effort-based tasks in rodents have the potential to quantify these antecedents, identify models (e.g. developmental, genetic) that produce deficits, and advance pharmacological treatments for social motivation deficits.

9. RESPONDING TO CHALLENGES: APPLYING NOVEL METHODS TO THE STUDY OF VIOLENCE IN PSYCHOSIS ACROSS THE LIFESPAN AND CULTURAL CONTEXTS

Unn Kristin Haukvik, *Institute of Clinical Medicine, University of Oslo*

Overall Symposia Abstract: Violence and aggression committed by persons with schizophrenia are major challenges to treatment, outcome, and societal safety, and lead to stigmatization of a large patient group. A key to prevent such events is to understand the complex biopsychosocial underpinnings of violence associated with severe mental disorders and their interaction with each other, across the lifespan and cultural contexts.

Adolescence is a critical time periods for emergence of disruptive behaviour as well as prodromal psychosis symptoms and constitutes a crucial developmental window for early intervention. Several overlapping environmental risk factors for antisocial behaviour and psychosis have been identified, e.g., childhood adversities and substance abuse. Neuroimaging studies have shown brain-based correlates of violence and anti-social behaviour in psychosis, such as abnormalities in the prefrontal and the limbic regions, central hubs of the emotion regulatory circuitry. Novel methods within imaging genetics research show distinct brain anatomical patterns involved in behavioural traits and mechanisms underpinning mental illness. This opens new possibilities for understanding the complex gene-environment-interactions and mechanistic underpinnings of violence in psychosis.

In this symposium, we will present how the application of state-of-the art methodologies in genetics and neuroimaging can provide novel insights about the neurobiology of violence in psychosis, the developmental trajectories and comorbidity during adolescence, and how risk-

factors for violent behaviour in psychosis manifest in a population from the global south. We will combine research using extensive datasets from international databases and collaborative mega-analyses conducted by research centers worldwide with research studying individual profiles, recognizing that the co-occurrence of disruptive behavior and psychotic symptoms leading to violence and criminal offending is observed only in a minority of psychosis patients.

The first presentation explores the genetic overlap between psychosis and anti-social traits by applying molecular genetic methods in a large cohort comprising 22 000 adolescents. With high heritability estimates of conduct disorder at 40-50% and psychosis at 40-80%, this study addresses the molecular genetic underpinnings of this vulnerability at the developmental stage.

The second presentation investigates the complex interactions between childhood trauma and aggression and how these factors affect social cognition, known to be impaired both in psychosis and violence. To expand the cultural context, this study is conducted among the Xhosa population in South Africa, which represents a sociodemographic marginalized and vulnerable population.

The third presentation addresses the fact that there is a striking inter-individual variability in neurobiology which is lost in regular case-control studies of brain morphology. By applying a novel computational method based on brain anatomical deviations from the norm (normative modelling), this heterogeneity can be mapped at the individual level.

Finally, the fourth study reveals a complex genetic relationship between antisocial behavior, substance use, and psychiatric traits. Significant genetic correlation and the identification of shared genetic loci associated with antisocial behaviour and related traits, suggest a common genetic basis for these conditions.

9.1. GENETIC ASSOCIATIONS BETWEEN PSYCHOTIC AND ANTISOCIAL TRAITS IN ADOLESCENTS

Natalia Tesli*¹, Piotr Jaholkowski², Andreas Jangmo³, Jaroslav Rokicki⁴, Viktoria Birkenæs⁵, Christine Friestad⁶, Ole A. Andreassen⁷, Martin Tesli⁸, Unn K. Haukvik⁹

¹University of Oslo and Oslo University Hospital, ²Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo and Oslo University Hospital,, ³Division of Mental and Physical Health, Norwegian Institute of Public Health, ⁴Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁵NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo⁶Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, University College of Norwegian Correctional Service,⁷NORMENT KG Jebsen Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo,Oslo University Hospital, ⁸Norwegian Institute of Public Health, Oslo, Norway; Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁹Norwegian Centre for Mental Disorders Research (NORMENT), University of Oslo, NORMENT, Oslo University Hospital, Oslo University Hospital, Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital,

Background: Antisocial behavior in youth has serious consequences for the individuals involved, close environment and the society at large. At the same time late childhood and

adolescence are critical time periods for emergence of prodromal psychosis symptoms. Co-occurrence between these two domains of psychopathology may aggravate aggression and later lead to adverse outcomes such as violent behaviour and criminality. Previous family studies have indicated common genetic determinants for psychotic and aggressive traits. However, we lack in-depth knowledge of putatively shared genetic liability between disruptive behaviour and psychosis symptoms using molecular genetic methods.

Methods: Firstly, we interrogated phenotypic overlap between disruptive traits and psychotic-like experiences in adolescents in the Norwegian Mother, Father and Child Cohort Study (n=22096). Secondly, we investigated bidirectional associations between polygenic risk scores (PRSs) for antisocial behavior and schizophrenia and disruptive traits and psychotic-like symptoms. We corrected the models for sex, age, and the first 10 ancestry principal components.

Results: We found phenotypic overlap between disruptive traits and psychotic-like experiences. This was reflected on the genetic level, as we found significant associations between PRS for antisocial behavior and psychotic-like symptoms [p-value FDR-corrected = .0007]. The associations between PRS for schizophrenia and disruptive behaviour (including conduct disorder [p-value FDR-corrected = .021] and oppositional defiant disorder traits [p-value FDR-corrected = .002]) were also present, but to a lesser degree.

Conclusions: The observed overlap between disruptive traits and psychotic-like symptoms in youth may be partially explained by common genetic liability. These findings highlight the importance of a broad clinical assessment and closely monitoring of youth at high risk for psychosis and disruptive traits, in order to prevent harmful consequences for the individuals and their environment.

9.2. LIFE HISTORY OF AGGRESSION IN A SOUTH AFRICAN STUDY OF XHOSA PEOPLE LIVING WITH SCHIZOPHRENIA

Christine Friestad¹, Christina Bell², Olivia Wootton^{*3}, Jaroslav Rokicki⁴, Natalia Tesli⁵, Anja Vaskinn⁶, Gabriela Hjell⁷, Thomas Fisher-Vieler⁸, Ruben Gur⁹, Ezra Susser¹⁰, Unn K. Haukvik¹¹, Dan Stein³

¹Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, College of Norwegian Correctional Service, ²University of Oslo, Oslo University Hospital, ³University of Cape Town, ⁴Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁵University of Oslo and Oslo University Hospital, ⁶Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, ⁷University of Oslo and Østfold Hospital, ⁸University of Oslo, Oslo University Hospital, ⁹University of Pennsylvania, ¹⁰Columbia University, ¹¹NORMENT, Norwegian Centre for Mental Disorders Research, Institute for Clinical Medicine, University of Oslo, Institute of Clinical Medicine, University of Oslo, Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital

Background: People living with schizophrenia (PLS) are at increased risk of committing acts of violence as well as experiencing violence themselves. The causes of violence in psychosis are multifactorial and many risk factors for violent behaviour have been identified, including adverse childhood experiences and social cognitive impairments. However, few studies have investigated the risk factors for violence in psychosis in low- and middle-income settings where differences in the socioeconomic context may affect the interaction between known risk factors and violent behaviour.

Methods: A subsample of participants (PLS = 179; controls = 357) from The Genomics of Schizophrenia in The South African Xhosa People Study completed The Childhood Trauma Questionnaire (CTQ), Life History of Aggression (LHA), Penn Emotion Identification Test, and Structured Diagnostic Interview for DSM-IV Axis I Disorders. Between group differences for childhood trauma, LHA, social cognition, and selected demographic and clinical factors were assessed using t-tests and chi-square tests. We tested if total scores for the LHA or CTQ were able to predict current social cognitive performance using multivariable linear regression.

Results: Scores for the CTQ and LHA were significantly higher for PLS and social cognitive performance was significantly worse for PLS compared to the control group. Current social cognitive performance was significantly associated with childhood trauma but not with aggressive behaviour over the lifetime.

Conclusions: The null relationship between current social cognition and lifetime aggression may be due to the relatively low rates of aggression reported in our sample. The significant relationship between social cognition and childhood trauma in this sample provides evidence that the effect of childhood trauma on social cognition in adulthood persists even in environments where adverse childhood experiences are relatively prevalent.

9.3. INDIVIDUAL-LEVEL DEVIATIONS FROM NORMATIVE BRAIN MORPHOLOGY IN VIOLENCE, PSYCHOSIS AND PSYCHOPATHY

Jaroslav Rokicki¹, Thomas Wolfers², Natalia Tesli³, Christina Bell⁴, Gabriella Hjel⁵, Thomas Fisher-Vieler⁶, Nina Bang⁷, Ingrid Melle⁸, Ole Andreassen⁹, Kirsten Rasmussen¹⁰, Ingrid Agartz¹¹, Lars Tjelta Westlye¹², Christine Friestad¹³, Unn Haukvik⁹

¹*Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital,*

²*University of Tübingen,* ³*University of Oslo and Oslo University Hospital,* ⁴*University of Oslo, Oslo University Hospital,* ⁵*Østfold Hospital Trust, Graalum,* ⁶*University of Oslo, Oslo University Hospital,* ⁷*Norwegian University of Science and Technology (NTNU),* ⁸*NORMENT Centre for Psychosis Research, University of Oslo,* ⁹*University of Oslo,* ¹⁰*Norwegian University of Science and Technology, NTNU,* ¹¹*NORMENT, Division of Mental Health and Addiction, University of Oslo, and Diakonhjemmet Hospital,* ¹²*Oslo University Hospital, NORMENT,* ¹³*Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway; University College of Norwegian Correctional Service*

Background: Neuroimaging research has shown brain morphological abnormalities associated with violence and psychosis, but individual differences are substantial and results not consistent across studies. Recently developed normative modeling of brain MRI-features provides a possibility to parse this heterogeneity by mapping inter-individual brain characteristics, which potential has not yet been explored in forensic psychiatry.

Methods: We explored brain heterogeneity in persons with a history of severe violence with or without a schizophrenia spectrum disorder (n=58), non-violent patients with schizophrenia spectrum disorders (n=138), and healthy non-violent controls from lifetime normative trajectories of cortical thickness, surface area, and subcortical volumes. Normative models were based on Freesurfer derived regions of interest from 58,836 individuals (ages 2-100) from 82 sites. Group differences and associations between brain deviations and psychopathy traits (PCL-R scores) were investigated.

Results: Across groups, we found an overall heterogeneous pattern of individual-level deviations, with a significantly higher frequency of extreme negative deviations in persons with a history of severe violence with or without a schizophrenia spectrum disorder (p=.020, d=.31) and non-violent patients with schizophrenia spectrum disorders (p=.019, d=.48), than healthy

non-violent controls. Group differences were mostly present in subcortical volumes and cortical area, but not thickness, with significant regional group-level differences within the subcallosal and insular cortices, and the cerebellum, and no significant associations to psychopathy traits.

Conclusions: By applying normative modeling, this proof-of-concept study demonstrates the heterogeneous pattern of brain morphometry deviations associated with violence and psychosis. While the results warrant replication, studies addressing individual brain deviations may contribute to improved understanding of the complex underpinnings of violence in forensic psychiatry.

9.4. THE SHARED GENETIC ETIOLOGY OF ANTISOCIAL BEHAVIOUR, SCHIZOPHRENIA, SUBSTANCE USE AND RELATED BRAIN MORPHOLOGY

Megan Campbell^{*1}, Olivia Wootton¹, Natalia Tesli², Unn K. Haukvik³, Dan Stein¹, Jaroslav Rokicki⁴

¹University of Cape Town, ²University of Oslo and Oslo University Hospital, ³NORMENT Norwegian Centre for Mental Disorders Research, Institute for Clinical Medicine, University of Oslo, Institute of Clinical Medicine, University of Oslo, Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁴Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital,

Background: Individuals with antisocial behaviour (ASB) exhibit increased risk of substance use disorders, likely linked to shared genetic vulnerabilities and overlapping neural pathways involved in reward processing and impulse control. This susceptibility is further accentuated by the comorbidity of ASB with various psychiatric disorders, suggesting common genetic underpinnings. Despite this there remains a paucity of work examining the shared genetic etiology of ASB, related neuropsychiatric traits and relevant brain regions.

Methods: Using GWAS of ASB (n=50,252), surface area and thickness of cortical frontal regions, volumes of the amygdala nuclei, psychiatric and substance use phenotypes, we utilized Linkage Disequilibrium Score Regression (LDSC) to assess the genetic correlation between these phenotypes. We then leveraged genetic overlap to boost discovery of genomic loci associated with ASB, and to identify specific shared loci associated with both ASB and each phenotype, using the conditional/conjunctional false discovery rate (cond/conjFDR) approach. FUMA was used for functional analyses.

Results: Using LDSC, we identified significant genetic correlations between ASPD and drinks per week (rg= 0.28; p=1.33×10⁻⁹), cannabis (rg= 0.37; p= 1.91×10⁻⁸), bipolar disorder (BD, rg= 0.20; p=1.95×10⁻⁵), major depressive disorder (MDD, rg= 0.53; p=1.09×10⁻¹⁵) and marginally significant correlations with caudal anterior cingulate surface area (rg=-0.17; p=0.04), superior frontal surface area (rg=0.18; p=0.03), and global measures of cortical surface area (rg=-0.15 ; p=0.02) and thickness (rg=-0.13 ; p=0.04) and ICV (rg=-0.2 ; p=0.01). A total of 54 loci, representing 127 independent SNPs, became significant after conditioning on related psychiatric disorders (8 SCZ, 7 BD, 11 MDD), substance use traits (18, drinks per week; 10, cannabis use) and the corpus callosum (11 anterior, 7 mid anterior, 8 central, 6 mid posterior, 9 total CC). These SNPs have been associated with schizophrenia, disruptive behaviour, risk taking behaviours, substance use disorders and cortical surface area in prior GWAS. Two biological processes were implicated: ethanol oxidation and metabolism.

Conclusions: Our results reveal a complex genetic relationship between substance use, psychiatric traits, and ASB. We provide strong evidence for existence of distinct genetic loci exhibiting pleiotropic effects in both ASB and related traits. Our findings provide convergent

evidence to suggest that substance use traits and psychiatric disorders have shared genetic underpinnings with ASB.

10. DIGITAL TECHNOLOGIES AND RECOVERY: CURRENT AND FUTURE DIRECTIONS TO IMPROVE CARE IN SCHIZOPHRENIA SPECTRUM DISORDERS

Élisabeth Thibadeau, *McGill University, Douglas Mental Health University Institute*

Overall Symposia Abstract: The use of digital technologies in schizophrenia spectrum disorders has significantly increased in the last decades and has several advantages to support recovery such as ecological momentary assessments, increased engagement, flexibility and empowerment. These technologies have been used for different purposes and encompass a wide array of methods to support different components of recovery, including clinical symptoms, cognitive impairments and return to work or to school. This symposium provides an overview of recent developments in digital technologies to support recovery in schizophrenia spectrum disorders. Further, given the very rapid development of these emerging technologies, this symposium also aims to provide insight into the development, co-design with service users and implementation of these technologies to ensure a coherent development between scientific and experiential knowledge to decrease research-to-practice gap.

Dr Haesebaert will present how digital technologies can be used to monitor and plan recovery goals. He will present the development and preliminary results of PLAN-e-PSY, a youth-friendly mobile application targeting goals planning and monitoring for first-episode psychosis. This application based on the recovery framework for first-episode psychosis care was developed through a user-centered design iterative co-building methodology. Positive preliminary results from the initial assessment of a feasibility and acceptability study will be presented.

Dr Raucher-Chéné will present how digital technologies can be used to deliver remote interventions. She will present the results from the ongoing iCog-CA trial, a multisite nationwide study in Canada assessing the acceptability, effects and implementation of remote group-based cognitive interventions targeting clinical symptoms and cognitive impairments in schizophrenia spectrum disorders, including the Metacognitive training (MCT) and the Action-Based Cognitive Remediation program (ABCR).

Dr Thibadeau will present how digital technologies can be used to treat social cognitive deficits remotely. She will present the results from an ongoing trial assessing the acceptability, feasibility, and preliminary effects of the remote administration of RC2S, an avatar-based cognitive remediation program for social cognitive impairments using paper and pencil exercises and digital relational simulations. The cultural adaptation of this intervention for North American English and French-Canadian languages will be presented, along with the preliminary results regarding the positive effects on social cognition, recovery, functioning and symptoms, as well as its acceptability and implementation both in people with lived experience and therapists.

Dr Smith will present how digital technologies can support functional recovery, using virtual reality job interviews (VR-JIT). He will discuss his recent work assessing the effectiveness, implementation outcomes and qualitative experiences of using VR-JIT within Individual Placement and Support (IPS) programs. This presentation will focus on both people with lived experience of schizophrenia spectrum disorders and IPS employment specialists and present

the positive outcomes observed in terms of effectiveness for competitive employment, interview skills, and interview anxiety as well as acceptability and implementation.

This symposium will provide insight about the development, use and implementation of digital technologies which represent a fast-growing approach to support recovery in schizophrenia spectrum disorders, from clinical to functional outcomes.

10.1. PLAN-E-PSY, A MOBILE APPLICATION CO-BUILT WITH ENDUSERS TO IMPROVE CASE MANAGEMENT FOR PATIENTS WITH FIRST EPISODE OF PSYCHOSIS (FEP)

Frederic Haesebaert¹, Mathilde Marchal², Amelie Pavard^{*3}, Laurent Magaud², Eric Fakra⁴, Julie Haesebaert⁵

¹PSYR2 Team, INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, Université Claude Bernard Lyon 1, ²Hospices Civils de Lyon, Public Health Center, Research and Clinical Epidemiology Department, F-69003 Lyon, France, ³CH Le Vinatier, Lyon, ⁴Pôle Psychiatrie, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, Rhône-Alpes, France., ⁵University Claude Bernard Lyon 1, Research on Healthcare Performance (RESHAPE), INSERM U1290

Background: First-episode psychosis (FEP) affects 3% of the population worldwide, mainly young adults. International guidelines for FEP are based on the principles of intensive case management (CM). To improve the relevance of CM and thus patient engagement and functional outcomes, the care objectives must not be solely clinical, but placed within an individualized "recovery" perspective, taking into account the patient's point of view, goals and context. The use of clinical tools co-built end users (patients, caregivers, carers) and adapted to recovery goals appears essential. In addition, the use of mobile applications as clinical tools can enhance the engagement of young patients.

Objective: Our research aims to co-build a youth-friendly mobile application (PLAN-e-PSY) based on the recovery framework for planning and monitoring FEP care goals.

Methods: We used a "user-centered design" iterative co-building methodology. Workshops were led by a psychiatrist and a psychologist. Two patients, 2 case managers, a caregiver, a peer-worker, a developer and an ergonomist were involved. Thematic content analysis following the workshops was conducted in order to refine the specifications of a beta version of the mobile application. Direct interviews were conducted with 3 CMs, 2 peer workers, a caregiver and a patient, after testing the beta version of PLAN-e-PSY.

Results: The application's architecture and content were defined on the basis of workshop participants' own representations of recovery, based on their own experiences. Participants also helped to define together the application's graphics, ergonomics and content. Interviews conducted following the beta test revealed that the beta version of PLAN-e-PSY was easy to use (4.5/5) and perceived as useful (3.5/5). They enabled us to improve the application: personalize it and include a joint crisis plan.

Conclusions: Co-building with end-users enabled us to create a relevant application for patients, their families and professionals. A funded randomized controlled trial on 168 patients will assess the app's effectiveness in FEP care settings.

10.2. ICOGCA: PRELIMINARY RESULTS ON RECOVERY BY PROMOTING COGNITIVE HEALTH THROUGH ONLINE INTERVENTIONS FOR PERSONS LIVING WITH A SCHIZOPHRENIA-SPECTRUM DISORDER.

Delphine Raucher-Chéné*¹, Élisabeth Thibaudeau², Genevieve Sauvé³, Katie Lavigne², Christopher Bowie⁴, Mahesh Menon⁵, Synthia Guimond⁶, Michael Best⁷, Michael Bodnar⁸, Todd Woodward⁹, Martin Lepage²

¹Douglas Research Centre, Montréal, ²Douglas Research Centre, Montréal, QC, Canada; McGill University, ³Douglas Research Centre, Montréal, QC, Canada; Université du Québec À Montréal, ⁴Queen's University, Kingston, ON, Canada, ⁵University of British Columbia, Vancouver, BC, Canada, ⁶The Royal's Institute of Mental Health Research, University of Ottawa, ON, Canada, ⁷University of Toronto Scarborough, Toronto, ON, Canada, ⁸The Royal Ottawa Institute of Mental Health Research, University of Ottawa, ON, Canada, ⁹BC Mental Health and Addictions Research Institute; University of British Columbia, Vancouver, BC, Canada

Background: To promote recovery in individuals living with schizophrenia-spectrum disorder (SSD), there is an important need to ameliorate overall cognitive health. Hence, cognitive impairments and biases collectively represent a core feature of SSD and adversely impact the social functioning and well-being of this population. By increasing access to cognitively stimulating activities, the iCogCA study - a national Canadian collaborative effort to implement online psychological interventions – aims to promote recovery in SSD.

Methods: Five sites across Canada (Quebec, Ontario, British Columbia) are part of the project. Participants living with SSD are recruited and assessed for symptoms, cognition, functioning and recovery pre- and post-intervention. Two evidence-based group interventions promoting cognitive health are conducted remotely through videoconference: Action-Based Cognitive Remediation (ABCR) and MetaCognitive Training (MCT) with each site running four groups annually (2 ABCR, 2 MCT).

Results: We will provide the first-year results of this entirely online trial. To date, among the 39 SSD participants screened, 22 enrolled in an intervention and 19 completed it (86%). Completers had a mean age of 33.84±7.4 years old, were in remission (i.e., mean PANSS-6 score LESS THAN 14), and had moderate to severe difficulties in at least one area of functioning before the intervention. Post-intervention assessment highlighted a progression in the process of recovery (i.e., a significant change in the Questionnaire about the Process of Recovery score; $t=-2.41$, $p=0.028$, $d=0.58$) with an increase in self-esteem ($t=-2.02$, $p=0.061$, $d=0.49$). No significant change was detected in symptoms, cognition, or functioning at that stage.

Conclusions: The iCogCA project has immense potential for reaching people in need who are otherwise unable to attend in-person settings, thus improving accessibility to care and health equity. These preliminary results on the effectiveness of remotely-delivered ABCR and MCT are encouraging, highlighting the potential impact of these interventions in the recovery process. By supplementing the results from the other groups given during the year, the impact of each intervention can be analyzed, as well as the other potential effects of these interventions on overall functioning and well-being.

10.3. A REMOTE AVATAR-BASED COGNITIVE REMEDIATION FOR SOCIAL COGNITION IN SCHIZOPHRENIA SPECTRUM DISORDERS: PRELIMINARY RESULTS OF THE ACCEPTABILITY, FEASIBILITY AND EFFECT OF RC2S

Élisabeth Thibaudeau*¹, Elodie Peyroux², Nicolas FRANCK³, Martin Lepage¹

¹McGill University, Douglas Mental Health University Institute, ²Le Vinatier Hospital,

³University of Lyon, Vinatier Hospital

Background: Social cognitive (SC) deficits are prevalent in schizophrenia spectrum disorders (SSD) and are associated with impairments in functional recovery. Cognitive remediation (CR) has shown its efficacy to improve these deficits, but the effect on functioning remains limited. Digital technologies could support the training and transfer of SC skills to daily life. The French program RC2S is a broad-based and personalized program using digital relational simulations to emulate real-life social interactions. While preliminary evidence of efficacy is available for RC2S, there is a need to increase remote access to culturally adapted CR for SC. The goals of this study were to 1) culturally adapt RC2S in North American English and French-Canadian and 2) to assess the feasibility, acceptability and preliminary effects of a remote version of RC2S in SSD.

Methods: For the first objective, the translation for the North American English version was performed by a professional agency. For both versions, all scenarios were revised to culturally adapt the expressions, turns of phrase, and names of places and characters. All audio files were recorded by professional actors. For the second objective, so far, we recruited eight (mean age 37.8, 5 men) symptomatically stable participants with SSD with objective and/or subjective SC impairments. A pre-post quasi-experimental design using mixed methods was used. Participants were assessed before and after the intervention for primary (SC, goal attainment) and secondary (symptoms, functioning, recovery) outcomes and completed in-session questionnaires assessing their motivation, perception of therapeutic alliance and appreciation of the remote intervention. RC2S includes 24 individual one-hour sessions with a therapist, twice a week with the first session dedicated to paper-pencil exercises to learn strategies and the second session using digital relational simulations with an avatar to practice skills. We also recruited five therapists offering the intervention with a graduate degree in psychology. They completed similar in-session questionnaires as participants with SSD. Descriptive statistics were used to summarize data and linear mixed models, along with effect-size d were used to assess the preliminary effect of RC2S on primary and secondary outcomes.

Results: The participants completed a mean of 20.4 sessions. For primary outcome, a significant effect was observed for goal attainment ($F(1,6.498)=62.031$, $p < 0.001$). The effects were marginally significant with medium-large effect sizes for theory of mind ($d=0.74$), subjective assessment of emotion recognition ($d=1.25$) and attributional bias ($d=0.75$). For secondary outcomes, the effect on cognitive biases was marginally significant, with small to moderate-large effect sizes for the scales Belief Inflexibility bias ($d=0.10$), Subjective complaints ($d=0.7$) and Safety behaviors ($d=0.11$). In addition, moderate-large effect sizes were observed for symptoms of social anxiety ($d=0.5$), depression ($d=0.52$), recovery ($d=0.75$), social functioning ($d=0.85$) and intimacy ($d=0.76$). Regarding the in-session questionnaires, for both participants with SSD and therapists, therapeutic alliance was perceived as good and remained relatively stable throughout the intervention ($p=0.082$), with a similar pattern for motivation (all scales > 0.05). High scores were obtained also obtained for the satisfaction questionnaires.

Conclusions: These preliminary results suggest that the remote administration of RC2S is feasible and acceptable and yields positive effects. While these results must be replicated in a randomized-controlled trial, they support the use of digital technologies to support SC impairments and functional recovery in SSD.

10.4. THE EVIDENCE FOR VIRTUAL JOB INTERVIEW TRAINING TO SUPPORT JOB-SEEKING ADULTS WITH SCHIZOPHRENIA

Matthew Smith^{*1}, Justin Smith², Shannon Blajeski³, Brittany Ross¹, Susan McGurk⁴, Kim Mueser⁵, Morris Bell⁶, Eugene Oulvey⁷, Jane Burke-Miller⁸, Neil Jordan⁹, Karley Nelson¹⁰, Tovah Lieberman¹⁰, Nicole Pashka¹⁰, Lisa Razzano¹¹

¹University of Michigan, ²University of Utah, ³Portland State University, ⁴Boston University, ⁵Center for Psychiatric Rehab, Boston University, ⁶Yale University School of Medicine, ⁷State of Illinois, Illinois Department of Human Services, Division of Rehabilitation Services, ⁸University of Illinois Chicago, ⁹Northwestern University, ¹⁰Thresholds, ¹¹University of Illinois, Chicago; Thresholds, Inc.

Background: About 20% of people with schizophrenia are employed and the field's gold standard vocational rehabilitation model, Individual Placement and Support (IPS), increases this employment rate to 55%. Thus, a large percentage of adults with schizophrenia remain unemployed, which contributed to an economic burden of \$343 billion in 2019 (largely driven by unemployment and productivity loss). Virtual Reality Job Interview Training (VR-JIT; a zoom-like job interview simulator with automated feedback) was developed with adults with serious mental illness and results from a randomized controlled trial (RCT) demonstrated initial efficacy that (within 6 months) trainees had more job offers compared to the control group (48% vs. 14%, $p < .05$). This initial data led to our current RCT evaluating VR-JIT effectiveness within IPS, initial implementation outcomes, and the qualitative experience of using VR-JIT.

Methods: First, ninety participants with schizophrenia or other serious mental illnesses were randomly assigned to IPS+VR-JIT (N=54) or IPS as usual (N=36). Intent-to-treat logistic regression, Cox proportional hazard and mixed-effects linear regressions evaluated the primary (employment rate, time-to-employment) and secondary outcomes (interview skills, interview anxiety). Fifty-one percent of participants were IPS nonresponders (i.e., no employment within their first 90 days of IPS). Second, a sequential, complementary mixed-methods design used qualitative data to gain greater depth of understanding of implementation process outcomes. Eleven IPS employment specialists trained to deliver VR-JIT completed VR-JIT acceptability, appropriateness, and feasibility surveys. Forty-two VR-JIT recipients completed acceptability and usability surveys. We then conducted five focus groups and thirteen semi-structured interviews with IPS staff and VR-JIT implementers and recipients, followed by an integrated analysis process. Lastly, we analyzed semi-structured interviews (n=8) with IPS employment specialists across four community IPS sites (distinct from the RCT site) implementing VR-JIT and analyzed secondary qualitative data from the implementation evaluation. All focus group and interview data were analyzed using grounded theory methodology.

Results: The IPS+VR-JIT group had greater odds of obtaining competitive employment as compared to the IPS-as-usual group (OR=3.0, $p=.027$). Moreover, IPS nonresponders in the IPS+VR-JIT group, as compared to the IPS-as-usual group, had greater odds of obtaining a job (OR=5.82, $p=0.01$) and shorter time to employment (HR=2.70, $p=0.04$). The IPS+VR-JIT as compared with the IPS as usual group had improved interview skills ($p=0.006$) and interview anxiety ($p=0.019$). IPS employment specialists found VR-JIT to be highly acceptable, appropriate for integration with IPS, and feasible for delivery. VR-JIT recipients reported the intervention to be highly acceptable. Qualitative results added perceived advantages for IPS employment specialists and adaptations for future delivery. The client experience yielded participants appreciated exposure to a simulated interview in a safe environment and receiving feedback which supported improved confidence and engagement in the job seeking process.

Conclusions: VR-JIT enhances access to competitive employment, interview skills, and interview anxiety among IPS clients with schizophrenia and other serious mental illnesses. The results were especially notable among IPS nonresponders who traditionally lag in their access

to employment. Moreover, IPS staff and clients view VR-JIT as acceptable and feasible to deliver within IPS as it provides a safe space to practice and get feedback on job interview skills. Staff reported that their clients were more engaged in the job search process after using VR-JIT. While the field seeks to understand the determinants of VR-JIT implementation, we recommend that IPS programs begin piloting delivery of VR-JIT to provide evidence-based practice for their most vulnerable IPS clients.

Plenary Session II: Raquel Gur - Brain Development and Psychosis

2:00 p.m. - 3:00 p.m.

11. BRAIN DEVELOPMENT AND PSYCHOSIS

Celso Arango, *Hospital General Universitario Gregorio Marañón*

11.1. BRAIN DEVELOPMENT AND PSYCHOSIS

Raquel Gur, *University of Pennsylvania*

Individual Abstract: Integration of brain-behavior measures in the study of psychosis has capitalized on advances in several research domains that are critical for progress and contribute to investigating the psychosis dimension neurodevelopmentally. In the domain of clinical phenotyping, it has been recognized that clinical manifestations are an evolving process ranging from subthreshold to schizophrenia spectrum disorder (SSD). To examine the emergence of psychosis, continuous measures were deployed for quantifying specific aspects of behavior that can be examined longitudinally.

In the domain of neurobiology, advanced measures of brain structure, function and connectivity are applied to large samples in collaborative efforts to parse the clinical heterogeneity based on the involvement of brain systems and the relation to neurobehavioral deficits that characterize SSD and are evident earlier in development.

Concomitantly, large-scale genetic studies have identified gene network associated with SSD that are implicated in brain development and are evident in other neurodevelopmental disorders such as autism spectrum disorders (ASD). Furthermore, large datasets on common and rare genetic variants, associated with increases incidence of SSD, have become available yielding sufficient power for probing underlying cellular-molecular mechanisms. The study of the exposome supports the contribution of the environment with advanced quantitative methodology for measuring its effects. Novel methodologies for mining such large data sets are needed and are applied increasingly incorporating artificial intelligence and machine learning approaches.

The presentation will illustrate efforts to integrate data across these domains and highlight challenges, opportunities, and future directions towards precision psychiatry applied to psychosis.

Concurrent Symposia

3:30 p.m. - 5:30 p.m.

12. BEYOND D2 BLOCKERS: NEW MECHANISTIC APPROACHES BASED ON GLUTAMATERGIC AND DOPAMINERGIC CIRCUIT TARGETS

Oliver Howes, *MRC LMS and KCL*

Overall Symposia Abstract: D2 blockers are the mainstay of drug treatment for schizophrenia but don't work for many patients and are poorly tolerated by many more. This highlights the need to identify new targets to guide the development of novel treatments. This symposium focuses on glutamatergic and dopaminergic circuits thought to underlie schizophrenia. It will cover new molecular and genetic data on regulators of these circuits.

The first talk (Sportelli) will present unpublished data on genetic regulators of the dopaminergic abnormalities implicated in psychosis, and integrate this with PET imaging data to identify proteins that modulate striatal dopamine circuit function. This identifies a number of targets, including the indirect dopamine pathway, that could be used to modulate striatal dopamine circuits to treat schizophrenia.

The second talk (Howes) will focus on the role of trace amine receptors in the regulation of dopaminergic circuits. It will present unpublished preclinical data showing that TAAR1 knock-out leads to the same meso-striatal dopaminergic dysfunction seen in schizophrenia, and an interventional study in patients showing that a TAAR1 agonist reduces meso-striatal dopamine dysfunction in schizophrenia, and that this is related to improvements in symptoms.

The third talk (Mizrahi) will present new in vivo imaging data in patients showing that cortical and striatal brain levels of MAO-B, an enzyme involved in both glutamatergic and dopaminergic circuits, are lower in people with a first episode of psychosis and in people at clinical high risk of psychosis. It will also present evidence that MAO-B brain levels are modulated by cannabis use, linking this system to a risk factor for the development of psychosis.

The final talk (Fan) will present new data from a prospective treatment study in antipsychotic naive first episode psychosis, showing that baseline cortical glutamate levels predict treatment response. It will also show that the gap between predicted and actual brain structural age increases during the first 3 months after the onset of psychosis during antipsychotic treatment irrespective of response status. These data identify cortical glutamate elevation as a potential treatment target for patients who do not respond to D2 blockers and highlight brain structural changes are not related to response to D2 blockers.

The discussant has expertise in the role of both the glutamatergic and dopaminergic circuits in schizophrenia, and in translational studies to identify and develop new treatments for the disorder. She will discuss the data presented and place it in this context to draw out the areas where findings converge. The discussion will also identify limitations and areas where the field needs to focus future studies to address key questions on the pathophysiology of the disorder. Finally, she will also consider the data in terms of other novel treatment strategies being developed in schizophrenia to consider the most promising approaches.

12.1. DOPAMINE AND SCHIZOPHRENIA FROM BENCH TO BEDSIDE: DISCOVERY OF A STRIATAL CO-EXPRESSION RISK GENE SET THAT PREDICTS IN VIVO MEASURES OF STRIATAL FUNCTION.

Leonardo Sportelli*¹, Daniel Eisenberg², Roberta Passiatore³, Enrico D'Ambrosio³, Linda Antonucci³, Qiang Chen⁴, Jasmine Czarapata², Aaron Goldman⁴, Michael D. Gregory², Kira

Griffiths⁵, Thomas M. Hyde⁴, Joel Kleinman⁴, Antonio Pardinas⁶, Madhur Parihar⁴, Teresa Popolizio⁷, Antonio Rampino³, Joo Heon Shin⁴, Mattia Veronese⁸, William Ulrich⁴, Caroline Zink¹⁰, Alessandro Bertolino³, Oliver Howes⁸, Karen F. Berman², Daniel Weinberger⁴, Giulio Pergola⁴

¹Lieber Institute for Brain Development, ²National Institute of Mental Health, National Institutes of Health, ³University of Bari 'Aldo Moro', ⁴Lieber Institute for Brain Development, Johns Hopkins Medical Campus, ⁵Holmusk Technologies Inc, ⁶MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, ⁷IRCCS Casa Sollievo Della Sofferenza,, ⁹Institute of Psychiatry, King's College London, ¹⁰Baltimore Research and Education Foundation

Background: Schizophrenia (SCZ) is characterized by a polygenic risk architecture implicating diverse molecular pathways important for synaptic function. However, how polygenic risk funnels through these pathways to translate into syndromic illness is unanswered. We aimed to identify a set of genes implicated both in genetic risk and in differential expression in a brain circuit of three brain regions and to study how gene-set-specific SCZ risk translated into brain circuit function.

Methods: To evaluate biologically meaningful pathways of risk, we used tensor decomposition to characterize gene co-expression in post-mortem brain of neurotypical controls (NC; N=154), patients with SCZ (N=84), and GTEx samples (N=120) from caudate nucleus (CN), hippocampus (HP), and dorsolateral prefrontal cortex (DLPFC). We associated the identified gene sets with SCZ diagnosis and genetic risk via ANCOVA and linear models respectively and assessed tissue, cell-type, and biological pathway specificity through gene enrichment analyses. We assessed the replication of the identified gene sets in the GTEx samples by means of Jaccard Index (JI: overlap/union of gene sets). We then computed a Parsed Risk Score (PaRS) by mapping risk polymorphisms within PGC3 SCZ loci to a dopamine-linked group of genes. We also computed a measure of cumulative SCZ risk burden based on GWAS risk genes not included in this gene set (complementary-PaRS) as negative control. We associated the PaRS and complementary-PaRS with in vivo striatal dopamine synthesis capacity measured by [18F]-FDOPA PET uptake in NC (N=65) and SCZ patients (N=20) by means of fixed-effect model meta-analysis. We replicated PET results in an independent NC cohort (N=150) through multiple linear regression. Finally, we associated the two type of scores to reward anticipation-related fMRI activation in an independent discovery sample of 86 NC and replicated the results in an independent cohort of 55 NC.

Results: We identified a CN-predominant gene set showing dopaminergic selectivity ($p[\text{FDR}] = 1.9 \times 10^{-57}$) that was enriched for genes associated with clinical state ($F[1,210] = 11.4$, $p = .0009$, $p[\text{FDR}] = .038$) and SCZ genetic risk ($t[93] = 1.67$, one-tailed $p = .048$). This gene set was also replicated in the NC GTEx cohort ($\text{JI} = .19$; empirical $p \text{ LESS THAN } .001$). Besides genes necessary for presynaptic dopamine biosynthesis, such as DRD2, TH and DDC, this gene set also included 17 genes preferentially expressed by indirect pathway medium spiny neurons, such as PENK, GPR6, HTR4 and again DRD2. Parsing polygenic risk score for SCZ based on this specific gene set (PaRS), we found that greater PaRS predicted greater in vivo striatal dopamine synthesis capacity in three independent cohorts of NC and patients (total N=235; discovery meta-analytic coefficient[95% CI]: $0.33[0.01, 0.65]$; $p = .0037$; $p[\text{Bonferroni}] = .037$; replication: $t[149] = 3.95$; $k = 16$; $p[\text{FWE}] \text{ LESS THAN } 0.05$) and greater fMRI striatal activation during reward anticipation in two additional independent NC cohorts (total N=141; discovery: $p[\text{TFCE-FDR}] = 0.01$; $Z = 3.54$; $x = 17$; $y = 15$; $z = -5$; 73 voxels; replication: $p[\text{TFCE-FDR}] = 0.03$; $Z = 4.04$; $x = 18$; $y = 17$; $z = 5$; 20 voxels). We found no significant association in any of the PET and fMRI samples using the complementary-PaRS.

Conclusions: We identified a dopamine-linked group of genes whose specific risk variants predict striatal presynaptic dopamine synthesis and striatal activity during reward anticipation in the living human brain, both outcomes concordant with known SCZ-associated phenotypes. Remarkably, the association was only seen with our parsed polygenic risk score and not with the scores including all all variants outside the pathway we considered. This unpublished translational body of work provides empirical evidence for striatal dopamine-relevant gene network involvement in the etiology of SCZ, pinpointing a specific biological pathway of risk that affect illness relevant striatal neurochemistry and neurofunction, and may open new possible avenues for studying clinical heterogeneity and drug treatment response.

12.2. TARGETING THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA: A COMBINED PRECLINICAL AND CLINICAL STUDY OF THE ROLE OF THE TRACE AMINE-ASSOCIATED RECEPTOR 1

Oliver Howes^{*1}, Luke Vano², Grazia Rutigliano², Alice Petty³, Sridhar Natesan², Courtney Zeni⁴, Dominic Withers⁵, Nina Dedic⁶, Stephen Kaar², Seth Hopkins⁴, Robert McCutcheon², Kenneth S. Koblan⁷

¹MRC LMS and KCL, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London,, ³Imperial College London, ⁴Sunovion Pharmaceuticals, ⁵LMS-MRC, Imperial College London, ⁶Sunovion Pharmaceuticals, Inc., , ⁷Sunovion Pharmaceuticals Inc

Background: Meta-analysis of PET evidence indicates that the major dopaminergic abnormality in schizophrenia is elevated dopamine synthesis and release capacity, and that this is associated with the development of the first psychotic episode and the severity of symptoms. The trace amine associated receptor 1 (TAAR1) has recently emerged as a promising target in the treatment of schizophrenia and other psychiatric disorders. TAAR1 is expressed in dopamine neurons and modulates their firing, suggesting it could target the dopamine pathophysiology of schizophrenia. This is further supported by recent results with ulotaront, a TAAR1/5-HT1A receptor agonist, which reduced dopamine synthesis capacity in a ketamine mouse model of hyperdopaminergia. However, it is not known whether the effects on dopamine synthesis capacity are directly linked to TAAR1 and/or translate to humans. To address this, we conducted two studies. The first study evaluated dopamine synthesis capacity in TAAR1 knockout (TAAR1-KO) mice, whilst the second tested the effect of ulotaront on dopamine synthesis capacity in patients with schizophrenia.

Methods: Study 1: Adult, male AAR1^{-/-}(B6-Taar1^{tm1}(NLSLacZ)Blt (TAAR1-KO) mice and wildtype littermates (8-12 weeks old) were used and experimental procedures were performed in accordance with EU directive 2010/63/EU. 18F-DOPA PET was utilized to measure striatal Ki (dopamine synthesis capacity) in TAAR1-KO (n=12) and WT (n=11) animals. In addition, locomotor activity at baseline and in response to amphetamine (2.5 mg/kg) i.p. was assessed in both genotypes. Study 2: Patients with a DSM-5 diagnosis of schizophrenia on a stable dose of a single antipsychotic medication participated. They received a baseline 18F-DOPA PET scan and symptom measures (PANSS ratings) followed by treatment with ulotaront up to 75mg/day added to their existing antipsychotic for a period of 14 days. On day 14, the 18F-DOPA PET scan was repeated approximately 2-4 h after the final ulotaront dose and PANSS ratings repeated. The primary endpoint was change from baseline in striatal Ki across its three functional subdivisions at day 14 measured by 18F-DOPA PET scan.

Results: Study 1: Striatal Ki was significantly elevated in TAAR1-KO animals (n=12; mean (sem) Ki=0.024 (0.0023)) relative to wildtype (n=11; mean (sem) Ki=0.018 (0.0015)),

$t(21)=2.09$, p LESS THAN 0.05) with an effect size of 0.85. There was no significant difference in locomotion between genotypes for the habituation or saline trials, however there was a significant increase in the locomotor response to amphetamine in the TAAR1-KO animals compared to wildtype controls (p LESS THAN 0.005). Study 2: 19 subjects (14 male); mean (SD) age, 32.9 (6.7) yrs; black ($n=8$), white ($n=8$), other ($n=3$) participated. Mean (SD) age at initial diagnosis-28.6 (6.5) yrs; baseline mean (SD) PANSS total score 79.3 (7.3), PANSS positive subscale 19.2 (4.6), PANSS negative subscale 22.8 (6.1). There was a significant effect of treatment (p LESS THAN 0.05) and striatal subregion (p LESS THAN 0.05) on Ki but no treatment by subregion interaction (p GREATER THAN 0.8). Treatment Cohen's d effect size were: associative striatum= -0.4 (95% CI: -0.89, 0.11); motor striatum= -0.4 (95% CI: -0.89, 0.11); and limbic striatum= -0.7 (95% CI: -1.28, -0.19). There was a significant correlation between change in striatal 18F-DOPA Kicer and change in Marder Positive Factor score on the PANSS ($r=0.5$, p LESS THAN 0.05) but no significant relationship with change in PANSS total symptom score ($r=0.2$, p GREATER THAN 0.05).

Conclusions: The knock-out of TAAR1 in mice results in elevated striatal dopamine synthesis capacity and locomotor response to amphetamine, showing that TAAR1 is involved in regulating dopamine synthesis and behavioural response to a dopaminergic challenge. Treatment with a TAAR1 agonist, ulotaront, is associated with a reduction in striatal dopamine synthesis capacity in people with schizophrenia that is related to clinical improvement. Together these results highlight the potential of targeting TAAR1 to address the dopaminergic pathophysiology underlying psychosis in schizophrenia.

12.3. IMAGING MONOAMINE OXIDASE B, AN ASTROGLIA MARKER KEY FOR NEUROTRANSMITTERS HOMEOSTASIS, IN EARLY PSYCHOSIS

Romina Mizrahi*¹, Kankana Aji², Pablo Rusjan¹

¹McGill University, ²CaTS lab, Douglas Hospital

Background: Astrocytes regulate homeostasis of neurotransmitters including dopamine and glutamate. Considering the fundamental involvement of astrocytes in glutamatergic processes, including biosynthesis, reuptake, and release, decreased astrocyte function could impact glutamatergic neurotransmission. For instance, altered astrocyte expression of excitatory amino acid transporter 1 (EAAT1) and EAAT2 may lead to impaired glutamate clearance from synapses, resulting in prolonged glutamate signaling. Interestingly, EAAT1 knock-out mice exhibited schizophrenia-like behavioural and cognitive disturbances, and postmortem brain tissue studies in schizophrenia patients have demonstrated reduced expression of EAATs in the cortical regions studied. Furthermore, diminished astrocyte function could relate to an impaired regulation of D-serine and glycine levels, both of which act as endogenous co-agonists for glutamatergic NMDARs. Notably, studies in schizophrenia patients have reported reduced serum and cerebrospinal fluid (CSF) D-serine levels implicating NMDAR hypofunction, resulting in overstimulation of glutamate release, consistent with the glutamatergic hypothesis of schizophrenia. Importantly, MAO-B is responsible for the independent catabolism of dopamine and other amines in brain. Thus, astrocyte dysfunction, as indexed by lower MAO-B levels, is consistent with both dopaminergic and glutamatergic transmission abnormalities previously reported in psychosis. However, this has never been tested in living brains of early psychosis patients. A novel radiotracer, [11C]SL25.1188 targets monoamine oxidase-B (MAO-B) enzyme primarily found in astrocytes, enabling in vivo astrocyte status quantification.

Methods: Objective: To investigate whether MAO-B distribution volume (MAO-B VT), an astroglia marker, is reduced in early psychosis. This is a cross-sectional study performed in a tertiary care psychiatric hospital, Ontario, from October 2018 to November 2019. Participants (n=38) included antipsychotic-free/minimally exposed patients with first episode psychosis (FEP), clinical high-risk (CHR) individuals and Healthy volunteers (HVs). Participants were excluded if tested positive on urine drug screen (except for cannabis and tobacco). All participants underwent a 90-minute positron emission tomography (PET) scan with [¹¹C]SL25.1188, to measure MAO-B VT, an index of MAO-B density.

Results: In total, 14 FEP patients (mean[SD] age, 25.7[5.7] years; 6 F), 7 CHR (mean[SD] age, 20.9[3.7] years; 4 F) and 17 HV (mean[SD] age, 31.2[13.9] years; 9 F) completed all study procedures. We found a significant effect of study group ($F(2,37.48)=5.30$, $p=0.009$, Cohen's $f=0.53$) on regional MAO-B VT, with significant reductions in CHR compared to HV (Cohen's $d=1.05$) and FEP (Cohen's $d=0.83$). We report a significant cannabis use effect on MAO-B VT ($F(1,39.47)=12.45$, $p=0.001$, Cohen's $f=0.56$), with a significant group-by-cannabis interaction ($F(2,37.35)=3.81$, $p=0.03$, Cohen's $f=0.45$), indicating lower MAO-B VT in cannabis using patients. We observed more pronounced MAO-B VT reductions in striatal regions compared to cortical regions, in both clinical groups ($F(12,46.07)=2.00$, $p=0.046$, Cohen's $f=0.72$) and in cannabis users ($F(6,46.07)=6.01$, $p < 0.001$, Cohen's $f=0.89$). All tests were controlled for tobacco use.

Conclusions: Reduced MAO-B levels could reflect diminished capacity to terminate dopaminergic synaptic signalling, resulting in the well replicated increased dopaminergic tone in psychosis, particularly in striatal regions. Further, reduced MAO-B could mean astrocyte dysfunction, which would also be consistent with glutamatergic transmission abnormalities previously reported in psychosis. Finally, reduced astrocyte status, or specifically MAO-B downregulation, also supports glial cell dysfunction, consistent with meta-analytic in-vivo evidence of reduced microglial density in schizophrenia. In this context, pharmacological interventions that restore MAO-B containing astrocytes or increase MAO-B density could potentially be targeted in patients.

12.4. THE ROLE OF CORTICAL GLUTAMATE LEVELS IN THE PATHOPHYSIOLOGY OF ANTIPSYCHOTIC NON-RESPONSIVE SCHIZOPHRENIA: A LONGITUDINAL IMAGING STUDY IN FIRST-EPISODE PSYCHOSIS

Lejia Fan^{*1}, Liangbing Liang², Xiaogang Chen³, Lena Palaniyappan⁴

¹Central South University, Changsha, ²Western University, ³The Second Xiangya Hospital, Central South University, ⁴Douglas Mental Health University Institute, McGill University

Background: A subgroup of patients with schizophrenia is believed to have aberrant excess of glutamate in the anterior cingulate cortex (ACC); this subgroup is thought to show poor response to first-line antipsychotic treatments that focus on dopamine blockade. Meanwhile, brain age gap (BAG), i.e., the difference between actual age and biologically predicted age based on brain structure, is higher in schizophrenia; this may relate to the effect of glutamate-mediated excitotoxicity and accelerated brain tissue loss. If we can identify a subgroup with higher glutamate and BAG early in the course of illness, we can reduce the repeated use of first-line antipsychotics and potentially stratify first episode patients to intervene early with clozapine. We must first establish if there is robust evidence linking elevations in BAG and glutamate metabolites to poor response, and determine if the use of antipsychotics worsens the glutamatergic excess and BAG in eventual nonresponders. We use proton magnetic resonance spectroscopy (1H-MRS) to measure glutamatergic metabolites (Glutamate and Glx (glutamate

plus glutamine)) to establish if stratification using MRS and structural imaging before starting antipsychotics in the future.

Methods: In this study, we obtained proton magnetic resonance spectroscopy of glutamatergic metabolites at perigenual (pACC) and dorsal (dACC) ACC and whole brain T1 imaging at 3-Tesla scanner in 42 drug-naïve patients with schizophrenia and 41 health controls (HC). We then treated schizophrenia patients with risperidone at a standard dose range of 2-6 mg/day (titrated as per clinician-patient shared decision making) and followed them up for 3 months to categorize their response status. Patients were divided into responders (N =27) and non-responders (N =15) based on whether the percent PANSS total score reduction was above or below 50%. Brain age was predicted by the model using XGBoost method.

Results: Nonresponders had higher glutamate than responders, but both patient groups did not differ in glutamate and Glx from HC group before treatment-onset ($F_{1,79} = 3.20$, $p = 0.046$, partial $\eta^2 = 0.075$). Glutamatergic metabolites did not change significantly over time in both nonresponders and responders over the 3 months of antipsychotic exposure ($F_{1,31} = 1.26$, $p = 0.270$, partial $\eta^2 = 0.039$). Both responders and nonresponders showed an improvement in symptom burden over 12 weeks, with the exception that nonresponders showed no notable improvement in negative symptoms ($t = -0.41$, $p = 0.688$). Contrary to our expectations, both responders and nonresponders had worsening BAG with time compared to healthy controls ($F_{2,77} = 3.20$, $p = 0.003$, partial $\eta^2 = 0.137$). Higher baseline Glu in dACC is associated with smaller BAG both at baseline ($r = -0.34$, $p = 0.032$) and 12 weeks ($r = -0.45$, $p = 0.005$) for patients as a group. Higher Glu ($r = -0.34$, $p = 0.032$) and Glx ($r = -0.32$, $p = 0.043$) in pACC is associated with smaller BAG at baseline for HC.

Conclusions: We note that while BAG and glutamate levels are correlated in patients, it is only the ACC glutamate signal that relates to non-response. Irrespective of responder status, all patients show worsening BAG. But glutamate levels do not continuously deteriorate over time. The use of antipsychotics without prior knowledge of later response delays symptom relief in a subgroup of first-episode patients. BAG may reflect a process that is related to hyperglutamatergia, but unrelated to response status. Given the current practice of nonstratified use of antipsychotics, longer-time follow-up MRS studies are required to see if improvement in symptoms accompanies a dynamic shift in glutamate profile.

13. UTILISING ENVIRONMENTAL RISK FACTORS TO IMPROVE PREDICTION AND PATHWAYS TO CARE IN ULTRA-HIGH RISK FOR PSYCHOSIS

Brian O'Donoghue, *University College Dublin*

Overall Symposia Abstract: There are a number of well-established, robust environmental risk factors for the development of a first episode of psychosis, including migrant or ethnic minority status, neighbourhood deprivation or fragmentation and cannabis use. However, these findings have not been utilised to improve prediction in the ultra-high risk (UHR)/ clinical high-risk (CHR) state for psychosis. In fact, it has been found that minority groups and individuals from more deprived areas are often under-represented within these cohorts. There has been a decline in the transition rates to a full-threshold psychotic disorder in those identified as UHR since the initial establishment of these services. Over 40% of UHR individuals transitioned to a full-threshold psychotic disorder in the initial studies in the mid-1990s and then there has been a steady decline in rates to approximately 15%. Therefore, it could be possible to further enrich the UHR cohorts based on the presence of environmental risk factors for psychotic disorders, thereby bringing the characteristics of the UHR cohort to resemble that of the FEP cohort more closely.

In this symposium, we will first explore the association between environmental risk factors and the symptoms and outcomes of the UHR state and then examine how this knowledge could assist in further refining the criteria or enriching UHR cohorts with individuals at greater risk of transition. In the first presentation, Dr Benson Ku, an assistant professor at the Emory University School of Medicine in the US, will discuss trajectories of impaired social functioning in childhood and young adulthood and their associations with area-level social fragmentation and school maladaptation among youth at clinical high risk for psychosis. He will be presenting additional unpublished findings from the North American Prodrome Longitudinal Study. This talk will be followed by Dr Mariapaola Barbato, who will present findings on the symptoms and outcomes of migrants who are identified as Ultra-high risk for psychosis. Associate Professor Brian O'Donoghue, a psychiatrist in Dublin, Ireland will present unpublished data on the accumulative effect of individual, family and neighbourhood level environmental risk factors on the transition rates in young people identified as ultra-high risk for psychosis from the PACE Clinic in Melbourne, Australia. Finally, Dr Dominic Oliver, a postdoctoral researcher from Oxford, UK, will describe the Psychosis Polyrisk Score (PPS), which was developed from 16 environmental risk factors and enables an UHR individual's risk of transition to be predicted. Dr Oliver will present findings on the validation of the PPS in large UHR cohort. Finally, Dr Sheri Oduola, who has published widely on pathways to care for psychosis, will act as a discussant for the symposium.

13.1. RELATIONS OF AREA-LEVEL SOCIAL FRAGMENTATION AND SCHOOL MALADAPTATION DURING CHILDHOOD ON SOCIAL FUNCTIONING AMONG YOUNG ADULTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

Benson Ku^{*1}, Jean Addington², Carrie Bearden³, Kristin Cadenhead⁴, Tyrone Cannon⁵, Michael Compton⁶, Barbara Cornblatt⁷, Benjamin Druss⁸, Sinan Guloksuz⁹, Daniel Mathalon¹⁰, Diana Perkins¹¹, Ming Tsuang⁴, Elaine Walker¹², Scott Woods⁵, Ricardo Carrion¹³

¹Emory University School of Medicine, ²University of Calgary, ³University of California, Los Angeles, ⁴University of California, San Diego, ⁵Yale University, ⁶College of Physicians and Surgeons, Columbia University, ⁷The Zucker Hillside Hospital, ⁸Emory University Rollins School of Public Health, ⁹Maastricht University, ¹⁰University of California, San Francisco, ¹¹University of North Carolina at Chapel Hill, ¹²Emory University, ¹³Institute of Behavioral Science, Feinstein Institutes for Medical Research

Background: Studies have identified area-level social fragmentation index as a significant risk factor for psychotic disorders. However, it is unknown whether it may impact social functioning. This study investigates whether social fragmentation during childhood predicts maladaptation to school as well as social functioning among healthy youth and those at clinical high risk (CHR-P).

Methods: This study sample included 133 young adults at CHR-P and 90 healthy comparisons from the baseline cohorts across 8 sites from the second North American Prodrome Longitudinal Study (N = 223, 54.7% males; average age range = 21.8). Area-level characteristics, including social fragmentation, were derived from county-level data from the U.S. Decennial Censuses. Cities or towns where individuals spent the majority of their childhood were linked to the primary county 5-digit Federal Information Processing Standards

codes. Social fragmentation was measured as the average of the z-scores of the following area-level characteristics which have been previously shown to measure social fragmentation and to be associated with psychotic disorders: residential instability (percent of residents who changed their address in the past five years), percent of residents with renter-occupied housing, percent of residents who are divorced, and percent single-parent households. Maladaptation to school and social functioning during childhood were assessed retrospectively and social functioning in adulthood was assessed at baseline. Generalized linear mixed regression models adjusted for covariates including age, sex, family history of mental illnesses, White non-Hispanic race/ethnicity, high school parental education, total traumatic events, area-level deprivation, and unique counties.

Results: During childhood, greater social fragmentation was associated with greater maladaptation to school in childhood (unadjusted $\beta = 0.25$; 95% CI: 0.08 to 0.42) even after adjusting for seven covariates (adjusted $\beta = 0.21$; 95% CI: 0.02 to 0.40). However, social fragmentation was not associated with social functioning in childhood (unadjusted $\beta = -0.08$; 95% CI: -0.31 to 0.15). In contrast, greater social fragmentation during childhood predicted poorer social functioning in young adulthood (unadjusted $\beta = -0.56$; 95% CI: -0.86 to -0.26) even after adjusting for seven covariates (adjusted $\beta = -0.43$; 95% CI: -0.79 to -0.07). Greater maladaptation to school during childhood predicted poorer social functioning in adulthood (adjusted $\beta = -0.38$; 95% CI: -0.61 to -0.15). Maladaptation to school had a significant indirect effect on the association between social fragmentation during childhood and social functioning in adulthood (adjusted $\beta = -0.07$; 95% CI: -0.17 to LESS THAN -0.01) and explained 15.7% of this association. CHR-P status significantly interacted with social fragmentation during childhood in predicting poorer social functioning in adulthood (adjusted $\beta = -0.42$; 95% CI: -0.82 to -0.02) such that the slope between social fragmentation and social functioning was more negative among youth at CHR-P compared with HC.

Conclusions: This is the first study to find associations between area-level social fragmentation during childhood and social functioning in early adulthood. This association is mediated by greater maladaptation to school during childhood. Moreover, this association is moderated by CHR-P status such that childhood social fragmentation has an even stronger association with adult social functioning among youth at CHR-P compared to HC. Perhaps, exposure to cumulative social stressors from area-level social fragmentation during childhood might impact social functioning through repeated and chronic adverse social experiences (e.g., lack of feeling of belongingness or not fitting in) at school. Further research will be needed to explore the mechanisms of these associations and better understand the perceived experiences of area-level social fragmentation, the specificity of the developmental time period of exposure in relation to its impact on social functioning, and how social fragmentation and genetic vulnerability might interact in contributing to poorer social functioning.

13.2. THE IMPACT OF MIGRANT STATUS ON CLINICAL SYMPTOMS AND FUNCTIONING IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

Mariapaola Barbato^{*1}, Lu Liu², Carrie E. Bearden³, Kristin S. Cadenhead⁴, Barbara A. Cornblatt⁵, Matcheri Keshavan⁶, Daniel H. Mathalon⁷, Thomas H. McGlashan⁸, Diana O. Perkins⁹, Larry J. Seidman⁶, William S Stone⁶, Ming T. Tsuang⁴, Elaine F. Walker¹⁰, Scott W. Woods⁸, Tyrone D. Cannon⁸, Jean Addington²

¹Zayed University, ²Hotchkiss Brain Institute, University of Calgary, ³University of California, Los Angeles, ⁴University of California San Diego, ⁵Zucker Hillside Hospital, ⁶Harvard Medical School, Beth Israel Deaconess Medical Center, ⁷University of California, San Francisco, ⁸Yale University, ⁹University of North Carolina, ¹⁰Emory University

Background: Migrant status is a known risk factor for schizophrenia and other psychotic disorders. Among migrants, the risk seems to vary according to several factors, including country of birth, host country, ethnic minority status and refugee status. The pathways to psychosis, however, for migrants and their offspring, are still largely unknown. Recent studies have begun to explore whether migrant status predicts transition to psychosis in individuals who are at clinical high risk (CHR) for psychosis. The results of systematic reviews and meta-analyses however have been inconclusive. Our study assessed the impact of migrant status on clinical symptoms and functional outcome in individuals at CHR for psychosis who took part in the North American Prodrome Longitudinal Study (NAPLS-3).

Methods: Participants' migrant status was classified as native-born, first-generation, or second-generation migrant. Clinical symptoms were assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS); functional outcome was measured using the Global Functioning Scales: Social and Role (GF:S; GF: R). Assessments were conducted at baseline, 12-months, 18-months, and 24-months follow-up. We used generalized linear mixed models for repeated measures to examine group differences and changes over time.

Results: The overall sample included 710 individuals at CHR for psychosis (54.2% males; Age: $M=18.19$; $SD=4.04$). A mixed model analysis was conducted, and no significant differences between groups in symptoms or functioning were observed at any time point. Over time, significant improvement in symptoms and functioning was observed within each group. The rate of conversion to full-blown psychosis was similar across the three groups (native-born: 20%; first-generation migrant: 20%; second-generation migrant: 21%; $X^2 = 0.27$, $p = 0.87$).

Conclusions: To the best of our knowledge our study was the first to focus on migrant status, clinical symptoms and functioning in CHR individuals, and our results await replication. Nevertheless, we will discuss potential factors that might explain the lack of group differences in our sample. Overall, migrants are a heterogeneous population. Discerning the impact of migration from that of neighborhood ethnic density, social disadvantage or socio-economic status of different ethnic groups could help better understand vulnerability and resilience to psychosis.

13.3. ENRICHING ULTRA-HIGH RISK FOR PSYCHOSIS COHORTS BASED ON ACCUMULATED EXPOSURE TO ENVIRONMENTAL RISK FACTORS FOR PSYCHOTIC DISORDERS

Brian ODonoghue^{*1}, Andrew Thompson², Patrick McGorry², Barnaby Nelson²

¹University College Dublin, ²Orygen

Background: Transition to psychosis rates within ultra-high risk (UHR) services have declined and the characteristics of UHR cohorts are often different from first episode psychosis (FEP) services. It may be possible to 'enrich' UHR cohorts based on the environmental risk factors seen more commonly in FEP cohorts. This study aimed to determine whether transitions rates varied according to the accumulated exposure to environmental risk factors at the individual, family and neighbourhood level.

Methods: The study included UHR young people aged 15-24 who attended the PACE clinic from 2012-2016. Information according to environmental risk factors at the individual (migrant status, asylum seeker/refugee status, indigenous population, cannabis/methamphetamine use), family (family history or parental separation) and neighbourhood (population density, social deprivation and fragmentation) level were collected at the time of presentation. The transition rates and the corresponding hazard ratios according to the level of accumulated exposure was determined.

Results: Of the 461 young people included, 55.5% were female and median follow-up was 307 days (I.Q.R.:188-557) and 17.6%(n=81) transitioned to a psychotic disorder. Of those who had no exposure to an environmental risk factor, 11.1% transitioned compared to 18% with one or two individual-level factors present. The proportion that transitioned increased incrementally with the accumulated exposure and 33.3% transitioned with exposure to five factors. Accumulated exposure to family or neighbourhood level environmental risk factors was not associated with transition.

Conclusions: There is a dose-response relationship between exposure to individual level psychosis-related environmental risk factors and transition to psychosis risk in UHR patients, although the numbers were small in the later groups and lacked statistical power. If replicated, this finding could be incorporated into a novel approach to identifying highest risk individuals within clinical services.

13.4. CONTRIBUTION OF THE PSYCHOSIS POLYRISK SCORE (PPS) AND POLYGENIC RISK SCORE IN PREDICTING PSYCHOSIS ONSET IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

Dominic Oliver*¹, Matthew Kempton², Daniel Stahl², Philip McGuire², Paolo Fusar-Poli³

¹University of Oxford, ²Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ³ Institute of Psychiatry, Psychology, and Neuroscience, King's College London, OASIS team, South London and the Maudsley NHS Foundation Trust, University of Pavia,

Background: The complex interplay between environmental factors and genetics in the development of psychosis remains poorly understood. Genetics, through the polygenic risk score (PRS), have been shown to explain between 9-12% of the variance in CHR-P transition risk (Perkins et al., 2020), which remains sub-optimal. To address this, the Psychosis Polyrisk Score (PPS) was developed, piloted and digitally implemented as a multivariate assessment of environmental risk factors for psychosis. The PPS combines information from 16 systematically selected environmental risk factors to predict an individual's psychosis risk. It can therefore be used to potentially improve prognosis of individuals at clinical high risk for psychosis (CHR-P). It is currently unknown what proportion of variance can be explained by the PPS and its combination with genetics.

Methods: N=410 CHR-P individuals were recruited as part of the EU-GEI study. We assigned a PPS score to all participants comprised of age, gender, non-right handedness, urbanicity, pollution, ethnicity, migrant status, paternal age, paternal socioeconomic status, parental severe mental illness, stressful life events, tobacco use, cannabis use, hearing impairments, childhood trauma and trait anhedonia. The weights for each factor were based on meta-analytic Odds Ratios from a previously published umbrella review (Radua et al., 2018). First, we compared PPS total score between CHR-P individuals who transitioned and those who did not using Welch's t-test. Second, we used a Cox proportional hazards model to estimate the risk of transitioning psychosis. Three models were conducted including: i) PRS alone; ii) individual PPS factors alone; iii) PRS and individual PPS factors. The primary outcome was the proportion of variance explained, indexed by Nagelkerke's pseudo R².

Results: N=57 (13.9%) CHR-P individuals transitioned over 730 days follow-up. PPS scores ranged from -3.5 to 40.5 with a mean (SD) of 16.7 (9.7). PPS scores were significantly higher in CHR-P individuals who transitioned to psychosis (MD=3.4, 95%CI=0.89-5.93, d=0.36, t(80)=2.7, p=0.009). PRS alone explained a small proportion of variance (R²=0.03). Individual PPS factors explained a greater degree of variance (R²=0.17). Combining PRS and PPS individual factors (R²=0.23) explained the most variance.

Conclusions: Significantly higher PPS total scores in individuals who transitioned to psychosis suggest heightened exposure in those most at risk. Preliminary results suggest that a simple multivariate environmental risk assessment for psychosis risk is able to explain substantially more variance in transition risk in CHR-P than more expensive and invasive genetic tests. However, we may gain more prognostic value by considering genetic and environmental risk as complementary approaches.

14. BEYOND THE BIOLOGICAL MODEL: INVESTIGATING SOCIAL DETERMINANTS, LONELINESS, AND ADVERSITY IN THE PSYCHOSIS SPECTRUM

Katrina Rbeiz, *Vanderbilt University*

Overall Symposia Abstract: Social determinants of health include socioeconomic status, social support and networks, cultural and social norms, racial/ethnic identity, and education levels, to name a few. The intersection between these factors and the development of psychosis is a critical area of study, carrying significant implications for addressing mental health disparities. The theory of social defeat stresses the importance of environmental factors in psychosis-risk, and posits that experiences of social adversity may amplify the risk for developing psychosis. The intricate relationship between these factors underscores the need to move beyond the traditional neurobiological models of schizophrenia to focus on the broader influence of social and environmental factors. In this symposium, we begin with an overview of how various forms of exclusion, discrimination, and adversity may play a role in the development of psychosis, particularly among marginalized groups of people across global contexts. Katrina Rbeiz will present data from a cross-sectional study investigating the risk and resilience factors associated with the development of psychosis, with a focus on Middle Eastern and North African immigrant experiences. Jill Laquidara's presentation will further explore the social defeat hypothesis, which posits that people with increased perceived discrimination and sense of inferiority will be at higher risk for psychosis. Renata Botello will explore the connection between social adversity and loneliness in first-episode psychosis patients, and will shed light on the psychosocial challenges faced by individuals as they navigate the early stages of the psychosis spectrum. Zeynep Akcaoglu will present experience sampling methodology findings from Belgium looking at moment-to-moment levels of distress and social isolation, and how they may be associated with psychotic experiences. This temporal investigation underscores the dynamic nature of these factors and how they may influence the trajectory of psychosis. Of note, the participants in each of these studies represent diverse and underrepresented populations, and their social identities will be at the crux of each presentation, providing new insights into culturally informed interventions. Finally, Dr. Hans Oh will synthesize the presentations and share his thoughts on future directions and interventions addressing social adversity, isolation, and risk factors in the development of psychosis spectrum disorders. Attendees will gain insights into the social determinants that may impact the development of psychosis across the schizophrenia spectrum, and will hopefully think critically about environmental factors and social networks when designing studies. This symposium challenges existing models rooted in biology by emphasizing the need to integrate people's social, cultural, and environmental contexts.

14.1. EXPERIENCES OF STIGMA AMONG PSYCHOLOGY TRAINEES WITH PSYCHOSIS SPECTRUM DISORDERS

Emily Turner*¹, Emily Treichler², Katrina Rbeiz³

¹*Psychin Out*, ²*University of California, San Diego*, ³*Vanderbilt University*

Background: Psychosis spectrum conditions (e.g., bipolar disorder, schizophrenia, psychosis) are highly stigmatized in our culture, and these systemic biases permeate mental health service professions despite this being contrary to the field's values and mission (Elliott and Ragsdale, 2020; Peris et al., 2008; Arboleya-Faedo et al., 2023). Mental illness stigma exacerbates feelings of burnout and reduces treatment-seeking among psychology trainees (Berger, 2022; Devendorf et al., 2023; Victor, Schleider, et al., 2022). While psychology trainees are clearly vulnerable to the effects of mental illness stigma (Grice et al., 2018), their unique experiences with psychosis spectrum conditions have not been studied. This exploratory study aims to investigate the levels of stigma of psychosis conditions and discrimination experienced by psychology trainees.

Methods: 200 psychology trainees (full-time predoctoral researchers and doctoral students in psychology) with mental health conditions were administered a battery of four validated scales to assess experiences of mental illness stigma and discrimination (Everyday Discrimination Scale, Williams et al., 1997; Internalized Stigma of Mental illness - Brief, Boyd-Ritscher et al., 2003; Berger Stigma Scale, Reinius et al., 2018; EMIC Community Stigma Scale, Chowdhury et al., 2001). Of these 200 participants, 65 trainees identified as having a psychosis spectrum condition. Using bivariate correlations, t-tests, and MANOVA, we will investigate whether experience with psychosis spectrum conditions is associated with higher levels of discrimination, internalized stigma, and community stigma. We will also investigate whether demographic variables (e.g., education, race, income, gender) play a role in increased stigma surrounding their given psychosis spectrum condition.

Results: We hypothesize that psychology trainees with experience of a psychosis spectrum condition will report higher levels of stigma and everyday discrimination than those with a history of other more common mental health problems. We also hypothesize that lower income and education, as well as people who identify as gender and racial minorities, will have increased reports of stigma and discrimination.

Conclusions: To our knowledge, this is the first study investigating stigma and discrimination among psychology trainees with a psychosis spectrum condition entering the mental health field. Understanding of lived experience of this population can inform anti-stigma and anti-discrimination efforts from graduate programs to professional organizations, to help support recruitment and retention of the next generation of diverse psychologists.

14.2. MEASURING PERCEPTIONS OF SOCIAL DEFEAT, DISCRIMINATION, AND SENSE OF INFERIORITY IN CLINICAL HIGH RISK FOR PSYCHOSIS

Madeline Ward*¹, Jill Laquidara¹, Taylor Johnson¹, Sarah Hope Lincoln¹

¹*Case Western Reserve University*

Background: The social defeat hypothesis of schizophrenia suggests that socially defeating or excluding experiences increase risk for psychosis (Selten et al., 2005). However, social defeat can be operationalized in several ways, including broad feelings of defeat, specific experiences of exclusion or discrimination, and perceptions of oneself as inferior (Schalbroeck, 2020). Various conceptualizations of social defeat may vary in how they are related to the psychosis spectrum. The present study aimed to explore three different measures of social defeat in a clinical high risk (CHR) population. We hypothesized that social defeat broadly, as well as perceived inferiority and discrimination more specifically, would be higher in clinical high risk

(CHR) participants than in healthy control (HC) participants, which would be in line with the social defeat hypothesis of schizophrenia.

Methods: Adults ages 18-35 (N = 66 [32 HC, 34 CHR], 58% female, M-age = 25.6 ± 4.17) completed self-report measures and clinical interviews in a research study conducted online, using the Zoom platform and REDCap. Measures included the Structured Interview for Prodromal Syndromes (McGlashan et al., 2001), Structured Clinical Interview for DSM-5 (First, 2015); Defeat Scale (Gilbert and Allan, 1998), Social Comparison Scale (Allan and Gilbert, 1995), Everyday Discrimination Scale (Williams et al., 1997), Brief Core Schema Scale (Fowler et al., 2006), Global Functioning: Social Scale (Carrión et al., 2019), and Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Analyses included between-groups t-tests and correlation analyses.

Results: Social defeat was significantly higher in the CHR group than the HC group when operationalized as Defeat Scale scores, $t(64) = 4.09$, $p < .001$ and Everyday Discrimination Scale scores, $t(63) = 3.66$, $p < .001$. However, when operationalized as feelings of inferiority, social defeat was not significantly different between groups, $p > .05$. Of note, the CHR and HC groups did not differ in terms of gender or sexual minority status ($p > .05$), but a greater proportion of the CHR group were people of color, $\chi^2(1, N=65) = 4.4$, $p = .04$.

Conclusions: Broad feelings of social defeat, and more specifically discrimination, were both higher in the CHR group. In contrast to our hypothesis, feelings of inferiority were not greater in the CHR group. Inferiority may be distinct from other aspects of social defeat in how it is experienced by individuals at risk for psychosis. It is notable that the CHR group had a greater proportion of people of color than the control group. Next steps will involve looking at the perceived reasons for discrimination endorsed by participants. Discrimination and defeat may be higher in the CHR group due to racial bias as well as other types of defeating experiences, perhaps those related to symptom presentation and mental health stigma. It is also possible that for CHR individuals, the defeat and discrimination they experience feels even more salient due to symptom-related attention to threat, social anxiety, or schemas involving danger. It is likely that these factors all play a role in helping to explain the finding that CHR individuals experience greater feelings of social defeat and discrimination than healthy controls. In line with the social defeat hypothesis, this study demonstrates higher reports of perceived social defeat in individuals with subthreshold psychosis.

14.3. SOCIAL ADVERSITY AND LONELINESS IN FIRST EPISODE PSYCHOSIS

Renata Botello^{*1}, Arti Gandhi¹, Nicholas Wagner¹, Hans Oh², Kim Mueser¹, Daniel Fulford¹

¹Boston University, ²University of Southern California

Background: Aspects of social adversity, including poverty, trauma, exposure to crime, and homelessness, may contribute to psychosis risk, at least partly through the effects of structural racism (Anglin et al., 2021; DeVlyder et al., 2023). Research has also shown that structural racism and other forms of social exclusion are highly prevalent in people with psychosis and are related to more severe symptoms of depression, anxiety, and positive symptoms (Berg et al., 2011). Loneliness, the subjective experience of social disconnection (Hawkey and Cacioppo, 2010), could result from various forms of social adversity and associated exclusion. Loneliness is more prevalent among both people with psychosis (Badcock et al., 2015) and marginalized individuals in the general population (Visser and El Fakiri, 2016). However, the extent to which social adversity contributes directly to loneliness among people with psychosis is relatively unknown. Thus, in the current study we aimed to understand the extent to which

social adversity contributes to loneliness, accounting for demographic and social network variables, in first episode psychosis.

Methods: Four-hundred and four participants ages 15-40 completed baseline assessments as part of the Recovery After an Initial Schizophrenia Episode-Early Treatment Program. Loneliness was measured using a composite set of self-report items from the Well Being Scale and the Stigma Scale (e.g., “I often feel lonely because I have few close friends with whom to share my concerns.”). Social network characteristics (e.g., degree of recent social contact, including close friends, relatives, and acquaintances) were measured using the Quality of Life Scale (QLS). We created a latent variable of social adversity that included trauma history (number of reported traumatic experiences), education (highest parental level of education), health insurance (Medicaid status), and poverty (deferral/food stamp receipt). We first tested measurement models of loneliness and social adversity, followed by estimating a path model of the relationships among these variables, accounting for race/ethnicity and social network characteristics.

Results: Our hypothesized measurement models of social adversity ($X^2 = 10.261$, CFI = 0.821, TLI = 0.643, RMSEA = 0.077, SRMR = 0.044) and loneliness ($X^2 = 5.185$, CFI = 0.992; TLI = 0.984; RMSEA = 0.049; SRMR = 0.050) both resulted in adequate fit. All items demonstrated adequate loadings (β s GREATER THAN 0.40, p LESS THAN 0.01). Our hypothesized path model of the association between social adversity and loneliness resulted in moderate fit ($X^2 = 86.56$, CFI = 0.76, TLI = 0.65, RMSEA = 0.067, SRMR = 0.061). Greater social connection (i.e., social network characteristics) was associated with significantly lower self-reported loneliness ($\beta = -0.384$, p LESS THAN .01) and social adversity ($\beta = -0.381$, p LESS THAN .001). Importantly, greater social adversity was associated with significantly higher self-reported loneliness ($\beta = 0.376$, p LESS THAN .01), after accounting for social network characteristics and race/ethnicity.

Conclusions: Findings highlight the potential contribution of social adversity to the experience of loneliness in first episode psychosis. Social adversity, including trauma, limited resources, and other stressful experiences, could contribute to feelings of loneliness by way of either reduced opportunities for meaningful social contact, or perceived discrimination or other racialized experiences. In future work, it will be important to identify the extent to which discrimination and other racialized experiences contribute directly to social disconnection. Nonetheless, this study emphasizes the need to consider markers of adversity and other important social determinants of health when developing loneliness interventions for marginalized individuals with first-episode psychosis.

14.4. THE TEMPORAL ASSOCIATION BETWEEN SOCIAL ISOLATION, DISTRESS AND PSYCHOTIC EXPERIENCES IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

Zeynep Akcaoglu^{*1}, Thomas Vaessen¹, Eva Velthorst², Ginette Lafit¹, Robin Achterhof³, Barnaby Nelson⁴, Patrick McGorry⁵, Frederike Schirmbeck⁶, . EU-GEI At Risk Study⁷, Craig Morgan⁸, Jessica A Hartmann⁹, Mark Van der Gaag¹⁰, Lieuwe De Haan¹¹, Lucia Valmaggia⁷, Philip McGuire¹², Matthew Kempton⁷, Henrietta Steinhart¹, Annelie Klippel¹³, Wolfgang Viechtbauer¹⁴, Tim Batink¹³, Ruud van Winkel¹, Thérèse van Amelsvoort¹⁴, Machteld Marcelis¹⁵, Evelyne van Aubel¹, Ulrich Reininghaus¹⁶, Inez Myin-Germeys¹

¹KU Leuven, ²GGZ Noord-Holland-Noord, ³KU Leuven, Center for Contextual Psychiatry, ⁴of Melbourne, ⁵Orygen Youth Health Research Centre, ⁶AMC, University of Amsterdam, ⁷Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ⁸Centre for Society and Mental Health, King's College London, ⁹Orygen, the National Centre of

Excellence in Youth Mental Health, ¹⁰VU University Amsterdam *Clinical Psychology*,
¹¹AMC-Academisch Psychiatrisch Centrum, ¹²King's College London, ¹³Open University,
¹⁴Maastricht University, ¹⁵Maastricht University Medical Center, ¹⁶Central Institute of
Mental Health, University of Heidelberg

Background: Psychotic experiences (PEs) and social isolation (SI) seem related during early stages of psychosis, but the temporal dynamics between the two are not clear. Literature so far suggests a self-perpetuating cycle wherein momentary increases in PEs lead to social withdrawal, which, subsequently, triggers PEs at a next point in time, especially when SI is associated with increased distress. The current study investigated the daily-life temporal associations between SI and PEs, as well as the role of SI-related and general affective distress in individuals at Clinical High Risk for psychosis (CHR).

Methods: We used Experience Sampling Methodology (ESM) in a sample of 137 CHR participants. We analyzed the association between SI, PEs and distress using time-lagged linear mixed-effects models.

Results: Social isolation did not predict next-moment fluctuations in PEs, or vice versa. Furthermore, although SI-related distress was not predictive of subsequent PEs, general affective distress during SI was a robust predictor of next-moment PEs.

Conclusions: Our results suggest that SI and PEs are not directly related on a moment-to-moment level, but a negative emotional state when alone does contribute to the risk of PEs. These findings highlight the role of affective wellbeing during early-stage psychosis development.

15. MULTI-SCALE, MULTI-SPECIES APPROACHES TO ADVANCE SCHIZOPHRENIA RESEARCH

Royhaan Folarin, *Olabisi Onabanjo University*

Overall Symposia Abstract: New approaches that bridge knowledge across genes and proteins to cells to whole-brain networks and to behaviour are beginning to transform our understanding of how the brain works in health and disease. Magnetic resonance imaging (MRI) is widely available for mapping brain structure, function, connectivity and neurochemistry safely and non-invasively, and can be done in human populations and in model organisms. However, a key barrier for translation of this information into the clinic is that we do not know how they are specifically linked to cells and molecules. Translation of novel neuroimaging results depend on this mechanistic understanding and is critical for the discovery of new druggable targets. This symposium will provide an in-depth view into state-of-the-art tools and approaches bridging the gap between the structural and functional organization of the brain and the underlying cellular and molecular mechanisms across humans and experimental animals.

First, Modinos (UK) will introduce translational approaches linking the effects of pharmacological modulation on multi-modal MRI profiles in individuals at clinical high-risk for psychosis (CHR-P) and bridge this to cross-species evidence from relevant animal models. She will also present new data linking MRI-based markers of brain function in CHR-P individuals and people with schizophrenia spectrum disorders to specific cellular and molecular signatures. Next, Di Biase (Australia) will illustrate the power of combining imaging and genetics/transcriptomics to bridge outstanding knowledge gaps in schizophrenia research, including the biological basis of heterogeneity and the impact of medical comorbidities. This will be complemented by Yee (Canada), who will describe brain structural covariance

networks, their biological basis, and applications to psychosis using multi-species imaging datasets (in mice and humans). Finally, van den Heuvel (Netherlands) will present data on how genetic vulnerability, cellular changes and MRI findings in schizophrenia are associated. The symposium will conclude with a discussion led by Folarin (Nigeria), expert in the broader basic science modelling of schizophrenia and other neuropsychiatric disorders, who will integrate this set of findings to facilitate a stimulating discussion with the audience. Overall, this interdisciplinary symposium will offer new insights and tools to investigate brain complexity at multiple spatial and temporal scales, to advance our understanding of the mechanisms underlying schizophrenia spectrum disorders and contribute to unlocking the discovery of new pharmacological targets.

15.1. STRUCTURAL COVARIANCE NETWORKS FROM RODENTS TO HUMANS: MULTI-SCALE METHODS AND APPLICATIONS TO PSYCHOSIS

Yohan Yee^{*1}, Jason Lerch², Mallar Chakravarty¹

¹*McGill University*, ²*University of Oxford*

Background: Structural covariance refers to group-wise correlations that are observed between the structural properties (cortical thickness, volume) of brain regions. These correlations have been shown to capture developmental processes and differ in states of disease. By examining correlations between every pair of brain regions, network neuroscience approaches can be used to understand inter-regional structural relationships, and the ability to construct structural covariance networks from conventional structural magnetic resonance imaging (MRI) scans makes it an appealing type of brain network from which symptom etiology can be understood.

Methods: Here, we will demonstrate the usefulness of structural covariance analyses in understanding psychosis. First, using high-resolution and longitudinal MRI of healthy mouse brains and linking these to viral tracing and transcriptomic datasets, we examined the biological basis of structural covariance, and further examined network differences in mouse models of disease. Next, using a human pediatric population dataset that consists of MRI scans and a neurocognitive battery (the Philadelphia Neurodevelopment Cohort; PNC), we constructed structural covariance networks for subgroups based on reported psychosis-related symptoms and measures.

Results: Using mouse imaging data, we show that structural covariance captures functional relationships, is sensitive (but not specific) to structural connectivity, and largely mimics transcriptomic similarity between regions. Using longitudinal data acquired at 9 postnatal timepoints, we find that regional correlations are highest at the earliest timepoints. Together, we posit that structural covariance networks primarily reflect early-life coordinated neurodevelopment, and through examining network differences in mouse models of disease, aberrant early neurodevelopment can be captured via structural covariance analyses. Subsequently, using human data (PNC), we demonstrate and interpret similarities and differences between these networks constructed for psychosis-related subgroups. Finally, as structural covariance is a group-wise measure, we highlight approaches in which data-driven subtypes can be obtained.

Conclusions: Using multiscale datasets on spatial gene expression and viral tracing, we examined the biological basis for structural covariance networks and provide evidence that these networks reflect early-life coordinated neurodevelopment. Using multispecies imaging

datasets (in mice and humans), we demonstrate that differences in these inter-regional relationships related to neurodevelopment can be assessed through structural MRI data.

15.2. MULTI-SYSTEM CHARACTERIZATION OF BRAIN-BODY HEALTH IN SCHIZOPHRENIA AND OTHER COMMON MENTAL DISORDERS

Ye Tian^{*1}, Maria Di Biase¹, Philip Mosley², Michelle Lupton², Ying Xia³, Jurgen Fripp³, Michael Breakspear⁴, Vanessa Cropley¹, Andrew Zalesky¹

¹The University of Melbourne, ²QIMR Berghofer Medical Institute, ³CSIRO Health and Biosecurity, ⁴The University of Newcastle

Background: Physical health and chronic medical comorbidities are underestimated, inadequately treated, and often overlooked in psychiatry. A multi-organ, system-wide characterization of brain and body health in mental illnesses will enable systematic evaluation of brain-body health status in patients and potentially identify new therapeutic targets. This study aims to systematically investigate brain and body health in four common mental health conditions, including schizophrenia, bipolar disorder, depression and generalized anxiety disorder.

Methods: Brain imaging data (structural and diffusion-weighted MRI), and physical and physiological data (where available) were sourced from the following consortia studies: the UK Biobank, the Australian Schizophrenia Research Bank, the Human Connectome Project Young Adult and the HCP Aging. T1-weighted MRI brain images were available for 22,005 individuals (age range 18-95 years, mean 60.8±11.5, 9,061 males), collectively sourced from the seven consortia; diffusion-weighted MRI brain images were available for 20,283 individuals (age range 18-95 years, mean 60.6±11.5, 8,139 males) from all cohorts except AIBL. Physical and physiological assessments were sourced from 175,944 individuals (age range 37-74 years, mean 54.8±8.1, 72,339 males) participating in the UK Biobank. Generalized additive models for location, scale and shape were used to establish sex-specific normative reference ranges (mean and centiles) across the adult lifespan for each brain and body phenotype, based on healthy comparison individuals (HC, n=87,420) without any neuropsychiatric disorders or other serious medical conditions. A principled approach was developed to summarize phenotypic deviation scores at an organ/system level, yielding composite organ health scores (OHS) indexing the health and function of the brain and 7 body (pulmonary, musculoskeletal, renal, metabolic, hepatic, cardiovascular, immune) systems in individuals with one or more neuropsychiatric disorders (n=92,254). Phenotypic deviation scores were used to predict diagnoses (disorder vs HC) and differentiating between diagnoses (disorder vs disorder).

Results: Body health, especially composite scores indexing metabolic (mean OHS range: -1.41~-0.45), hepatic (-0.82~-0.21) and immune (-0.65~-0.19) health significantly deviated (p LESS THAN 0.05, FDR corrected) from normative reference ranges for all four mental disorders studied (schizophrenia: N=2,100; bipolar disorder: N=5,853; depression: N=81,631; anxiety: N=11,456). Poor body health was a more pronounced illness manifestation compared to brain changes. Body phenotype deviation scores provide the most accurate diagnostic classification for schizophrenia (body: AUC (area under the curve)=0.82; brain: AUC=0.80), bipolar disorder (body/brain = 0.68/0.57), depression (0.67/0.58), and anxiety (0.63/0.57). However, brain health enabled more accurate differentiation between distinct mental illness diagnoses than body health (average AUC: body/brain, schizophrenia-others: 0.70/0.79; bipolar disorder-others: 0.60/0.65; depression-others: 0.61/0.66; anxiety-others: 0.63/0.66).

Conclusions: Mental disorders share a substantial and largely overlapping imprint of poor body health. Despite the unequivocal neural basis of common mental disorders, we conclude

that poor body health and function are important illness manifestations that require ongoing management in patients. Routinely monitoring body health and integrated physical and mental health care in psychiatric practice may provide cost-effective targets for reducing the adverse impact of physical comorbidity on people with mental illness.

15.3. UNCOVERING AND MODULATING BIOLOGICAL SIGNATURES OF BRAIN VULNERABILITY FOR PSYCHOSIS

Gemma Modinos*¹

¹*King's College London*

Background: Preclinical evidence has shown that hyperactivity of the hippocampus due to neural excitatory (glutamatergic) – inhibitory (GABAergic) imbalance leads to psychosis-relevant electrophysiological and behavioural abnormalities. Importantly, peripubertal exposure to the GABA-enhancing drug diazepam prevented such psychosis-like phenotypes from emerging in adulthood in experimental animals. In humans, previous functional MRI work, including our own, found that hippocampal hyperactivity (by resting cerebral blood flow, rCBF) is a robust feature in individuals at clinical high-risk for psychosis (CHR-P). We also recently demonstrated a link between specific GABAergic interneuron disruption and increased hippocampal rCBF by back-translation in a genetic rodent model. Here, I will present novel findings on (1) whether diazepam exposure can restore hippocampal rCBF in individuals at CHR-P, and (2) the specific cellular and neurochemical signatures of rCBF-based profiles from CHR-P individuals and people with schizophrenia spectrum disorders (SSD).

Methods: Our first experiment used a within-subject, double-blind, placebo-controlled, randomised, cross-over design in 24 CHR-P individuals. Participants underwent MRI scanning twice, once under a single dose of diazepam (5mg) and once under placebo, with a minimum 3-week washout period between visits. rCBF was measured using pseudo-continuous arterial spin labelling, and a T1-weighted structural scan was acquired for co-registration. The hippocampus and its subfields were segmented for each subject per hemisphere and mean rCBF values were extracted in native space. Statistical/imaging analyses were done in R/4.2.2, including mixed ANCOVA models (healthy controls (HC) vs. CHR-P placebo, covarying for age, sex, and global CBF) and linear mixed-effects models (CHR-P placebo vs. CHR-P diazepam, covarying for subject_ID as random effect). Significance was set at pFDR LESS THAN 0.05. Our second study linked case-control rCBF alterations to gene and neuroreceptor expression in individuals with SSD (n=122) and people at CHR-P (n=129) versus their matched HC (n=116 and n=58, respectively). Case-control t-maps produced in SPM12 were parcellated into 100 cortical and 22 subcortical regions (Schaefer+Xiao atlases) with the mean value across each region z-scored to ease comparison across maps. Gene expression data was accessed via the Allen Human Brain Atlas (AHBA). Neuroreceptor maps were constructed from 19 publicly available PET images, covering nine neurotransmitter systems. Gene expression and receptor maps were all parcellated into the same 100 cortical and 22 subcortical regions as the rCBF maps. Correlations between case-control rCBF differences and (1) gene expression and (2) neurotransmitter systems were assessed with Spearman's rank correlations and dominance analyses. Significance was determined using FDR-corrected spatial-autocorrelation preserving null models.

Results: Diazepam (vs placebo) significantly reduced hippocampal and subfield (subiculum, CA1, CA4/dentate gyrus) rCBF in CHR-P individuals (all pFDR LESS THAN 0.05), to the extent that it was no longer significantly different from HC. At the whole-brain level, diazepam

(vs placebo) significantly reduced rCBF globally in CHR-P, greatest in pre/postcentral gyrus, dorsolateral prefrontal cortex, cingulate, hippocampus, insula, and striatum (all pFDR LESS THAN 0.05). The rCBF profile of CHR vs HC alterations tracks the distribution of oligodendrocyte, oligodendrocyte progenitor, and endothelial cell gene markers, as well as of D2, DAT, NET and NMDA receptors (all pFDR LESS THAN 0.05). In contrast, the SSD vs HC rCBF profile tracks the distribution of oligodendrocyte, pericyte, oligodendrocyte precursor and microglia gene markers, and of 5-HT2A and GABA-A receptors (all pFDR LESS THAN 0.05).

Conclusions: These novel mechanistic insights into the effects of diazepam on rCBF in CHR-P individuals support the development of GABA-enhancing compounds for psychosis, ideally with more selectivity for hippocampus. Furthermore, our findings implicate cell-types involved in stress response and inflammation, as well as dopamine, GABA-A, and NMDA receptors as distinct cellular and neurochemical signatures of rCBF profiles in SSD and CHR-P. Decoding the biological properties underlying MRI-based markers in CHR-P and SSD may unlock their translational potential to inform mechanisms that may be amenable to treatment.

15.4. TOWARDS CROSS-SCALE PSYCHIATRY: LINKING MICRO- AND MACRO FINDINGS OF MENTAL CONDITIONS

Martijn van den Heuvel*¹

¹*VU Amsterdam*

Background: The human brain is a complex multi-scale system with neural elements working at multiple levels of organization concurrently. At the microscale level, neurons, dendritic and axonal projections form the basic elements of brain architecture and at the meso- and macroscale system level, large-scale brain regions, functional pathways and white matter connections form the infrastructure for system-level brain communication. How disease effects manifest across these different scales at the same time remains an open question. In this talk we will discuss recent insights into how disease-related alterations at one level of organization may underlie alterations observed at other scales of brain network organization and discuss the importance of a cross-call understanding of the ethology of neuropsychiatric conditions.

Methods: Examining schizophrenia, we will discuss results of integration of genetic, transcriptomic, cellular and system-level MRI findings, discussing a particular vulnerability of higher-order cognitive brain areas at multiple levels of brain organisation. Data from GWAS and regional and single-cell gene expression is combined with recordings from macroscale functional resting-state networks across multiple datasets and cohorts. Cross-scale correlations across brain patterns are examined and tested by means of specific null-models and statistical tests.

Results: We show evidence of strong concordance of disease involvement of genetic, transcriptomic, cellular and macroscale system effects in schizophrenia. Regional gradients of expression of schizophrenia risk genes across cortical areas are found to show significant overlap with MRI disease patterns (p LESS THAN 0.001), combined with consistent patterns of changes in pyramidal structure at the cellular level. Results will be presented across several sensitivity and validation analyses and discussed in light of several studies showing cross-scale relationships.

Conclusions: Our findings suggest a robust relationship between disease effects across multiple levels of brain organisation in schizophrenia. We will discuss our findings in light of a developing field of multiscale neuroscience studies that illustrate the importance of studying

cross-scale interactions among the genetic, molecular, cellular, and macroscale levels of brain circuitry and connectivity and behavior.

16. COMPUTATIONAL APPROACHES FOR STUDYING FORMAL THOUGHT DISORDER: CURRENT AVENUES AND FUTURE PROSPECTS

Isaac Fradkin, *Max Planck UCL Centre for Computational Psychiatry and Ageing Research*

Overall Symposia Abstract: Disturbances in thought processes play a key role in historical and current conceptualizations of schizophrenia. Such disturbances, referred to as Formal Thought Disorder (FTD), are usually inferred based on alterations in the form and organization of speech. Yet, the complex and dynamic nature of language complicates objective measurement of FTD. Furthermore, the inherently covert nature of thought processes themselves hinders analysis of mechanisms involved in FTD based on linguistic output alone. A rapidly growing approach meeting these challenges involves the use of computational approaches to assess dynamics of language and thought. Two types of computational approaches can be identified. First, recent advances in natural language processing (NLP) are becoming an increasingly popular tool to quantify language incoherence, and even predict transition to psychosis. Whereas these methods hold promise to transform FTD measurement, their inherent biases and interface with traditional clinical ratings scales remain underexplored. A second type of model focuses on formalizing the covert cognitive dynamics governing the emergence and regulation of thought and its dynamic expression in language in FTD. In this symposium we will introduce up-to-date research in these two adjacent approaches, and endeavor to outline future prospects for progress and integration in the field.

Following a brief introduction by I. Fradkin, N. Lundin will discuss recent work focused on understanding potential cognitive processes underlying FTD through a semantic foraging framework. She will show how suboptimal semantic retrieval among individuals with psychosis may reflect a reduced ability to use the patchy structure of semantic memory to aid retrieval and discuss the emerging roles of hippocampal and cerebellar neural activity in semantic foraging and FTD.

Broadening the scope of computational-mechanistic approaches from the analysis of experimental cognitive tasks to the study of naturalistic speech, M. Nour will present a novel NLP pipeline that allows us to cast free speech as trajectories through semantic spaces. The potential of this approach to improve our understanding of the cognitive processes involved in naturalistic speech in FTD will be demonstrated in a large and diverse clinical sample.

Considering the potential biases involved in NLP methods for FTD, N. Mota will discuss the effects of formal education on clinical and computational assessment of FTD. She will show how patients' attained education and educational deficits can bias state-of-the-art NLP metrics of FTD but also serve as protective factors.

Finally, A. Voppel will present an application of a novel NLP framework for analyzing FTD symptom dimensions, as defined across different ratings scales. He will show how NLP methods can be used not only to quantify patients' speech output, but also as a tool for integrating different clinical views of FTD, thereby clarifying its fundamental clinical conceptualization.

To conclude the symposium, L. Palaniyappan will lead a discussion regarding the promises, limitations, and potential integration of the different computational approaches, while focusing on theoretical and clinical implications.

16.1. SUBOPTIMAL FORAGING IN SEMANTIC SPACE: POTENTIAL MECHANISMS OF THOUGHT DISORDER IN PSYCHOSIS

Nancy Lundin*¹

¹*The Ohio State University Wexner Medical Center*

Background: Advances in natural language processing have increased capacity to quantify speech organization and content, bolstering the widespread study of thought disorder among individuals with psychosis. Despite these advances, further research is needed to understand the underlying mechanisms of thought disorder. Semantic foraging is a novel framework which holds promise for understanding these mechanisms. Just as bears search for berries by alternating between local exploitation and global exploration in physical space, humans may search their memories for related concepts using an explore-exploit trade-off in semantic space. This has been studied using word search retrieval tasks such as verbal fluency tests (VFT). Individuals with higher VFT response rates tend to alternate between clustering and switching between groups of semantically similar items aligning with predictions within optimal foraging theories. While studies have broadly found VFT impairments among individuals with psychosis, open questions include how semantic foraging strategies vary among individuals with psychosis and the neural correlates of semantic foraging.

Methods: Samples included participants with schizophrenia (SZ), first-episode psychosis (FEP), schizotypal personality disorder (SPD) traits, and individuals without psychiatric illness. Participants completed 1–3 minute VFT in which they named as many items as possible from a particular category. Responses were transcribed. In a non-clinical sample, participants completed VFT during functional magnetic resonance imaging. VFT responses were designated as cluster or switch-related in various ways based on semantic similarity thresholds (using BEAGLE or word2vec), common subcategories, and participant evaluations of their own responses. Search metrics analyzed included: the number of generated responses, interitem semantic similarity and response times, indices of clustering and switching, and neural activity during search phases.

Results: Findings across studies revealed that participants with SZ and FEP generated fewer correct VFT responses than non-psychiatric and SPD comparison groups. During local search within patches of related words, participants with SZ had prolonged search times, and participants with FEP produced responses that were lower in semantic similarity. Among individuals with FEP, generating more VFT responses and a higher percentage of clustered responses related to lower disorganized and negative (but not positive) psychotic symptom severity, as well as greater processing speed and overall cognitive function. Finally, in a non-clinical sample, individuals showed greater neural activation during switching than clustering in the hippocampus or posterior cerebellum, depending on how patch boundaries were operationalized. Neural activity in these regions was also found to increase during within-patch search and reset at switch responses, potentially indexing a cognitive monitoring process guiding the search.

Conclusions: This work provides evidence of altered semantic foraging patterns among individuals with persistent and early course psychotic illness, while also highlighting the heterogeneity of cognitive search strategies among individuals with psychosis. Future studies will focus on consolidating methods to improve replicability, optimizing algorithms to define patch boundaries, and identifying neural correlates of semantic search strategies among individuals with psychosis. Finally, future work will investigate whether semantic explore-

exploit processes serve as a reliable index for organization of speech and narrative more broadly to identify intervention targets for recovery from thought disorder.

16.2. TRAJECTORIES THROUGH SEMANTIC SPACES IN PSYCHOSIS

Matthew Nour^{*1}

¹*University of Oxford*

Background: The ‘aberrant cognitive mapping’ hypothesis proposes that psychotic symptoms such as conceptual disorganisation and delusions stem from abnormalities in how the brain forms structured representations of the world. Current measurement tools are inadequate to test this hypothesis: symptom rating scales lack connection to theories of neural computation, while behavioural tasks offer a shallow window onto internal representations, and lack scalability and ecological validity. Advances in natural language processing (NLP) – notably, transformer-based large language models (LLMs, like chat-GPT) - signal a step change in our ability to extract cognitively-rich information from language behaviour, and thus test cognitive mapping hypotheses in clinical samples. In this presentation I will showcase work that applies novel machine learning and NLP tools to free speech transcripts from patients across a psychosis spectrum, and illustrate how these tools can inform neurocognitive theories of schizophrenia - including those pertaining to how related concepts are represented and retrieved. The talk will begin with a brief primer on foundational computational principles, followed by a detailed walkthrough of a novel analytic pipeline for speech data, and end with a presentation of unpublished empirical results from a clinical study of speech in psychosis.

Methods: The analytic pipeline has been developed and validated on study data comprising free speech samples from 200 individuals across a psychosis spectrum (from ‘at risk’ to chronic schizophrenia) and healthy volunteer controls. Participants were asked to provide free speech samples under 3 experimental contexts (paradigms) chosen to elicit speech with differing levels of directedness and constraint by external stimuli. These contexts were: picture descriptions, storyboard descriptions, and story recall. Participant speech was first transcribed, and then subjected to a novel NLP pipeline designed to track the temporal evolution of semantic and emotional information. This pipeline comprises sentence parsing (splitting the sequence of words into utterances, e.g., using BERT LLM to predict probability of period after each token), semantic embedding (embedding each utterance in LLM vector space, e.g., OpenAI ‘embeddings’ models), and cluster-based topic modelling (using the Uniform Manifold Approximation and Projection [UMAP] nonlinear dimensionality reduction algorithm and Hierarchical Density-Based Spatial Clustering of Applications with Noise [HDBSCAN] algorithm). These algorithms yield ‘topic solutions’, which can be tuned to have higher or lower numbers of topics (topic granularity) through tuneable UMAP and HDBSCAN hyperparameters. This pipeline signals an advance over extant approaches that track superficial semantics (e.g., word similarity) or eschew temporal or semantic information altogether (‘bag-of-words’ or ‘speech-graph’ methods).

Results: I will present three key results. The first demonstrates the validity of the NLP pipeline to detect semantically-coherent topic clusters in free speech. I will show how the pipeline can be fine-tuned to increase sensitivity to detect recurrent topics across participants, and topic variability within participants. Second, I will show that the intermediate NLP variables extracted by the pipeline are sensitive to subtle differences in speech structure collected across different experimental paradigms (contexts). Such main effects include an increased semantic

trajectory tortuosity in picture description vs storyboard contexts. Finally, I will show how NLP speech variables (e.g., semantic path tortuosity) are correlated with psychotic symptoms and differentiate early-stage vs. chronic patients.

Conclusions: These findings demonstrate the feasibility of indexing the structure of internal conceptual organisation in clinical samples using advanced NLP tools applied to free speech data, thus speaking to cognitive mapping hypotheses of symptoms. This work contributes new methods that can be applied to the study of speech and cognition in psychiatric samples with minimal attentional or task-comprehension requirements for participants. These methods and associated proof-of-concept findings, lay the foundation for future transdiagnostic studies, with the ultimate aim of developing NLP-based diagnostic and treatment-prediction tools for patients.

16.3. THE IMPACT OF FORMAL EDUCATION IN LANGUAGE DISTURBANCES IN PSYCHOSIS: CRUCIAL CONSIDERATIONS FOR AN UNBIASED CLINICAL PRACTICE

Natália Mota*¹

¹*Federal University of Rio de Janeiro*

Background: Recently, with the advance of natural language processing tools and artificial intelligence algorithms, different strategies have been applied to quantify language disturbances related to mental suffering. Word recurrence graphs have been applied to study word trajectories in the past decade. The method was inspired by the descriptions of formal thought disorders associated with psychosis and successfully demonstrated low connectedness related to non-affective psychosis in different stages. To advance knowledge in applicable strategy, it is crucial to understand confounder effects that could jeopardize actual clinical practice, such as access to education. In this talk, I will summarize studies on how this novel strategy to look into language is impacted by written language contact. Considering that by learning and practicing reading and writing, a child masters grammar and syntax rules, adopting this formal communication in oral storytelling, access to formal education is a vital confounder effect.

Methods: We will discuss how word recurrence graphs and sentiment analysis are associated with negative symptomatology in the early stages of psychosis. To address educational attainment impact, we will also study associations between language markers and years of education in different stages of disorder and how it could be a confounder or even a protective factor.

Results: In a sample under chronic psychosis, there was no association between low connectedness and years of education, unlike a control sample. Chronical psychosis seems resistant to traditional formal education, or symptomatology independently explains this variance. Moreover, in a first-episode psychosis sample, low connectedness was independently associated with symptoms and years of education, demonstrating a protective effect of education at this stage (in a significant multilinear correlation – R^2 0.67, negative symptoms were positively associated with a low connectedness – coefficient 0.41, while years of education were negatively associated – coefficient -0.53). A similar result was also found for a clinical high-risk sample. Alternatively, educational attainment seems to mediate the association between symptoms and emotional expression in the early stages of psychosis.

Conclusions: The results reveal crucial considerations regarding the social impact of psychosis, how formal education could protect communication, and the need to consider this factor on novel language markers in an unbiased clinical practice.

16.4. HOW COHERENT ARE OUR RATING SCALES? APPLYING NLP ON FTD ITEM DESCRIPTIONS

Alban Voppel^{*1}, Manaan Karray², Sohee Park³, Lena Palaniyappan⁴

¹McGill University, ²Princess Alexandra Hospital, Brisbane, ³Vanderbilt University, ⁴McGill University, Douglas Mental Health University Institute; Western University, Robarts Research Institute

Background: Formal thought disorder (FTD), a core symptom of schizophrenia-spectrum disorders, is commonly rated using scales such as TLC, TALD or PANSS. The design of these rating scales (choice and description of items) are informed by clinical observations and historical concepts of FTD pursued by the authors. As a result, different items of these scales may map on to the same or a small number of clinical phenomena presenting as disorganized speech, thoughts, or communication disturbances. For example, one scale might rate words per minute, others posit subjective poverty of speech or rate difficulties upholding a flow of information, which could all be grouped under “poverty of thought”. As a result, factor analysis undertaken with different scales often produce cross-cutting factors with inconsistent item loading across scales, and varying number of factors. Here, we probe the conceptual construct of FTD elicited using these rating scales by employing a semantic language model. We also provide a limited two-scale comparison in a single cohort, to illustrate the conceptual overlap. Natural Language processing has resulted in more theory-neutral methods of assessing language through the usage of large models, such as BERT or GPT. These models can be used to assess the semantic content of language and to quantify and compare language produced by participants. Here, we apply this methodology to the scales themselves; we use semantic models to examine the item-level description of 7 commonly used thought disorder different rating scales and compare them. Through the usage of NLP, we perform content clustering on these descriptions across scales, to extract the “backbone” of FTD from item-level descriptions.

Methods: We collected 7 commonly used FTD rating scales and used a sentence-level Bidirectional Encoder Representations from Transformers (BERT; all-mpnet-base-v2) model to perform item-level embedding of each item for each rating scale. These 7 scales were TALD, SAPS-SANS, PANSS, TLI, TLC, BIT and CLANG. We filtered out examples but kept all other content. We calculate item-to-item sentence similarity, resulting in a connectivity matrix for 100+ FTD item scales, with each rating-scale item receiving a similarity between 0 and 1 to each other item. The resulting similarity matrix allowed a range of operations, including the assessment of the relation between item-descriptions of FTD scales. We sparsified the matrix, leaving the “backbone” of the network, and detected similar communities of items, clustering content-similarity rating-scales items together. Finally, we applied these clustered item-level descriptions of different rating scales and see how they perform compared to classic factor analysis.

Results: We computed embeddings of TALD, SAPS-SANS, PANSS, TLI, TLC, BIT and CLANG item-scale descriptions. We noted differences in richness of scale descriptions as a quantitative comparison, such as the presence of examples or floridness of descriptions. We found 4 major groups of item-level symptoms when using the TLC network as a backbone; we repeated this finding using the TALD. Rating all items as semantically either more positive and negative FTD and showed high concurrence with published factors (81% overlap with TALD division). Ranked CLANG and TLC item correlation and canonical factor loadings from a cohort of 98 subjects overlap 72.2% with semantic clustering, with 88.8% of items within communities of clusters.

Conclusions: We found finite clusters of meaning in different rating scales-based item-level descriptions. These descriptions can be unified using NLP methods. Resulting unified

descriptors overlap with previously reported conceptual divisions, such as positive and negative FTD but allowing other divisions to be made. Our approach serves as an “intuition pump” for integrating different clinical views and rating scales of FTD, thereby clarifying its clinical conceptualization. This approach can be extended and applied to other symptom rating scales. Finally, new rating scales would benefit from the approach here to test descriptive validity of their measures.

17. LET’S FOCUS ON CLINICAL RECOVERY – IN LONG-TERM MODERN COHORTS OF INDIVIDUALS DIAGNOSED WITH SCHIZOPHRENIA FOLLOWED FOR MORE THAN TWO DECADES ON SEVERAL CONTINENTS – AND PROPOSE A CONSENSUS DEFINITION?

Nikolai Albert, *Copenhagen Research Center for Mental Health – CORE*

Overall Symposia Abstract: The course of schizophrenia is complex and therefore the concept of clinical recovery is present and relevant but as of now we still do not have a consensus definition. More than 100 years ago, Kraepelin was the first to use the term recovery in the field of psychiatry. He reported that 2.6% of his patients with schizophrenia had a “permanent recovery” and 13% experienced time-limited periods of recovery. So, what we as clinicians could ask ourselves now is: “Do modern cohorts of individuals diagnosed with schizophrenia experience more favorable outcomes?” Or is the prognosis still as Kraepelin reported back in the 19th century or in other words “Are we getting better at getting our patients better?”

Over the years, several meta-analyses among individuals with schizophrenia have found recovery rates ranging between 13.5% to 57%. These inconsistencies in recovery percentages have been hard to uncover since meta-analytic methods could not explain the variation due to clinical study characteristics such as chronic or first episode illness, gender, duration of follow-up or strictness criteria of the recovery definition. Older WHO-led studies have found significant differences between continents as well as developed- and developing-countries but the mechanisms behind this are still not fully understood.

With the criteria for symptomatic remission presented by the Remission in Schizophrenia Working Group (RSWG), we now have a foundation to build on a consensus definition for clinical recovery.

Bringing this panel of experts together we hope to develop the concept of recovery further and enlighten the audience on the inconsistencies on clinical recovery rates among long-term modern cohorts diagnosed with schizophrenia followed for more than two decades on several continents. Firstly, Dr. Hansen will present data from the 20-year follow-up of the OPUS trial including 578 individuals diagnosed with first episode schizophrenia focusing on remission status and clinical recovery through 20 years. Secondly, Dr. Weibell will present new data on a 20-year follow-up of a prospective cohort of individuals with a first episode of psychosis in Norway. Thirdly, Dr. Jonas will present data on remission and recovery rates from the Suffolk County Mental Health Project Cohort, including 628 individuals followed longitudinally for 25 years after a first episode of psychosis in the US. Finally, Dr. Chan will present preliminary results from a 20-years follow-up of patients with first-episode schizophrenia spectrum disorder in Hong Kong and elaborate on predictors of clinical remission and functional recovery.

Overall, the presenters will be able to discuss how we define clinical recovery in different studies and what measurements are used? Also, which patients recover and what do they have in common? Furthermore, are there any differences between continents among those who recover? AND finally let's propose a consensus definition on clinical recovery in order to promote long-term positive outcomes for individuals diagnosed within the schizophrenia spectrum.

17.1. DESCRIPTIVE PATTERNS OF CLINICAL RECOVERY AND SYMPTOM REMISSION FOLLOWING 547 INDIVIDUALS DIAGNOSED WITH FIRST-EPISODE SCHIZOPHRENIA OVER 20 YEARS - RESULTS FROM THE OPUS TRIAL

Helene Gjervig Hansen^{*1}, Marie Starzer², Carsten Hjorthøj³, Nikolai Albert⁴, Merete Nordentoft⁵

¹*Copenhagen Research Centre for Mental Health, University of Copenhagen*, ²*Copenhagen University Hospital, Mental Health Center Copenhagen, Copenhagen Research Center for Mental Health - CORE*, ³*Mental Health Center Copenhagen, University of Copenhagen, Denmark*, ⁴*Copenhagen Research Center for Mental Health – CORE*, ⁵*Mental Health Centre Copenhagen*

Background: Through decades, clinical recovery outcomes among individuals diagnosed with schizophrenia have been highly inconsistent ranging from 13.5%-57%. The primary objective of this study was to report on 20-year patterns of clinical recovery and symptom remission in a clinical cohort of individuals diagnosed with a first episode of schizophrenia.

Methods: A total of 547 individuals with a first episode schizophrenia spectrum disorder were included into the trial between 1998 to 2000 and allocated to either two years of Early Intervention Services (EIS) or Treatment As Usual (TAU). Over the years multiple follow-ups of the entire clinical cohort has been conducted at one-, two-, five-, ten- and now 20 years. For the analyses of symptom remission and clinical recovery rates, individuals diagnosed with schizotypal disorders were excluded, since a diagnosis of schizotypal disorder excludes any major psychotic symptoms.

Results: A total of 164 participants (30%) out of 547 were reassessed at the 20-year follow-up, (mean [SD] age, 45.9 [5.6] years, 51.8% female sex). Approximately, 40% (n=53) of the participants obtained symptom remission and 18% (n=23) of participants were in clinical recovery at the 20-year follow-up. Symptom remission accounted for 37.5% (n=24) in the EIS-group and 42% (n=29) in the TAU-group, P=.59. Clinical recovery accounted for 14.1% (n=9) in the EIS-group and 21.2% (n=14) in the TAU-group, P=.27. Furthermore, in total 28.8% (n=57) of participants (observed cases) experienced clinical recovery at least once through the past 20 years. Only 35% of individuals in symptom remission were in treatment with antipsychotics. Also, 50% of individuals in symptoms remission receiving no antipsychotic treatment were in clinical recovery at the 20-year follow-up. Of individuals reporting self-perceived recovery (n=47) only 28% were in clinical recovery. Investigating psychotic illness trajectories over 20 years, significantly higher clinical recovery rate (22%) was found among those with continues remission of psychotic symptoms. Also, 37% of individuals following a trajectory of remission of negative symptoms over 20 years were in clinical recovery. Stratifying for parenthood, we found that significantly more parents were in symptom remission (59.5% vs. 22.4%, P LESS THAN .001) and in clinical recovery (29.7% vs. 11.1%, P=.002) compared to non-parents at the 20-year follow-up. Finally, of the entire sample, a total

of 82 individuals (14.4%) had died over the past 20 years. Predictors of high mortality were substance use and chronic somatic illness whereas predictors of low mortality were symptom remission without antipsychotic treatment and clinical recovery.

Conclusions: A clinical recovery rate of 18% and symptom remission of 40% was found at the 20-year follow-up of the OPUS trial. No significant differences were found on clinical recovery and symptom remission between the EIS-group compared to TAU, implying that modern era treatment facilities have not enhanced these outcomes in schizophrenia. Overall, a substantial proportion of 14-18% were in clinical recovery over 20 years with app. 30% (n=57) of participants experiencing clinical recovery at least once through the past 20 years. These results imply that new initiatives for individuals with schizophrenia are needed to improve the rates of both clinical recovery and symptom remission.

17.2. CIOMPI REVISITED: TRAJECTORIES OF REMISSION AND RECOVERY IN FIRST EPISODE PSYCHOSIS OVER 25 YEARS

Katherine Jonas^{*1}, Sara Tramazzo², Wenxuan Lian¹, Olesya Ajnakina³, Gabrielle Carlson¹, Evelyn J. Bromet¹, Roman Kotov¹

¹*Stony Brook University*, ²*Hofstra University*, ³*Institute of Psychiatry KCL*

Background: Understanding prognosis is critical to anticipating public health needs and providing care to individuals with psychotic disorders. However, the long-term course of remission and recovery remains unclear. Cross-sectional estimates of remission and recovery vary widely, and there are relatively few studies with a follow-up greater than 10 years. In this cohort of individuals followed for 25 years since first admission for psychosis, we describe the most common trajectories of illness course.

Methods: Participants are from the Suffolk County Mental Health Project, an epidemiological study of first-admission psychosis. Data for the present study was gathered from six follow-ups. 311 individuals were assessed at the 25-year follow-up. Symptom remission was operationalized according to Andreasen's definition, while recovery was defined according to criteria from Liberman's definition. Tetrachoric correlations were used to assess stability of remission and recovery across follow-ups. Common patterns of remission and recovery were assessed in the baseline cohort of 591 individuals and the subsample observed at the 25-year follow up. Multinomial regression was used to identify predictors of patterns of remission and recovery.

Results: Among those ascertained at first admission, 41.9% of those with other psychotic disorders and 27.2% of those with schizophrenia spectrum disorders were recovered 6 months after first admission. However, rates declined over time, and at the end of the 25-year follow-up only 28.1% of those with other psychoses and 14.2% of those with schizophrenia spectrum disorders were in recovery. Remission rates followed a similar trajectory, beginning at 46.2% in other psychotic disorders and 24.9% in schizophrenia spectrum disorders, and falling to 20.0% and 7.4%, respectively. Among those with schizophrenia spectrum disorders, the most common pattern in both the baseline and 25-year cohort was a trajectory of no remission and no recovery. Among those with other psychotic disorders, the modal pattern in both the baseline and the 25-year cohort was one of intermittent remission and recovery. Those with other psychotic disorders were more likely to experience stable remission (15.1%) and stable recovery (21.1%), outcomes that were rare in schizophrenia spectrum disorders (0% and 0.6%, respectively). Gender, diagnosis, and avolition predicted patterns of both remission and recovery. Race and treatment with mood stabilizers at discharge predicted recovery, while socioeconomic predicted remission.

Conclusions: The most common trajectory for individuals with schizophrenia spectrum disorders is one of no remission and no recovery. The increasing stability of symptoms across the follow-up period indicates more effective treatments are needed to impact the course of remission and recovery in schizophrenia spectrum disorders, and illuminates the need for sustained intervention and support for this population. The modal longitudinal pattern for those with other psychoses is one multiple transitions into and out of symptomatic and functional recovery. Engagement in a long-term health care plan may help individuals with other psychotic disorders detect and respond to changes. Our results emphasize a need for continued research and treatment for individuals with psychotic disorders in midlife and beyond.

17.3. 20-YEAR REMISSION AND RECOVERY IN FIRST EPISODE PSYCHOSIS

Melissa Weibell*¹, Jone Bjørnstad², Inge Joa³, Carmen Simonsen⁴, Torill Ueland⁵, Ingrid Melle⁶, Wenche ten Velden Hegelstad³

¹Stavanger University Hospital, ²TIPS Centre for Clinical Research in Psychosis, Stavanger University Hospital, University of Stavanger, ³TIPS Centre for Clinical Research in Psychosis, Stavanger University Hospital, . Network for Medical Sciences, University of Stavanger, ⁴NORMENT, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Early Intervention in Psychosis Advisory Unit for South East Norway, Oslo University Hospital, ⁵NORMENT, University Hospital and Institute of Clinical Medicine, University of Oslo, University of Oslo, ⁶NORMENT Norwegian Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo University Hospital,

Background: The TIPS 20-year sample encompasses patients followed up more than 20 years after their first-episode of psychosis in one early, and one usual detection area. Recovery is a key element, and patients are assessed through multiple instruments and interviews. The aim of the overall long-term follow-up is to investigate long term outcomes in an early versus a usual detection area. In the sub-study presented here, the aim was to establish rates of remission and recovery across both areas.

Methods: 281 patients, 18-65 years old with a first episode of non-affective psychosis were included between 1997-2001. Of these, 74 patients have by October 2023 been followed up at more than 20 years and assessed for symptoms and recovery defined as living independently, seeing friends at least weekly, and being competitively employed (if not retired, homemaker or not working due to other circumstances than mental illness) in addition to being in stable remission (GREATER THAN 6 months with no scores above 3 on the PANSS positive subscale).

Results: Forty-six participants (62,2%) had been in symptom remission for at least the last six months. Preliminary analyses indicate that 24 (32,2%) out of the participants hitherto assessed were in stable long-term recovery. Seventeen (22,9%) participants were currently psychotic, and 10 (13,5%) had been continuously psychotic since inclusion. 57 (77%) were living independently, 23 (31,3%) were in stable relationships, and 19 (25,6%) were competitively employed or studying part- or full time. In addition, 49 (66.2%) had digital contact with friends or equivalent at least once per week and 45 (60.8%) saw their friends at least weekly. Data presented in this abstract should be considered preliminary, pending detailed analyses and publication.

Conclusions: Rates of symptomatic remission as well as recovery including adequate functioning and remission increased from 10-20 years. After 20 years, it becomes apparent that

our definition of recovery does not take into account that as time passes, other reasons than psychosis could be the reason for patients not working or studying.

17.4. CLINICAL REMISSION AND FUNCTIONAL RECOVERY OF PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA-SPECTRUM DISORDER: COMPARISON OF 10 YEAR AND 20 YEAR FOLLOW UP

Sherry Kit Wa Chan*¹

¹*The University of Hong Kong*

Background: Schizophrenia-spectrum disorder is a chronic condition and most of the long-term follow up suggested that only about 20-30% of patients recovered. Some earlier studies of very long-term follow up study suggested that some patients recover at later stages. The current study aimed to compare the clinical remission and functional recovery of patients with first-episode schizophrenia-spectrum disorders at 10 year and 20 year follow up. Baseline demographic and clinical information as possible factors associated with the 20 year clinical remission and recovery will also be explored.

Methods: Patients with first-episode schizophrenia-spectrum disorders with age 15-25 who attended the public psychiatric service in Hong Kong between June 2000- July 2002 were identified and face-to-face interviews with clinical and functional assessment at 10 year and 20 year follow up were conducted. Their baseline demographics and clinical information, and clinical information over the initial three years of service attendance were obtained from the electronic and written clinical records. PANSS was used for clinical assessment, SOFAS was used for functional assessment. Employment and general living conditions at 10 and 20 year follow up were assessed. SF 36 was used to assess subjective quality of life. Within subject comparison was conducted between the 10 year and 20 year follow up time point. Association analysis was conducted to examine the relationship of the baseline demographics and early clinical factors and longer-term recovery and remission. Andreasen cross-sectional criteria was used to define the clinical remission and functional recovery. Patients who fulfil criteria of both are considered as having complete recovery.

Results: A total of 110 patients were interviewed at both 10 year and 20 year follow up and were included in the analysis. At 20 year follow up, the mean age was 43.2 with 50% male. 61.8% of patients had clinical remission, 60.9% had functional recovery, 50% had complete recovery, 55.5% were engaged in open employment at 20 year follow up. Though no significant differences in clinical remission rate between 10 and 20 year follow up, significantly more patients were in functional recovery and complete recovery between 10 and 20 year follow up. 49% and 39.3% who were recovered functionally and completely recovered respectively at 10 year follow up were considered functionally recovered and completely recovered at 20 year follow up. Though no significant differences in employment rate between 10 and 20 year follow up, 42.1% patients who were unemployed at 10 year follow up were engaged in open employment at 20 year follow up. Educational years was consistently associated with clinical remission and functional recovery. No significant changes of subscore of SF 36 between 10 and 20 years follow up apart from a trend significant increase ($p=0.051$) of subscale of pain between the two time points.

Conclusions: Though clinically there is not much improvement between the 10 years, a substantial number of patients have improved in functioning as well as employment status. However, there are no significant changes in quality of life between the two time points apart from a possible deterioration of experience of physical pain. This suggests that there are different trajectories for domains of recovery over time.

Plenary Session III - Sara Evans-Lacko: Stigma and Economic Determinants

9:00 a.m. - 10:00 a.m.

18. STIGMA AND ECONOMIC DETERMINANTS

Nicolas Crossley, *Facultad de Medicina, P. Universidad Catolica de Chile*

18.1. THE ROLE OF STIGMA AND SOCIO-ECONOMIC FACTORS IN PERPETUATING INEQUALITIES FOR PEOPLE WITH PSYCHOSIS

Evans-Lacko Sara, *Care Policy and Evaluation Centre, London School of Economics and Political Science*

Individual Abstract: This presentation considers the intricate relationship between socio-economic factors and the stigma experienced by individuals with psychosis. It will highlight how socio-economic disadvantage and stigma are intertwined, impacting a range of life domains and contributing to ongoing inequalities that those with psychosis face. By addressing the stigma embedded within structures, institutions, policies, and cultural attitudes, alongside explicit consideration of socio-economic factors, the presentation will propose actionable strategies to mitigate these inequalities. It will emphasise the need for integrated approaches that not only confront stigma directly but also robustly address the socio-economic underpinnings that hinder recovery and perpetuate disparities in outcomes. The presentation will advocate for interventions that are embedded within policy and societal change, aiming to dismantle both the overt and subtle forms of stigma while addressing socio-economic factors as a core component of mental health recovery and to chart a pathway towards equity,

Concurrent Symposia

10:30 a.m. - 12:30 p.m.

19. THE CHANGING WORLD OF ANTIPSYCHOTIC MEDICATION USE: THE LATEST EVIDENCE FROM THE INTERNATIONAL TRIALS IN THE TAPER (TAPERING ANTI-PSYCHOTICS AND EVALUATING RECOVERY) CONSORTIUM

Marieke Begemann, *University Medical Center Groningen*

Overall Symposia Abstract: During the last few years, the risk-vs-benefit debate on antipsychotic medication use has intensified. This is partly due to the growing emphasis on the patient perspective, as many wish to discontinue their medication due to side effects or stigma. While most guidelines advise to use medication for at least 1 year after remission of a first psychotic episode, up to 58% of patients discontinue early - without clinical consultation. In addition, growing findings on the impact of antipsychotic medication are being published, including alarming side effects such as metabolic disease, heart disease, cognitive impairment, and potential brain volume reductions. To help patients make informed choices, clinicians and researchers face the responsibility of providing evidence-based counselling. However, evidence on the long-term impact of maintenance treatment vs early tapering is scarce when it

comes to an outcome prioritized by patients: personal and functional recovery. The two randomized trials completed so far have left us with contradictory results. Moreover, formal guidelines on how to safely reduce antipsychotic dosage to minimize the risk of withdrawal effects and relapse are scant. Recent suggestions of gradual, hyperbolic tapering as opposed to abrupt discontinuation have not yet been tested in RCTs, and tapering strategies may need to differ for first-episode compared with multi-episode psychosis.

This symposium will present the latest evidence from clinical trials and observational studies on optimal tapering. Presenters are members of the TAPER Research Consortium, uniting researchers involved in previous and current trials from Australia, China, Denmark, France, the Netherlands, Taiwan, and the UK. We extend the traditional focus on relapse risk by also examining the impact of tapering on social functioning and quality of life, providing a more holistic view of the risk-vs-benefit ratios of antipsychotic medication.

Dr. Horowitz will kick-off this symposium by premiering the results from RADAR (UK). This RCT compared a gradual and structured method of dose reduction to maintenance treatment in 253 people with recurrent psychosis. Next to relapse rates and social functioning at 24-months follow-up, he will share qualitative data on how RADAR participants had experienced dose reduction.

Dr. Liu will complement the current evidence by presenting 2-year outcomes from GARMED (Taiwan). This RCT applied a pragmatic-based tapering protocol, empowering 51 patients with remitted psychosis to evaluate their readiness for a next tapering attempt. Different dose-tapering patterns were identified and linked to functioning and quality of life.

Shiral Gangadin continues the discussion on tapering trajectories by evaluating tapering speed as predictor for relapse risk. He will present a subset of the data from the ongoing Dutch HAMLETT trial (450 FEP patients). As self-report data on medication use is not always accurate, he included unique dispensation data from pharmacies.

Dr. Ødegaard Nielsen shares evidence from three Danish studies in first-episode as well as multi-episode psychosis. Apart from survival curves and relapse rates, she will discuss qualitative data showing that clinicians still seem reluctant to let service users make decisions and how tapering affected patients' attitude towards drugs. This will form the foundation for discussing the upcoming priorities in the field.

19.1. RANDOMISED CONTROLLED TRIAL OF ANTIPSYCHOTIC DOSE REDUCTION AND DISCONTINUATION VERSUS MAINTENANCE TREATMENT IN PEOPLE WITH SCHIZOPHRENIA AND OTHER RECURRENT PSYCHOTIC DISORDERS (THE RADAR TRIAL)

Mark Horowitz*¹, Joanna Moncrieff²

¹*North East London NHS Foundation Trust*, ²*University College London*

Background: Antipsychotics reduce psychotic symptoms in the short-term, have some unpleasant subjective effects and some negative health consequences. Many patients wish to stop these medications. A previous Dutch RCT involving people with FEP found improved functioning and the same level of relapse in people who reduce or stop their antipsychotics compared to those who maintain their dose at long follow-up. We wished to determine whether these results could be replicated in the UK in people with recurrent disorders.

Methods: An RCT was conducted in 19 NHS Trusts in England comparing maintenance of antipsychotic medication in people with chronic psychotic conditions versus gradual, supported dose reduction and/or cessation (RADAR trial). Patients were excluded if they had experienced a mental health crisis in the last month, were deemed a serious risk by the treating clinician or were legally mandated to take antipsychotics. The intervention was evaluated quantitatively and qualitatively, with primary outcome being social functioning (measured by the Social Functioning Scale).

Results: 253 people with psychotic conditions were randomised from 4100 people screened: 126 to dose reduction and 127 to maintenance. At 24 months the median dose reduction was 33% in the discontinuation group and 0% in the maintenance group. At 24 month follow up there was no difference in the Social Functioning Scale between the two groups. 25.4% of people in the reduction group had a severe relapse whilst 13.4% did so in the maintenance group. In qualitative interviews, dose reduction patients reported a reduction in negative effects, primarily in mental clouding, emotional blunting and sedation and a positive effect in terms of social functioning and sense of self. They also reported withdrawal effects, symptom recurrence and relapse. Some people experienced an increased sense of empowerment, regardless of the outcome.

Conclusions: Similarly to the previous Dutch trial, there was no difference in social functioning between dose reduction and maintenance at medium term follow-up, and a near doubling in relapse rate. The majority of patients who reduced or stopped medication did not relapse. Longer follow-up is taking place. A more gradual, hyperbolic approach to tapering might improve outcomes. Patients reported a number of subjective and functional benefits to dose reduction.

19.2. 2-YEAR TRAJECTORIES AND OUTCOMES OF GUIDED ANTIPSYCHOTIC REDUCTION TO REACH MINIMUM EFFECTIVE DOSE (GARMED TRIAL) IN PATIENTS WITH REMITTED PSYCHOSIS

Chen-Chung Liu*¹

¹*National Taiwan University Hospital and College of Medicine, National Taiwan University*

Background: Patients in remitted state of schizophrenia face a dilemma whether they could improve their quality of life by reducing antipsychotics or they should maintain on stable dose to prevent from relapse. We tested in real world practice if an operationalized exponential guided-dose-reduction algorithm can help them reach a lower effective dose not at expense of increased risks of relapse. We also depicted and examined dose-tapering trajectories as to explore factors associated with different dose-reduction patterns and provide insights for re-evaluating the risk-to-benefit balance.

Methods: A 2-year open-label randomized prospective comparative cohort trial from Aug 2017 to Sep 2022 in Taiwan. Patients with a history of schizophrenia-related psychotic disorders under stable medications and symptoms were eligible, randomized 2:1 into guided dose reduction group (GDR) versus maintenance treatment group (MT1), together with a group of naturalistic maintenance controls (MT2). We examined if patients of GDR group could have a relapse rate not higher than the other two comparison groups by Kaplan-Meier survival estimates, how much dose they could reduce within 2 years, and if dose reduction correlated with improved functioning and quality of life compared by paired t-test. We also depicted the trajectories of individual GDR patients, grouped them based on dose-tapering patterns, and explored who were more likely to take which tapering strategies by logistic regression analysis.

Results: A total of 96 patients, comprised 51, 24, and 21 patients in GDR, MT1, and MT2 groups, respectively. During 2-year follow-up, 14 patients (14.6%) relapsed, including 6, 4,

and 4 from GDR, MT1, and MT2 (2 GDR and 2MT1 patients confessed discontinuing medications before relapse), statistically no difference between 3 groups. Among the 51 GDR patients, only 18 (35.3%) reduced 4 steps consecutively following the hyperbolic tapering algorithm (sequential reducers, SR, on average 58.5% baseline dose reduced), 14 (27.5%) reduced 1 to 3 steps (modest reducers, MR, 40% dose reduced), 3 (5.9%) re-escalated to previous level (alert reducers, AR, 28.7% dose reduced), 7 (13.7%) returned to baseline level (baseline returners, BR, no dose reduced), 6 (11.7%) relapsed (failed reducers, FR) and 3 (5.9%) withdrew without relapse (early exits, EE). Only SR subgroup of GDR exhibited improved clinical outcomes and endorsed better quality of life. Patients with a history of relapse were strongly correlated to taking a conservative dose-tapering pace, while no variables identifiable for predicting SR or FR.

Conclusions: Guided dose reduction seems to be a feasible approach as the majority of patients successfully tapered antipsychotics to certain extents. However, even though the risk of relapse, 11.8%, is comparable to their maintenance counterparts, in total 25.5% of GDR patients failed to decrease any dose, a fact to be deliberate while trying dose-reduction. Moreover, guided dose reduction comprises dynamic processes with differences between individual trajectories. Longer term observation, more flexible tapering processes, and closer monitoring of factors related to successful or failed tapering, are anticipated to improve outcomes of dose-reduction trials.

19.3. ANTIPSYCHOTIC TAPERING SPEED AS PREDICTOR FOR PSYCHOTIC RELAPSE AFTER FIRST-EPISODE PSYCHOSIS

Shirah Gangadin^{*1}, Franciska de Beer¹, Martijn Kikkert², HAMLETT and OPHELIA consortium³, Iris Sommer¹

¹UMCG, ²Arkin Mental Health Care Amsterdam, ³HAMLETT and OPHELIA Consortium,

Background: The prevention of relapse is a crucial treatment target in first episode psychosis (FEP) patients, as up to 85% of FEP patients experience a psychotic relapse within 5 years of remission from their first episode. Current guidelines recommend continuation of antipsychotic (AP) treatment during the first year after remission to prevent relapse, but patients and clinicians may have prominent reasons to reduce or discontinue AP medication early (e.g., unfavourable side-effects). However, evidence on safe tapering is scarce. Although gradual dose reduction may intuitively reduce relapse risk as compared to rapid discontinuation, this notion has not been supported by a large body of evidence. Therefore, this study will investigate the association between AP tapering speed, the type of AP drug, and psychotic relapse in the first 1.5 years after recovery from FEP in 250 patients.

Methods: We include data from the HAMLETT study (Begemann et al., 2020), a randomised controlled discontinuation trial. Participants were included in the trial when in remission from FEP for 3 to 6 months. Half of the participants is randomised to the continue group, the other half to the dose reduction/discontinuation group. Participants who tapered/discontinued antipsychotic medication, irrespective of randomized group, with available follow-up data for at least 1.5 years were included. We defined relapse as hospitalisation due to worsening of psychotic symptoms, the clinical judgement of the treating psychiatrist, or an increase of ≥ 10 points on the total score of the positive and negative syndrome scale (PANSS). Antipsychotic medication use was based on data from the Dutch Foundation for Pharmaceutical Statistics (SFK). SFK collects dispensation data from community pharmacies in the Netherlands. Tapering speed (in olanzapine equivalents/day) is calculated as the difference of AP dose at remission and at the end of AP discontinuation, divided by the number of days in between. AP

drugs are divided into partial agonists (PA, e.g. aripiprazole) and groups with high affinity (HA, e.g. haloperidol) and low affinity (LA, e.g. olanzapine) D2-receptor antagonism. Data were analysed using binary logistic regression models including AP tapering speed and AP type as predictors for relapse. Covariates were measured at baseline, 3-6 months after remission, and included age, sex, years of education (YOE), and duration of FEP (in months).

Results: The current patient group was on average 28.3 ± 8 years of age at baseline and consisted of 33% females. The average PANSS total score was 43.9 ± 9.4 and GAF score was 66.5 ± 12.4 . Preliminary analyses show that within the first year after recovery from FEP, 50% ($n=78$) experienced a relapse after dose reduction. The average tapering speed of all patients was equivalent to the discontinuation of a daily dose of 10mg olanzapine in 100 days (~ 0.1 olanzapine equivalents/day), starting from an average dose of 12.5 mg olanzapine. Male sex was a significant predictor for relapse $p < 0.05$, but other covariates were not significantly related to relapse.

In a model adjusted for age, sex, years of education and FEP duration, tapering speed was not significantly related to relapse ($OR=2.26$, $p=0.51$). A long total duration of the tapering trajectory ($OR=0.99$, $p=0.001$) and low dose after tapering ($OR=0.86$, $p=0.01$; complete discontinuation was not required) were significant predictors for relapse. AP type might be related to relapse, for which PA users might have a lower risk for relapse compared with HA users ($p < 0.10$).

Conclusions: Preliminary analyses indicate that AP tapering speed may not be related to relapse in patients who have recently recovered from their first FEP. It is important to emphasize that all patients were relatively well functioning individuals that participated in a discontinuation trial and were therefore closely monitored. As a result, all patients tapered off very gradually. A shorter tapering trajectory and lower end dose as significant predictors for relapse are possibly reflections of the protective effects of antipsychotics. In addition, the risk for relapse after tapering may be dependent on specific AP types. Evidence for the relationship between AP tapering speed and psychotic relapse is a valuable addition to current clinical knowledge, since there are still many persistent unknowns regarding AP discontinuation.

19.4. MOTIVATIONAL FACTORS, CLINICAL OUTCOMES, AND MENTAL HEALTH PROFESSIONALS' POSITIONS: RESULTS FROM FOUR DANISH STUDIES ON TAPERING ANTIPSYCHOTICS

Mette Ødegaard Nielsen^{*1}, Helene Speyer², Alexander Nøstdal³, Anne Emilie Stürup², Kickan Roed⁴, Jimmi Nielsen³

¹Copenhagen University Hospital, ²Copenhagen Research Center for Mental Health-CORE; Mental Health Center Copenhagen, Copenhagen University Hospital, ³Psychiatric Centre Glostrup, Mental Health Services in the Capital Region of Denmark, ⁴Centre for Applied Research in Mental Health Care, Mental Health Center, Glostrup, Copenhagen University Hospital - Mental Health Services CPH

Background: The need for lifelong antipsychotic maintenance treatment has been increasingly challenged. Questions have emerged regarding the characteristics of patients who can safely taper off antipsychotic treatment and the most effective way to reduce the antipsychotic dose. However, the idea of tapering antipsychotic medication can be met by negative attitudes among clinical staff.

Methods: In Denmark, three clinical studies on tapering antipsychotics have been conducted during the past 5 years: One randomized controlled study on remitted first-episode patients (n

= 26), one naturalistic study following patients with schizophrenia spectrum disorders who taper their antipsychotics (n=52), and one study on patients with schizophrenia enrolled in a specialized tapering clinic (n=88). Despite different inclusion-criteria and study designs, all projects were challenged in the recruitment of patients. Also, a qualitative study was conducted with 39 mental health staff divided into six focus groups to investigate their accounts of tapering antipsychotics.

Results: For the three clinical studies, 1-year follow-up data showed a total relapse rate of 35%, whereas 45% remained stable on a dosage of LESS THAN 50% of the baseline dosage. In the specialized tapering clinic, motivational factors for tapering were side-effects (71%), thoughts about the continuous need for medication (29%), the feeling of being stigmatized (12%) or disagreeing with the diagnoses (7%). For patients who remained stable, the level of function increased, and the reported side-effects decreased. For patients experiencing a relapse, level of function was stabilized after the relapse. Predictive models were weak but identified higher levels of general symptoms and lower baseline antipsychotic dose as predictors of relapse after one year.

The qualitative study identified three distinctive positions among mental health staff towards tapering antipsychotics, and points to a reluctance among mental health staff to let service users make decisions. This may leave limited possibilities for people with schizophrenia to have their request for tapering of their antipsychotic medication met by mental health staff.

Conclusions: The results from the clinical studies indicate that a significant proportion of patients with a schizophrenia spectrum disorder can benefit from a decreased antipsychotic dose in terms of an improved level of function and reduced adverse effects without a worsening in symptoms. For patients who experienced a relapse, a close monitoring resulted in a relatively swift stabilization of symptoms and level of function. The improved attitude towards antipsychotic medication following a relapse may potentially improve the treatment alliance and future adherence.

The randomized study struggled with recruitment, partly due to unwillingness to let randomization decide. Patients' preference to taper their medicine conflicts with mental health staffs' critical attitude towards tapering and may result in patients quitting the medicine on their own. To date, there are no strong evidence to identify who can safely taper their medication and the most secure method to do so. We argue that, at present, a closely monitored, slowly progressing tapering process based on active shared decision making, stands as the most effective and safe approach to identify individuals who can manage without medication and ensure the minimum necessary antipsychotic dose for those who require continuous antipsychotic treatment.

A limitation of the Danish studies lies in their relatively short follow-up period. It is essential to elucidate the long-term impact of the tapering process on the participants, a task that can, to some extent, be accomplished by examining the Danish registers.

20. NOVEL SOLUTIONS TO OLD QUESTIONS: USING ARTIFICIAL INTELLIGENCE TO PREDICT SEX, DRUGS, AND PSYCHOSIS PREVENTION

Paris Alexandros Lalousis, *Institute of Psychiatry, Psychology, and Neuroscience, King's College London*

Overall Symposia Abstract: Modern psychiatry largely deals with the same questions it did 100 years ago, but our selection of tools to answer them is increasingly growing. The recent Artificial Intelligence (AI) revolution provides hope for innovation and advancement that can

translate into transformative change in patient care. In this symposium, we will present work in which AI techniques have been implemented using biological markers and clinical presentation to improve prediction of sex, treatment response, and psychosis prevention.

In the first talk, Maria Fernanda Urquijo Castro presents work in which she uses machine learning to predict biological sex based on brain structure among patients with psychosis and depression. Drawing insights from the European Personalised Prognostic Tools for Early Psychosis Management (PRONIA) study, this presentation showcases the power of supervised machine learning in forecasting functioning outcomes. Her work showcases the connection between brain structure, sex and clinical trajectories.

In the second talk, Madaliva-Octavia Buciuman shows from resting-state fMRI (rs-fMRI) and their potential as early risk-stratification tools. Using supervised machine learning techniques, the talk explores the predictive value of static and dynamic rs-fMRI metrics, including local fractional amplitude of low-frequency fluctuations and functional connectivity measures. In a second phase, the talk explores the use of semi-supervised clustering methods, particularly Heterogeneity through Discriminative Analysis (HYDRA). These methods unveil transdiagnostic biologically-defined subtypes among clinical high-risk for psychosis, recent-onset depression, and recent-onset psychosis individuals based on rs-fMRI measures. These subtypes offer a deeper understanding of the complexities of these conditions, paving the way for more precise risk-stratification and personalized treatment approaches.

In the third talk, Dominic Oliver explores dynamic risk prediction for psychosis, reimagining how we detect individuals at risk. Utilizing vast patient data from electronic health records, the talk introduces a paradigm shift with time-varying Cox proportional hazards modelling and dynamic survival random forests to capture evolving symptoms over time. By refining a transdiagnostic risk calculator, this research demonstrates how incorporating longitudinal data can transform existing clinical prediction models and approaches to detection.

In the final talk, Paris Alexandros Lalousis presents a comprehensive journey into clinical and biological heterogeneity within depression and psychosis. Using a systematic review of structural neuroimaging studies, we uncover potential transdiagnostic patterns of gray and white matter volume reductions. Leveraging clinical, neurocognitive, and neuroanatomical support vector machine (SVM) learning models, we showcase the separability of depression from psychosis and provide insights into affective comorbidity. Semi-supervised machine learning further identifies distinct clusters of schizophrenia with varying immune signatures, GMV, and neurocognitive function, offering potential for targeted treatments. This work challenges traditional diagnostic boundaries, showcasing the promise for a new era of precise and transdiagnostic approaches to mental health care.

Together, these talks explore uncharted territories in prediction, risk assessment, and patient stratification, offering a glimpse of a future where early detection, dynamic risk prediction, and personalized treatments become the standard of care. Here we provide an overview of the ways that artificial intelligence is redefining our understanding of mental health.

20.1. UNDERSTANDING SEXUAL DIMORPHISM IN EARLY PSYCHIATRIC DISORDERS: A MULTIMODAL MACHINE LEARNING APPROACH

Maria Urquijo*¹, Linda A. Antonucci², Anne Ruef³, Frauke Schultze-Lutter⁴, Anita Riecher-Rössler⁵, Peter Falkai³, Rachele Sanfelici⁶, Lana Kambeitz-Ilankovic⁷, Dominic Dwyer⁸, Nikolaos Koutsouleris³, The PRONIA Consortium⁹

¹*Clinic for Psychiatry and Psychotherapy - LMU Clinic*, ²*University of Bari "Aldo Moro"*, ³*Ludwig-Maximilian-University*, ⁴*University Hospital of Child and Adolescent Psychiatry and Psychotherapy*, ⁵*University of Basel Psychiatric Clinics, Center for Gender Research and Early Detection*, ⁶*Ludwig Maximilian University, Max Planck School of Cognition*, ⁷*University of Cologne*, ⁸*Orygen, University of Melbourne*, ⁹*EU*

Background: Sexual dimorphisms contribute to the heterogeneity observed in psychotic and affective disorders across various disease stages. Despite evident sex-specific patterns in the expression of both disorder groups, prevailing diagnostic and treatment approaches rely on a one-size-fits-all paradigm. This may stem from a limited understanding of the intricate interactions among diverse bio-psycho-social variables that underlie the differences between females and males.

Methods: Here, our objective was to comprehensively investigate sex-related differences in the early stages of psychiatric diseases through a normative modeling lens. We initially constructed models of sexual dimorphism at the neuroanatomical level (BrainSex) and the phenotypical level (PhenotypicSex) using data from healthy individuals (N= 521). Subsequently, we applied these models to data from a total of 994 subjects with Clinical High-Risk (CHR) states for psychosis, Recent Onset Psychosis (ROP), and Recent Onset Depression (ROD) to evaluate whether deviations from the norm were associated with psychopathology. We also combined the initial two models to assess the gains of multimodal data integration.

Results: The BrainSex classifier exhibited a balanced accuracy (BAC) of 85.7% (p < 0.001), the PhenotypicSex model achieved a BAC of 69.6% (p = 0.001), while the multimodal classifier predicted sex with a BAC of 88.9% (p = 0.001). Additionally, when applying the BrainSex model to clinical samples, a gradual decrease in BAC for CHR, ROD, and ROP subjects was observed. In contrast, the PhenotypicSex model demonstrated improved performance in CHR and ROD subjects but not in ROP subjects, indicating a more pronounced influence of sex-related heterogeneity in the latter group.

Conclusions: Our findings affirm the existence of interactions between neuroanatomical and phenotypical patterns related to individuals' sex and psychopathology, even in early stages, with an increasing impact as the illness progresses. Risk stages of psychosis exhibited a marked sex-based dichotomization at the phenotypical level, highlighting the potential for these variables to offer prognostic insights and facilitate better-tailored treatment selection that could delay or even impede disease progression. Moreover, merging the models yielded greater accuracy in characterizing both healthy and clinical populations. These results underscore the imperative need for sex-based stratification in clinical practice for patients even in the early stages of psychiatric disorders as well as the integration of different modalities when aiming for an understanding of their etiopathology.

20.2. RESTING-STATE FMRI METHODS FOR TRANSDIAGNOSTIC PREDICTION OF FUNCTIONING OUTCOMES AND HETEROGENEITY CHARACTERIZATION IN EARLY STAGES OF PSYCHOSIS AND DEPRESSION

Madalina-Octavia Buciuman*¹, Paris Alexandros Lalousis², Shalaila Haas³, Linda A. Antonucci⁴, Lana Kambeitz-Ilankovic⁵, Anne Ruef¹, Stefan Borgwardt⁶, Joseph Kambeitz⁵, Christos Pantelis⁷, Rebekka Lencer⁶, Alessandro Bertolino⁴, Paolo Brambilla⁸, Rachel Upthegrove⁹, Stephen J. Wood¹⁰, Peter Falkai¹, Anita Riecher-Rössler¹¹, Stephan

Ruhrmann⁵, Frauke Schultze-Lutter¹², Eva Meisenzahl¹², Jarmo Hietala¹³, Raimo K.R. Salokangas¹³, Dominic B. Dwyer¹⁰, Nikolaos Koutsouleris¹, PRONIA study group¹⁴

¹Ludwig-Maximilian-University, ²Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ³Icahn School of Medicine at Mount Sinai, ⁴University of Bari Aldo Moro, ⁵University of Cologne, ⁶University of Lübeck, ⁷The University of Melbourne, Melbourne Neuropsychiatry Centre, ⁸University of Milan, ⁹University of Birmingham, ¹⁰Orygen, the National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, University of Melbourne, ¹¹University of Basel, ¹²Heinrich-Heine University Düsseldorf, ¹³University of Turku, ¹⁴EU Consortium

Background: Impairments in daily functioning are prevalent in the early stages of psychosis and depression and are of increasing interest as clinical outcome metrics, due to their high impact on patients' quality of life. However, individualized risk stratification of functional outcomes is currently limited and would benefit from the exploration of novel methods and data modalities. In this context, group-level brain functional abnormalities have been extensively reported in psychotic and depressive disorders, but their value as early prognostic tools within the framework of precision psychiatry has been insufficiently explored. Moreover, delineating biologically informed patient subgroups within the highly heterogeneous early illness stages may further aid the development of optimal tools for functional prognosis.

In the current work, we assess the prognostic value of state-of-the-art resting-state fMRI (rs-fMRI) measures for the stratification of functioning outcomes in clinical high-risk for psychosis (CHR) and recent-onset depression (ROD). In the second stage of the project, we explore whether rs-fMRI-based transdiagnostic subgroups within the early stages of psychosis and depression further improve the prediction of functional outcomes.

Methods: A total number of 218 CHR individuals and 197 ROD patients coming from eight European sites within the multi-center European Personalised Prognostic Tools for Early Psychosis Management (PRONIA) study were used for the current analyses. We trained support vector machine classifiers within a leave-site-out nested cross-validated framework to predict functional outcomes at the 9-month follow-up, as well as the persistence of high functioning from the 9-month to the 18-month follow-up based on several rs-fMRI metrics. As sufficient samples were available for the prediction of the 9-month functional outcome, we split our total sample into a model training (N=211) and a model validation (N=204) sample for these analyses, to further assess the generalizability of the models. Functional outcomes were measured using the Global Assessment of Functioning: Disability scale (Pedersen et al., 2007), with high functioning defined as more than 80 points on this scale. The rs-fMRI measures used as predictors were voxel-wise multiband fractional amplitude of low-frequency fluctuations and static and dynamic functional connectivity based on a group-level network model. In the second stage of the project, we plan to use the rs-fMRI metrics to identify transdiagnostic biological subtypes within CHR, ROD, and recent-onset psychosis (ROP) using semi-supervised clustering methods. Lastly, we aim to characterize the obtained subgroups at clinical, cognitive, and genetic levels, and explore their prognostic value for a more precise risk-stratification of functional outcomes.

Results Distributed fALFF and functional connectivity increases/decreases were transdiagnostically predictive of functioning outcomes at the 9-month follow-up above chance level, with a maximal balanced accuracy obtained by stacking the rs-fMRI metrics (Balanced accuracy = 65.8%, Sensitivity = 72.5%, Specificity=59.1%, P LESS THAN .001). Interestingly, the models generalized to the ROD patients in the replication sample, but not to

the CHR individuals, with maximum accuracy for the stacked model combining the different rs-fMRI metrics (BAC = 63.4%, Sensitivity = 72.7%, Specificity = 54%, P LESS THAN .001). Moreover, we found that the persistence of high functioning from the 9-month to the 18-month follow-up point could be predicted with higher performance based on the stacked rs-fMRI metrics (BAC = 71.6%, Sensitivity = 59.3%, Specificity = 84.0%, P LESS THAN .001), with predictive patterns predominantly spanning regions of the default-mode, frontoparietal and salience networks.

Conclusions: We provide evidence that resting-state fMRI measures are predictive of functioning outcomes in prodromal risk syndromes and early depression stages. We highlight the value of transdiagnostic model training for ROD patients and the potential presence of multiple pathways leading to functioning deficits in the CHR state, suggesting the need to further delineate more homogeneous subgroups in terms of risk etiology. Our results open the avenue for the further establishment of the generalizability and complementary prognostic value of rs-fMRI measures to other data domains within multimodal approaches.

20.3. USING DYNAMIC METHODS TO IMPROVE INDIVIDUALISED, TRANSDIAGNOSTIC CLINICAL PREDICTION MODELS FOR ENHANCING PSYCHOSIS PREVENTION

Dominic Oliver^{*1}, Maite Arribas², Kamil Krakowski³, Daniel Stahl⁴, Philip McGuire¹, Paolo Fusar-poli²

¹University of Oxford, ²King's College London, ³University of Pavia, ⁴Institute of Psychiatry, Psychology, and Neuroscience, King's College London

Background: Detection of individuals at clinical high risk of psychosis is sub-optimal and inefficient, limiting the potential of effective primary indicated prevention. To address this, we previously developed and validated a clinical prediction model for individuals at risk of psychosis in secondary mental health care using Natural Language Processing (NLP) symptom and substance use predictors. However, this model can only produce a single risk estimation at baseline, whereas individuals' symptoms and substance use changes over time, and so does their psychosis risk. We therefore aimed to refine our model using dynamic methods.

Methods: We included n=125,855 patients receiving a first index diagnosis of non-organic, non-psychotic mental disorder within the South London and Maudsley NHS Foundation Trust between 1st January 2008 and 10th August 2021. We refined a previously developed static individualized, transdiagnostic risk calculator employing NLP in secondary Electronic Health Records (EHRs) (C-index=0.85). We employed a i) time-varying Cox proportional hazards model; ii) dynamic survival random forest to allow for dynamic/longitudinal representation of predictors to estimate psychosis risk compared to the static model (Least Absolute Shrinkage and Selection Operator (LASSO)-regularized Cox proportional hazards model) according to TRIPOD statement. Performance was assessed via discrimination (C-index) in internal-external validation.

Results: Mean (SD) age was 34 years old (19.5), 48% were female, 66% were of White ethnicity. The most common index diagnostic spectra were anxiety disorders and non-bipolar mood disorders (both 25%). Mean follow up period was 1510 days. The cumulative incidence of psychosis was 0.031 (95% CIs: 0.030-0.033). The time-varying Cox model showed improved discrimination performance (C-index=0.88) compared to the static model (C-index=0.83).

Conclusions: These preliminary findings demonstrate that incorporating longitudinal data on symptoms and substance use substantially improves prediction performance. The study

provides novel evidence for refining detection strategies of individuals at risk of psychosis in secondary mental health care using dynamic prediction models. Further work is needed to mitigate against potential overfitting e.g. incorporating penalisation, test the impact of antecedent features and investigate more complex modelling techniques.

20.4. TRANSDIAGNOSTIC BIOTYPES OF DEPRESSION AND PSYCHOSIS: A MACHINE LEARNING APPROACH

Paris Alexandros Lalouis^{*1}, Lianne Schmaal², Stephen Wood², Renate Reniers³, Raimo Salokangas⁴, Christos Pantelis⁵, Eva Meisenzahl⁶, Paolo Brambilla⁷, Stefan Borgwardt⁸, Dominic Dwyer⁶, Rachel Upthegrove³, Nikolaos Koutsouleris⁶

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London*, ²*Orygen, the National Centre of Excellence in Youth Mental Health*, ³*University of Birmingham*, ⁴*University of Turku*, ⁵*Melbourne Neuropsychiatry Centre, The University of Melbourne, VIC, Australia*, ⁶*Ludwig Maximilian University*, ⁷*University of Milan*, ⁸*University of Lübeck*,

Background: Current nosological categories are not reflective of underlying brain pathology. Patients whose symptoms are potentially caused by different biological processes being placed in the same category and patients whose symptoms are potentially caused by same biological processes being placed in different categories with detrimental effects to disease and treatment course prediction. This lack of biological validity is thought to be one of the major reasons for the lack of biomedical translation in psychiatry. Depression and psychosis specifically share hippocampal grey matter volume (GMV) reductions and they have both been found to be pro-inflammatory states with certain cytokines such as IL-6 and CRP detected at elevated levels. This study aimed to identify prototypes of pure depression and pure psychosis to investigate the heterogeneity of depression and psychosis with common, comorbid transdiagnostic symptoms.

Methods: HYDRA (Heterogeneity through Discriminant Analysis) was trained on whole-brain volumetric measures from 577 participants from the discovery sample of the multisite PRONIA study to identify neurobiologically driven clusters, which were then externally validated in the PRONIA replication sample (n = 404) and three datasets of chronic samples (Centre for Biomedical Research Excellence, n = 146; Mind Clinical Imaging Consortium, n = 202; Munich, n = 470).

Results: The optimal clustering solution was two transdiagnostic clusters (cluster 1: n = 153, 67 ROP, 86 ROD; cluster 2: n = 149, 88 ROP, 61 ROD; adjusted Rand index = 0.618). The two clusters contained both patients with ROP and patients with ROD. One cluster had widespread gray matter volume deficits and more positive, negative, and functional deficits (impaired cluster), and one cluster revealed a more preserved neuroanatomical signature and more core depressive symptomatology (preserved cluster). The clustering solution was internally and externally validated and assessed for clinical utility in predicting 9-month symptomatic remission, outperforming traditional diagnostic structures.

Conclusions: We identified two transdiagnostic neuroanatomically informed clusters that are clinically and biologically distinct, challenging current diagnostic boundaries in recent-onset mental health disorders. These results may aid understanding of the etiology of poor outcome patients transdiagnostically and improve development of stratified treatments.

21. LARGE-SCALE COLLABORATIVE NETWORKS TO UNDERSTAND RISK AND RESILIENCE FOR SCHIZOPHRENIA

Gemma Modinos, *King's College London*

Overall Symposia Abstract: Current understanding recognises that schizophrenia spectrum disorders (SSD) exist on a continuum, whose symptoms are distributed from health to (psychotic) illness. Recent large-scale collaborative networks leveraging brain scans from thousands of individuals worldwide across the psychosis continuum are advancing our understanding of the brain mechanisms that predispose to and/or protect from pathophysiology and poor outcomes. This symposium will offer the latest insights arising from such global neuroimaging analyses, across healthy individuals with self-reported schizotypy, individuals at clinical high-risk for psychosis (CHR), those with first-episode psychosis (FEP), and with established SSD. This will be achieved through four inter-related talks, comprehensively characterising brain morphometry across the psychosis continuum to highlight both predictive and protective pathways for the development of adverse clinical outcomes. Matthias Kirschner (Switzerland) will begin by presenting recent work from the global ENIGMA Schizotypy consortium on multiscale differentiation of cortical differences related to positive and negative dimension schizotypy in over 3,000 individuals. The vulnerability for SSD approach will be complemented by Maria Jalbrzikowski (USA), who will describe use of a neuroimaging summary score to detect those at greatest risk for later developing psychosis within the ENIGMA CHR cohort. Next, delving deeper into brain morphometric features with translational potential to predict clinical outcomes at the FEP stage, Dominic Dwyer (Australia) will show how brain risk and resilience biotypes influence prognoses over 5- to 10-year periods. Finally, Ryota Hashimoto (Japan) will present data derived from large-scale mega-analyses of cortical and subcortical structure in SSD and other three major psychiatric disorders. The symposium will conclude with a discussion led by world-leading expert Raquel Gur (USA), who will integrate this set of findings across the psychosis continuum to facilitate a stimulating discussion with the audience. In view of the increasing attention devoted to open science, big data and global collaboration, this timely symposium bringing together large-scale collaborative networks will offer new insights and tools to relevant for the prediction of risk and resilience for SSD from a dimensional perspective.

21.1. MULTISCALE DIFFERENTIATION OF POSITIVE AND NEGATIVE SCHIZOTYPY RELATED CORTICAL SIGNATURES: A WORLDWIDE ENIGMA STUDY

Matthias Kirschner^{*1}, Benazir Hodzic-Santor², Leda Kennedy³, Theo van Erp⁴, Jessica Turner⁵, Paul Thompson⁶, Andre Aleman⁷, Alain Dagher⁸, Stefan Kaiser⁹, Gemma Modinos¹⁰, ENIGMA Schizotypy Working Group¹¹

¹*University Hospitals of Geneva*, ²*Montreal Neurological Institute, McGill University*,

³*University of California - San Diego*, ⁴*University of California Irvine*, ⁵*The Ohio State University Wexner Medical Center*, ⁶*University of Southern California*, ⁷*University Medical Center Groningen*, ⁸*Montreal Neurological Institute*, ⁹*Geneva University Hospitals*, ¹⁰*King's College London*, ¹¹*Worldwide*

Background: Positive and negative schizotypy are associated with impaired neurodevelopment and increased risk for schizophrenia. While cortical alterations have been associated with both schizotypy dimensions, a comprehensive characterization of shared and dimension-specific neuroanatomical signatures is lacking. Here, we present a large-scale meta-analysis of the relationship between positive and negative schizotypy and cortical thickness in

healthy individuals. We further contextualized how these cortical patterns of schizotypy dimensions are shaped by local multiscale variations of brain organization.

Methods: The sample comprised 2,730 unmedicated healthy individuals (12-68 years, 47% male) from 29 cohorts of the worldwide ENIGMA-Schizotypy working group. Cortical effect size maps of positive and negative schizotypy scores were generated using standardized methods. We systematically compared these cortical profiles of schizotypy dimensions to case-control differences in schizophrenia, ADHD, ASD, and 22q11DS-psychosis, as well as microarchitecture, structural connectome measures, and specific neurotransmitter systems.

Results: Higher positive schizotypy was associated with thinner inferior frontal gyrus (pars-opercularis: $r=-.07$, pars-orbitalis: $r=-.06$), while higher negative schizotypy was associated with thicker medial orbitofrontal cortex ($r=.07$), and thicker rostral anterior cingulate ($r=.06$) (all $pFDR$ LESS THAN .05). Cortical maps of positive schizotypy-related cortical profiles were correlated with those of schizophrenia, ADHD and 22q11DS-psychosis. Negative schizotypy-related cortical profiles were correlated with those of schizophrenia, ADHD and ASD (all r GREATER THAN .29, p spin LESS THAN .05). Overall, the cortical profiles of both schizotypy dimensions were better explained by molecular and neurotransmitter features compared to structural connectome measures. In positive schizotypy, variation in gene expression and D1 receptor density, and in negative schizotypy, myelination and histamine receptor density were the best predictors of cortical differences.

Conclusions: This study revealed both shared and unique cortical thickness profiles of positive and negative schizotypy. Cortical pattern similarity of both dimensions with schizophrenia suggests neuroanatomical continuity across the psychosis phenotype, while distinct associations with 22q11DS-psychosis and ASD support additional separate neurodevelopmental pathways in positive and negative schizotypy. Regional facets of microarchitecture, connectomics and neurotransmitter that contribute differently to the cortical profiles of each schizotypy dimension further support distinct neurobiological mechanisms. Altogether, our work yields novel insights in the multiscale differentiation of cortical alterations in positive and negative schizotypy and their relationship to neuroanatomical patterns of related neuropsychiatric disorders.

21.2. NEUROIMAGING SUMMARY SCORES AS AN INDICATOR OF PSYCHOSIS RISK IN THE ENIGMA CLINICAL HIGH RISK FOR PSYCHOSIS COHORT

Maria Jalbrzikowski^{*1}, Rebecca Cooper¹, Rebecca Hayes², Rashmi Sahasrabudhe², Dennis Hernaes³, NA ENIGMA Clinical High Risk for Psychosis Working Group⁴

¹Children's Hospital/Harvard Medical School, ²Boston Children's Hospital, ³Maastricht University, ⁴NA ENIGMA Clinical High Risk for Psychosis Working Group

Background: Structural brain alterations are well-established features of schizophrenia, but do not effectively predict disease or elevated risk for disease. We recently developed a “Schizophrenia Neuroscore” that integrated multifactorial aspects of brain structure and found that this score significantly differentiated schizophrenia cases from controls (Cohen’s d [d]=0.56) to a greater degree than individual brain regions. Analogous to methods used to calculate polygenic risk scores, we created a single neuroimaging score (i.e., the Schizophrenia Neuroscore) by summing the weighted effects of many structural brain regions. Weights were determined via group difference effect sizes from ENIGMA Schizophrenia Working Group publications. The overall pattern of structural brain alterations in individuals at clinical high risk for developing psychosis (CHR) compared to healthy controls is similar to patterns of alterations observed in individuals with schizophrenia; however, the effectiveness of the Schizophrenia Neuroscore has not yet been tested in CHR.

Methods: Cross-sectional T1-weighted magnetic resonance imaging (MRI) data were pooled from a subset of the 32 international sites included in the ENIGMA Clinical High Risk for Psychosis Cohort (26 sites, total N=2681). CHR status was assessed using the Comprehensive Assessment of At-Risk Mental States or the Structured Interview for Prodromal Syndromes, at the baseline assessment and follow-up clinical visits. We processed MRI scans using harmonized protocols. After regressing out the effects of age and sex on each individual brain measure, we z-scored all regions of interest (ROIs) across the entire sample. We then multiplied each ROI by the Cohen's d effect sizes from case vs. control summary-level statistics obtained from ENIGMA Schizophrenia Working Group publications. We then summed the weighted values from all regions to create one cumulative score, with a higher score indicating greater neuroanatomical liability for psychosis. We examined differences in Schizophrenia Neuroscores between individuals at CHR and healthy controls, as well as differences between participants at CHR who later developed a psychotic disorder (CHR-PS+) and those who did not (CHR-PS-). Specifically, we conducted separate linear regressions with Schizophrenia Neuroscore as the dependent variable and group status (CHR vs. healthy controls; CHR-PS+ vs. CHR-PS- vs. healthy controls) as the independent variable. We calculated Cohen's d effect sizes for each group comparison.

Results: Of the 2681 included participants, 1160 (43.3%) were female, and the mean age was 21.5 (SD=5.0; range=9.5-39.9) years. This study included 1516 individuals at CHR and 1165 healthy controls [HC]. Using longitudinal clinical information, 225 individuals were in the CHR-PS+ group, 1074 participants were in the CHR-PS- group, and 217 CHR individuals did not have follow-up data. In comparison to HC, CHR individuals had significantly higher Schizophrenia Neuroscores ($d=0.24$, 95% Confidence Interval [CI]=0.16-0.32, $p=7.5e-10$). Schizophrenia Neuroscores were also associated with psychosis conversion ($F=18.6$, $p=9.5e-09$). In comparison to HC, CHR-PS+ had significantly elevated Schizophrenia Neuroscores ($d=0.31$, CI=0.16-0.45, $p=2.5e-05$). CHR-PS- also had significantly elevated Schizophrenia Neuroscores in comparison to HC ($d=0.22$, CI=0.15-0.31, $p=7.1e-08$). However, CHR-PS+ and CHR-PS- had similar Schizophrenia Neuroscores and did not significantly differ from one another ($d=0.07$, CI=-0.11-0.26, $p=0.28$).

Conclusions: These preliminary results suggest that the development of a cumulative brain-based score of psychosis liability carries potential to identify individuals at clinical high risk for psychosis. Further refinement of such scores could be used in future to accurately predict psychosis onset in individuals at risk.

21.3. THE DISCOVERY OF BRAIN RISK AND RESILIENCE BIOTYPES IN THE PHENOM CONSORTIUM

Dominic Dwyer^{*1}, Ganesh Chand², Junhao Wen³, Alessandro Pigoni⁴, Adyasha Khuntia⁵, Mathilde Antoniades¹⁵, Gyujoon Hwang⁶, Erus Guray³, Jimit Doshi³, Dhivya Srinivasan³, Erdem Varol⁷, Rene Kahn⁸, Stephen Wood⁹, Geraldo Busatto¹⁰, Benedicto Crespo Facorro¹¹, Christos Pantelis¹², Chuanjun Zhuo¹³, Marcus Zanetti¹⁰, Robin Murray¹⁵, Daniel Wolf³, Barnaby Nelson¹⁶, Theodore Satterthwaite³, Raquel Gur³, Christos Davatzikos¹⁷, Nikolaos Koutsouleris¹⁸, Paola Dazzan¹⁵

¹Ludwig Maximilian University, ²Washington University ³University of Pennsylvania, ⁴IMT School for Advanced Studies - Lucca, ⁵Max-Planck Institute of Psychiatry, ⁶University of Pennsylvania, ⁸Columbia University, ⁹University Medical Centre Utrecht, Brain Centre Rudolf Magnus, ¹⁰Orygen, the National Centre of Excellence in Youth Mental Health, ¹¹Universidade De São Paulo, ¹²Hospital Universitario Virgen del Rocio, CIBERSAM, Universidad de Sevilla, IBiS, Sevilla, ¹³Melbourne Neuropsychiatry Centre, The University of

Melbourne, VIC,¹⁴Nankai University Affiliated Tianjin Anding Hospital, Tianjin Medical University,¹⁵Institute of Psychiatry, Psychology, and King's College, London,¹⁶Orygen,¹⁷University of Pennsylvania Perelman School of Medicine,¹⁸Ludwig-Maximilian-University,

Background: Biological heterogeneity underlying psychosis has prevented mechanistic understanding and treatment development. It has also historically led to misdiagnosis with associated morbidity and mortality. Differences in underlying brain morphology have long been suspected, but numerous top-down studies demonstrating associations between brain patterns with diagnoses, illness stages, or symptoms have not resulted in any increases in research or clinical precision. Using machine learning, we recently took a bottom-up approach and decomposed the neuroanatomical heterogeneity of established schizophrenia to discover two volumetric subgroups—a ‘lower brain volume’ subgroup (SG1) and an ‘higher striatal volume’ subgroup (SG2) with otherwise normal brain structure and higher educational attainment. In this presentation, we will report on a series of follow-up studies where aimed to determine if: a) the brain subgroups were present in earlier illness stages; b) they could be found as endophenotypes in the general population. We hypothesised that the brain subgroups may represent brain risk (SG1) and brain resilience (SG2) endophenotypes.

Methods: The work was conducted as part of the PHENOM consortium, consisting of seven international sites in the USA, Europe, South America, and China. We previously created a two-group structural MRI statistical model with participants from USA, Germany, and China in addition to controls from the same sites (n=671). In our follow-up work, we used a first-episode psychosis sample of individuals from Sao Paulo, Santander, London, and Melbourne (n=996). To test endophenotypes, we used population samples from the UK Biobank (n=836) and the Philadelphia Neurodevelopmental Cohort (n=359). We preprocessed all data using a pipeline consisting of multi-atlas segmentation (MUSE) to obtain grey, white, and CSF regional volumes. We also obtained voxel-wise volumetric maps for later comparison of subgroup differences. Our original work in the chronic schizophrenia sample applied a novel semi-supervised learning technique called HYDRA (heterogeneity through discriminative analysis) to cluster brain MRI volume with internal validation to ensure reproducibility of the results (i.e., cross, split-half, and leave-site-out validation). We then applied these models to the first-episode and population samples. We assessed relationships in longitudinal symptoms, functioning, cognition, and genetic risk for schizophrenia (polygenic risk scores).

Results: The SG1 and SG2 subgroup solutions were detected across first-episode psychosis and population samples. In the first-episode sample, SG2 membership was associated with a baseline pattern of higher education, higher positive symptoms, and female sex (p LESS THAN 0.05). During a 5- to 10-year follow-up period, SG2 membership was also associated with higher remission of psychotic diagnoses (SG1, 57%; SG2, 78%; $\chi^2(8)=9.8$, $p=0.02$). In comparing subgroups in population samples, SG2 membership was associated with less incidence of subthreshold psychosis symptoms ($\chi^2=11.67$, $df=1$, p LESS THAN 0.05) and better cognitive performance ($\rho=0.13$, p LESS THAN 0.05). Whereas, SG1 was associated with worse cognitive performance ($\rho=-0.28$, p LESS THAN 10⁻⁴) and increased schizophrenia polygenic risk (Wilcoxon test; $z=2.69$, p LESS THAN 0.05).

Conclusions: Our results challenge common conceptualisations of schizophrenia as a disease involving changes to brain matter volume. Instead, they suggest that a brain risk phenotype is present in the healthy population and is enriched in schizophrenia samples. Such a hypothesis aligns with the concept of clinical risk that occurs along dimensions of severity. For the first time, we also discovered a potential brain resilience subgroup that is present in healthy populations and is associated with less impairment and better long-term outcomes. The results have the potential to lead to precision medicine approaches that employ biological stratification to improve mechanistic understanding and clinical care.

21.4. MEGA-ANALYSIS STUDY OF CEREBRAL CORTICAL AND SUBCORTICAL STRUCTURE IN FOUR MAJOR PSYCHIATRIC DISORDERS AND A DATA-DRIVEN APPROACH FOR CLASSIFICATION

Ryota Hashimoto^{*1}, Naohiro Okada², Junya Matsumoto³, Kenichiro Miura³

¹National Center of Neurology and Psychiatry, ²The University of Tokyo, ³ National Institute of Mental Health, National Center of Neurology and Psychiatry

Background: According to the operational diagnostic criteria, psychiatric disorders such as schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), and autism spectrum disorder (ASD) are classified based on symptoms. While its cluster of symptoms defines each of these psychiatric disorders, there is also an overlap in symptoms between the disorders. We hypothesized that there are also similarities and differences in cortical structural neuroimaging features among these psychiatric disorders. And the creation of a novel diagnostic system using objective biomarkers using brain structural features is expected to take place the current diagnostic system.

Methods: T1-weighted magnetic resonance imaging scans were performed for over 5500 subjects including SZ, BP, MDD, ASD and healthy subjects recruited from 14 sites. Cortical thickness and surface area and subcortical volumes were calculated using FreeSurfer method. Effect sizes were determined using a linear regression model within each protocol, and these effect sizes were meta-analyzed. The similarity of the differences in cortical thickness and surface area of each disorder group was calculated using cosine similarity, which was calculated from the effect sizes of each cortical regions.

Results: The thinnest cortex was found in SZ, followed by BD and MDD. The cosine similarity values between disorders were 0.943 for SZ and BD, 0.959 for SZ and MDD, and 0.943 for BD and MDD, which indicated that a common pattern of cortical thickness alterations was found among SZ, BD, and MDD. Additionally, a generally smaller cortical surface area was found in SZ and MDD than in BD, and the effect was larger in SZ. The cosine similarity values between disorders were 0.945 for SZ and MDD, 0.867 for SZ and ASD, and 0.811 for MDD and ASD, which indicated a common pattern of cortical surface area alterations among SZ, MDD, and ASD. Patterns of alterations in cortical thickness and surface area were revealed in the four major psychiatric disorders. We demonstrated larger lateral ventricles volume in schizophrenia, bipolar disorder, and major depressive disorder, smaller hippocampus volume in schizophrenia and bipolar disorder, and schizophrenia-specific smaller amygdala, thalamus, and accumbens volumes and larger caudate, putamen, and pallidum volumes. In addition, we observed a leftward alteration of lateralization for pallidum volume specifically in schizophrenia. Moreover, as our main objective, we clustered the 5,604 subjects based on subcortical volumes, and explored whether data-driven clustering results can explain cognitive/social functioning in the subcohorts. We showed a four-biotype classification, namely extremely (Brain Biotype [BB] 1) and moderately smaller limbic regions (BB2), larger basal ganglia (BB3), and normal volumes (BB4), being associated with cognitive/social functioning. Specifically, BB1 and BB2-3 were associated with severe and mild cognitive/social impairment, respectively, while BB4 was characterized by normal cognitive/social functioning.

Conclusions: To our knowledge, this is the first report of a cross-disorder analysis conducted on cortical and subcortical structures of four major psychiatric disorders. Our results may lead to the future creation of novel biological data-driven psychiatric diagnostic criteria, which may be expected to be useful for prediction or therapeutic selection.

22. GLOBAL INEQUITIES IN EXCESS MORTALITY IN SCHIZOPHRENIA: NOVEL PERSPECTIVES TO TACKLE THE INEQUITABLE HEALTH GAP

Jayati Das-Munshi, *Institute of Psychiatry, Psychology and Neuroscience, King's College London*

Overall Symposia Abstract: People with severe mental health conditions, such as schizophrenia and bipolar affective disorders, die on average 15-20 years before the general population. This has been noted across international contexts, has persisted over time and across settings, and may have worsened during the COVID-19 pandemic. Most causes of death are from common preventable physical health conditions, and there is now widespread acknowledgement that a narrow focus on individual health behaviours is inadequate to tackle this inequity.

The aim of this symposium is to bring together research and perspectives from multiple international contexts (UK, Denmark, Ethiopia and Australia), to consider commonalities underlying physical health inequities impacting this group. We will draw upon systems-thinking to consider the role of social determinants and structural inequalities in impacting mortality risks in people with schizophrenia and bipolar disorders. Two of the presentations will consider the impact of the COVID-19 pandemic across different contexts (UK, Ethiopia) to understand how the pandemic may have further magnified inequities in people with schizophrenia.

Dr Ali will present her work which has developed causal loop diagrams to consider how systems-thinking can help inform an understanding of causal relationships, impacting mortality in people with schizophrenia. This will set the context, highlighting the role of stigma, social support and economic disadvantage in impacting physical health in people with schizophrenia.

Ms Chen will present findings from an analysis of whole-population data from Denmark, on the association between schizophrenia and cause-specific mortality with individual-level socioeconomic position data. Her findings suggest that people with schizophrenia experience a shorter life expectancy even compared to the general population in the lowest income bracket.

Dr Mihretu will present findings from a mixed methods study conducted in Ethiopia, which will highlight how the COVID-19 pandemic exacerbated stigma and discrimination towards people with schizophrenia and other severe mental health conditions, having a direct impact on physical health. The talk will reflect on how future emergency responses could prioritise the human rights, health, social and economic needs of people with mental health conditions.

Dr Das-Munshi will present a study of more than 20,000 people in the UK, which assessed mortality trends up to and including the COVID-19 pandemic, in people with schizophrenia and bipolar affective disorders. Mortality risks in this group increased steadily over a 13 year period. Higher mortality was evident in Black Caribbean and Black African people with these conditions, during the pandemic, relative to earlier years. The presentation will consider structural and systemic inequities which accounted for trends. The symposium will be co-chaired by Dr Plana-Ripoll and Dr Das-Munshi. The discussant will be Professor John McGrath, who will draw from his expertise based on many years of research in this area, to consider how we can effectively tackle the gap in life expectancy which continues to impact upon people living with schizophrenia and other severe mental health conditions.

22.1. SOCIOECONOMIC INEQUALITIES IN EXCESS MORTALITY AND LIFE YEARS LOST ASSOCIATED WITH SCHIZOPHRENIA AND OTHER MENTAL DISORDERS: A NATIONWIDE COHORT STUDY IN DENMARK

Danni Chen^{*1}, Linda Ejlskov¹, Julie Werenberg Dreier², Henrik Toft Sørensen¹, Oleguer Plana-Ripoll¹

¹Aarhus University and Aarhus University Hospital, ²National Centre for Register-based Research, Aarhus University,

Background: Schizophrenia and other mental disorders are associated with elevated mortality rates and shorter life expectancy. Although low socioeconomic position (SEP) is associated with both mental disorders and excess mortality, it is unknown to what extent SEP explains the excess mortality among people with mental disorders. Individuals with low SEP may be more often exposed to many risk factors (i.e., poor diet, smoking, alcohol, drugs, obesity, and social exclusion), and have limited access, continuity, and quality of healthcare; therefore, this population may be more sensitive to the adverse association of mental disorders with mortality. Based on our recent literature review, we observed that relative risks for mortality for people with vs. without mental disorders were similar across SEP levels. However, absolute differences in mortality risks between the two groups might differ by SEP, and this information was rarely reported in previous studies. In addition, evidence on specific types of disorders and cause-specific mortality was scarce. This study aims to investigate the associations between schizophrenia and other types of mental disorders with cause-specific mortality according to SEP.

Methods: We designed a cohort study including all individuals living in Denmark on January 1, 2000 (~5.2 millions) and followed them up until December 31, 2020. Information on schizophrenia and other mental disorders was obtained from the Danish Psychiatric Central Research Register, while the date and cause of death were obtained from the Danish Registry of Causes of Death. Individual SEP was defined based on the equated household disposable income as percentile ranks relative to all individuals of the same age and sex. We used Poisson regression models to estimate mortality rate ratios (MRR) comparing people with and without each diagnosis and stratified by SEP. Population attributable fractions (PAF) of all-cause and cause-specific mortality for each diagnosis were also calculated for each SEP stratum. We compared the average life expectancy between people with mental disorders and the general population depending on SEP levels by calculating excess life years lost (LYLs) for all-cause mortality, and for cause-specific deaths. The analysis plan was pre-registered in Open Science Framework (OSF).

Results: In preliminary analyses, we observed that people with mental disorders have higher all-cause and cause-specific mortality rates than those without regardless of SEP level. Specifically, in the bottom SEP quintile, MRR comparing people with and without schizophrenia was 1.96 (95%CI 1.88–2.04) for all-cause mortality, 3.80 (3.31–4.36) for external causes and 1.86 (1.79–1.94) for natural causes, and PAFs were 1.5%, 4.3%, and 1.4%, respectively; whilst the corresponding MRRs in the top SEP quintile were 2.94 (2.65–3.27), 14.92 (11.74–18.97), and 2.43 (2.17–2.73) and PAFs were 0.7%, 4.6%, 0.5%. The gap in average life expectancy between people with schizophrenia and the general population in the top SEP quintile was 11.2 years (73.0 vs. 84.2 years), whereas this difference was smaller in the bottom SEP quintile (9.2 years; 69.9 vs. 79.1 years). For specific causes of death, we found that people with schizophrenia and belonging to the highest rather than lowest SEP quintile lost fewer years due to natural causes, whilst similar LYLs due to external causes. Results for other mental disorders including bipolar disorders showed a similar pattern.

Conclusions: Our study confirms that whereas people in the general population experience a social gradient in mortality risk, people with schizophrenia and bipolar affective disorders experience a substantially shorter life expectancy and elevated mortality, even compared to the general population in the lowest income bracket.

22.2. IMPACT OF THE COVID-19 PANDEMIC ON HEALTH CARE AND PEOPLE WITH SEVERE MENTAL HEALTH CONDITIONS IN ETHIOPIA: THE MASC MIXED-METHODS STUDY

Awoke Mihretu^{*1}, Wubalem Fekadu¹, Azeb Alemu¹, Beakal Amare¹, Eleni Misganaw², Abebaw Ayele³, Ousman Esleman³, Zewdu Assefa⁴, Atalay Alem¹, Graham Thornicroft⁵, Charlotte Hanlon⁵

¹Addis Ababa University, ²Mental Health Service Users Association, Addis Ababa, ³Ministry of Health, Ethiopia, ⁴Ethiopian Public Health Institute, ⁵King's College, London,

Background: The COVID-19 pandemic has had far-reaching effects on the mental health of populations around the world, but there has been limited focus on the impact on people with existing mental health conditions in low-income countries. The aim of this study was to examine the impact of the pandemic on health care and people with severe mental health conditions (MHC), such as Schizophrenia, in Ethiopia.

Methods: A convergent mixed methods study was conducted. We systematically mapped information from publicly available reports on impacts of the pandemic on mental health care. Monthly service utilisation data were obtained from Amanuel Mental Specialised Hospital, the main psychiatric hospital, and analysed using segmented Poisson regression (2019 vs. 2020). In-depth interviews were conducted with 16 purposively selected key informants. Framework analysis was used for qualitative data. Findings from each data source were integrated.

Results: There was low priority given to the overall needs of people with severe MHCs during the COVID-19 pandemic in Ethiopia. Mental health-related stigma and discrimination were evident, complicating care and referrals for pre-existing physical health conditions especially among people with psychoses. People with severe MHCs were reportedly denied COVID-19 treatment because of an attitude from health care providers that they were unpredictable, unreliable and uncontrollable. Scarce mental health service settings were diverted to become COVID-19 treatment centres. Quality of health care was poor due to infrequent visits and follow-up, and there were also suicidal attempts and injuries. Lack of reliable medication supplies increased relapse and the chance of becoming chained at home, abandoned or homeless. At tertiary hospitals, there was a significant reduction in the number of admissions since March 2020. Infection control procedures did not adequately safeguard those with severe MHCs and basic needs were also not fully met. Many people with severe MHCs and their families could not afford to sustainably buy protective equipment due to the impoverishing effects of mental illness.

Conclusions: The COVID-19 pandemic had substantial negative impacts on the lives of people with severe MHCs in Ethiopia. Future emergency response should prioritise the human rights, health, social and economic needs of people with severe MHCs. Integration of mental and physical health care would expand access to care, improve individual outcomes and increase resilience of the mental health system.

22.3. LONG TERM MORTALITY TRENDS IN PEOPLE WITH SEVERE MENTAL ILLNESSES (SMI) AND HOW COVID-19, ETHNICITY AND OTHER CHRONIC

MENTAL HEALTH COMORBIDITIES CONTRIBUTED: A RETROSPECTIVE COHORT STUDY

Jayati Das-Munshi^{*1}, Ioannis Bakolis², Laia Bécaries², Hannah Dasch², Jacqui Dyer³, matthew Hotopf⁴, Rosanna Hildersley¹, Josephine Ocloo², Robert Stewart¹, Ruth Stuart², Alex Dregan¹

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London*, ²*King's College London*, ³*NHS England and NHS Improvement (NHS-E/I)*, *Black Thrive Global*,

⁴*Psychological Medicine, Institute of Psychiatry, King's College London*, ,

Background: The COVID-19 pandemic worsened pre-existing inequalities in health outcomes and healthcare access for the most disadvantaged groups, particularly in countries with the highest levels of social inequities. Racialised and minority ethnic communities, and people living with mental disorders, including severe mental illnesses (SMI), such as schizophrenia and bipolar affective disorders, were noted to be at a higher risk of SARS-Cov2 infection and death. Chronic comorbid physical health conditions such as cardiovascular disease and diabetes have been shown to exacerbate mortality following SARS-CoV-2 infection. A growing body of work has also highlighted the additional contributions which long-term mental health conditions play in heightening the risk of death following infection, such as substance use disorders, dementia, anxiety, depression and learning disabilities. The interplay of these comorbidities with other vulnerability factors, associated with a higher risk of death following SARS-CoV-2 infection, in people already living with SMI, remains unclear. In particular, the impact of the COVID-19 pandemic on potentially exacerbating underlying longer-term trends, in addition to exacerbating other inequalities, for example with respect to ethnicity, remains unclear. The aim of this study was to explore longer term trends in mortality in SMI, including over the COVID-19 pandemic period, with a focus on additional vulnerabilities for mortality (psychiatric comorbidities and race/ ethnicity) in this group.

Methods: We conducted a retrospective cohort study using electronic health records from secondary mental healthcare, covering a regional UK catchment of 1.3 million people. Data from adults with clinician-ascribed ICD-10 diagnoses for schizophrenia-spectrum and bipolar disorders were used to assess mortality trends spanning fourteen years, which also included the COVID-19 pandemic period (2020-2021). Parametric regression survival models were used to assess all-cause mortality trends over time, and cause specific mortality was estimated using a competing risks regression model. Age and sex- standardised mortality ratios were estimated for the sample over the pre-pandemic period of 2019 and over 2020 (pandemic).

Results: The sample comprised 22,361 people with SMI, with median follow-up of 10.6 years. Standardised mortality ratios (SMRs) for people with SMI were more than double the population average pre-pandemic, increasing further during the pandemic, with substantial increases in those with mental health comorbidities, particularly in people with SMI and comorbid learning disabilities (SMR: 6.08 (95% CI: 4.13, 8.63) and comorbid substance use disorders (SMR: 6.88 (95% CI: 5.65, 8.31)). All-cause mortality risk was 16% higher (Risk Ratio (RR): 1.16 (95% CI: 1.04-1.29)) in the sample over the first year of the COVID-19 pandemic (2020-2021), compared to reference years (2014-2015). Mortality risk increased steadily among people with SMI and comorbid depression, dementia, substance use disorders and anxiety over a 13-year period, increasing further during the pandemic. Higher mortality was also evident in Black Caribbean (RR: 1.40; 95% CI: 1.11-1.77) and Black African (RR: 1.59; 95% CI: 1.07-2.37) people with SMI during the COVID-19 pandemic years, relative to reference years (2014-2015). During the pandemic period (2020-2021), COVID-19 mortality

was especially elevated in people with SMI and comorbid dementia (sub-Hazard Ratio (sHR): 1.96, 95% CI: 1.26-3.04; p LESS THAN 0.001) and in people with SMI and learning disabilities (sHR: 2.30; 95% CI: 1.30-4.06; p LESS THAN 0.001), compared to people with SMI alone. Deaths from non-COVID-19 causes were also elevated in people with SMI and comorbid dementia (sHR: 2.62; 95% CI: 2.10-3.26; p LESS THAN 0.001) and in people with SMI and comorbid substance use disorders (sHR: 1.31; 95% CI: 1.06, 1.61; p=0.01), over the COVID-19 pandemic period.

Conclusions: Mortality risks have increased over time in people with SMI, with the pandemic exacerbating pre-existing trends. Marked inequities were noted for people with SMI and comorbid conditions, such as dementia and learning disability. A higher risk of death during the pandemic was noted in Black Caribbean and Black African people with SMI, compared to pre-pandemic years. The pandemic may have magnified pre-existing structural inequities. Actionable solutions, focused on structural and social determinants, are needed.

22.4. USING A SYSTEMS THINKING APPROACH TO EXPLORE THE COMPLEX RELATIONSHIPS BETWEEN SCHIZOPHRENIA AND PREMATURE MORTALITY

Suhailah Ali¹, Eryn Wright¹, Fiona Charlson¹

¹*The University of Queensland*

Background: People with schizophrenia have a higher risk of mortality compared to the general population, which has not improved over time. The majority of premature deaths are due to comorbid physical diseases, driven by interrelated factors operating at the individual level, through health systems and influenced by social determinants of health. A holistic understanding of this problem and the causal pathways linking these factors together is lacking.

Methods: This study aims to understand why the mortality gap between people with schizophrenia and the general population is not improving by developing a causal loop diagram (CLD), a systems thinking approach which enables empirical research and theoretical knowledge to be combined into a visual representation of causal relationships and feedback loops. The CLD was constructed using published literature, including both quantitative and qualitative studies, to identify key variables and relationships, and refined through consultation with experts in the topic area.

Results: A total of 21 variables and 68 connections were included in the CLD, with 23 distinct feedback loops identified. Stigma and social support had the most connections, while unemployment was involved in the greatest number of feedback loops. Most feedback mechanisms served to reinforce behavioural risk factors, inadequate healthcare and social disadvantage.

Conclusions: The CLD has created a holistic and dynamic understanding of the causal pathways driving the mortality gap between people with schizophrenia and the general population, providing insights into why it has persisted over time. One of the key findings was the critical role of social determinants in shaping health outcomes, highlighting the need for person-centred models of care and multisectoral government action.

23. SOCIAL DISCONNECTION IN SCHIZOPHRENIA SPECTRUM DISORDERS

Sarah Hope Lincoln, *Case Western Reserve University*

Overall Symposia Abstract: Social connection is important for individuals' mental health. Individuals across the psychosis spectrum experience higher rates of a variety of types of social disconnection, including loneliness, social exclusion, and social isolation. Research on social disconnection could offer new insight into the psychological processes associated with social experiences for individuals across the psychosis spectrum. Additionally, work examining various aspects of social disconnection may identify critical intervention and treatment targets for individuals with schizophrenia spectrum disorders. This symposium brings together four projects focused on social disconnection across a continuum of psychotic experiences.

Examining qualities of embodied loneliness in psychosis, Baxter, Lee, and Park (Vanderbilt University, United States) examine the association among loneliness, hallucinations, and self-disturbances. They find that the embodiment of loneliness is felt in the torso, but the quality of embodiment differs between individuals with schizophrenia and controls, potentially reflecting interoceptive difficulties and degree of self-disturbance in individuals with psychosis.

Furthering our understanding of the role of loneliness and psychosis, Gandhi, Botello, Mueser, and Fulford (Boston University, United States) test a model of the temporal relationships among loneliness and paranoia in 404 individuals with first-episode psychosis. Their work indicates robust associations between loneliness and paranoia across two years. They also find that elevated paranoia may contribute to greater loneliness in the later stages of recovery.

In line with this work, Lincoln, Ward, Laquidara, and Barrick (Case Western Reserve University, United States) investigated the relationship between social isolation and social dysfunction in individuals with schizophrenia and suicidal thoughts and behaviors using self-report, clinical interviews, and ecological momentary assessment. Preliminary results indicate that social isolation and disconnection at baseline is associated with suicidal thoughts and behaviors, and will examine whether these social factors predict suicidal thoughts and behaviors at a 1-month follow-up. These findings may highlight an important target in reducing suicide risk for individuals with schizophrenia spectrum disorders.

Finally, Riehle, Brauer, Lincoln, and Pruessner (Universität Hamburg and Universität Heidelberg, Germany) find in a one-week diary study that young adults with attenuated negative symptoms use less interpersonal emotion regulation strategies in their daily lives than either young adults with attenuated positive symptoms or a control group, and find interpersonal emotion regulation strategies less helpful. These results may further explain emergent and consequential features of social disconnection in individuals with elevated psychosis risk.

Collectively, the work in this symposium furthers our understanding of the experiences, causes, and consequences of social disconnection for individuals with schizophrenia spectrum disorders. This more nuanced understanding of how social disconnection both develops and affects individuals across a continuum of psychotic experiences could inform interventions targeting psychotic symptoms and psychosocial dysfunction.

23.1. EMBODIMENT OF LONELINESS AND SELF-DISTURBANCES IN THE SCHIZOPHRENIA-SPECTRUM

Tatiana Baxter¹, Hyeonseung Lee², Sohee Park²

¹*Vanderbilt University*, ²*Vanderbilt University, Dept of Psychology*

Background: Prevalence of loneliness among individuals with schizophrenia (SZ) is as high as 80% (Badcock et al., 2020). The Social Deafferentation Hypothesis (2007) posits that isolation causes social hallucinations (e.g., felt presence (FP) or hearing voices). Indeed, social isolation is associated with bodily self-disturbances and disembodiment, two core features of SZ. Whilst the negative impact of loneliness on outcome is established, the relationship between loneliness and bodily self-disturbance of SZ remains obscure. The aim of this study was to further elucidate how loneliness, social hallucinations and self-disturbances might be manifested and experienced in the SZ-spectrum conditions.

Methods: Individuals with SZ, matched control participants (CO), people at-risk for psychosis (HR) and those at low-risk (LR) for psychosis participated in visuospatial mapping tasks that required localizing bodily sensations associated with feelings of loneliness (plus 13 emotions) and components of self-disturbances. UCLA Loneliness Scale, Sensed Presence Questionnaire (SenPQ), Body Disturbance Inventory (BODI), and Brief Trauma Questionnaire (BTQ) were administered to assess loneliness, FP, Out-of-Body Experiences (OBE) and trauma, respectively. SANS and SAPS were used to rate the severity of SZ symptoms.

Results: Loneliness was significantly associated with FP and OBE across all groups; self-disturbances were elevated in lonelier participants. Loneliness was embodied primarily in the torso for SZ and CO but there was a noteworthy difference; CO reported deactivation of sensations similar to their map of sadness, but the map of SZ showed activation. In addition, the bodily maps of loneliness differed between the HR vs LR such that the sensations associated with loneliness were distributed more diffusely across the body in the HR. Mapping of sensations associated with self-disturbances revealed that the topography of the core self, voices and FP diverged between SZ and CO, qualitatively and quantitatively. With respect to self-disturbance, the rates of FP and OBE were elevated in SZ and the HR. Among CO, those with both FP and OBE were at the highest risk for psychosis. Lastly, trauma was associated with OBE but not with FP.

Conclusions: We examined embodiment of loneliness and self-disturbances in the schizophrenia-spectrum to document the phenomenology of these experiences and to further elucidate the role of social isolation in self-disturbances. We found that loneliness is felt in the torso, as has been described previously in first-person narratives as a gnawing, hunger-like sensation. However, CO vs. SZ diverged in the quality of the embodiment, which might reflect interoceptive difficulties in the SZ and/or the extent of the self-disturbance. Lastly, embodiment and self-disturbance are rarely considered as treatment-targets, but it would be important to re-evaluate the utility of the core symptoms of schizophrenia as potential targets for intervention.

23.2. INTERPERSONAL EMOTION REGULATION IN YOUNG PSYCHOSIS-PRONE ADULTS: A 7-DAY DIARY STUDY

Marcel Riehle*¹, Saskia Brauer¹, Tania M. Lincoln¹, Luise Pruessner²

¹Universität Hamburg, ²Universität Heidelberg

Background: Emotion regulation difficulties and social disconnect are recognized in psychosis-risk populations. However, little research has been conducted to investigate how psychosis-prone young adults turn to others when regulating their emotions. Such interpersonal emotion regulation (IER) strategies can include contacting others to upregulate positive or downregulate negative emotions. Based on prior research, we hypothesized that young adults with attenuated levels of negative symptoms would make less use of IER strategies and that people with attenuated levels of positive symptoms would use IER strategies more than those

without these symptoms. Our second hypothesis was that people with either attenuated negative or positive symptoms would perceive using IER strategies as less helpful.

Methods: We included three groups of young adults (age 18-29) based on a priori defined psychometric cut-offs for the Community Assessment of Psychic Experiences: psychosis-prone – negative symptoms (PP-NES, $n=37$), psychosis-prone – positive symptoms (PP-POS, $n=20$), and low psychosis proneness (control group, CG, $n=52$). We excluded people with concurrent moderate and concurrent high levels of positive and negative symptoms. Participants provided daily online diary entries in the evenings over one week (min. 3 entries). The diaries assessed the frequency and efficacy of using IER strategies, daily negative symptoms, paranoia levels, and positive and negative affect. Our assessment of IER strategies was based on the Interpersonal Emotion Regulation Questionnaire and included separate measures for regulating positive and negative emotions.

Results: The data were analyzed with multi-level linear models. PP-NES reported using IER strategies for upregulating positive emotions less frequently than both other groups (vs. CG: Cohen's $d = -0.87$, $p < .001$; vs. PP-POS: $d = -0.76$, $p = .017$), and there were no significant group differences in the frequency of using IER strategies for reducing negative emotions. However, the groups differed in their affect levels and after controlling for positive and negative affect, respectively, there were no longer group differences for the upregulation of positive emotions, but PP-NES were found to report using IER strategies to downregulate negative emotions less frequently than both other groups (vs. CG: $d = -0.69$, $p = .003$; vs. PP-POS: $d = -0.63$, $p = .025$). Regarding the efficacy of IER, only PP-NES reported that using IER strategies for positive emotions was less helpful than did controls (upregulating pos. emotions: $d = -0.78$, $p = .005$; downregulating neg. emotions: $d = -0.58$, $p = .018$). Additional analyses showed significant within-person associations, most notably for diary negative symptoms predicting lower scores on all IER variables (i.e., frequency and efficacy).

Conclusions: Our results suggest that young adults with attenuated negative symptoms apply IER strategies less frequently. For upregulating positive emotions this was contingent on low levels of positive affect. For downregulating negative emotions, the effect became only observable after controlling for this group's elevated negative affect levels. Those with attenuated negative symptoms also perceived IER to be less helpful. Particularly the latter may contribute to the social disconnect in this group. The analyses for attenuated positive symptoms were limited by the small group size. Future research should investigate temporal directions of the within-person effects reported here and whether the lower efficacy of using IER strategies in young adults with attenuated negative symptoms has behavioral or psychophysiological correlates.

23.3. SOCIAL ISOLATION AND SUICIDAL BEHAVIORS IN SCHIZOPHRENIA

Sarah Hope Lincoln^{*1}, Madeline Ward¹, Jill Laquidara¹, Elyssa Barrick¹

¹*Case Western Reserve University*

Background: Suicide is the leading cause of premature death in individuals with psychotic disorders, with a lifetime prevalence rate of death by suicide at approximately 4-5% (Palmer et al., 2005). Social isolation, the disruption to or lack of interpersonal interactions, is implicated in both the development of psychotic disorders (van Os et al., 2000) and suicide behaviors (Fisher et al., 2015; Trout, 1980), and thus is a strong candidate mediating the association between psychosis and suicide behaviors. Previous studies have identified social isolation as associated with both self-injurious and suicide behaviors (Endo, et al., 2017), thus social isolation might be a factor in the high rates of suicide behaviors in individuals with schizophrenia. The current research clarifies the association between psychosis and suicide

behaviors by testing a specific mechanism, social isolation, which may explain high rates of suicide behavior in this population.

Methods: Participants, ages 18-30 years old, have been recruited from mental health facilities, community clinics, and online platforms. Inclusion criteria included: 1) United States residents, 2) diagnosis of schizophrenia or schizoaffective disorder (confirmed with clinical interview) (SZ group) or no history of psychiatric diagnosis (HC group), 3) English as a primary language. At baseline, participants complete clinical interviews assessing positive, negative, and disorganized psychotic symptoms using the Psychotic Symptom Rating Scale, Brief Negative Symptom Scale, and the Thought and Language Index, as well as an assessment of suicidal thoughts and behaviors using the Self-Injurious Thoughts and Behavior Inventory (SITBI). Social connection is assessed with several self-report measures focused on social network, perceived social support, and loneliness. Participants then complete five days of ecological momentary assessment assessing symptoms and social connection, and finally complete a 1-month follow-up of psychotic symptoms and suicide behaviors.

Results: Preliminary results indicate that the SZ group reports lower perceived social support, less informational support, and less companionship relative to the HC (ps LESS THAN .05). The SZ group also reports higher endorsement (frequency) of suicidal ideation and suicidal behaviors. Of note, the SZ group also endorses significantly higher rates of depressive symptoms (p LESS THAN .05).

Conclusions: The work of this study thus far supports differences in social behavior (e.g., less effective) and experiences (e.g., lower social support) in individuals with schizophrenia and related disorders relative to healthy controls, as well as demonstrating higher suicide thoughts and behaviors. The interaction of psychological and social factors may contribute significantly to the development of psychiatric symptoms and behaviors in psychosis. Specifically, social difficulties such as exclusion, rejection, loneliness, and isolation may be implicated in risk for suicide behaviors in this population, and could be an important intervention target.

23.4. SOCIAL DISCONNECTION IN SCHIZOPHRENIA: LONELINESS & PARANOIA IN THE YEARS FOLLOWING A FIRST EPISODE OF PSYCHOSIS

Arti Gandhi¹, Renata Botello¹, Kim Mueser¹, Daniel Fulford¹

¹*Boston University*

Background: Loneliness is a common experience in individuals with psychosis and is associated with dire mental and physical health outcomes. Emerging evidence and theories suggest that paranoia plays a key role in the emergence and persistence of loneliness. However, existing research primarily consists of cross-sectional studies in people with chronic psychosis, leaving gaps in our understanding of the early stages of psychosis. This study explores the temporal relationship between loneliness and paranoia over two years in patients with a first episode of psychosis in the United States.

Methods: Four hundred and four people aged 15 to 40 participated in the Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP), where sites were randomly assigned to either coordinated specialty care, or standard community treatment. Participants completed assessments of psychiatric symptoms and social experiences every 6 months for two years. We calculated a composite loneliness score by averaging four self-report items, including three items from the Well-Being Scale ("I often feel lonely due to a lack of close friends to share my concerns with") and one item from the Stigma Scale ("I often feel alone because of my mental health problems"). We then assessed psychometrics of the scale, including exploratory factor analysis and correlations between loneliness and paranoia (suspiciousness item of the Positive and Negative Syndrome Scale [PANSS]) at each time

point. We analyzed longitudinal associations between paranoia and loneliness using latent growth curve models to understand how changes in paranoia impacted changes in loneliness over time.

Results: Loneliness items exhibited strong internal consistency (omega values = 0.63-0.79) and adequate item loadings (lambda values = 0.41-0.79) across all time points. Self-reported loneliness was moderate across all time points ($M[SD] = 3.52-3.95 [1.22-1.38]$; possible range = 1-7), with the highest levels at baseline, and decreased significantly over time (average loneliness did not differ between groups). We examined trajectories of loneliness and paranoia separately. Both paranoia and loneliness showed significant variability in their intercepts, but only loneliness exhibited variability in the slope. Contemporaneous associations revealed that higher loneliness was related to higher paranoia at 6 ($\beta=0.71$, $SE=0.17$), 12 ($\beta=0.53$, $SE=0.16$), and 18 ($\beta=0.58$, $SE=0.17$) months, but not at 24 months ($\beta=0.04$, $SE=0.18$). Lagged associations showed that increased paranoia at 18 months predicted significantly greater loneliness at 24 months ($\beta=0.64$, $SE=0.19$), but not at previous time points.

Conclusions: Moderate levels of loneliness were observed in patients with a first episode of psychosis, decreasing significantly over time in the context of intervention. Initial severity of loneliness and paranoia varied between individuals. The rate of decline in loneliness differed between individuals while the decline in paranoia was stable. Paranoia and loneliness were related to one-another in the early stages of recovery, which diminished in later stages. Furthermore, elevated paranoia contributed to future loneliness, but only in the later stage of recovery. This study provides evidence that paranoia may lead to greater loneliness, independent of the effect of time, and may have a stronger influence on loneliness in later stages of recovery. In further analyses, we plan to examine these relationships bidirectionally.

24. FROM ALOGIA TO VERBIGERATION: UNDERSTANDING SPEECH AND LANGUAGE DISTURBANCE IN PSYCHOSIS

Sunny Tang, *Zucker Hillside Hospital*

Overall Symposia Abstract: Understanding speech and language disturbances in psychosis and other mental disorders is critical for elucidating key mechanisms underlying these disorders as well as developing novel opportunities to capture objective biomarkers through computational analysis of speech. The objective of this symposium is to discuss current theoretical, trans-nosological, and data-driven understandings of speech and language disturbance in psychosis as part of an international collaborative effort by the DISCOURSE consortium to harmonize the clinical assessment of these phenomena.

Speech and language disturbances are among the canonical features of major psychiatric disorders, particularly including psychosis and schizophrenia-spectrum disorders. The linguistic content of speech and the manner in which it is represented have been interpreted as representing internal thought processes. Disturbances in thought process are related to distinct findings on neuroimaging, poor outcomes and greater disability.

Recent advances in artificial intelligence and natural language processing have launched a wave of new and promising investigations that use computationally derived speech and language features to predict or model key clinical outcomes. For example, natural language processing and acoustic analysis has been used to classify schizophrenia diagnosis relative to individuals with other psychotic disorders, to predict the development of threshold psychotic disorders among youths at clinical high risk, and to model changes in psychosis symptoms over the course of hospitalization.

The DISCOURSE consortium is an international collaboration of researchers studying speech and language in psychosis. This symposium will present ongoing efforts by the consortium to achieve a clinically-informed and evidence-based consensus on how speech and language disturbances should be assessed and understood clinically. First, Dr. Sreeraj will present an overview of clinical and psychometric approaches to describing speech and language disturbances in mental disorders, as well as examining prevalence of different symptom types. Then, Dr. Voppel will use sentence-embeddings from BERT, a large language model, to group and represent rating scale descriptions of speech and language-related symptoms. Next, Dr. Stein will examine factor analysis findings from a large cross-diagnostic sample, along with neurobiological correlates on MRI. Finally, Dr. Tang will relate factor analysis findings based on clinical ratings to computational features derived from acoustic analysis and natural language processing.

24.1. APPROACHES TO CLINICAL CHARACTERISATION OF THOUGHT DISORDER IN SCHIZOPHRENIA

Vanteemar Sreeraj*¹, Kiran Bagali¹, Sonika Nichenametla¹, Nilanjan Datta¹, Swarna Buddha Nayok¹, Venkataram Shivakumar¹, Lena Palaniyappan², Ganesan Venkatasubramanian¹

¹*National Institute of Mental Health and Neurosciences (NIMHANS)*, ²*Douglas Mental Health University Institute*

Background: Thought disturbance is a core symptom dimension of schizophrenia captured by multiple clinical symptom rating scales. However, interoperability/convertibility of thought disorder ratings among the existing assessment scales is necessary to support cross-study comparisons and meta/mega-analysis that are lacking in this domain. The variations in terminology related to thought disturbance pose a challenge. Here, we analyse the definitions of thought disturbance items in different psychopathology rating scales. Further, we estimate the impact of varying definition on the prevalence estimates of thought disorder.

Methods: The clinical rating scales measuring the formal thought disorder in schizophrenia were systematically searched. Individual items of the scales that followed a descriptive psychopathological approach with full texts of descriptions available in the English language were enlisted. The scales' administration methods and item descriptions were collated. Similarities and differences in the item descriptions and their conceptual contexts were evaluated. The items were further rated for their descriptive psychopathological and phenomenological characters. We evaluated the prevalence rates of FTDs in 306 drug-naïve first-episode psychosis (55%males, mean(SD)age=31(7.9)yrs) with SANS/SAPS and 49 schizophrenia patients in remission of positive symptoms (mean illness duration=7.3yrs) using EASE(Examination of Anomalous Self-experience). The impact of differences in item definitions on these ratings was analysed from schizophrenia patients' rating scores.

Results: A total of 15 different scales were identified, 9 of which were used for further item analysis. 72 disjoint items (i.e., minimal conceptual overlapping) were consolidated. The ratings were recommended to be conducted on speech samples from clinical interviews, eliciting speech samples during a conversation, and using neutral and/or standard stimuli. Different technical terms are used to describe similar concepts and vice versa. For eg., the definition of “tangentiality” and “thought block” in the thought language communication (TLC) scale matches that of “cross-talk” and “rupture of thought” in the thought and language disorder(TALD) scale, respectively. Most of these can be construed as positive(n=56), and few

as negative/deficit(n=16) thought disorders. Ten of these items were purely subjective and needed a phenomenological approach to recognise. Nearly 57% of our drug-naïve early schizophrenia cohort had thought disorder. Over 39% of remitted patients had subjective thought disturbance. The prevalence estimates based on the rating scales (TALD vs SAPS-SANS) are being evaluated in a subset of patients with schizophrenia.

Conclusions: The contexts of evaluation and variations in the definitions of terms in rating scales should be considered while comparing scores across studies. Harmonisation of terminology for these symptoms is needed. Theoretical/conceptual backgrounds tended to influence the description of the terms/items in rating scales. Validating the items with objective computational measures may enhance the measurability of thought disorder.

24.2. USING SEMANTIC INFORMATION TO CLUSTER FORMAL THOUGHT DISORDER RATING SCALES

Alban Voppel^{*1}, Lena Palaniyappan²

¹*McGill University*, ²*Douglas Mental Health University Institute*

Background: Schizophrenia-spectrum disorders often involve the manifestation of Formal Thought Disorder (FTD), assessed using clinical rating scales. Scales are designed to capture clinical symptoms associated with the construct of FTD but differ among each other in their approach. Cross-scale analyses using yield variable results; this situation has led to conceptual grouping of symptoms, the most used one being positive (posFTD) and negative FTD (negFTD). Here, we propose a new method to assess on, and expand on this conceptual division. We employ Natural Language Processing (NLP) with semantic models to scrutinize descriptions from commonly used thought disorder rating scales, compare the semantic descriptions to the positive and negative division and to free community detection.

Methods: Using the positive and negative thought disorder symptom division, we assess textual descriptions of formal thought disorder items in multiple clinical rating scales for their semantic content through a transformer model. We compare each semantic item to the description given by Kircher et al. in defining posFTD and negFTD, and thus their semantic relation to the positive and negative division FTD descriptions in the literature. Finally, we perform a conceptually free approach where we use community detection algorithms to detect the most meaningful related groups of symptoms.

Results: Semantic embeddings and their distance to posFTD and negFTD descriptions aligned with 75%+ accuracy with the posFTD and negFTD scales. Antonyms were noted for when alignment was reversed (i.e. “an absence of...”), or referrals to other items within clinical rating scales.

We find four distinct semantically related clusters:

Group 1 features result in muddled communication with some incomprehensible elements. Meaning distortion, word substitution, and weak context association occur; confusion and word sequencing difficulties are associated with group 1.

Group 2 features involve abrupt topic shifts in response to stimuli, repeated words or subjects, speech interruptions, and memory lapses regarding previous speech.

Group 3 features include unfounded conclusions, irrelevant replies, a lack of thought continuity, off-topic wandering, disjointed ideas, and a dearth of meaningful connections, resulting in inconsistent narrative structure.

Group 4 features entail restricted speech, brief concrete answers, omission of additional information, overly concise replies, uninformative or indirect responses with vague, repetitive, or abstract language, hindering meaningful information extraction by interviewers.

Conclusions: From descriptions of clinical rating scales, we were able to replicate the posFTD and negFTD conceptual division, although antonyms in item descriptions muddled the results. Conceptually free community detection algorithms unveiled four distinct clusters of FTD symptoms within item-level descriptions from different scales through the usage of sentence transformers and network community methodologies. Our approach serves as a valuable tool for harmonizing diverse conceptual perspectives and clinical rating scales related to FTD.

24.3. EXPLORING SPEECH AND LANGUAGE DISTURBANCES AND THEIR BRAIN STRUCTURAL CORRELATES IN AFFECTIVE AND PSYCHOTIC DISORDERS

Frederike Stein^{*1}, Tilo Kircher¹

¹*University of Marburg,*

Background: Formal thought disorder (FTD) is highly prevalent in schizophrenia (SZ) and also occurs in in major depressive (MDD) and bipolar disorder (BD). However, the association between alterations in brain structure and FTD across affective and psychotic disorders remains unknown. In two studies, we investigate transdiagnostic symptom dimensions of FTD and their association with both local brain structural alterations and global macroscopic structural brain networks.

Methods: Using FTD symptoms from the SANS and SAPS, we performed exploratory and confirmatory factor analyses in over 1000 patients with MDD, BD, and SZ to identify psychopathological FTD dimensions. Both T1- and diffusion-weighted magnetic resonance imaging were used to investigate local gray matter volume (GMV) alterations, white matter fractional anisotropy (FA) alterations, and structural brain networks being associated with FTD. Interaction analyses were employed to investigate the influence of categorical diagnosis.

Results: Cross-validation factor analyses revealed three psychopathological FTD factors: disorganization, emptiness, and incoherence. Disorganization was negatively correlated with a GMV cluster comprising parts of the middle occipital and angular gyri and positively with FA in the right posterior cingulum bundle and inferior longitudinal fascicle. Emptiness was negatively associated with the left hippocampus and thalamus GMV. Incoherence was negatively associated with FA in bilateral anterior thalamic radiation, and positively with the hippocampal part of the right cingulum bundle. Network-based statistics identified macroscopic subnetworks being associated with the FTD dimensions disorganization and emptiness but not with the FTD dimension incoherence. Confirmatory analyses showed a substantial overlap of nodes from both subnetworks with cortical brain regions previously associated with FTD in SZ. None of the GMV, FA, and macroscopic network associations interacted with diagnosis.

Conclusions: Our results provide a refined mapping of cross-disorder FTD phenotype dimensions, highlighting their neuroanatomical signatures linked to language-related local and global brain structural measures, independent of diagnosis. Our findings open a promising avenue for transdiagnostic, psychopathology-informed, dimensional studies in pathogenetic research.

24.4. DISTINCT RELATIONSHIPS BETWEEN DIMENSIONS OF SPEECH AND LANGUAGE DISTURBANCE AND COMPUTATIONAL FEATURES

Sunny Tang*¹, Amir Nikzad¹, Yan Cong¹, Sunghye Cho², Katrin Hänsel¹, Sarah Berretta³, Leily Behbehani³, Aarush Mehta⁴, Majnu John¹, Sameer Pradhan², Mark Liberman⁵

¹*Zucker Hillside Hospital*, ²*Linguistic Data Consortium*, ³*Northwell Health*, ⁴*Feinstein Institutes for Medical Research*, ⁵*University of Pennsylvania*

Background: Quantitative features derived from speech are increasingly recognized as valuable predictors and objective biomarkers for psychiatric disorders, notably including schizophrenia spectrum disorders (SSD). Significant advancements have been made in SSD to identify clinically relevant speech features, include a wide range of acoustic (e.g., pitch, amplitude), timing (e.g., pauses, speaking rate), lexical (e.g., sentiment, concreteness), syntactic (e.g., parts-of-speech, discourse connectives), and discourse-level measures (e.g., graph analysis, semantic similarity). Presumably, speech features predict clinical characteristics by reflecting speech-related symptoms, but the nature of the relationships are not clear. Here, we identify latent factors for speech and language disturbances which show consistency across language and diagnoses, and describe their distinct relationships to computational speech and language features.

Methods: Clinical ratings for speech and language disturbance were generated across 14 items from the Scale for the assessment of Thought Language and Communication (TLC) and the Scale for the Assessment of Negative symptoms (SANS). We evaluated a cross-diagnostic sample (N=343), including SSD (n=90), individuals with other or unverified psychotic disorders (n=47), those with non-psychotic psychiatric disorders (n=130), and healthy comparison participants (HC, n=76). Participants spoke English proficiently and were ascertained in a diverse area of New York (U.S.A.). Speech features were quantified using an automated pipeline for brief recorded samples of narrative free speech. Factor models for the clinical ratings were generated using exploratory factor analysis, then tested with confirmatory factor analysis in the cross-diagnostic and SSD groups. Correlations and network relationships among factor scores and computational speech features were examined across acoustic, timing, lexical, syntactic, and discourse-level measures.

Results: We found a 3-factor model with good fit in the cross-diagnostic group and acceptable fit for the SSD subsample. The model identifies an impaired expressivity factor and two interrelated disorganized factors for inefficient and incoherent speech. These findings are largely consistent with those of an independent study conducted in German, using the SANS and Scale for the Assessment of Positive Symptoms. We found that incoherent speech was relatively specific to psychosis groups (SSD and other psychotic disorders), while inefficient speech and impaired expressivity showed intermediate effects in people with nonpsychotic disorders compared to HC. Each of the three factors had significant and distinct relationships with speech features. In the SSD group, insufficient speech was most closely related to higher speaking rate ($r=0.63$) and mean age of acquisition ($r=0.54$); incoherent speech was most closely related to decreased positive valence ($r=-0.50$) and greater use of particles ($r=0.41$) and mean speaking rate ($r=0.41$); and impaired expressivity was most closely related to decreased mean pitch ($r=-0.41$) and higher mean turn latency ($r=0.41$).

Conclusions: We identified a 3-factor model that describes speech and language disturbance with good statistical properties in SSD and cross-diagnostically, concordance with an independent study, clinical relevance, and distinct relationships with computational speech and language features. A larger, collaborative effort is underway to replicate and generalize these findings in 700 participants from this site, and several thousand participants internationally.

Plenary Session IV - Oliver Howes: Could the Synaptic Hypothesis Explain All of Schizophrenia?

2:30 p.m. - 3:30 p.m.

25. COULD THE SYNAPTIC HYPOTHESIS EXPLAIN ALL OF SCHIZOPHRENIA?

Peter Falkai, *Psychiatric University Hospital Munich*

25.1. COULD THE SYNAPTIC HYPOTHESIS EXPLAIN ALL OF SCHIZOPHRENIA?

Oliver Howes, *MRC LMS and KCL*

Individual Abstract: The synaptic hypothesis of schizophrenia is one of the leading hypotheses of the pathoetiology of schizophrenia. However, advances in genetics, cellular biology and neuroimaging in the last few years have led to a step change in understanding of the nature and role of synaptic alterations in schizophrenia, their links to symptoms and the mechanisms underlying them. A key advance has been the development of novel neuroimaging techniques that enable synaptic terminal proteins to be measured in vivo in patients. This talk will consider these new lines of evidence and present the latest in vivo neuroimaging data on synaptic terminal markers in people with schizophrenia, and their links to symptoms and glutamatergic function, as well as the effects of antipsychotic treatment. Finally, it will consider the potential of the synaptic hypothesis to explain the cognitive, negative and psychotic symptoms of the disorder, and the implications for pharmacological and psychosocial treatments.

Plenary V - Padmavati Ramchandran: Research to Practice - Understanding the Schizophrenia Conundrum

8:30 a.m. - 9:30 a.m.

26. RESEARCH TO PRACTICE: UNDERSTANDING THE SCHIZOPHRENIA CONUNDRUM

Paola Dazzan, *Institute of Psychiatry, Psychology and Neuroscience, King's College London*

26.1. RESEARCH TO PRACTICE - UNDERSTANDING THE SCHIZOPHRENIA CONUNDRUM

Padmavati Ramchandran, *Schizophrenia Research Foundation, India*

Individual Abstract: The Schizophrenia conundrum remains a management challenge despite the advances in research, globally. However, contemporary expectations of course and outcome of this inherently chronic and deteriorating condition are optimistic given the evidence-based developments in culturally informed intervention across the globe.

The Schizophrenia Research Foundation (SCARF, India) India is a non-governmental, not-for-profit organization that has committed to mental health care and research over the past 4 decades. Forging national and international collaborations, SCARF has consciously focussed

on the translation of research findings to practice. In this process we have tried to make sense of the condition, especially to understand the interplay between culture and psychosis.

Our research over 40 years has encompassed epidemiology, untreated illness, course and outcome, untreated psychoses, and understanding the patient/family perspectives of psychoses. An example of the Madras Longitudinal study, carried out over 35 years when compared with other longitudinal studies has emphasized the multifaceted role of culture. A series of studies have examined schizophrenia under the lens of gender, marriage, employment, and stigma. Genetic research of studies has helped understand some facets of the condition. Over one and half decades of research with a population of persons with a first episode of psychoses has informed the development of protocols for interventions at the clinics. Research on metabolic comorbidity has contributed to the understanding of lifestyles of the persons with schizophrenia and the effects of antipsychotic medications. The lessons learned informed an appropriate re-orientation of psychosocial interventions whether in the facility-based setting or the community. The use of technology in testing a low-cost app-based intervention using the DIALOG + and online compensatory cognitive interventions is currently under investigation. More recent investigations have included persons with lived experience, the research establishing the acceptability and feasibility of peer support volunteer programs. On a broader scale, recognising the need for appropriate sharing of information, SCARF's public awareness programs have systematically included the findings of research, through the past 4 decades.

This talk will discuss challenges in providing equitable mental health care across diverse cultural contexts will be critically examined, emphasizing the importance of dismantling cultural barriers to accessing appropriate and effective treatments. The presentation advocates for a global mental health perspective that recognizes and respects the diversity of cultural narratives surrounding mental illness.

Concurrent Symposia

10:00 a.m. - 12:00 p.m.

27. NOVEL PSYCHOLOGICAL TREATMENTS FOR PSYCHOSIS – CURRENT EVIDENCE, LIMITATIONS, AND FUTURE IMPLICATIONS

Kerem Böge, *Charite CBF*

Overall Symposia Abstract: Psychosis is considered one of the most impairing mental health disorders worldwide, with significant major long-term consequences on individuals' psychological and physical health, relationships, and employment. National and international clinical guidelines recommend cognitive behavioral therapy, next to psychopharmacology, as a treatment of choice for psychosis. However, the effect sizes of these interventions are still limited to the medium range. Moreover, they do not reach all patients because they either do not have access to care with psychotherapy in the face-to-face setting or because the available treatments are not sufficiently adapted to the cultural and ethnic background of those affected. Together, this underscores the dire need for novel interventions with improved efficacy that are accessible to a broader range of consumers and that can be adapted to the individual and cultural needs of the patients. Therefore, this symposium aims to showcase new research and treatment developments to improve the psychological treatment of patients with psychotic disorders. Alexandra Moussa-Tooks (Indiana University Bloomington) will discuss and address current developments and outcomes from the cultural adaptation of CBT, particularly for Black Americans. She will give novel insight into the role of systematic racism in the

therapy process and treatment gaps for minority populations throughout series of cases. Louise Birkedal Glenthøj (University of Copenhagen) will present new outcomes from a randomized controlled trial (N=239) on Virtual-Reality-augmented CBT (VR-CBT) compared to CBT for the treatment of paranoia. Tania Lincoln (University of Hamburg) will discuss the findings of the RELATE trial (N=85) testing a new behavioral intervention aiming to reduce voice-related distress compared to the current mental health care system in Germany (treatment-as-usual) in a multicenter randomized controlled trial. Geraldine Pijnenborg (University of Groningen) will expand the focus to new technologies such as VR-assisted psychotherapy and present findings of a randomized controlled trial (N=81) examining therapeutic potentials on social functioning but also discuss limitations and future implications. Accordingly, she will present novel developments in the field of VR for psychosis, focusing on the quality of social contacts, leisure activities, and overall participation in society. Together, the speakers in this symposium will provide insight into novel developments in the psychological treatment of people with psychotic disorders. We will discuss implications as well as directions for future research building up on these findings.

27.1. BEING ASSERTIVE TO DISTRESSING VOICES? FEASIBILITY AND PRELIMINARY EFFICACY OF ADDING RELATING THERAPY TO STANDARD CARE. FINDINGS FROM THE RELATE TRIAL

Tania Lincoln^{*1}, Björn Schlier¹, Mark Hayward², Rebecca Müller¹, Thomas Lang³, Gonther Uwe⁴, Cornelia Exner⁵, Kerem Böge⁶, Jürgen Gallinat⁷, Candalaria Mahlke⁷, Antonia Zapf⁷, Annika Buchholz⁷, Katharina Stahlmann⁷, Matthias Pillny¹

¹University of Hamburg, Institute of Psychology, ²School of Psychology, University of Sussex, ³Jacob University Bremen, ⁴AMEOS Klinik, Bremen, ⁵Universität Leipzig, ⁶Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, ⁷University Medical Center Hamburg-Eppendorf,

Background: Auditory verbal hallucinations (AVH) such as hearing voices are a common and distressing experience in psychotic disorders. Accordingly, patients report the reduction of voice related distress amongst their most important treatment goals for AVH. However, available treatment options show only limited efficacy on AVH related distress. Relating Therapy (RT) is a novel translational approach that tackles the distress related psychological mechanisms by exploring the experience of hearing voices within interpersonal frameworks and by rebalancing the hearer-voice relationship through the development of assertive responding.

Methods: We conducted a multi-centered and randomised-controlled pilot feasibility trial that aimed to evaluate the feasibility of trial procedures and to examine effect-size estimates of a 16-session RT module compared with Treatment-as-usual (TAU) in different German mental healthcare settings. Single-blind assessments were done at baseline, post-treatment at five months (T1) and at nine months follow-up (T2). Primary outcome was the distress factor score of the AVH subscale of the Psychotic Symptoms Rating Scale at T2 adjusted for the baseline value. Secondary outcomes included change in depressive symptoms, quality of life, daily-life activity engagement as well as relating to voices and to other people.

Results: From October 2020 to April 2022, 85 patients with persistent distressing AVH were included in the trial. Of these, 43 received either 16 sessions of RT plus TAU and 42 received TAU only. 82% of the participants completed the primary outcome assessment at 5 and 86% at 9 months. Of those participants assigned to RT, 88% received the pre-specified minimum

treatment dose of at least 8 sessions. The rating of therapist adherence with the RT protocol reached the predefined quality criterion in 98% of the rated therapy audio tapes. The number of reported adverse events did not differ between the conditions. Auditory-related distress decreased after 9 months in both conditions, with a non-significant trend towards greater improvement in the RT plus TAU condition (PSYRATS AVH distress $b=-2.40$ (1.52), $p = 0.121$, (-4.94 to 0.15). The effect size of this difference remained stable with significant confidence intervals in two of four sensitivity analyses. Descriptive changes on all but one of the secondary outcomes were in the expected direction.

Conclusions: We conclude that adding a RT module to standard care is feasible and well accepted by patients and has the potential to lead to reduced hallucination related distress. Further research should examine the benefit of RT compared to TAU in a full-scale trial using a mixed method approach by adding a qualitative assessment of the consumer's experiences with RT. This would add substantially to our understanding of the positive and adverse effects associated with RT.

27.2. VIRTUAL REALITY-BASED CBT VS. CBT FOR PARANOIA: PRELIMINARY FINDINGS FROM THE FACEYOURFEARS RANDOMIZED CLINICAL TRIAL

Ulrik Nykjær Jeppesen¹, Ditte Lammers Vernal², Anne Sofie Due³, Mariegaard Lise⁴, Amy Pinkham⁵, Mads Juul Christensen², Wim Velting⁶, Merete Nordentoft⁷, Louise Birkedal Glenthøj^{*8}

¹Copenhagen Research Center for Mental Health (CORE), , ²Aalborg University Hospital, Psychiatry, Research Unit for Child and Adolescent Psychiatry, ³Mental Health Centre Copenhagen, University of Copenhagen, ⁴Copenhagen Research Center for Mental Health - CORE, VIRTU Research Group, ⁵The University of Texas at Dallas, ⁶University Medical Center Groningen, ⁷Mental Health Centre Copenhagen, ⁸Mental Health Centre Copenhagen University of Copenhagen

Background: Paranoia is a frequently occurring symptom in schizophrenia spectrum disorders (SSD). While cognitive behavioral therapy (CBT) has proven small to moderate effect in alleviating this symptom, there is a need to advance therapy approaches stressing the behavioral component of CBT. Virtual reality (VR)-based therapy offers the potential of exposing the individual to paranoid inducing situations in a safe and controlled manner and may hold great potential in increasing CBT benefits.

Methods: The FaceYourFears trial is a randomized, single-blind, clinical trial allocating 256 patients with SSD to either 10 sessions of CBT or 10 sessions of virtual reality-based CBT (VR-CBT) for paranoia. Assessments are carried out at baseline, at treatment cessation, and at 9-months post-baseline. Primary outcome is ideas of persecution and secondary outcomes: ideas of reference, social anxiety, safety behavior, emotion recognition, and daily life-functioning. Additionally, health economic analyses will elucidate cost-effectiveness of the interventions.

Results: A total of 239 participants have been included in the study. Participant enrollments will be completed in November 2023, and 9-months follow-up data are expected in August 2024. Data on baseline characteristics of the study sample along with data on feasibility and acceptability (drop-out rate, adverse events etc.) of both interventions will be presented at the conference. Additionally, this presentation will elucidate patients' experiences with the interventions at a case level.

Conclusions: The FaceYourFears trial will elucidate whether VR-CBT can enhance therapy efficacy for paranoid ideations in a cost-effective manner. This may guide the possible

dissemination and implementation into clinical practice. Within this scope, it is essential to outline the acceptability and safety of the intervention. In a long term perspective, VR-based CBT may be the preferred non-pharmacological treatment option for paranoia.

27.3. CONCEPTUALIZING AND INTEGRATING CULTURE INTO CONTEMPORARY COGNITIVE-BEHAVIORAL THERAPIES FOR PSYCHOSIS

Alexandra Moussa-Tooks*¹, Julia Sheffield², Daniel Freeman³, Aaron Brinen²

¹*Indiana University Bloomington*, ²*Vanderbilt University Medical Center*, ³*University of Oxford*

Background: Racial threat (RT) is increasingly recognized as a critical factor in the diagnosis, assessment, and treatment of psychosis. Threat-based worry and hypervigilance in Black Americans and other minoritized individuals is higher due to systemic racism, which has a long-standing history in the United States. RT has been associated with increased risk for psychopathology like clinically significant paranoia. Although there has been a rise in the accessibility of CBT for psychosis (CBTp), there have been no adaptations of cognitive-behavioral therapies for Black Americans with psychosis. These interventions are needed to address the unique challenges associated with experiences of RT, to increase engagement from clients and enhance the impact of the intervention.

Methods: We present the first step towards developing an adapted cognitive-behavioral intervention for Black and minoritized Americans with psychosis. The case is of a Black American man diagnosed with schizoaffective disorder. He enrolled in a clinical trial of a worry intervention for persecutory delusions. This adaptation of an empirically supported worry-based treatment for persecutory delusions was accomplished by comprehensive conceptualization and integration of how systemic racism and minoritization drive the prevalence and perception of threats. This contrasts with conceptualizing racism-related hypervigilance and cognitions as worry or ignoring these critical experiences altogether, which is invalidating and neglects optimal identification and intervention on behavioral targets. He was assessed for change in persecutory beliefs, worry, and activity engagement at various timepoints including baseline, mid-way through the intervention (4 weeks), end of the intervention (8 weeks), and a 24-week follow-up.

Results: At the onset of establishing the therapy rationale, we intentionally acquired information about the role of RT in daily life on worry. Using a validating and normalizing approach, the individual was able to identify how frequent threats related to systemic racism resulted in increased worry, vigilance, and distress. We were careful to conceptualize these experiences as threats, not worry behaviors or thoughts. Over the course of the intervention, we saw a clinically meaningful improvement in worry that persisted to follow-up (Reliable Change Index = 2.29-8.64). He also exhibited improvement in delusional content per self- and clinician-report with distress, conviction, and preoccupation all trending downward (RCI = 3.95-7.77). He reported improved self-efficacy and treatment satisfaction during the therapy.

Conclusions: By identifying and intervening on the perception of threat and associated worry, the individual engaged in more helpful responses to the threat, which in turn increased participation in more meaningful activities and reduced worry and clinical paranoia. This case illustrates how accurate conceptualization clarifies behavioral targets and increases patient engagement, which together enhance the effectiveness of the intervention for minoritized individuals. This case also provides a path towards improving the conceptualization of culture in treatment models and increasing adaptations across groups and interventions.

27.4. VR TREATMENT FOR IMPAIRED SOCIAL FUNCTIONING IN PSYCHOTIC DISORDERS

Marieke (Gerdina) Pijnenborg*¹, Saskia Nijman², Ivo Meins¹, Dauw Muijsson³, Elisabeth van der Stouwe³, Wim Veling³

¹University of Groningen, ²GGZ Drenthe, ³University Medical Center Groningen

Background: Social functioning is often impaired in psychotic disorders while effective treatment options are few. Virtual Reality (VR) may be an ecological valid tool for practicing social interactions. Currently, several new treatments are being evaluated.

Methods: In this presentation two VR interventions targeting social functioning in psychotic disorders. First, results of an RCT on DISCOVR (social cognition training in VR, n=81) will be discussed. Second, we will present the outline of VR SOAP. This brandnew VR intervention offers various modules that contribute to improving the amount and quality of social contacts, leisure activities and participation in society.

Results: DISCOVR was compared to an active control condition, and appeared not more effective in improving social cognition or social functioning than the control condition, probably because the intervention was not realistic enough to improve emotion perception and mindreading in real life. However, learning did occur, as participants did demonstrate within session improvement on emotion recognition in VR. Pilot data (n=5) show that VR SOAP was acceptable and beneficial by therapists and participants.

Conclusions: Although VR has the potential to contribute to the treatment of people with psychotic disorders, it is critical to evaluate what can and cannot be trained in VR.

28. ETHICAL CONSIDERATIONS ON THE USE OF AI IN MENTAL HEALTH

Sophia Frangou, *Icahn School of Medicine at Mount Sinai*

Overall Symposia Abstract: This proposal has been put together by the Ethics Committee of SIRS to stimulate ethical scrutiny of the increasing use of algorithmic and data-driven technologies, commonly grouped under the term artificial intelligence (AI), in mental health research and clinical care. Properly designed AI solutions securely utilized can improve mental health research and service delivery, improve patient engagement and well-being, and allow more flexible allocation of resources. Conversely, the potential risks are undeniable such as breaches of therapeutic records, and algorithms that may discriminate or disadvantage specific patient populations to mention two examples. Concerns also arise, not necessarily from the misuse or malfunctioning of technologies, but from their intended operations that may have intrinsic harmful potential such as technologies that implement extensive observation, recording, digitization, and prediction of human behaviour. The four speakers of the proposed symposium are thought leaders in the field of AI ethics and bring a range of perspectives given their diverse and multi-disciplinary backgrounds. Each presentation will focus on different aspects of ethical challenges impacting policies, new forms of embodied AI treatment options, and research integrity and will also discuss how and who could potentially act to regulate AI use in mental health.

28.1. THE ETHICS OF MACHINE LEARNING APPLICATIONS AND BIG DATA IN MENTAL HEALTHCARE

Giovanni Rubeis*¹

Background: Machine learning techniques commonly referred to as AI in combination with big data approaches offer a wide spectrum of possibilities for mental healthcare. These technologies enable the integration and modelling of multimodal data from different sources, e.g. combining patient data from electronic health records and diagnoses with behavioral and environmental data form

self-reports and monitoring via sensors (either wearable or stationary). By using data mining technologies, analyzing this data may enable a better risk assessment, stratification and predication, tailoring of treatment to the individual needs of each patient, preventing the onset of episodes or symptoms, and empowering the patient's self-management. Focusing on the complex connections between individual symptoms and behavior with specific situations and environment of patients may furthermore help to understand the specific needs of groups and individuals with a complex help-seeking behavior that are otherwise under-served. Hence, the use of AI and big data may support decision-making and the personalization of treatment.

Methods: Narrative synthesis of the existing research literature in the ethics of AI and big data in mental healthcare.

Results: The intensive use of highly sensitive data from various sources as well as the operational logic of machine learning algorithms pose several ethical risks. I will discuss three types of risks, namely security risks like data safety and privacy protection, epistemological risks such as digital positivism and reductionism, and risk for the therapeutic alliance, namely overstraining autonomy and reduced personal contact.

Conclusions: Realizing the potential of AI and big data for accuracy, efficacy, and personalization requires combining the skills of care givers for building a meaningful, patient-centered therapeutic alliance that centers around the uniqueness of the patient.

28.2. THE USE OF GENERATIVE LARGE LANGUAGE MODELS LIKE CHATGPT AND BARD FOR CITATION SEARCH AND LITERATURE REVIEW: THE PROBLEM OF ACCURACY

Alessia McGowan¹, Yunlai Gui¹, Matthew Dobbs¹, Sophia Shuster¹, Alexandria Selloni¹, Matthew Cotter¹, Marianne Goodman¹, Agrima Srivastava¹, Guillermo A. Cecchi², Cheryl Corcoran*¹

¹Icahn School of Medicine At Mount Sinai, ²IBM, Thomas J. Watson Research Center

Background: Large language models such as OpenAI's ChatGPT (Generative Pre-Trained Transformer) and Google's Bard are neural networks that have learned information and patterns of language use from the internet. These language models are generative in that they can respond to queries in a conversational manner. They have been identified as having several uses, including the provision of companionship and assistance in the writing of music, code, and text, including essays, protocols and even jokes. However, there are concerns that such models may replace jobs and even lead to catastrophic consequences (through scams and misinformation). Also, several ethical concerns have been identified, including with respect to security, privacy, copyright (plagiarism), bias and accuracy. Here we describe our experience in using ChatGPT and Bard to identify references relevant to a literature review for a manuscript on the linguistic correlations of suicidal behavior in spontaneous spoken language in individuals at clinical high risk for psychosis, highlighting the problem of accuracy.

Methods: In March 2023, we queried ChatGPT 3.5 for citations relevant to a literature review in preparation of a manuscript on linguistic correlations of suicidal behavior in individuals at clinical high risk (CHR) for psychosis. Our initial query was "What has been published regarding suicidal behavior in individuals at high risk for psychosis?", followed by requests to list specific papers that used NLP (natural language processing). Citations provided by ChatGPT were compiled and verified for accuracy. In June 2023, we again similarly queried ChatGPT, and as it no longer provided references or citations, we then queried Google's Bard 2.0, using the same prompt as was used in March 2023, also verifying produced citations for accuracy. Error patterns were characterized for output from ChatGPT in March 2023 and from Bard in June 2023.

Results: In March 2023 ChatGPT provided 35 citations after a series of prompts/queries. Of these, only 2 (6%) were accurate. Of the 33 inaccurate citations, 12 had titles that were "near-matches" for existing real articles, whereas 21 could not be readily linked to any real manuscripts. For the 12 "near-matches", 9 listed incorrect first authors, 10 listed incorrect years of publication, and 4 listed incorrect journal names. A common error pattern was that for titles, original terms (e.g. "bipolar disorder") were replaced with terms from our queries ("clinical high risk for psychosis"; "suicidal ideation"). In June 2023, ChatGPT no longer provided citations, writing "Unfortunately, as an AI language model, I don't have direct access to databases or the ability to perform real-time searches". However, in June 2023, Bard 2.0, in response to the same query "What has been published regarding suicidal behavior in individuals at high risk for psychosis?", responded "Talk to someone now", providing a number for a suicide crisis hotline. It then generated 8 references, none of which were accurate. Of these, 5 were "near-matches" for real articles (1 with an erroneous title; 4 with incorrect authors) and 3 could not be matched to any real articles. Overall, the accuracy for provided citations was low for ChatGPT in March 2023 (2/35 or 6%) and for Bard in June 2023 (0/8 or 0%), and error patterns were similar.

Conclusions: While it is now more widely known that programs like ChatGPT and Bard can be highly inaccurate, nonetheless the assured tone of language they produce can be misleading. For example, in response to our query for a list of relevant papers, ChatGPT provided citations, adding "While this list is not necessarily exhaustive, it is a comprehensive sample of existing research in this field". Similarly, Bard generated 8 citations (none of which were accurate), adding "I hope this is comprehensive and exhaustive!" Our research team assiduously spent hours looking for citations and manuscripts they assumed to be real, until they had an "aha" moment when they realized ChatGPT was fabricating citations - pastiches of real titles and authors and journals. But not all users will be so diligent. For example, two lawyers used ChatGPT to find cases and citations for a legal brief which was then submitted unchecked, resulting in fines and public castigation by a judge (<https://www.nytimes.com/2023/06/22/nyregion/lawyers-chatgpt-schwartz-loduca.html>). Overall, our experience suggests caution in using these models in research, where accuracy is paramount.

28.3. CONSIDERATIONS FOR EMBODIED AI AND MENTAL HEALTH CARE

Amelia Fiske^{*1}, Peter Henningsen¹, Alena Buyx¹

¹*Technical University of Munich*

Background: Research in embodied artificial intelligence (AI) has increasing clinical relevance for therapeutic applications in mental health services. With innovations ranging from 'virtual psychotherapists' to social robots in dementia care and autism disorder, to robots for sexual disorders, artificially intelligent virtual and robotic agents are increasingly taking on

high-level therapeutic interventions that used to be offered exclusively by highly trained, skilled health professionals. In order to enable responsible clinical implementation, ethical and social implications of the increasing use of embodied AI in mental health need to be identified and addressed.

Methods: Based on a thematic literature search and established principles of medical ethics, an analysis of the ethical and social aspects of currently embodied AI applications was conducted across the fields of Psychiatry, Psychology, and Psychotherapy. To enable a comprehensive evaluation, the analysis was structured around the following three steps: assessment of potential benefits; analysis of overarching ethical issues and concerns; discussion of specific ethical and social issues of the interventions.

Results: From an ethical perspective, important benefits of embodied AI applications in mental health include new modes of treatment, opportunities to engage hard-to-reach populations, better patient response, and freeing up time for physicians. Overarching ethical issues and concerns include: harm prevention and various questions of data ethics; a lack of guidance on development of AI applications, their clinical integration and training of health professionals; ‘gaps’ in ethical and regulatory frameworks; the potential for misuse including using the technologies to replace established services, thereby potentially exacerbating existing health inequalities. Specific challenges identified and discussed in the application of embodied AI include: matters of risk-assessment, referrals, and supervision; the need to respect and protect patient autonomy; the role of non-human therapy; transparency in the use of algorithms; and specific concerns regarding long-term effects of these applications on understandings of illness and the human condition.

Conclusions: Embodied AI is a promising approach across the field of mental health; however, further research is needed to address the broader ethical and societal concerns of these technologies to negotiate best research and medical practices in innovative mental health care. I conclude by indicating areas of future research and developing recommendations for high-priority areas in need of concrete ethical guidance.

28.4. ETHICAL CONSIDERATION OF NORMATIVE MODELING OF BRAIN IMAGING DATA

Sophia Frangou*¹

¹*Icahn School of Medicine at Mount Sinai*

Background: Neuroimaging offers a unique window into the living brain but its translational application of neuroimaging to mental health has been minimal, largely due to the lack of normative reference frameworks for neuroimaging measures. This contrasts with other medical fields where diagnosis and prognosis are aided by criteria on how biological measures deviate from established normative ranges (e.g., height, weight, blood glucose). However, determination of "normality" in terms of brain structure is philosophically and ethically complex because it is intrinsically linked with societal concepts of the ideal human.

Methods: We developed CentileBrain, a normative model of brain morphometry and brain-age-gap-estimates (brainAGE) that belongs to the category of standard life charts; it is derived from a large, international, and diverse pool of healthy individuals and thus represents the healthy pattern of age-related brain changes. CentileBrain currently contains lifespan charts of measures of regional cortical thickness, surface area, and subcortical volumes and brainAGE derived from neuroimaging data of 37,407 healthy individuals (53.33% female; aged 3 to 90 years) collated from 86 international MRI datasets

Results: CentileBrain was generalizable to different ethnoracial groups but the predictive value of brain morphometry and brainAGE for behavioural and cognitive outcomes in healthy individuals was limited. Normal variation in these measures was very wide.

Conclusions: These findings argue for a "soft normativism" in terms of neuroanatomical features. Soft normativism comes with a moderate degree of relativism, and argues that normative models have a role to play as they enrich our understanding of processing models but should not be used to inform idealistic notions of human beings.

29. PREVENTING PSYCHOSIS IN LOW RESOURCE SETTINGS: UNIQUE PERSPECTIVES FROM ULTRA-HIGH RISK FOR PSYCHOSIS RESEARCH IN LOW- AND MIDDLE-INCOME COUNTRIES

Alexandre Loch, *University of Sao Paulo*

Overall Symposia Abstract: Given the social and economic burden associated with psychotic illnesses, research efforts have increasingly focused on early stages of the disorder. In this sense, the ultra-high risk for psychosis (UHR) criteria were created to identify subjects before they developed their first psychotic episode. Despite the many advances made in the field, most data come from high-income countries.

A recent systematic review (Loch et al., 2023) showed this discrepancy, with only 112 articles on UHR coming from low- and middle-income countries (LAMIC), as compared with more than 500 for manuscripts on UHR in more developed countries. This review identified obstacles in the conduction. of prospective UHR research in LAMIC, including mainly lack of funding, and cultural issues and stigma. However, data collected in such scenarios, in face of these adversities, is of utmost importance as they can bring up unique perspectives such as inovative screening methods and new insights into the psychosis continuum.

In this symposium, we will address examples of country-specific experiences in UHR research, including in Brazil, Turkey and Tunisia, that may be common to other LAMIC countries, or in some cases different. We describe challenges and obstacles, as well as success in overcoming these, to provide important data on UHR from LAMIC that will complement that from more developed countries. We hope this will generate a lively discussion in the audience as to experiences in other LAMIC countries as well.

First, in Brazil, we will show how technology can help in the identification of UHR individuals at the population level. Alexandre Loch will present data that shows that automated facial expression analysis can be used to identify UHR individuals, as compared to healthy individuals, and to predict transition from the UHR state to psychosis and psychiatric illnesses in general. Research was conducted with non-help seeking, medication-naïve individuals from an epidemiological general population sample from Sao Paulo, Brazil.

Second, Ruben Valle will present a systematic review of multicomponent interventions available for LAMIC. He will show how antipsychotic medication, psychoeducation, family support and cognitive behavioral therapy are used in LAMIC.

Third, Gresshma Mohan, from India, will explain the components about first episode psychosis services from the Indian SCARF project. She will discuss which aspects of this innovative project can be used in other high-income and LAMIC countries.

Finally, Feten Fekih-Romdhane will present results from a Tunisian initiative to prevent psychosis, showing the challenges and facilitative factors in implementing a psychosis prevention service in a low-resource setting.

With this symposium, we wish to bring new data on this under researched area. We also wish to discuss new ideas to conduct research in this scenarios, and how data from these different settings might shed light into psychosis prevention initiatives across the world.

29.1. USING MACHINE LEARNING ENSEMBLES AND FACIAL FEATURES TO DETECT INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS AND PREDICT THEIR OUTCOME

Alexandre Loch^{*1}, João Medrado Gondim², Ana Caroline Lopes-Rocha³, Felipe Argolo⁴, Anderson Ara⁵

¹*University of Sao Paulo*, ²*Federal University of Bahia*, ³*Institute of Psychiatry, Laboratory of Neuroscience (LIM 27), University of Sao Paulo*, ⁴*Universidade de São Paulo (USP)*,

⁵*Federal University of Paraná*

Background: Detection of individuals at risk for psychosis and outcome prediction poses a great challenge for several reasons. First, very long interviews by trained mental health professionals are resource consuming. This is particularly critical in low resource settings such as low and

middle-income countries, where there is an insufficient regular mental healthcare delivery. Second, there is a help-seeking barrier, given that these are psychotic phenomena which are intrinsically related to lack of judgement and insight. Third, transition to psychiatric illnesses among those at risk is erratic, with heterogeneous transition rates observed across studies. Taking all that into account, our study aimed to develop two machine learning ensembles. The first was intended to distinguish subjects at "ultra-high risk for psychosis" (UHR) from control subjects from the general population based on facial data extracted from short video-recordings. The second was developed to predict transition from the UHR state to psychosis and/or general psychiatric illnesses using the same approach.

Methods: 58 non-help-seeking medication-naïve UHR and 70 healthy subjects were screened from a representative general population sample. At-risk status was assessed with the Structured Interview for Prodromal Syndromes (SIPS). Presence of psychiatric disorder was evaluated with the Structured Interview for DSM-5 diagnosis (SCID-5). Two videos of the participant's interview were recorded at baseline. The first consisted in the "Subject's Overview" section of the SIPS (3-5 min), in which participants were asked to talk about their relationship with their parents during their childhood. The second video was recorded during a memory recall free speech task, in which

individuals were asked to talk about a recent dream, an old dream, and to tell stories based on three positive affective pictures. Several features were extracted, e.g., eye and mouth aspect ratio, Euler angles, coordinates from 51 facial landmarks. This elicited 649 facial features, which were further selected using Gradient Boosting Machines (AdaBoost combined with Random Forests). The selected features entered a first machine learning model to discern UHR from control subjects. Data was split in 70/30 for training, and Monte Carlo cross validation

was used. UHR subjects were then followed-up for two years and assessed for transition to psychosis or any psychiatric disorder. After this period, 51 UHR subjects could be reassessed, of whom 9 converted to psychosis, and 21 to other psychiatric diagnosis. The same procedures were made for a second machine learning model, to predict transition from the UHR state to psychiatric disorders.

Results: The first model, to detect UHR, reached 83% of mean F1-score, and balanced accuracy of 85%. Mean area under the curve for the receiver operator curve classifier was 93%. Convergent validity testing showed that two features included in the model were significantly correlated with Avolition (SIPS N2 item) and expression of emotion (SIPS N3 item). The second model, to predict conversion among UHR subjects, reached 82% of mean F1-score, and balanced accuracy of 85%. Sensitivity of the classifier was of 79%, and specificity was of 84%. Convergent validity testing showed that features included in the model were significantly correlated with Avolition (SIPS N2 item) and ideational richness (SIPS N5 item).

Conclusions: Our model capitalized on short video-recordings from individuals recruited from the general population, effectively distinguishing between UHR and controls, and predicting their

transition to psychiatric diagnoses, including psychosis. Results are encouraging for large-screening purposes in low-resource settings.

29.2. MULTICOMPONENT INTERVENTIONS IN EARLY PSYCHOSIS AVAILABLE IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW

Ruben Valle^{*1}, Nora Morrison¹, Srividya Iyer¹

¹*McGill University*

Background: Early intervention in psychosis (EIP) is a multicomponent intervention aimed at identifying and treating psychotic symptoms in their early phases. EIP services have been well-established in high-income countries. However, EIP services in low-and middle-income countries are still in their infancy. Most EIP services in those countries were adapted from high-income countries to fit with the available local resources. Although we are aware of the existence of EIP services in low-and middle-income countries, the components offered and their efficacy when used within such services is unknown. The present systematic review seeks to determine the multicomponent interventions offered to individuals at clinical-high risk and with first-episode psychosis in low-and middle-income countries; and determine the efficacy of these interventions when used in these settings.

Methods: We conducted a systematic review in PsycInfo, Embase, and Medline from inception until February 2023. We included search terms such as: prodromal phase of psychosis, first-episode psychosis, early intervention in psychosis services and low-and middle-income countries. Records of studies which were: conducted in low-and-middle income countries, provided multicomponent interventions to people at clinical high risk or with first episode psychosis, reported on at least one EIP component in addition to assessment of individuals with first episode psychosis and antipsychotic medication, reported at least one EIP component beyond clinical assessment of individuals at clinical high risk, and reported on the long-term provision of such multicomponent interventions, were included in the review. Data on the number and name of components provided and the efficacy of such components was synthesized.

Results: We identified 110 records across 15 low-and middle-income countries. Most EIP services were located in tertiary health facilities located in urban areas, with only a single site per country. Multicomponent interventions for individuals with first-episode psychosis comprised a mean of 4.6 components provided over 23 months, most commonly including clinical assessment, antipsychotic medication, patient psychoeducation, family education and support and cognitive-behavioral therapy. Multicomponent interventions for individuals at clinical-high risk included a mean of 4.4 components provided over 19 months, namely clinical assessment, evaluation by a specialist, monitoring by a specialist, and interventions for health problems. Multicomponent interventions were found to be beneficial in many clinical and functional outcomes for people with first-episode psychosis from low-and middle-income countries. Three randomized clinical trials showed multicomponent intervention is more effective than standard treatment in first-episode psychosis.

Conclusions: Multicomponent interventions for early psychosis in low- and middle-income countries closely mirror high-income country models in the number and type of EIP components offered. Also, multicomponent interventions for early psychosis are also effective in improving outcomes. However, most of these interventions are offered within short-term research studies rather than integrated into routine care and have limited cultural adaptation. Specifically, for individuals with first-episode psychosis, it's noteworthy that first-generation antipsychotics are commonly used and cognitive behavioral therapy is moderately applied. Also, for those at clinical high risk, antipsychotic medications are prominently featured, while cognitive behavioral therapy is less frequently utilized. Leveraging the review's findings, this presentation will highlight implications for further development and scale-up of EIP in low-and middle-income countries.

29.3. EARLY PSYCHOSIS SERVICES: AN INDIAN PERSPECTIVE

Greeshma Mohan*¹, Rangaswamy Thara², R Padmavati², Swaran Singh³, Ashok Malla⁴, Srividya Iyer⁵

¹Schizophrenia Research Foundation, India and University of Warwick, ²Schizophrenia Research Foundation, ³University of Warwick, ⁴McGill University, ⁵McGill University and Douglas Hospital Research Institute

Background: FEP in the Indian Context: India has a large pool of undetected and untreated patients with psychosis and a treatment gap exceeding 75%. Evidence-based packages of care have been piloted, but delivery of interventions still remains a challenge. Even when patients access treatment, there is minimal to no continuity of care. Much of the data and experience from India is provided from the First Episode Psychosis (FEP) program at Schizophrenia Research Foundation (SCARF) located in the Southern state of Tamil Nadu, India. Collaboration with PEPP, Montreal: The FEP program at SCARF was initiated in 2003 as a research collaboration with the Prevention and Early Intervention Program for Psychoses (PEPP), affiliated with McGill University, Montreal. A series of collaborative studies was carried out from 2003-2017 which focused on patients with previously untreated FEP who received clearly defined and similar treatment for two years. Partnering with the WIC group: While the collaboration with PEPP, Montreal furthered understanding of the nature of early psychosis presentation in India and the impact on patients and their families, a need was felt to develop culturally-sensitive interventions that could expand mental health services to communities that currently have no access in India. This brought together four internationally recognized institutions with a single aim – to develop protocol for management of first episode psychosis, thereby reducing burden of psychotic disorders. Partners included University of

Warwick (Coventry, UK); All India Institute for Medical Sciences (New Delhi, India); McGill University (Montreal, Canada) along with SCARF; collectively called the WIC group. During this presentation, we will describe the main findings resulting from both collaborations. To identify and discuss the components of FEP services in India that are best suited to wider implementation.

Methods: The first half of the presentation will focus on the outcome indicators and distinct characteristics of the FEP patients in India. The second part of the presentation will highlight the core components of FEP services in India with an emphasis of emerging symptoms, care pathways and duration of untreated psychosis based on 283 participants who were recruited as part of research collaborations.

Results: Our unique findings will be presented (eg., very low to no service disengagement, relatively high rates of medication discontinuation with maintained symptom remission, no delay in overall DUP when first contact is with healer as compared to other sources of help). We will also discuss the core components that provide a foundation for broader implementation and provide an evidence-based understanding.

Conclusions: Our unique findings will be presented (eg., very low to no service disengagement, relatively high rates of medication discontinuation with maintained symptom remission, no delay in overall DUP when first contact is with healer as compared to other sources of help). We will also discuss the core components that provide a foundation for broader implementation and provide an evidence-based understanding.

29.4. CHALLENGES OF IMPLEMENTING AN EARLY PSYCHOSIS INTERVENTION PROGRAMME IN TUNISIA

Feten Fekih-Romdhane*¹

¹*Tunis El Manar University*

Background: In Tunisia, psychiatric healthcare has long been mainly hospital-based and secondary care, with no community-based care or rehabilitation and recovery services available for youth with mental health problems. During the last decade, the public mental health strategy was approved, particularly with the adoption of the 2013 Tunisian National Strategy for the Promotion of Mental Health. Since then, a specific emphasis has been placed on mental health prevention efforts. This presentation seeks to describe the structural characteristics of a new early intervention in psychosis service in a real-world low-resource setting in Tunisia, i.e. the Tunisian Center of Early Intervention in Psychosis (TCEIP) program, and to discuss the benefits and challenges of implementing an early psychosis intervention programme in Tunisia within the local economic, social, and cultural context.

Methods: A literature review was undertaken.

Results: The Tunisian Center of Early Intervention in Psychosis (TCEIP) program has been created in 2017 in response to a lack of policies, staff training, and specialized early intervention services in the country. It is located at the Razi Psychiatric Hospital, and integrated into an existing service structure. The TCEIP was implemented with the financial support of civil societies, as well as the support and encouragement of the Ministry of Health. To the best of our knowledge, it is, so far, the first early detection and intervention in psychosis center based in Tunisia and the Middle East-North Africa region. The TCEIP targets individuals between the ages of 16 and 35 years, who are considered at risk for developing psychosis or presenting with a first episode of psychosis. It offers extensive clinical assessment and evidence-based interventions. However, there exists important barriers and challenges to be currently considered for the functioning, strengthening and sustainability of the TCEIP,

including a substantial burden of chronic underfunding of public mental health services, resource scarcity, financial obstacles to staff recruitment, lack of availability of and recurrent shortages in psychotropic medications, stigma toward the psychiatric hospital, and poor communication/collaboration with primary health care providers.

Conclusions: Because of the economic, social and cultural peculiarities, simply translocating early intervention programs previously implemented and tested in the Western, high-income world to the Tunisian context may be inappropriate.

30. RACISM AND PSYCHOSIS: FUTURE DIRECTIONS

Hans Oh, *University of Southern California*

Overall Symposia Abstract: Racism and psychosis: Future directions In a rapidly changing world where systemic inequities adversely affect population health, people of color are disproportionately impacted and appear to have higher psychosis risk. Race is a social construct used to categorize people based on secondary physical characteristics, such as skin tone, hair texture, and facial features. Historically, the concept of race was erroneously used to infer biological, genetic, and essential differences across groups; and as such, race has served as the basis of marginalization and oppression. Like in other mental health fields, psychosis researchers have treated ethnicity and race without proper contextualization, namely, without acknowledgement of racism –the complex system of oppression that operates through multiple pathways, including structures, institutions, culture, and interpersonal interactions to privilege the dominant (white) group while disadvantaging people of color. By and large, the field of psychosis research has employed underdeveloped conceptualizations of race and racism. Thus, we begin with an overview of anti-racist praxis when examining race and ethnicity in research to properly establish race as a proxy for exposure to racist experiences. Dr. Els van der Ven will present data from a meta-analysis showing ethnoracial risk variation across multiple psychosis outcomes, calling attention to diagnostic biases and systemic influences such as structural racism. Ms. Katrina Rbeiz will then present data from the US showing psychosis risk within the Middle Eastern/North African population, which is often treated as a monolith, with little regard for the socio-cultural variability in terms of exposure to discrimination and presence of resilience. Dr. Benson Ku will present data from the US showing associations between neighborhood racial diversity, peer victimization, perceived racial discrimination, and attenuated positive symptoms among youth at Clinical High Risk for Psychosis, shedding light on the social determinants of psychosis and stimulating discussion on potential early interventions for schizophrenia. Dr. Frederike Schirmbeck will present findings from the Netherlands, showing significantly longer time-to-treatment interval for ethnic minorities when compared with their white counterparts. Finally, Dr. Srividya Iyer will synthesize the presentations and share her thoughts on implications for service delivery and population health. Those in attendance will come away with greater awareness of racialization, race and ethnic minority status and racism in relation to psychosis, and hopefully become inspired to interrogate studies that make claims about race or ethnicity, adopt more measures of racism in data collection, and uphold antiracist practices in research to address racial disparities in psychosis.

30.1. ETHNORACIAL RISK VARIATION ACROSS THE PSYCHOSIS CONTINUUM IN THE UNITED STATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Els van der Ven*¹

¹*Vrije Universiteit Amsterdam*

Background: Studies suggest higher risk of schizophrenia diagnoses in Black versus White Americans, yet a systematic investigation of disparities that include other ethnoracial groups and multiple outcomes on the psychosis continuum is lacking. The objective of this study was to identify ethnoracial risk variation in the U.S. across three psychosis continuum outcomes (ie, schizophrenia and other psychotic disorders, clinical high risk for psychosis [CHR-P], and psychotic symptoms [PS] and experiences [PE]).

Methods: PubMed, PsycINFO and EMBASE were searched up to December 2022. Observational studies on ethnoracial differences in risk of three psychosis outcomes were selected. Data extraction and synthesis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Using a random-effects model, estimates for ethnoracial differences in schizophrenia and PS/PE were pooled and moderation by sampling and setting was determined, along with the assessment of heterogeneity and risk of bias. Main outcomes included risk of schizophrenia and other psychotic disorder, CHR-P and conversion to psychosis among CHR-P, and PS/PE.

Results: Of 32 studies on schizophrenia, 3 on CHR-P, and 29 on PS/PE included in the systematic review, 47 were included in the meta-analysis. Compared to White individuals, Black Americans had increased risk across two outcomes, ie, schizophrenia (pooled odds ratio [OR], 1.80 [95% CI, 1.36-2.38]) and PS/PE (pooled standardized mean difference [SMD], 0.10 [95% CI, 0.03-0.16]), Latinx individuals for PS/PE (pooled SMD, -0.15 [95% CI, -0.22-0.08]), and individuals classified as ‘Other’ ethnoracial group for schizophrenia (pooled OR, 1.81 [1.31-2.50]). The results regarding CHR-P studies were mixed and inconsistent. Sensitivity analyses showed elevated odds of schizophrenia in Asian individuals in inpatient settings (pooled OR, 1.84 [95% CI 1.19-2.84]) and increased risk of PE among Asian compared to White individuals specifically in college samples (pooled SMD, 0.16 [95% CI, 0.02-0.29]). Heterogeneity across studies was high and there was substantial risk of bias in most studies.

Conclusions: Findings suggest widespread ethnoracial risk variation across multiple psychosis outcomes. In addition to diagnostic, measurement and hospital bias, systemic influences such as structural racism should be considered as drivers of ethnoracial disparities in outcomes across the psychosis continuum in the U.S.

30.2. NAVIGATING DISCRIMINATION AND BUILDING RESILIENCE: INSIGHTS FROM MIDDLE EASTERN AND NORTH AFRICAN POPULATIONS IN THE U.S.

Katrina Rbeiz*¹, Sohee Park¹

¹*Vanderbilt University*

Background: Ethnic identity plays a significant role in people's psychological outcomes, experiences of discrimination, and the coping mechanisms that may emerge from these negative experiences. This study aims to delve into the emotional experiences, ethnic identity, and resilience of people from Middle Eastern and North African (MENA) populations. MENA individuals are among the most vulnerable populations, as they have been historically understudied due to the erasure of representation in key demographic questionnaires (i.e., the U.S. Census) as well as in psychological research, leading to major gaps in the literature regarding the culturally specific discrimination and ethnic trauma they endure. Even less is known about the development of psychotic experiences in MENA populations.

Methods: Participants will include community-dwelling adults from MENA backgrounds living in the United States. Using bivariate correlations and t-tests, we investigated whether ethnic and religious identity, immigrant status, gender, social defeat (via SDS), and everyday experiences of discrimination (via PDS) were associated with higher reports of psychosis-risk (via PQ-16), trauma (via BTQ), psychological distress (i.e., depression, anxiety, and stress; via DASS-21), as well as resilience (via BCRS) and belongingness (via CSBS). Further, categories within the PDS were created to measure race-, religion-, and gender-based discrimination, to investigate their associations with outcomes.

Results: We hypothesize that lower income and education will be associated with increased reports of trauma. We also predict that US-born MENA populations will report higher psychosis-risk, discrimination, social defeat, trauma, and psychological distress. We believe that ethnic and religious identity and feelings of belongingness will also serve as protective factors against trauma and psychosis-risk, and that these will be correlated with higher scores of resilience. All categories of discrimination (including total scores) will predict higher psychosis-risk, trauma, and psychological distress.

Conclusions: MENA populations are often treated as a monolith, with little regard for the socio-cultural variability that exists within them. We urge future researchers to use intersectional frameworks to explore MENA identities and experiences, such as immigrant status, race-, religion-, and gender-based discrimination, and their relationships to adverse psychological outcomes (i.e., psychosis-risk, trauma, distress), as well as resilience. This may address a public health concern by promoting inclusivity in research and clinical work for an understudied ethnic identity group, who are unlikely to access mental health resources to promote resiliency and protection.

30.3. THE RELATIONSHIPS OF NEIGHBORHOOD RACIAL DIVERSITY, PEER VICTIMIZATION, DISCRIMINATORY EXPERIENCES, AND POSITIVE SYMPTOMS AMONG YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

Benson Ku^{*1}, Emerald Yuan¹, Regine Haardorfer¹, Jean Addington², Carrie Bearden³, Kristin Cadenhead⁴, Tyrone Cannon⁵, Barbara Cornblatt⁶, Benjamin Druss⁷, Matcheri Keshavan⁸, Daniel Mathalon⁹, Diana Perkins¹⁰, William Stone¹¹, Scott Woods⁵, Elaine Walker¹, Deidre Anglin¹²

¹Emory University School of Medicine, ²University of Calgary, Department of Psychiatry,

³University of California, Los Angeles, ⁴University of California, San Diego, ⁵Yale

University, ⁶The Zucker Hillside Hospital, ⁷Emory University Rollins School of Public

Health, ⁸Harvard University, ⁹University of California, San Francisco, ¹⁰University of North

Carolina At Chapel Hill, ¹¹Harvard Medical School / Beth Israel Deaconess Medical Center,

¹²The City College of New York (CCNY)

Background: Racial diversity is an important factor in promoting inclusivity, productivity, and wellness. Greater racial diversity in schools has been associated with less bullying. Neighborhood-level factors including ethnoracial minority density and social fragmentation have been shown to be important in the development of psychosis. However, the relationships between neighborhood-level racial diversity and psychosis have yet to be investigated. In this study, we hypothesize that greater neighborhood-level racial diversity will be associated with lower psychotic symptoms among youth at clinical high risk for psychosis (CHR-P). In addition, we hypothesize that this relationship will be explained by less peer victimization and discriminatory experiences.

Methods: Data is collected at baseline from North American Prodrome Longitudinal Study Phase 2 (NAPLS-2) among youth at CHR-P. Neighborhood racial diversity was constructed using the Simpson Index using participants' census tract characteristics derived from their baseline addresses. The Simpson Index measures the probability that two racial groups randomly selected from a census tract will belong to different racial groups. The value of this index ranges between 0 and 1, the greater the value, the greater the sample diversity. Peer victimization was derived from the Life Event Stress Scale: (1) were bullied/got in a fight; (2) were excluded from a peer group and (3) were the subject of a cruel rumor. Discriminatory experiences included having experienced discrimination in their lifetime due to (1) skin color; (2) ethnicity; and (3) appearance. Both peer victimization and discriminatory experiences were constructed with the specified items above as latent variables. Attenuated positive psychotic symptoms were derived from the SOPS. Structural equation modeling (SEM) was employed to assess serial mediation of peer victimization and discriminatory experiences in the relationship between neighborhood racial diversity and attenuated positive symptoms. All models have been clustered by sites and adjusted for the following covariates: age, sex, neighborhood-level poverty, and depressive symptoms. Subgroup analyses explored whether the relationship of these variables differs based upon the racial minority status of the participant.

Results: The study included 437 participants at CHR-P. The median age was 18.0, 57.9% were male. The median neighborhood racial diversity index was 0.46. Median neighborhood poverty was 6.6%. All models reported had adequate model fit statistics. The final main model showed that greater neighborhood racial diversity was associated less attenuated positive symptoms (Std. Est = 0.28, 95% CI = 0.10 to 0.47, $p = 0.003$). This relationship was serially mediated by less peer victimization (Std. Est. = -0.14, 95% CI = -0.24 to -0.03, $p = 0.017$) and less discriminatory experiences (Std. Est. = 0.45, 95% CI = 0.26 to 0.63, $p < 0.001$), both of which explained 16.67% of the relationship between neighborhood racial diversity and positive symptoms. In subgroup analyses, the relationships between these variables were statistically significant among racial minorities, but not among white non-Hispanic participants.

Conclusions: This study demonstrates the associations between neighborhood racial diversity, peer victimization, perceived racial discrimination, and attenuated positive symptoms among youth at CHR-P. These findings help us better understand the social determinants of psychosis, which also shed light on potential early interventions for schizophrenia.

30.4. RISK CLUSTERS OF MULTIPLE SOCIAL DETERMINANTS IN THE PREDICTION OF DURATION OF UNTREATED PSYCHOSIS

Hannah Edelhoff^{*1}, Frederike Schirmbeck², Ulrich Reininghaus¹, GROUP Investigators³

¹*Central Institute of Mental Health, Mannheim*, ²*AMC, University of Amsterdam*, ³*GROUP*

Background: A longer duration of untreated psychosis (DUP) is associated with several short-term and longer-term negative outcomes, including higher symptom severity, longer time until remission, poorer overall functioning and quality of life. Despite efforts to implement early-intervention services and specialized care, DUP are still considerably long. Improving our understanding of predictors and barriers for a delay to adequate care for a first episode psychosis (FEP) may display important targets for intervention. Studies investigating individual and environmental factors influencing DUP, highlighted associations with several social determinants such as ethnoracial group, education, premorbid social, and academic functioning. Instead of focussing on single factors recent findings propose to use multiple characteristics of social determinants to identify potential clusters of risk/privilege. In addition,

potential barrier to care, measured at first contact might shed light on important variables on the pathway to treatment initiation.

Methods: In a cohort studies of recent onset psychosis (n=447) sociodemographic characteristics on gender, ethnicity, employment status, living arrangement, education, urbanicity, cannabis use and proportion of unmet needs were collected and included in latent class analysis to identify clusters of individuals based on these variables. Subsequently, differences in outcome (DUP) were compared with ANOVA and post-hoc comparisons.

Results: Preliminary analysis revealed 4 clusters. Cluster 1 was the largest cluster (31.1%) of individuals characterized as being predominantly white, male, living alone, being employed, with high educational degree and no cannabis use over the last 12 months. Cluster 2 (27,7%) differed from Cluster 1 by frequent cannabis use and a higher proportion of unmet needs. Cluster 3 (23.5%) consisted of predominantly female, white, more often being married or living together, not using cannabis and reporting little unmet needs. Finally, cluster 4 (17,7%) was characterized as male, non-white individuals with lower educational degree, higher proportion of unemployment, living in urban regions and reporting several unmet needs. Between cluster comparisons with regard to the DUP revealed significant longer time-to-treatment interval for individuals in cluster 4 compared with individuals in cluster 1 and 3.

Conclusions: Preliminary findings suggest that duration of untreated psychosis differs between clusters combining several social determinants. Accounting for their combination and potential interaction might increase early detection of subjects most vulnerable for a delay to adequate care.

31. ENVIRONMENTAL RISK FACTORS AND PSYCHOPATHOLOGIC DOMAINS: FROM MOLECULAR MECHANISMS TO THERAPEUTIC INTERVENTION

Marco Andrea Riva, *University of Milan*

Overall Symposia Abstract: A strong relationship exists between psychiatric disorders, such as schizophrenia, and disturbances of neurodevelopment. Indeed, a derangement in the maturational pattern of specific cellular subtypes, because of a genetic predisposition or exposure to adverse life events, may lead to alterations in brain circuits critical for the manifestation of key psychopathologic domains. With this respect, a better understanding of the relationship between early life adversities, psychopathologic domains, and key neurobiological mechanisms is crucial to identify potential targets for pharmacological intervention. Our symposium will summarize and discuss authoritatively important recent findings in this field by integrating basic and clinical research to highlight key molecular mechanisms and circuits that will ultimately guide future research efforts toward better phenotyping of ‘at risk’ individuals as well as for the identification of novel therapeutic strategies intervention.

At the preclinical level, Marco A. Riva (Italy) will discuss how stress exposure during gestation leads to vulnerability or resilience for specific behavioral constructs in adolescence, which are associated with altered function and responsiveness of selected brain circuits. He will also discuss the contribution of neuronal plasticity and immune mechanisms and the role of pharmacological intervention. Considering the relevance of adolescent experiences for disease susceptibility, Felipe V. Gomes (Brazil) will focus on the effects produced by stress exposure during this critical time frame and how such experience leads to impaired sociability and cognitive deterioration with significant changes in excitatory/inhibitory (E/I) balance due to oxidative stress (OxS) and altered mitochondrial function. Moreover, he will show how

treatment with N-acetylcysteine (NAC) may be able to prevent and/or attenuate the schizophrenia-related changes caused by stress exposure.

The central role of OxS in mediating the etiopathological role of genes and environment will be further addressed by Danielle Dwir (Switzerland) using a translational approach both in animal models and in early psychosis patients (EPP). She will show how OxS may interact with inflammation to produce long-term dysfunction of parvalbumin interneurons. She will also show how EPP with a genetic vulnerability to OxS, may display alteration of redox markers in plasma that are associated with reduced prefrontal GABA levels, potentially predicting a central E/I imbalance. Interestingly, sub-chronic NAC treatment may counteract such changes leading to an improvement in cognition and clinical symptoms.

Lastly, considering that a dysfunction of the hypothalamic-pituitary axis represents a key element in stress response and may also interact with some of the mechanisms discussed above, Alexis E. Cullen (Sweden) will focus on cortisol abnormalities among individuals with psychotic disorder and those at high-risk for the disorder. She will show data from five unique cohort studies conducted in the UK and she will discuss how cortisol measures may indeed show robust association with established psychosis and psychosis high-risk status thus providing useful information for a better characterization of affected individuals.

Together with the discussant (Marta Di Forti; UK), this expert panel of speakers will discuss how these findings can advance the understanding of etiological mechanisms for schizophrenia toward the identification of novel and more targeted strategies for preventive and therapeutic interventions.

31.1. VULNERABILITY AND RESILIENCE TO PRENATAL STRESS EXPOSURE IN RODENTS AT ADOLESCENCE: FROM BRAIN MECHANISMS AND CIRCUITS TO PSYCHOPATHOLOGIC DOMAINS.

Marco Andrea Riva*¹

¹*University of Milan*

Background: Exposure to adverse conditions early in life represents an important risk factor for the onset and development of mental disorders, including schizophrenia. Adverse perinatal events are indeed associated with profound changes in the progeny, which often become manifest at the transition between adolescence and adulthood. With this regard, animal models are particularly useful to investigate the molecular and functional mechanisms that are persistently affected after exposure to stressors early in life (ELS). The characterization of the timing for such alterations is instrumental in developing pharmacological interventions aimed at normalizing or preventing the behavioral consequences associated with ELS exposure. In our studies, we employed the prenatal stress model (PNS) in rats to investigate the behavioral and molecular alterations that develop because of this adverse experience in adolescent rats, also considering sex differences.

Methods: Pregnant rats were exposed to the prenatal stress (PNS) paradigm, consisting of 3 daily sessions of immobilization for 45 minutes from gestational day 14 to birth, while control dams were left undisturbed. During adolescence, the behavior of male and female offspring was investigated to analyze psychopathologic domains, including sociability, anhedonia, and anxiety, that are shared across different mental disorders. Following sacrifice, transcriptomics as well as candidate gene analyses were performed in different brain regions to identify

mechanisms that may be relevant for the behavioral phenotypes observed in animals exposed to PNS. Furthermore, a subgroup of animals was exposed to a 5 min of forced swim before sacrifice to investigate the differential responsiveness to the acute challenge.

Results: We found that PNS exposure produces emotional dysregulation in male and female adolescent offspring, including anhedonia, anxiety, and impaired sociability. Based on a two-step cluster analysis of the behavioral data, we identified 30% of PNS animals as resilient (PNS-res), whereas the remaining 70% were classified as vulnerable to PNS exposure (PNS-vul). At the molecular level, we found that such behavioral patterns were associated with selective changes in the expression of activity-dependent genes as well as of immune-related mechanisms in different brain regions, which are known to play a crucial role in emotional regulation. Moreover, while control or PNS-exposed rats show a similar activation of different brain structures following an acute stress in adolescence, some differences were found in the prefrontal cortex with an imbalance between excitatory and inhibitory circuits.

Conclusions: Overall, we showed that stress exposure during gestation produces emotional dysregulation only in a sub-group of adolescent male and female offspring. The characterization of the neurobiological mechanisms contributing to resilience or vulnerability to stress will be instrumental in identifying mechanisms that may be targeted by therapeutic approaches to counteract specific pathologic domains of mental disorders, including schizophrenia.

31.2. SCHIZOPHRENIA-RELATED HIPPOCAMPAL EXCITATORY/INHIBITORY IMBALANCE CAUSED BY ADOLESCENT STRESS: INVOLVEMENT OF REDOX DYSREGULATION AND MITOCHONDRIAL DYSFUNCTION

Felipe Gomes^{*1}, Thamyras Santos-Silva¹, Icaro Freitas¹, Caio Lopes², Doğukan Ülgen³, Francisco Silveira Guimaraes¹, Luciane Alberici², Carmen Sandi³

¹Ribeirao Preto Medical School, University of Sao Paulo, ²Ribeirão Preto Pharmaceutical Sciences School, University of São Paulo, ³Brain Mind Institute, École Polytechnique Fédérale de Lausanne

Background: The developing adolescent brain is highly susceptible to social experiences and environmental insults, influencing how personality traits emerge. We previously found that adolescent stress leads to long-lasting behavioral changes and excitatory/inhibitory (E/I) balance dysregulation in the ventral hippocampus (vHip) associated with neurodevelopmental disorders, including schizophrenia. The neurobiological mechanisms of psychiatric disorders have been linked with oxidative damage and reduced antioxidant capacity in the brain. However, the impact of severe stressors during adolescence, a critical neurodevelopmental period, on mitochondrial function, redox balance, and their functional consequences are not completely understood. We hypothesized that mitochondrial respiratory function and redox homeostasis in the vHip are affected by adolescent stress, leading to behavioral and electrophysiological changes associated with schizophrenia.

Methods: First, we performed a behavioral characterization during late adolescence (postnatal day, PND 47 – 50), including naïve animals and animals exposed to stress from PND 31 until 40 (10 days of footshock and 3 restraint sessions) by assessing sociability (social interaction test) and cognition function (novel-object recognition test). Then, we uncovered changes in E/I balance by analyzing the activity of glutamate pyramidal neurons, and the number of parvalbumin (PV)-containing GABAergic interneurons and their possible association with oxidative stress. To address the dynamic impact of stress on mitochondrial redox homeostasis, we performed high-resolution respirometry, DHE staining, MitoSox™ and AmplexRed® assays one (PND 41) and ten days (PND 51) after stress protocol. Also, we evaluated

glutathione (GSH) and glutathione disulfide (GSSG) levels at PND 51. We also assess the genome-wide transcriptomic signature of vHip of stressed animals by performing bulk RNA-sequencing following the behavioral tests. Finally, we tested whether the treatment with the antioxidant N-acetylcysteine (NAC) would attenuate the deleterious impact of adolescent stress.

Results: One week after stress, adolescent-stressed animals exhibited: loss of sociability and cognitive impairment; enhanced vHip pyramidal neuron activity; and reduction in the number of PV-positive cells and their associated perineuronal nets. These changes were associated with an increase in 8-oxo-DG, a marker of oxidative stress, in the vHip that was co-localized with PV interneurons. By performing high-resolution respirometry analysis, we found that stress impacted mitochondrial uncoupled efficiency (PND 41) and the phosphorylation capacity (PND 51). In addition, stressed animals displayed long-lasting redox dysregulation in the vHip, as revealed by molecular analysis. GSSG levels were increased in the vHip and serum of stressed animals and negatively correlated with social and cognitive performance, indicating that GSH was previously oxidized by ROS in stress conditions, and may affect behavioral phenotype. In another cohort of animals, we identified three cluster subgroups by performing a principal component analysis of behavioral assessment: naïve higher-behavioral z-score (HBZ), naïve lower-behavioral z-score (LBZ), and stressed animals. Genes encoding subunits of oxidative phosphorylation complexes were significantly down-regulated in both naïve LBZ (Cox7c) and stressed animals (Coa5), while the Txnip gene that encoded thioredoxin-interacting protein was up-regulated in stressed animals and negatively correlated with behavioral performance. The treatment with NAC during adolescent stress attenuated the behavioral and electrophysiology abnormalities caused by adolescent stress.

Conclusions: Our results identify mitochondrial genes associated with distinct adolescent behavioral phenotypes and highlight the negative impact of adolescent stress on vHip mitochondrial respiratory function and redox regulation, in which are partially associated with E/I imbalance and behavioral abnormalities related to schizophrenia. In addition, redox dysregulation and mitochondrial dysfunction may be potential targets to prevent and/or attenuate schizophrenia-related changes caused by stress.

31.3. MMP9/RAGE AS A COMMON MECHANISM INDUCED BY ENVIRONMENTAL RISK FACTORS IN THE DEVELOPMENTAL PSYCHOPATHOLOGY OF SCHIZOPHRENIA: A PROMISING TARGET FOR EARLY INTERVENTION IN EARLY PSYCHOSIS PATIENTS.

Daniella Dwir^{*1}, Jan Harry Cabungcal¹, Basilio Giangreco¹, Lijing Xin², Enea Parietti¹, Larissa Allgäuer¹, Catherine Yzydorczyk³, Raoul Jenni¹, Philippe Conus⁴, Michel Cuénod¹, Paul Klauser¹, Pascal Steullet¹, Kim Q. Do¹

¹Center for Psychiatric Neuroscience, Lausanne University Hospital, ²Center for Biomedical Imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne, ³, ⁴Service of General Psychiatry, Lausanne University Hospital, Switzerland

Background: The complexity of SZ comes from its multifactorial origins, involving both genetic and environmental factors. Environmental stressors occurring during gestation, at birth or during childhood increase the risk for SZ. The interaction between environmental risk factors and a genetic background of vulnerability converges to increased oxidative stress (OxS) and inflammation during early brain development, which may affect the proper maturation of cortical circuitry, specifically the highly metabolically active PVI, as a hallmark of SZ. In a translational approach both in animal models and in early psychosis patients (EPP), we aimed (1) to identify a precise mechanism induced by environmental stressors and leading to the

interaction between OxS and neuroinflammation, affecting PVI, and (2) to interfere with the proposed mechanism by using the antioxidant N-acetyl-cysteine (NAC) and environmental enrichment (EE) to rescue PVI maturation.

Methods: This study was conducted on three rodent models of environmental stressors with relevance for SZ: the transgenic GSH deficit (GCLM KO) model with an additional OxS during childhood, the gestational methylazoxymethanol acetate (MAM) model and the intrauterine growth restriction (IUGR) model. The animal findings were then validated in a well-characterized cohort of EPP. A rescue experiment was conducted on the GCLM-KO+GBR mice with NAC and EE during juvenile/adolescent period and morphological/functional analysis were conducted on adult animals. EPP underwent blood sampling, magnetic resonance spectroscopy (MRS) and clinical assessment. This cohort is composed of N=68 healthy controls (37% females; 14.7% ethnic minority) and N=111 EPP (25% females; 30% ethnic minority). A part of this cohort joined a double-blind, randomized, placebo-controlled clinical trial of NAC supplementation for 6-months and underwent blood sampling, MRS and clinical assessment at baseline and after treatment. This cohort is composed of N=16 placebo (44% females; 31% ethnic minority) and N=15 NAC (14% females; 26% ethnic minority).

Results: In the three rodent models with an environmental stressor, we identified a mechanism that maintained a feedforward loop of increased OxS and neuroinflammation, leading to PVI impairments. This mechanism involved the activation of MMP9, leading to the cleavage of the extra- and intra- cellular domains of RAGE (RAGE shedding). The intracellular domain of RAGE translocated to the nucleus, leading to the activation of NFkB, and further pro-inflammatory cytokines and microglia activation. These effects were completely reversed by the combination of NAC treatment and EE in the GCLM KO+GBR mice. This recovery was mediated by NAC, possibly via the inhibition of OxS induced MMP9/RAGE pathway, interrupting this deleterious feedforward mechanism, and allowing PVI maturation. A subsequent EE during adolescence promoted the final maturation of PVI, providing a long-term neuroprotection to PVI network. The fast-rhythmic oscillations reflecting neuronal synchronization of PVI was decreased in the GCLM KO+GBR, and recovered by NAC/EE. In EPP with a genetic vulnerability to OxS, an increase in RAGE shedding, measured as soluble form of RAGE (sRAGE) in the plasma, was associated with low prefrontal GABA levels, potentially predicting a central inhibitory/excitatory imbalance, in line with our preclinical model. Interestingly, 6-month NAC treatment decreased RAGE shedding in the plasma of EPP, in association with increased prefrontal GABA level, improvement of cognition and clinical symptoms, suggesting similar neuroprotective mechanisms.

Conclusions: MMP9/RAGE pathway represents a key regulatory mechanism by which OxS interacts with neuroinflammatory conditions, which is particularly damaging to PVI. The long-lasting effects on PVI can be reversed by a combined NAC/EE, even after the challenge. In analogy, patients carrying genetic risks to redox dysregulation potentially vulnerable to early-life insults could benefit from a combined pharmacological and psycho-social therapy. Our translational study establishes sRAGE as a peripheral marker for CNS inhibitory circuit impairments. The activation of MMP9 by OxS, on its redox-sensitive site, represents a mechanism-based peripheral proxy for brain neuroinflammation and OxS. Our findings highlight the MMP9/RAGE pathway as a promising target for novel drug development in psychiatry.

31.4. CORTISOL MEASURES ACROSS CLINICAL STAGES OF PSYCHOSIS: AN INDIVIDUAL PATIENT DATA (IPD) META-ANALYSIS

Senta Haussler¹, Uzma Zahid¹, Mahnoor Hassan¹, Fern Day², Simone Ciufolini¹, Natalia Petros¹, George Gifford¹, Luis Alameda³, Diego Quattrone¹, Kareen Heinze⁴, Helen Fisher¹,

Kristin Laurens⁵, Marta Di Forti⁶, Stephen Wood⁷, Robin Murray⁶, Philip McGuire¹, Valeria Mondelli¹, Alexis Cullen*⁸

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London*, ²*South London and Maudsley, NHS Foundation Trust*, ³*Institute of Psychiatry, Psychology and Neuroscience, King's College London/South London and Maudsley*, ⁴*University of Birmingham, UK*, ⁵*Queensland University of Technology/University of New South Wales*, ⁶*Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK*, ⁷*University of Melbourne*, ⁸*Karolinska Institutet*

Background: Studies conducted over the past five decades have provided evidence of cortisol abnormalities (indexing hypothalamic-pituitary axis dysregulation) among individuals with psychotic disorder and those at high-risk for the disorder. However, attempts to synthesise evidence from these studies indicate that findings are extremely heterogeneous. There are several factors that may explain this heterogeneity, including diversity in the cortisol measures, variable approaches accounting for potential confounders, and differences in illness stages across study populations. To address these issues, we will conduct an individual participant data (IPD) meta-analysis to examine five distinct cortisol measures across psychosis clinical stages. Our primary aim is to identify cortisol measures that differ in established psychosis and high-risk populations relative to controls. Our secondary aim is to conduct subgroup analyses comparing cortisol measures across clinical stages of psychosis.

Methods: As our aim is to harmonise and pool data across cohorts that had adopted similar methods of data acquisition, we have not conducted a systematic review to identify all studies reporting cortisol measures in psychosis/high-risk populations, but instead included a reasonably representative sample of studies that employed similar protocols and were accessible to us through existing consortia. Studies are required to (a) have measured cortisol in either saliva or hair using a clearly-defined protocol, (b) have data on a minimum set of potential confounders (age, sex, ethnicity, tobacco use, cannabis use, psychotropic medication), (c) have clinical data, obtained using a validated/reliable instrument, to determine illness stage, and (d) included at least one psychosis clinical stage and a healthy control group. Clinical stages are defined as mild psychotic symptoms and/or depression anxiety (stage 1a), clinical high-risk for psychosis (stage 1b), first-episode of psychosis (stage 2), relapsing/remitting illness (stage 3), or chronic illness (stage 4). A two-stage IPD meta-analysis will be conducted using the 'ipdmetan' package in Stata 17. In the first stage, correlational analyses will be used to investigate the relationship between potential confounders and cortisol measures within each cohort. Linear regression models will then be performed in each cohort to obtain standardised beta coefficients (StB), adjusted for potential confounders, representing the difference in cortisol measures between each clinical stage and healthy control group. In the second stage, StB's will be pooled using random effects meta-analyses.

Results: We have obtained six datasets from five unique cohort studies conducted in the UK. From the available datasets, we derived four salivary cortisol measures and a single measure of hair cortisol (indexing chronic HPA axis function). The number of cohorts and total sample size (N) for each cortisol measure is as follows: awakening response (5 cohorts, N=794), basal cortisol (5 cohorts, N=623), diurnal slope (5 cohorts, N=581), overall daytime cortisol release (5 cohorts, N=761), and hair cortisol (4 cohorts, N=255). We are currently performing stage 1 of the IPD meta-analysis, in stage 2 we will first compare healthy controls with all high-risk groups (stages 1a and 1b) and all individuals with established illness (stages 2, 3, and 4). Subgroup analyses will then be used to compare individual stages with healthy controls. The results from this analysis will be presented at the meeting.

Conclusions: Based on the results of the study, we will identify the cortisol measures that are the most robustly associated with established psychosis and psychosis high-risk status and provide recommendations for advancing scientific research in this field.

32. NEW FRONTIERS FOR PSYCHOSIS PREDICTION AND PREVENTION IN CHILDREN AND ADOLESCENTS

Ian Kelleher, *University of Edinburgh*

Overall Symposia Abstract: This symposium will explore new approaches to identifying risk for psychosis, in particular in childhood and adolescence.

Dr Kelleher will begin by discussing the current state of the art with regard to psychosis prediction research, especially for children and adolescents.

Dr Jalbrzikowski will then discuss new U.S. research looking at risk for psychosis in young people who have been followed up for 5 years+ after presenting to clinical services with self-harm. Her findings will demonstrate that this is a group at significantly elevated risk for later psychosis.

Dr Healy will discuss his research on risk for psychosis associated with 2 different approaches: (1) the classic Familial High Risk approach, looking at offspring of parents with a history of psychosis, and compare this to (2) offspring of parents who have attended specialist mental health services for any reason (not limited to psychosis). He will compare data on both the absolute risk of psychosis in each of these two groups but also on the total proportion of cases of psychosis that are captured by each of the two approaches.

Dr Lang will discuss data from Finland looking at risk of psychosis in young people who have attended adolescent psychiatry services who are followed into adulthood. She will demonstrate that this is a high risk group for later psychosis and present data on additional variables that help to identify subgroups of adolescent psychiatry patients who are at particularly high risk.

Dr O'Hare will present UK biobank data on risk for psychosis among young people who have attended child and adolescent mental health services (CAMHS). She will also present data on risk factors within these patients that predict a higher risk of later psychosis.

Dr Moriyama will summarise the four talks and lead our discussion, including discussing global health implications of the findings.

32.1. LEVERAGING ELECTRONIC HEALTH RECORDS TO IMPROVE RISK PREDICTION FOR PSYCHOSIS AND BIPOLAR DISORDER

Maria Jalbrzikowski*¹, Rashmi Sahasrabudhe²

¹*Children's Hospital/Harvard Medical School*, ²*Boston Children's Hospital*

Background: Psychosis and bipolar disorder are debilitating psychiatric disorders that prevent individuals from reaching their optimal level of functioning and are associated with significant economic and medical burden in society. Currently established risk prediction models for psychosis or bipolar disorder were built using specialized, costly, help-seeking samples and are focused on a single psychiatric disorder. While these approaches are valuable, only ~4-13% of individuals who present with first episode psychosis to mental health care centers were

previously seen through these programs prior to diagnosis. Furthermore, early diagnoses of psychosis and bipolar disorder are often unstable, suggesting that a transdiagnostic approach may be more effective. A recent study used data from a Finland registry to find that hospital presentation with self-harm was an indicator of elevated risk for later development of psychotic or bipolar disorder. Among children and adolescents who presented with self-harm, ~20% later received a diagnosis of psychosis or bipolar disorder. Yet, such an approach has not been validated in the United States of America (USA). Electronic Health Records (EHRs) offer a unique opportunity to assess self-harm presentation as a marker of psychiatric risk in the USA primary health care system.

Methods: We extracted EHR records from Boston Children's Hospital (Oct 2015-August 2023) on individuals 6-28 years old at the first incidence. After excluding individuals with less than 2 years of active diagnostic records, and those missing ICD-10-CM information, our final sample consisted of 157,708 individuals (mean age (SD)=12.98 (3.89) years, 52.5% female). We used ICD-10-CM diagnosis codes to identify records of presentation with self-harm and first diagnoses of psychotic and bipolar disorder. We conducted Cox proportional hazard analyses, to assess the relationship between hospital presentation with self-harm and receiving a diagnosis of psychotic or bipolar disorder. We also examined presentation with self-harm to any type of medical center (including outpatient settings) as a possible predictor. We then examined the ability of other known risk factors for psychosis and bipolar disorder (e.g, post-traumatic stress disorder, childhood maltreatment) to predict these outcomes. Covariates for all models included race, ethnicity, and birth year.

Results: Hospital presentation with self-harm was associated with a greater likelihood of developing a psychotic or bipolar disorder (hazard ratio [HR]=9.1, 95 % Confidence Interval [CI]=5.0-16.5, $p=2.9\text{e-}13$). 11% of individuals who presented with hospital presentation of self-harm went on to receive a diagnosis of a psychotic or bipolar disorder. This association between hospital presentation of self-harm and psychotic/bipolar disorder remained present (HR=2.9, CI=1.6-5.2, $p=5.2\text{e-}04$) when we included an ICD-10 diagnosis of a depressive disorder in the model (HR=6.5, CI=5.8-7.3, $p=5.8\text{e-}239$). With hospital presentation of self-harm also included in the model as a predictor, other notable predictors of psychotic or bipolar disorder included anxiety disorders (HR=5.8, CI=5.2-6.4, $p=4.1\text{e-}214$), attention-deficit hyperactivity disorder (HR=4.2, CI=3.8-4.7, $p=1.6\text{e-}143$), post-traumatic stress disorder (HR=7.8, CI=6.6-9.3, $p=1.6\text{e-}121$), obsessive-compulsive disorder (HR=4.3, CI=3.4-5.4, $p=1.6\text{e-}36$), childhood maltreatment (HR=3.4, CI=2.0-5.6, $p=4.4\text{e-}06$). Presentation to any type of medical center with self-harm was also associated with increased likelihood of developing a psychotic or bipolar disorder (HR=4.3, CI=2.9-6.4, $p=6.6\text{e-}13$).

Conclusions: This study adds to the building body of research showing that individuals with hospital presentation of self-harm are at significantly elevated risk for developing a diagnosis of psychotic or bipolar disorder. This research highlights the need to monitor and provide treatment to this high-risk group. Furthermore, to our knowledge, this is the first documentation of this relationship in a U.S. cohort and shows that this relationship is not restricted to European registry samples. In the future, we plan to look at the ability to improve our risk prediction model by including all significant univariate predictors combined. We also plan to test how our ability to predict those at greatest risk improves when we use natural language processing models to gather self-harm information from clinical notes.

32.2. CAPACITY FOR PSYCHOSIS PREDICTION USING THE FAMILIAL HIGH RISK APPROACHES: A FINNISH TOTAL POPULATION STUDY

Colm Healy*¹

¹University College Dublin

Background: Psychotic disorders have a strong hereditary component. Children who have a parent with a psychotic disorder have an increased risk of developing psychosis themselves. However, despite many studies demonstrating this increased risk, no research to date has quantified what proportion of all psychosis cases in the population are captured by this familial high-risk (FHR-P) approach. This is essential information for prevention research and health service planning, as it tells us the total proportion of psychosis cases that this high risk approach stands to prevent if we were to identify an effective treatment. Beyond this, we also wished to assess the same questions using a broader familial risk approach: looking at psychosis risk in individuals who have a parent who has attended mental health services for any mental disorder (not just psychosis), FHR-MD.

Methods: Data linkage from multiple Finnish registries were used to; 1) identify all individuals born between 1987-1992 (the index children); 2) examine their history of non-affective psychosis and schizophrenia based on a secondary care registry with inpatient and outpatient data; and 3) examine their parent's history of mental disorder which was based on inpatient registries. FHR-P and FHR-MD were defined as a parental diagnosis that occurred prior to the index child's 13th birthday and were based on a harmonized grouping of ICD-8, 9 and 10 codes. Outcome diagnoses in the index children, by ages 25-30, of non-affective psychosis and schizophrenia were defined using ICD 10 coding (F2X and F20, respectively).

Results: Of the index children (n=384,549), 1.5% (n=5,754) had FHR-P and 10.2% (n=39,313) had FHR-MD. By their late 20s, 1.7% (n=6,333) of the index children had been diagnosed with non-affective psychosis and 0.5% (n=1,799) had been diagnosed with schizophrenia. Of all non-affective psychosis cases in the index children, 5.3% (n=333) were captured by FHR-P and 20.4% (n=1292) were captured by FHR-MD. Of all schizophrenia cases in the index children, 6.4% (n=114) were captured by FHR-P and 21.5% (n=386) were captured by FHR-MD. The absolute risk of non-affective psychosis in the index children with FHR-P or FHR-MD was 5.8% and 3.3%, respectively. The absolute risk of schizophrenia in the index children with FHR-P or FHR-MD was 2.0% and 1.0%, respectively. Sensitivity analysis indicated that the absolute risk and capacity from FHR-P and FHR-MD were equivalent in mothers and fathers of the index children.

Conclusions: The FHR-P approach captures only a small proportion of all future psychosis cases but this is similar to the proportion of cases captured with the Clinical High Risk approach. The FHR-MD approach captures a substantially larger proportion of future psychosis cases. The absolute risk for non-affective psychosis from both FHR approaches was low but additional factors may improve prediction precision of these approaches and may ultimately aid in the prevention of psychosis.

32.3. PREDICTING PSYCHOTIC DISORDERS WITHIN ADOLESCENT PSYCHIATRY SERVICES – NATIONWIDE REGISTER-BASED STUDY

Ulla Lång*¹

¹*Finnish National Institute of Health and Welfare*

Background: We recently showed that as many as half of all psychotic disorders in the population emerge in individuals who have attended child and adolescent psychiatry services. There are, therefore, enormous opportunities for psychosis prediction and prevention within these services. In the current study, we wished to assess whether it is possible to stratify the level of risk among subgroups of patients attending adolescent psychiatry services.

Methods: Finnish healthcare registers capture extensive data on population healthcare usage, including all contacts with specialist mental health services. We linked Finnish population wide health care register data for all individuals born in 1987-1992 who had attended adolescent

psychiatry services between ages 13-18 years (N=26,195). Using logistic regression models, we assessed whether psychotic disorders after age 18 were predicted by 1) adolescent mental disorder diagnoses and 2) other clinical and demographic factors, including sex, season of birth, personal history of inpatient psychiatric treatment in adolescence, parental history of psychosis, and mother's education level.

Results: Of all individuals who had attended adolescent psychiatry, 9.8% (N=2,556) went on to be diagnosed with a psychotic disorder in adulthood. Looking at adolescent mental disorder diagnoses as risk factors for later psychosis, risk was broadly distributed across diagnoses. However, being assigned diagnoses from multiple mental disorder categories in adolescence was associated with higher risk of adult psychosis. The absolute risk of psychosis was 7.8% in individuals who left adolescent psychiatry services (at age 18 years) with 1 mental disorder category, 12.4% for 2 mental disorder categories, and 20.0% for 3 or more mental disorder categories. Higher risk of adult psychosis was predicted by (1) inpatient psychiatric treatment in adolescence (OR 2.0 95% CI 1.8-2.1), (2) parental history of psychosis (OR 1.7 95% CI 1.4-2.1), and (3) lower socio-economic status (OR 1.3 95% CI 1.0-1.5), but not by sex, season of birth or mother's education level. The absolute risk of psychosis among adolescent psychiatry patients varied from 4.7% for those who did not have an inpatient adolescent psychiatry admission, had no parental history of psychosis, and had the highest socioeconomic status to 28.7% for those who had one or more inpatient adolescent psychiatry admission, had a family history of psychosis, and were in the lowest socioeconomic status group.

Conclusions: Our findings show that there are important opportunities to identify risk for psychosis in young patients attending adolescent psychiatry services and highlight the need for research on psychosis prevention within this clinical population.

32.4. RISK FACTORS FOR LATER PSYCHOSIS IN INDIVIDUALS WHO ATTENDED CHILD AND ADOLESCENT MENTAL HEALTH SERVICES IN THE UNITED KINGDOM

Kirstie O'Hare*¹

¹*University of Edinburgh*

Background: Recent findings indicate that a large proportion of psychosis diagnoses occur in individuals who had attended Child and Adolescent Mental Health Services (CAMHS) earlier in life. CAMHS therefore appears to represent a high-risk, high-capacity system for identifying individuals at risk of psychosis. The ability to further refine prediction of psychosis within a CAMHS sample could facilitate the delivery of preventative interventions to those most at risk. Our aim was to examine whether sociodemographic and clinical factors could be used to enhance the prediction of psychosis within a CAMHS sample.

Methods: Using data from the UK Biobank, we investigated whether a range of risk factors were associated with lifetime diagnoses of psychosis within a sample of individuals who had attended CAMHS at least once. Risk factors included: male sex, ethnicity, immigrant status, age at first CAMHS attendance, season of birth, low birthweight, maternal smoking, educational achievement, cigarette smoking, self-harm, cannabis use, and adverse childhood experiences. Univariate and multivariate logistic regression was used to examine associations between these risk factors with lifetime diagnoses of psychosis (including non-affective psychosis and bipolar disorders).

Results: Of all individuals who had attended CAMHS, 10.3% had a lifetime diagnosis of psychosis. In univariate models male sex, minority ethnic group, a first CAMHS attendance in adolescence, not having a secondary school qualification, and self-harm, were all associated

with an increased risk of psychosis. In multivariate models only male sex, minority ethnic group, and a first CAMHS attendance in adolescence were associated with a diagnosis of psychosis. The absolute risk of psychosis ranged from 4.7% for individuals who were female, belonged to a white ethnic group, and had first attended CAMHS during childhood, through to 35.7% for individuals who were male, belonged to a minority ethnic group, and had first attended CAMHS during adolescence.

Conclusions: A small number of sociodemographic and clinical factors that are readily available to clinicians may be useful for aiding in the identification of individuals at a very elevated risk of psychosis.

Plenary Session VI - Jari Tiihonen: Antipsychotic Treatment of Schizophrenia: Real-World Evidence from National Cohorts

2:00 p.m. - 3:00 p.m.

33. ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA: REAL-WORLD EVIDENCE FROM NATIONAL COHORTS

Laila Asmal, *University of Stellenbosch*

33.1. ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA: REAL-WORLD EVIDENCE FROM NATIONAL COHORTS

Jari Tiihonen, *Karolinska Institutet*

Individual Abstract: The current treatment guidelines are largely based on randomized controlled trials (RCTs), but also observational studies have provided substantial contributions to evidence-based medicine. RCTs provide information on the efficacy of treatments in standardized settings in selected patient populations, i.e. they tell us if the treatment can work in optimal conditions. Well-conducted observational studies can inform us about the effectiveness of drugs, indicating whether or not these treatments actually work in a real-life setting. Both of these approaches have their pros and cons. In RCTs, randomization eliminates the selection bias, which is a problem in observational studies. On the other hand, highly selected patient populations, limited number of participants, and relatively short follow-up periods in RCTs make it very difficult to study relatively rare outcomes such as death, suicide, or severe adverse effects of medications. Using large unselected nation-wide patient cohorts can overcome these obstacles. Nordic countries with comprehensive nation-wide registers provide good possibilities for pharmacoepidemiological research. During the last decade, within-individual analysis has been utilized increasingly to eliminate selection bias related to time-invariant characteristics, such as sex, genetics, and initial severity of illness. This research has increased the knowledge on the effectiveness of the pharmacological treatments in schizophrenia, and has contributed to national treatment guidelines in several countries. This lecture will review how the big data have provided new insights to the associations between antipsychotic treatments and mortality, risk of relapse, risk of long-term adverse effects such as breast cancer, hematological cancer, and general physical morbidity, dopamine supersensitivity and breakthrough psychosis, and occupational functional outcome among patients with schizophrenia. Development of new methodological tools has enabled also modelling of dose-response effects of medications with these outcomes.

Concurrent Symposia

3:00 p.m. - 5:00 p.m.

34. APPROACHES TO IMPROVING THE QUALITY OF EARLY PSYCHOSIS INTERVENTION SERVICES

George Foussias, *Centre for Addiction and Mental Health*

Overall Symposia Abstract: Early psychosis intervention (EPI) offers timely, comprehensive treatment for young people with psychosis and their families. While it has been widely implemented, there is a high degree of variation in how the model is delivered. Furthermore, models have failed to improve psychosis recovery rates and functional outcomes at the population level. Increasingly, evaluation mechanisms are being implemented to help to ensure model fidelity, quality, and access with the aim of improving outcomes in EPI. This symposium will examine some of the mechanisms being used to improve EPI service delivery and outcomes. First, N. Kozloff (Ontario, Canada) will present the “EPI-SET” study, which implemented the NAVIGATE model of coordinated specialty care in 6 EPI programs in Ontario, Canada. She will present on the primary objectives at one year, including fidelity, individual-level outcomes, and youth and family engagement. M. Ferrari (Quebec, Canada) will present the 3-year implementation evaluation of “SARPEP,” the first rapid learning health system for first-episode psychosis in Canada. I. Bello (New York, USA) will present the development of a data visualization dashboard to support OnTrackNY, a state-and federally funded learning healthcare system for early psychotic disorder. N. Stefanis (Greece) will discuss his experience leading the first system-wide implementation of EPI services in Greece. L. Dixon, who directs the Center for Practice Innovations (CPI) at the New York State Psychiatric Institute which oversees OnTrackNY as well as a range of other evidenced based practices for persons diagnosed with serious mental illness, will highlight key themes across these efforts to improve EPI service delivery and lead a discussion to help attendees consider application to their local contexts. The highlighted research initiatives advance EPI service delivery and evaluation with the potential to improve patient and family experience and outcomes and clinician experience related to this population.

34.1. IMPROVING OUTCOMES IN EARLY PSYCHOSIS INTERVENTION THROUGH NAVIGATE IMPLEMENTATION: ONE-YEAR FINDINGS OF THE ONTARIO “EPI-SET” STUDY

Nicole Kozloff¹, George Foussias¹, Marleine Saliba¹, Emily Panzarella¹, Rakshita Kathuria¹, Kiran Jassal¹, Rsha Soud¹, Augustina Ampofo¹, Lillian Duda¹, Alexia Polillo¹, Janet Durbin¹, Paul Kurdyak¹, Sanjeev Sockalingam¹, Aristotle Voineskos¹

¹*Centre for Addiction and Mental Health*

Background: While Ontario has a relatively well-developed system of over 50 early psychosis intervention (EPI) programs delivering care informed by a set of program standards, surveys and fidelity reviews suggest that programs struggle to consistently deliver evidence-based, recovery-oriented services. NAVIGATE is a manualized model of coordinated specialty care integrating evidence-based interventions for early psychosis. NAVIGATE was implemented in 6 geographically diverse EPI programs across Ontario starting in 2019 in the “Early Psychosis Intervention: Spreading Evidence-based Treatment (EPI-SET)” study. The primary

objectives of this implementation-effectiveness study were to 1) assess implementation of NAVIGATE and whether this leads to improvement in fidelity to the EPI standards; 2) determine longitudinal change in functioning and symptoms among individuals receiving NAVIGATE; 3) evaluate youth and family member engagement in the study; 4) compare system-level outcomes (i.e. health service utilization, suicide attempts, mortality and system costs) associated with receipt of NAVIGATE. One-year results were measures for the first 3 objectives.

Methods: We assessed fidelity to EPI standards using the First Episode Psychosis Services Fidelity Scale (FEPS-FS; Addington et al, 2020), with 31 items rated on a scale from 1 (not implemented) to 5 (fully implemented). Trained assessors conducted baseline assessments prior to NAVIGATE implementation (T1) and a second assessment 20 months later after most clients had at least one year of exposure to the model (T2). Fidelity ratings were based on staff interviews, administrative data and client chart data. We calculated mean T1 and T2 fidelity scores at the item, domain and total scale levels. For the individual-level outcomes, we recruited 100 participants ages 14 to 35 years who met criteria for a DSM-5 schizophrenia spectrum disorder, substance-induced psychotic disorder, or mood disorder with psychotic features and had received less than 2 years of services in an EPI-SET site prior to enrolment between 2020-2022. Participants complete outcome measures at baseline and every 6 months over 2 years, including the Quality of Life Scale (QLS), the Social and Occupational Functioning Assessment Score (SOFAS), the World Health Organization Disability Assessment Schedule 2.0 (WHODAS), and Brief Psychiatric Rating Scale (BPRS). Change in outcome measures over the first 12 months was evaluated using linear mixed models. Youth advisors completed the modified Public Patient Engagement Evaluation Tool (PPEET) tool every 3 months and family advisors completed the tool monthly (their preferred frequency) to measure their experience of engagement. We administer the PPEET to YAC members every 3 months and FAC members monthly as recommended by participating advisors. Responses are rated on a scale from 1 (strongly disagree) to 5 (strongly agree). Percentage who rated each item at least 4 were calculated for each advisory group for each year of the study.

Results: The mean fidelity score across the 6 EPI-SET sites increased from 3.82 to 4.05 from T1 to T2. At the domain level, mean ratings increased for team practice (4.14 to 4.45) and psychosocial treatments (2.79 to 3.77). Participants were a mean age of 22.7 ± 4.2 years, 58% were male, 62% identified as White, and 33% were unemployed and not in school. Participants exhibited a significant improvement in QLS scores ($F(82.2,2) = 13.129$, $p < .001$), and SOFAS score ($F(53.9,1) = 47.890$, $p < .001$). There was also a trend for improvement in overall symptoms as measured by the BPRS ($F(87.6,2) = 2.802$, $p = .066$). There were no significant changes over time in WHODAS scores. Percentage of youth advisors with a favourable response to the engagement items ranged from 84-87% in the first year and 93-96% in the third year of the study. Eighty-three to eighty-six percent of family advisors in year 1 and 82-87% in year 3 had favourable responses to the engagement items.

Conclusions: Early data following the implementation of the NAVIGATE model of coordinated specialty care in Ontario EPI programs suggest that it was associated with improvements in fidelity to the EPI standards and patient outcomes. Youth and family advisors were highly engaged in the project. Evaluation at the study endpoint at 2 years is required to inform efforts aimed at sustaining quality of services and positive outcomes over the long term.

34.2. DEVELOPMENT OF DATA VISUALIZATION TO IMPROVE THE DELIVERY OF ONTRACKNY EARLY INTERVENTION SERVICES

Iruma Bello^{*1}, Ana Stefancic², Igor Malinovsky¹, Marleen Radigan³

¹*College of Physicians and Surgeons, Columbia University*, ²*Columbia University Medical Center*, ³*New York State Office of Mental Health*

Background: OnTrackNY (OTNY) is a state-and federally funded learning healthcare system (LHS) providing specialized early intervention services to adolescents and young adults with early psychotic disorder across New York state. It was awarded funding by the National Institute of Mental Health to become a regional hub within the Early Psychosis Intervention Network (EPINET), a national LHS for young adults with early psychosis. OTNY consists of 28 CSC teams receiving support from an intermediary organization, OnTrack Central, on CSC model implementation. OnTrack Central is supported by the New York State Office of Mental Health as an intermediary purveyor organization. It oversees the implementation of the OTNY model through the delivery of training and technical assistance, data collection, and fidelity assessments. Programmatic and outcome data for all OTNY participants are submitted by primary clinicians on a quarterly basis using standardized admission, follow-up, and discharge forms. OnTrack Central coordinates with OMH to aggregate de-identified participant and program data and provides monthly reports to teams for quality improvement. However, to impact individual-level care, the OTNY LHS recognized the need have providers access participant-level data. This presentation will describe the process for developing a data visualization dashboard that provides teams with participant-level data that can be utilized to guide treatment decisions and model implementation.

Methods: A User-Centered Design framework, Discover, Design, Build and Test (DDBT) was used to maximize key stakeholder engagement at each phase of the project. The Discover phase involved 12 provider key informant interviews (KII) eliciting feedback on key data elements to include. Findings were shared with OnTrack Central, who identified additional data elements in response to provider feedback. Design and Build Phases: A 10-member key stakeholders committee (KSC) met monthly for one year, to discuss the feedback received and design a dashboard in Tableau. An iterative process was used to inform the KSC that included two focus groups (FGs) and a survey with a total of 11 stakeholders and five cognitive walk throughs for usability testing.

Results: The Discover phase indicated that providers preferred a dashboard that was accessible to different team members, depicting outcomes that were important to participants, and could be connected to fidelity indicators, to guide model implementation. During the Design and Build phases, feedback from the FGs and interviews highlighted the need to use clear language and formatting to facilitate understanding of data represented. Providers emphasized the need to be provided with flags and suggestions related to data trends. Overall, the survey data indicated consensus (100% of 11 respondents) that the content of the dashboard was useful to the work.

Conclusions: The use of data to guide treatment decisions could be facilitated by a visualization dashboard that reflects the priorities of program participants and providers. Results indicate that to increase the usability of a dashboard, it needs to be easily accessible, the data need to be presented in an intuitively clear format and represent key elements and outcomes of CSC. Connecting the dashboard to data collection process by including reminders and fidelity indicators was also deemed very important by providers. The next phase of this project will consist of piloting the dashboard with all teams throughout the network and creating mechanisms for feedback within the LHS to understand how it is being used to make individual level care decisions and whether it can impact the implementation of OTNY to fidelity.

34.3. IMPLEMENTING A RAPID-LEARNING HEALTH SYSTEM IN EARLY INTERVENTION SERVICES FOR PSYCHOSIS IN QUÉBEC, CANADA: REFLECTING ON INDICATORS AND TECHNOLOGIES

Manuela Ferrari^{*1}, Marc-André Roy², Srividya N. Iyer³, Camille Arbaud⁴, Annie LeBlanc⁵, Amal Abdel-Baki⁴

¹*McGill University and Douglas Mental Health Institute*, ²*l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec*, ³*McGill University; Douglas Mental Health University Institute*, , ⁴*Centre Hospitalier de l'Université de Montréal*, ⁵*Université Laval*

Background: Psychosis typically emerges during the major developmental period between ages 15-30, with profound personal, family and socio-economic impacts, and has a lifetime prevalence of 3%-3.5%. The risks are high for social and vocational difficulties, long-term disability, and tragic outcomes like violence or suicide. Early intervention services (EIS) are the treatment of choice for psychosis in Québec/Canada, Australia, the US, and Denmark. More effective than routine care, EIS respond to problems of treatment delay and challenges arising in the first crucial 2-5 years, like poor service engagement and medication nonadherence. EIS for psychosis have operated for over 20 years in Canada, with Québec, British Columbia, Nova Scotia, and Ontario leading the creation of guidelines. Yet, similar to experience elsewhere, EIS implementation in Canada shows a lack of standards in some jurisdictions. Systematic monitoring of quality indicators and outcomes is lacking, and problems persist in integrating essential organizational components, despite the availability of fidelity measures. Rapid learning health systems (RLHS) embed data collection in clinical settings for real-time, problem-focused learning and continuous quality improvement. SARPEP (Système Apprenant Rapide pour les Programmes de Premiers Épisodes Psychotiques), the first rapid learning health system for first-episode psychosis in Canada, was designed and implemented to test the feasibility and acceptability of the new RLHS, bridging the gap between evidence and practices.

Methods: The first 3-year implementation of the SARPEP project, which involved 11 early intervention services (EIS) from urban, semi-rural, and rural areas, was evaluated using a mixed method design grounded in the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. Six focus groups were conducted with participants (n=24) from different stakeholder groups (two with service users, and one each with family members, psychiatrists, managers, and team leaders) who shared their experiences with the implementation of the RLHS.

Results: All invited EIS agreed to participate in the RLHS and completed all components (systematic monitoring of program and patient-level indicators; capacity-building activities). Study participants confirmed the value of introducing a standardized, measurement-based, digital system through SARPEP for routine collection and sharing of program-level data. Reach: SARPEP recruited 11 clinics, 90+ healthcare professionals, 33 psychiatrists, 12 team leaders, five patient and four family partners. All invited EIS agreed to participate in the RLHS and completed all components (systematic monitoring of program and patient-level indicators; capacity-building activities). The 11 SARPEP clinics currently care for 2,050+ active patients, adding 734 new cases per year. Effectiveness: key program indicators improved (e.g., time from referral to first contact, continuing education, patient-to-provider ratios), informing the revision of provincial standards. Adoption: all EIS monitored program indicators every 4 months, gradually improving data completion and accuracy. Participation in satisfaction questionnaires by youth and family members remained low, but varied across programs. Stakeholders (n=20-35) attended capacity-building events (knowledge exchange,

implementation meetings). Implementation: the completion time for data collection decreased over the study period from 10 to 3 weeks, as the REDCap system underwent continuous adaptation, creating tools and rapid supports for team leaders. Maintenance: all EIS pledged to maintain their participation and 9 new EIS joined SARPEP after completion of the study.

Conclusions: Implementing SARPEP proved feasible and successful, reaching targeted EIS/participants, who adopted and maintained the RLHS, improving in key program indicators despite the pandemic, and providing a new Québec database of quality care indicators.

34.4. NATIONWIDE COVERAGE OF EARLY INTERVENTION SERVICES FOR PSYCHOSIS IS UNDERWAY IN GREECE

Nikos Stefanis*¹

¹*National and Kapodistrian University of Athens*

Background: What can only be described as an unprecedented thrust in mental health reform is currently underway in Greece. Responding to the recommendation from the Ministry of Health, the Ministry of Finances announced in March 2022 the allocation of considerable funds drawn from the Recovery and Resilience Facility of the European Commission (RRF) for the establishment and operation of initially eight Early Intervention Services for Psychosis (EISP) providing nationwide coverage. Consequently, the Ministry of Health in August 2022 announced a tender in which local mental health Non-Government Organisations could apply either as a single entity or forming partnerships with public mental health institutions, such as University Departments, to claim the establishment of community-based EISP in eight predetermined major cities of the country. The final eight winners of the bid were announced in early December 2022 with an allocated budget of 500,000 Euros per year per service and a mandate to deliver operational services by late 2023. This fortunate development is the accumulation of combined efforts on the one hand by numerous colleagues and stakeholders who have tirelessly advocated for Mental Health Reform in Greece, and on the other a receptive Ministry of Health who responded favorably to public demand.

If one was to trace the origins of the effort, one would probably date it back to 2015, when the Athens First Episode Psychosis (FEP) research study was launched by the A' Department of Psychiatry in Athens, consequently evolving in the first prospective study of FEP in the country. The study provided much-needed local information on clinical outcomes such as the high one-year relapse/readmission rates after initial hospitalization under the existing “treatment as usual” model. This was a prominent argument utilized in consequent debates over the necessity of establishing such community-based EIP services and a sign for a change in policy to occur. Consequently, a committee under the Ministry of Health was formed in late 2018 with a mandate to examine the legal and organizational framework for the implementation of EISP. The current government adopted the recommendations of the committee and proceeded to bring the legislation to Parliament (Official Government Gazette of the Hellenic Republic, A 256 - 23.12.2020) thus establishing EISP as a legal entity within the NHS. Public awareness amongst colleagues and mental health professionals grew even further thanks to the highly successful international WPA Thematic Congress on Early Intervention in Psychiatry, held in Athens in June 2022 (www.wpathematic.org) under the auspice of the Greek Psychiatric Association, the University of Athens, and the Early Intervention in Mental Health international Network (IEPA).

Methods: NONE

Results: NONE

Conclusions: As of October 2023, six such EISP are operational. Even though there is still much to be done, such recent advances raise justified optimism for a new era of reform in community mental health in Greece. However, complacency is unwarranted. The sustainability of government-based funding should be secured in the long run and integration of EISP with existing mental health services may prove to be a challenging process. Nevertheless, it is now undisputed, Greece joins the selected few countries that provide government-based and nationwide coverage of EISP.

35. DECONSTRUCTING THE NEGATIVE SYMPTOM CONCEPT

Emilio Fernandez-Egea, *University of Cambridge*

Overall Symposia Abstract: The reborn interest in the negative symptoms of schizophrenia has led to new assessment tools, large epidemiological studies, new cognitive paradigms.... and the perennial lack of novel and effective interventions. Increasingly, some researchers are moving away from considering negative symptoms a single entity but a construct with at least two dimensions, loosely defined as experiential (motivation) and expressive (emotion), or even five different domains. This is not a semantic discussion as the two dimensions (or five domains) might have distinct pathophysiology and, crucially, treatment. This symposium will explore recent work in against (and in favour) an unitary view of the negative symptoms (Prof Mucci and Dr Fernandez-Egea's talks). Then, we will explore two different approaches to negative symptoms: as a transdiagnostic dimension, with shared pathophysiology in affective, psychotic and neurodegenerative disorder (Dr Robert's talk) or as a specific symptom in schizophrenia, by exploring the clinical and imaging predictors of the primary negative symptoms (Dr Mane talk). We hope this symposium will stimulate a debate about how should negative symptoms be reconceptualised in order to progress in our understanding and treatment.

35.1. EXTERNAL VALIDATION OF NEGATIVE SYMPTOM DOMAINS WITH COGNITIVE AND FUNCTIONING-RELATED VARIABLES IN SUBJECTS WITH SCHIZOPHRENIA

Armida Mucci¹, Giulia Maria Giordano¹, Francesco Sanmarchi², Paola Rucci², Paola Bucci¹, Paola Rocca³, Alessandro Rossi⁴, Alessandro Bertolino⁵, Silvana Galderisi¹, Mario Maj¹

¹*University of Campania Luigi Vanvitelli*, ²*University of Bologna*, ³*University of Turin*,

⁴*University of L'Aquila*, ⁵*University of Bari*

Background: Recent confirmatory factor-analytic studies suggested that the bi-dimensional model (Motivational Deficit-MAP and Expressive Deficit-EXP) may not capture the complexity of negative symptoms (NS) structure, and a 5-factor or a hierarchical model, in which the five NS domains are the first-order factors, and MAP and EXP the second-order factors are proposed. A validation of these models is needed to define the structure of NS.

Methods: To evaluate the validity and temporal stability of the five-factor or the hierarchical structure of the Brief Negative Symptom Scale (BNSS) in individuals with schizophrenia (SCZ), exploring associations between these models with cognition, social cognition, functional capacity, and functioning at baseline and at a four years follow-up.

Clinical variables were assessed using state-of-the art tools in 612 SCZ at two time points. The validity of the five-factor and the hierarchical models was analyzed through structural equation models.

Results: The two models had both a good fit and showed a similar pattern of associations with external validators at the two time points, with minor variations. The five-factor solution had a slightly better fit. The associations with external validators favored the five-factor structure.

Conclusions: Our findings suggest that both the five-factor and the hierarchical models provide a valid conceptualization of NS in relation to external variables and that the 5-factor solution provides the best balance between parsimony and granularity to summarize the BNSS structure. These findings have implications for the study of pathophysiological mechanisms to develop new treatments for negative symptoms.

35.2. CASES: A EUROPEAN STUDY USING DIFFERENT MEASURES OF APATHY AND NEGATIVE SYMPTOMS.

Emilio Fernandez-Egea^{*1}, Stefan Kaiser², Anna Mane³, Armida Mucci⁴, Silvana Galderisi⁴, Gabriel Robert⁵, Philippe Robert⁶

¹*University of Cambridge*, ²*Geneva University Hospitals*, ³*Hospital del Mar*, ⁴*University of Campania Luigi Vanvitelli*, ⁵*University of Rennes*, ⁶*Université Côte d'azur*

Background: Apathy is a quantitatively reduction of goal-directed activity either in behavioural, cognitive, emotional or social dimension in comparison to person's previous level of functioning in these areas. Apathy is prevalent across many neurodegenerative, neurological, and psychiatric disorders. However, the definition and terminology employed to refer to apathy can vary in the context of different conditions and specialties and the diagnostic criteria have evolved overtime and little progress has been achieved in assessing the validity of the same construct across different disorders (eg.

neurodegenerative disorders, schizophrenia or affective disorders). The first diagnostic criteria for apathy (DCA) in neuropsychiatric disorders were published in 2009

(Robert et al. 2009) A group of experts reached a novel consensus in 2018 using Delphi panel methodology (Robert et al. 2018). The validity of this new consensus has yet to be assessed among all relevant populations. This Multicentre PanEuropean study had two aims: The first aim of the present multicenter survey was to test the prevalence of apathy, measured with the 2018 DCA, in patients diagnosed with schizophrenia. The second aim will focus on the relationship between DCA and other measures of apathy and negative symptoms in schizophrenia.

Methods: Cross sectional assessment of schizophrenia patients (18-60 years old) stable on medication from six different centres in France (Rennes and Nice), Switzerland (Geneva), Italy (Naples), Spain (Barcelona) and UK (Cambridge). Sociodemographic and clinical data was collected, as well as structured psychometric scales including: 1) 2018 DCA: Diagnostic criteria for apathy (Robert et al. 2018); 2) PANSS: positive and negative symptoms scale (Kay et al. 1987); 3) BNSS: brief negative symptoms of schizophrenia (Kirkpatrick et al. 2011); 4) AMI: apathy and motivation index (Ang et al. 2017); 5) PSP: Personal and social performance scale (Morosini et al. 2000); 6) BACS: brief assessment of cognition in schizophrenia (Keefe et al. 2004); 7) CDS: Calgary depression scale (Addington et al. 1993); 8) SHRS: St. Hans Rating Scale for extrapyramidal symptoms (Gerlach et al. 1993); 9) M.I.N.I: Mini International Neuropsychiatric Interview (Sheehan et al. 1998).

Results: The study recruited between April 2021 and March 2023, with data consolidated in August 2023. A total of 151 cases were recruited (107 males and 44 female) in all six sites (ranging from 5 to 38 per site) with a mean age of 39.8 years old (SD 11.2). Ninth-one out of the 151 met criteria for apathy using the DCA. Further analysis of the relationship between the DCA, BNSS and AMI will be unveiled at the meeting.

Conclusions: It is crucial that neurology, geriatry and psychiatry find a common lexicon to describe the decrease of goal directed activity. Here, we compared three different system: dichotomic (DCA), clinician rated (BNSS and PANSS) and patient-rated (AMI). DCA might represent a first step towards the convergence of the three fields.

35.3. APATHY AS A TRANSDIAGNOSTIC SYNDROME IN CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS: WHAT ARE THE FACTS?

Gabriel Robert^{*1}, Jean-Charles Roy¹, Dominique Drapier¹

¹*Rennes University*

Background: Apathy is one of the dimension or facet of negative symptoms in schizophrenia. It is frequently described across central nervous system diseases and disorders (CNS-DD) and iteratively associated with pejorative outcomes, independently of the underlying CNS-DD. Therefore, it raises the question of a trans-diagnostic syndrome. However, it is still unclear how cognitive and cerebral correlates of apathy overlap and what are the differences across and within CNS-DD. Our overarching goal is to systematically identify the cognitive and cerebral correlates of apathy in schizophrenia and other CNS-DD. The secondary goal is to identify the clinical (age, medication, disease duration, socio-educative level) factors that best explain the heterogeneity of cognitive and cerebral correlates of apathy.

Methods: A systematic review following the PRISMA guidelines will be performed using the following term (apathy [title] OR motivation [title] OR goal-oriented [title/abstract]) AND (cogni* [title/abstract] OR neurocogni* [title/abstract] OR dementia [title/abstract] OR schizo* [title/abstract] OR Parkin* [title/abstract] OR alzhei* [title/abstract] OR vascular [title/abstract] OR small vessel [title/abstract] OR lewy [title/abstract] OR depress* [title/abstract]) AND (imaging [title/abstract] OR MRI [title/abstract] OR PET [title/abstract] OR EEG [title/abstract] OR MEG [title/abstract] OR SPECT [title/abstract]) in MEDLINE, EMBASE, PsycINFO, The Cochrane Library, Health Technology Assessment Database, and Web of Science. Two independent reviewers will select the articles and a third will choose for inclusion when conflictual situations. The review is registered in Prospero, currently under review.

Results: The analysis has not been performed yet and following are only preliminary findings. Our search a total of 373 articles have been retrieved, after excluding doubles. However, based on our previous knowledges about apathy cognitive and cerebral correlates, we expect some general findings. Goal-oriented behaviors and cognition, anchored in computational decision making field as well as the executive system, with planning and anticipating positive outcomes, are the two cognitive pillars of apathy in schizophrenia, which are also found in degenerative and major depression disorders. From the cerebral literature, the dopamine-dependent ventral striatum and its projection to the medial prefrontal cortex is also found across CNS-DD, including in schizophrenia. The anterior cingulate and its role in effort devaluation seems also to contribute to apathy pathophysiology in schizophrenia. From a network perspective, the interplay between the central executive, the salience and the default mode networks is also described in schizophrenia. However, other cerebral structures are less robustly found such as the hippocampus and the cerebellar basal ganglia projections. The

systematic review will be able to provide a comprehensive view of the moderating effect size of the clinical factors (age, medication, disease duration, socio-educative level).

Conclusions: The literature of apathy in schizophrenia suggest that there might be cognitive and cerebral correlates across CNS-DD and the vision of a trans-diagnostic apathy syndrome is very appealing. However, some cerebral structures are less robustly found and within and between CNS-DD that influences the results are not known. Additionally, the mechanistic explanations that disrupt these cerebral pathways and cognitive functions vary across CNS-DD, thereby reducing trans-diagnostic therapeutic approaches.

35.4. CAN NEUROIMAGING DETECT THE VULNERABILITY TO PERSISTENT NEGATIVE SYMPTOMS?

Anna Mane*¹, Laura García-Blanco¹, Alba Toll¹

¹*Hospital del Mar,*

Background: Negative symptoms remain a major unmet therapeutic need for people with schizophrenia. Epidemiological studies suggest an increase of the severity of negative symptoms over time. Still, it is unclear whether these are primary negative symptoms or secondary to other factors (psychosis, depression, etc..). In this study, we aimed to predict the presence of persistent negative symptoms after a year of the onset of the disorder, using a multimodal approach of neuroimaging and peripheral biomarkers.

Methods: We recruited 50 drug-naïve patients with first-episode psychosis and 50 age- and sex-matched healthy controls to study brain volumes. We performed univariate and multiple and logistic regression analyses to determine the association between baseline clinical and neurobiological variables, score on the PANSS negative subscale and persistent negative symptoms after 1 year of follow-up.

Results: Low baseline serum BDNF levels ($p = 0.011$), decreased left amygdala relative volume ($p = 0.001$) and more severe negative symptomatology ($p = 0.021$) predicted the severity of negative symptoms at 1 year, as measured by the PANSS negative subscale. Low baseline serum BDNF levels ($p = 0.012$) and decreased left amygdala relative volume ($p = 0.010$) predicted persistent negative symptoms at 1 year.

Conclusions: This study shows that a set of variables at baseline, including low BDNF levels, smaller left amygdala relative volume and score on the PANSS negative subscale are significant predictors of outcome in first-episode psychosis. These findings might offer an initial step for tailoring treatments in first-episode psychosis

36. PROMISES AND PITFALLS OF CLINICAL TRIAL DESIGN: HOW CAN WE BETTER EVALUATE NOVEL TARGET ANTIPSYCHOTICS?

Anthony Grace, *University of Pittsburgh*

Overall Symposia Abstract: Clinical trials are an essential means to evaluate clinical efficacy of new medications. However, many agents that appeared to be highly effective in preclinical studies and early stage evaluations failed in the multi-center trials. This could be due to several factors, including the lack of efficacy across a broad population, or a trial design that is ineffective at identifying novel target compounds. These limitations could prevent the entry of more effective medications that may be highly beneficial to the patient populations. For example, it may be that some medications are only effective in subgroups of patients, and denying their entry would limit the ability of these patients to receive effective treatment. The other issue is the trial design itself. Thus, many clinical trials for e.g. antipsychotic drugs have

relied on the principle that once a drug is washed out of the system over a 1-2 week period, a new medication can be introduced. While this has been effective in identifying “me-too” D2 antagonist antipsychotic drugs, there is the strong potential that the drug that the patient had been given for long periods of time has altered the system in such a way that only another drug of the same class can be effective. Indeed, in preclinical studies it has been shown that the D2 supersensitivity induced by 3 weeks of treatment with the D2 antagonist haloperidol interfered with the efficacy of a novel GABAergic drug that was found to be highly effective in non-pre-exposed animal models. In this panel, we will discuss the potential limitations of current clinical trial design, and how these shortcomings may be circumvented. Dr. Ines Khadimallah will present data showing that the antioxidant N-acetyl cysteine is only effective in patients in the early phase psychosis showing high oxidative status and mitochondrial impairments. In a randomized double blind clinical trial with supplementation of NAC, patients’ subgroup with high baseline plasma exosomal levels of microRNA-137, the key regulator of mitochondrial oxidative stress, showed significant improvements of cognitive and functional outcomes. The latter was associated with a reduction in exosomal microRNA-137 levels. Dr. Stefan Gold will present the EU-PEARL project, an IMI-funded private-public partnership that jointly developed an adaptive platform trial for treatment resistant depression and how this may serve as a blueprint for clinical trials that can increase efficiency, speed, comparability, and patient-centricity in mental health. Dr Stephen Wood will discuss the benefits of clinical trials networks as platforms for delivering rapid, high quality trials of novel treatments, with a particular focus on the Australian early psychosis network. Dr. Anthony Grace will present preclinical data showing that drugs such as pomaglumetad, which failed in large multicenter trials, was highly effective in reversing the pathophysiology in a developmental disruption model of schizophrenia. A reason for this discrepancy is suggested by his studies showing that prior exposure to D2 antagonist antipsychotic drugs interfere with potential therapeutic actions of a novel target compound, a GABA A alpha 5 PAM. He will also present a unique approach for investigating novel target antipsychotic drugs without extended withdrawal periods. Dr. Pat McGorry will then provide an integration and describe how trial designs may be modified to more effectively test novel compounds for efficacy.

36.1. N-ACETYL-CYSTEINE (NAC) INTERVENTION AND MITOCHONDRIAL MECHANISMS IN EARLY PSYCHOSIS: COGNITIVE AND FUNCTIONAL IMPROVEMENTS

Ines Khadimallah^{*1}, Martine Cleusix², Raoul Jenni¹, Paul Klauser¹, Kim Do³, Philippe Conus², Luis Alamedad²

¹*Center for Psychiatric Neuroscience, Lausanne University Hospital*, ²*Service of General Psychiatry, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL)*, ³*Lausanne University*

Background: Schizophrenia (SZ) is associated with neurocognitive dysfunction already in the early phase of the disease. However, cognitive impairments are poorly treated by pharmacological interventions, leaving severe problems in functioning (Green et al., 2000). Redox dysregulation and oxidative stress emerge as a central pathological mechanism underlying schizophrenia (Cuenod et, 2023). Individuals with SZ show increased oxidative damage and reduced antioxidant capacity. Impairments of fast-spiking GABA parvalbumin interneurons (PVI), leading to cortical excitatory-inhibitory imbalance, underlie cognitive deficit. A variety of models relevant to SZ and psychotic disorders, converge on oxidative

stress induced PVI integrity impairment as a common underlying pathway (Steullet and Cabungcal et al, 2017). In a proof-of-concept trial in patients with early psychosis (EPP), the antioxidant N-acetyl-cysteine (NAC) increased prefrontal glutathione levels in a small subgroup of patients, thus suggesting target engagement. NAC improved moderately processing speed (Conus et al., 2017) with no effect on other clinical symptoms. However, in a subgroup of patients with high blood oxidative markers at baseline, NAC improved positive symptoms, in parallel with changes in peripheral redox status, (Conus et al., 2017).

To search for biomarkers capturing circuitry dysfunction needed for patient stratification, we have identified a molecular mechanism linking mitochondria and oxidative stress induced PVI impairments. Oxidative stress upregulates the microRNA miR-137 in PVI, a gene strongly associated with SZ (Ripke et al., 2011), leading to decreased COX6A2, a subunit of cytochrome c oxidase complex IV specific to PVI, and impaired mitophagy with mitochondrial damage accumulation (Khadimallah et al., 2022). In EPP, high miR-137 and low COX6A2 plasma exosomal biomarkers allow to select with high accuracy patients with worse psychopathological status and neurocognitive performance, and impaired global and social functioning. We now aim to compare the effect of NAC between subgroups of patients with and without mitochondria dysfunction.

Methods: The study was a 6-month, double-blind, randomized, placebo-controlled trial of NAC supplementation (2700 mg/d) to standard medications. Sixty-one patients (31 NAC, 30 placebo) with a diagnostic of psychotic disorder and less than 12 months of antipsychotic treatment were enrolled. We assessed and compared in NAC and placebo groups at baseline and at the end of treatment: 1) Neurocognition using with the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). b) Global assessment of functioning (GAF), c) Brain-derived exosomal levels of miR-137 and COX6A2.

Results: Patients with high baseline plasma exosomal miR-137 levels in the NAC group showed significant improvements in processing speed, attention/vigilance, and GAF. The amelioration in processing speed within the NAC group was inversely correlated with exosomal miR-137 levels. Moreover, an improvement of GAF was positively linked to higher COX6A2 exosomal levels in both NAC and placebo groups.

Conclusions: The addition of NAC significantly improved neurocognition and functional outcome in early psychosis patients, particularly in those with mitochondrial dysfunction, in parallel with associated biomarkers miR-137 and COX6A2. If replicated in larger studies, in particular with treatment focusing on mitochondrial mechanisms, our results would open the way for personalized and mechanistically guided treatments.

36.2. THE EU-PEARL INTEGRATED PLATFORM TRIAL FOR MAJOR DEPRESSION

Stefan Gold*¹

¹*Charite University Medical Center Berlin*

Background: Clinical trials are at the core of evidence-based medicine. However, in psychiatry, the trials conducted often fail to inform clinical practice because many are underpowered. Moreover, the available treatments only work for a subset of patients and the number of new regulatory approvals in psychiatry has consistently lagged behind other areas of medicine, such as oncology, infectious diseases, or neurology. Thus, there is an urgent need for a more efficient, faster and more collaborative way of evaluating the safety and efficacy of new and repurposed drugs as well as comparative effectiveness data for medications already in use.

Traditionally, treatments are evaluated in individual trials, with participants randomized to the intervention or a control group, each trial conducted in a specific setting and requiring its own infrastructure, which is dismantled after completion of the trial. This approach is slow, not very efficient, and limits comparability across trials. In contrast, a platform trial uses a shared infrastructure for many treatments, a shared control group, and allows new treatments to be added over time. Importantly, platform trials also require fewer participants overall and fewer participants will receive control/placebo treatments in this setting. This approach can thus increase the speed at which data on safety and efficacy are obtained, reduce operational costs and participant burden, and increase statistical power and comparability. Platform trials have successfully been used in fields like oncology, and – more recently – during the COVID pandemic.

Methods: The EU-PEARL project, an EU-funded public private partnership, has thus developed a similar approach for the mental health field by building a reusable multinational infrastructure, operated by an open collaborative consortium, to run an integrated platform trial for new and repurposed treatments for depression.

Our integrated platform trial (IPT) consists of 3 components: A trial site network, a longitudinal observational cohort (LOC), and the platform trial itself. The platform trial will evaluate investigational (new as well as repurposed) drugs for treating treatment-resistant depression (TRD) in a proof of concept (PoC) / phase 2 setting.

Results: This IPT has been co-designed with lived experience experts and informed by extensive trial simulations to test the efficacy and safety of combination or augmentation strategies over a 6-week period with long-term follow-up within the observational cohort. The trial can accommodate different routes of administration (“domains” of the trial) and the protocol allows for flexibility in the samples size of each arm (ranging from N=40 to N=120), with blinding ensured and controls shared within each domain (but not across domains).

Conclusions: In this presentation, I will describe the development of this platform trial and discuss its advantages and challenges for accelerating evidence generation in mental health.

36.3. CLINICAL TRIALS NETWORKS AS PLATFORMS FOR DELIVERING BETTER TRIALS: THE AUSTRALIAN EARLY PSYCHOSIS COLLABORATIVE CONSORTIUM

Stephen Wood*¹, Patrick McGorry², Michael Berk³, Sue Cotton², Eóin Killackey², Barnaby Nelson², Alison Yung³, G Paul Amminger², Brian O'Donoghue⁴, Aswin Ratheesh², Mario Alvarez-Jimenez², Deborah Rickwood⁵, Andrew Thompson²

¹University of Melbourne, ²Orygen; The University of Melbourne, ³Deakin University,

⁴University College Dublin, ⁵Headspace

Background: Although early intervention services for psychosis now have Cochrane level 1 evidence for their effectiveness for many outcomes, real-world outcomes at a population level such as quality of life, cognitive and physical health impairments, and social and occupational disability for many young people could be improved. Trialling new interventions in early psychosis populations can be challenging because of the large number of young people required for eligibility screening to secure suitable study-specific clinical trial participation, especially for important sub-groups such as those with delayed recovery. There are similar challenges in the area of indicated prevention for psychosis and the Ultra High Risk paradigm which has also developed rapidly over the last few decades. Whilst profiling risk and new treatments have

emerged, no first line treatment has been firmly established and larger trials and co-ordinated monitoring of outcomes are needed to further progress the field.

Methods: One option to significantly enhance the depth, breadth, and quality of the evidence base is through a Clinical Trials Network (CTN). CTNs bring together clinicians, primary healthcare, and research professionals to design and conduct clinical trials that provide high-level evidence about which treatments work and are most cost-effective in clinical practice and other real-world practice settings. CTNs provide access to multiple health service centres, a myriad of healthcare practitioners and academic professionals, and thousands of participants/patients. In addition, through the establishment of standard training, processes and research operational documents, CTNs reduce the variation between health services, clinical trials sites, and jurisdictional requirements while streamlining budget and governance negotiations in order to shorten start up times and reduce duplication of resource effort.

Results: In Australia we have set up a CTN for early psychosis as part of the Australian Early Psychosis Collaborative Consortium (AEPCC). Australia is already a world leader in the design and conduct of high impact clinical trials across the investigator-initiated and commercial sectors, a reputation which is built on a strong, collaborative foundation of CTNs. We particularly wanted our CTN to have a strong translational role and therefore have intentionally labelled ourselves as a Clinical Trials and Translation Network (CTTN), and have adopted a “Facilitating Network” organisational model in which the network facilitates the set-up, national reach and delivery of clinical trials but does not conduct them.

Conclusions: CTNs can provide leadership for world-class, large, and cost-effective multicentre trials answering the key clinical research questions relevant to schizophrenia. They can optimise value for research investment by ensuring the most important questions are prioritised and also develop ‘living’ systematic reviews and guidelines, implement and evaluate uptake of Clinical Care Standards and facilitate closer collaboration with our stakeholders, to ensure evidence is more rapidly taken up into practice, policy and education curricula. Through training and mentoring of clinicians and researchers at all career stages they can also enable the next generation to continue this work.

36.4. PRECLINICAL STUDIES OF STANDARD AND NOVEL TARGET ANTIPSYCHOTIC DRUGS IN ANIMAL MODELS OF SCHIZOPHRENIA: INSIGHTS INTO WHY CLINICAL TRIALS MAY HAVE FAILED TO RECAPITULATE PRECLINICAL FINDINGS

Anthony Grace^{*1}, Daniela Uliana¹, Susan Sonnenschein¹

¹*University of Pittsburgh*

Background: Accumulating evidence suggests that the DA system is not the primary driver of pathology in schizophrenia. Instead, substantial research has focused on hippocampal dysregulation driving the DA dysfunction underlying psychosis and contributing to cognitive and negative symptoms. However, several agents that target normalization of the hippocampal circuit, while showing promise in preclinical studies and in early clinical trials, have failed in large multicenter studies. However, we posit that classic clinical trial design may not be effective at evaluating novel target agents. Indeed, we found that pomaglumetad was highly effective in developmental disruption and prepubertal stress models of schizophrenia in its ability to normalize hippocampal function and reverse the hyperdopaminergic state, but despite showing early promise in initial trials, this drug also failed in large clinical trials. Based on evidence presented here we posit that prior treatment of patients with D2 antagonist antipsychotic drugs, by inducing D2 supersensitivity, obscured the potential therapeutic actions

of these novel compounds. We then examined if there was a way in which we can circumvent the confound of prior drug administration when testing the actions of novel target compounds.

Methods: Pregnant Sprague Dawley rats were administered with MAM (20mg/kg) at gestational day 17 and the male offspring were tested as adults. We tested the effects of acute and repeated (3 weeks) treatment with pomaglumetad or a novel GABA A alpha 5 positive allosteric modulator (PAM) on DA and hippocampal neuron activity. In another cohort of rats, we examined the impact of aripiprazole vs olanzapine on DA neuron activity. DA neuron population activity was assessed by making 9 electrode tracks through the ventral tegmentum and assessing number of DA neurons active, firing rate and pattern.

Results: We found that MAM-treated offspring showed increased activity in the limbic ventral hippocampus and an increase in the number of DA neurons spontaneously active, consistent with studies in schizophrenia patients. Acute administration of the GABA A alpha 5 PAMs (2 types) consistently reversed hippocampal hyperactivity and normalized DA neuron firing as well as amphetamine hyperlocomotion in the MAM model. However, after pretreatment of MAM rats with haloperidol for 3 weeks and 1 week withdrawal, this compound was no longer effective at reversing DA dysfunction, which we propose is due to D2 supersensitivity. Pomaglumetad was also effective in normalizing DA neuron function and hippocampal hyperactivity via a direct action within the hippocampus. In another study, animals that were treated with olanzapine for 3-4 weeks were found to exhibit an induction of DA neuron depolarization block; we posit that this inactivation of DA neuron firing drove the induction of DA supersensitivity. In contrast, when we administered aripiprazole, a D2 partial agonist, either acutely or for 3-4 weeks, there was an inhibition of DA neuron firing in the MAM model; however, this was not accompanied by depolarization block, but instead appears to be due to a direct DA agonist inhibition of DA neuron activity.

Conclusions: These data support the hypothesis that prior administration of a D2 antagonist drug and a short withdrawal period interfered with the actions of novel target compounds by confounding D2 supersensitivity. While withdrawing patients from antipsychotic drugs for a sufficient period to normalize D2 receptors, which may require months, is not ethically feasible, our data suggest that transitioning patients from an effective compound that does not induce supersensitivity, such as aripiprazole, may be a more effective strategy. Alternately, while it is not ethically feasible to withdraw patients from an antipsychotic drug for extended periods, it is known that a large number of patients are not compliant with their current medication. If we can test novel compounds either on demonstrably noncompliant patients or patients early in their treatment, we may have a more effective strategy for testing the efficacy of these compounds in the treatment of schizophrenia.

37. PREVENTION AND PREDICTION IN PSYCHOSIS; FROM IMAGING TO ETHICS WITH PROTEINS, SOCIAL FACTORS AND METABOLISM ON THE JOURNEY

David Cotter, *Royal College of Surgeons in Ireland*

Overall Symposia Abstract: In psychosis, as in medicine, we aim to treat better by treating early. If tools become available to allow the prediction of psychotic disorders, then primary prevention could be facilitated, or the trajectory of illness diverted. However, prediction is imperfect and the gains from early treatments must outweigh the risks at both population and individual levels. Ethical issues come to the fore here, and perhaps these issues need to be reconsidered before we proceed too far down the road of prevention. This symposium aims to do just that.

First, Sophia Frangou will focus on the prediction of symptoms and diagnosis using normative models of brain morphometry. Using cortical and subcortical regional brain imaging data from over 37,000 healthy individuals, the model parameters were applied to the regional morphometric data of individuals at clinical high-risk for psychosis, and individuals at the early stages of psychosis from the Human Connectome Project – Early Psychosis. The study found that the distribution of the normative regional morphometric measures from Individuals in the HCP-EP and CHR-P groups overlapped nearly completely with that of the healthy individuals. These findings challenge the usefulness of macroscale morphometric measures as predictive biomarkers of psychosis. Jonah Byrne will present the performance of an a priori-specified proteomic prediction model of transition from clinical high-risk to psychotic disorder. In the largest study of its kind to date, plasma samples were collected from participants in three CHR cohorts: the North American Prodrome Longitudinal Studies 2 and 3, and the NEURAPRO randomized control trial (total n=754). This study did not confirm the findings from a previous protein-based prediction model of transition from CHR to psychosis, although certain complement proteins may be weakly associated with transition at a group level. Benjamin Perry focuses on cardiometabolic dysfunction in young people with psychotic disorders across the globe as the most important contributor to a shortened life expectancy of 15-20 years. The Psychosis Metabolic Risk Calculator (PsyMetRiC) has been externally validated in the UK and internationally. Here Benjamin Perry will detail consistent evidence that PsyMetRiC maintains its predictive performance and potential for clinical usefulness across borders. Tecelli Dominguez will present an investigation into psychosocial factors associated with the risk of developing psychosis in a Mexican general population. Overall, the findings highlight a distinction between psychosocial contributors to psychosis vulnerability in different sociocultural contexts, which will contribute to better context-targeted preventive intervention efforts. Finally, Natalie Lane as discussant will overview the presentations and bring an overarching ethical perspective to this area of prevention and prediction in psychosis.

37.1. PREDICTING SYMPTOMS AND DIAGNOSIS USING NORMATIVE MODELS OF BRAIN MORPHOMETRY

Sophia Frangou*¹

¹*Icahn School of Medicine at Mount Sinai*

Background: The lack of robust neuroanatomical predictors of psychosis has been traditionally attributed to heterogeneity. Here we tested the alternative hypothesis that the neuroanatomical measures in the majority of individuals with psychosis or at psychosis risk are not discriminative as they are nested within the normal variation.

Methods: We created CentileBrain an empirically validated framework for the normative modeling of FreeSurfer-derived cortical and subcortical regional morphometric measures from an international, pooled sample of 37,437 healthy individuals through our collaboration with the ENIGMA Lifespan Working Group. The model parameters are freely available at <https://centilebrain.org/>. The model parameters were applied to the regional morphometric data of individuals at clinical-high-risk for psychosis (CHR-P; N= 1,340) from the ENIGMA CHR-P Working Group and individuals at the early stages of psychosis from the Human Connectome Project – Early Psychosis Study (HCP-EP; N=

For each morphometric measure, the normative deviation z-scores were used to define supranormal (z GREATER THAN 1.96) and infranormal ((z LESS THAN -1.96) values.

Results: The distribution of the normative regional morphometric measures from Individuals in the HCP-EP and CHR-P groups overlapped nearly completely with that of the healthy individuals. The proportion of individuals in the HCP-EP and CHR-P groups with infranormal or supranormal values in any regional measure was low (LESS THAN 12%) and similar to that of healthy individuals. CHR-P converters versus CHR-P non-converters had a higher percentage of infranormal values in temporal regions (5–7% vs 0.9–1.4%). Neither observed nor normative morphometric measures distinguished cases (CHR-P or HCP-EP) from controls. In both groups, normative deviation scores explained a trivial amount of variance in psychotic symptoms and general cognitive ability

Conclusions: These findings challenge the usefulness of macroscale morphometric measures as predictive biomarkers of psychosis.

37.2. PROTEOMIC BIOMARKERS FOR THE PREDICTION OF TRANSITION TO PSYCHOSIS IN INDIVIDUALS AT CLINICAL HIGH RISK - A MULTI-COHORT MODEL DEVELOPMENT STUDY

Jonah Byrne^{*1}, Colm Healy², Melanie Föcking², Subash Raj Susai², David Mongan³, Kieran Wynne⁴, Eleftheria Kodosaki⁵, Meike Heurich⁵, Lieuwe de Haan⁶, Ian Hickie⁷, Stefan Smesny⁸, Andrew Thompson⁹, Connie Markulev⁹, Alison Ruth Yung¹⁰, Miriam Schaefer⁹, Anita Riecher-Rössler¹¹, Nilufar Mossaheb¹², Gregor Berger¹³, Monika Schlögelhofer¹⁴, Merete Nordentoft¹⁵, Eric YH Chen¹⁶, Swapna Verma¹⁷, Dorien H. Nieman⁶, Scott Woods¹⁸, Barbara Cornblatt¹⁹, William Stone²⁰, Daniel Mathalon²¹, Carrie Bearden²², Kristin Cadenhead²³, Jean Addington²⁴, Elaine Walker²⁵, Tyrone D. Cannon¹⁸, Mary Cannon², Patrick McGorry⁹, Paul Amminger⁹, Gerard Cagney⁴, Barnaby Nelson⁹, Clark Jeffries²⁶, Diana Perkins²⁶, David Cotter²

¹Royal College of Surgeons in Ireland, ²RCSI University of Medicine and Health Sciences, ³Queen's University Belfast, ⁴Proteome Research Centre, University College Dublin, ⁵Cardiff University, ⁶Academic Medical Center, University of Amsterdam, ⁷Brain and Mind Centre, University of Sydney, ⁸University Hospital Jena, ⁹Orygen, The National Centre of Excellence in Youth Mental Health, ¹⁰University of Manchester, ¹¹University of Basel, ¹²Medical University of Vienna, ¹³University of Zurich, ¹⁴BioPsyC, ¹⁵University of Copenhagen, ¹⁶The University of Hong Kong, ¹⁷Institute of Mental Health, Singapore, ¹⁸Yale University, ¹⁹Zucker Hillside Hospital, ²⁰Harvard Medical School/Beth Israel Deaconess Medical Center, ²¹University of California, San Francisco, ²²University of California, Los Angeles, ²³University of California, San Diego, ²⁴University of Calgary, ²⁵Emory University, ²⁶University of North Carolina at Chapel Hill

Background: Psychosis risk prediction is one of the leading challenges in psychiatry. Previous investigations have suggested that plasma proteomic data may be useful in accurately predicting transition to psychosis in individuals at clinical high risk (CHR). We hypothesized that an a priori-specified proteomic prediction model would have strong predictive accuracy for psychosis risk and aimed to replicate longitudinal associations between plasma proteins and transition to psychosis.

Methods: Plasma samples were collected from participants in three CHR cohorts: the North American Prodrome Longitudinal Studies 2 and 3, and the NEURAPRO randomised control trial (total n=754). Plasma proteomic data were quantified using mass spectrometry. The

primary outcome was transition to psychosis over the study follow-up period. Logistic regression models were internally validated, and optimism-corrected performance metrics derived with a bootstrap procedure.

Results: In the overall sample of CHR participants (age: 18.5, SD: 3.9; 51.9% male), 20.4% (n=154) developed psychosis within 4.4 years. The a priori-specified model showed poor risk-prediction accuracy for the development of psychosis (C-statistic: 0.51 [95% CI: 0.50, 0.59], calibration slope: 0.45). At a group level, Complement C8B, C4B, C5 and leucine-rich α -2 glycoprotein 1 (LRG1) were associated with transition to psychosis but did not survive correction for multiple comparisons.

Conclusions: This study did not confirm the findings from a previous protein-based prediction model of transition from CHR to psychosis. Certain complement proteins may be weakly associated with transition at a group level. Previous findings, derived from small samples, should be interpreted with caution.

37.3. THE PSYCHOSIS METABOLIC RISK CALCULATOR (PSYMETRIC): VALIDATION & REFINEMENT ACROSS CONTINENTS

Benjamin Perry^{*1}, Emanuele Osimo², Graham Murray¹, Rachel Upthegrove³

¹University of Cambridge, ²Imperial College London, ³University of Cambridge, ³University of Birmingham

Background: Cardiometabolic dysfunction is common in young people with psychotic disorders across the globe, and is the most important contributor to a shortened life expectancy of 15-20 years in people with psychotic disorders. Recently, the Psychosis Metabolic Risk Calculator (PsyMetRiC) was developed and externally validated in the UK, predicting up-to six-year risk of metabolic syndrome (MetS) from routinely collected data. However, clinical risk prediction algorithms can only be confirmed to be suitable for populations they have been tested in, and international populations are likely to vary in ethnicity; culture and dietary habits; average population health, healthcare access; social norms, behaviours and attitudes, and legislation.

Methods: In order to bring PsyMetRiC closer to a globally-useful tool for clinicians and researchers, we performed detailed external validation analysis of PsyMetRiC in multiple continents including Europe (Spain, Switzerland, Finland); North America (Quebec); East Asia (Hong Kong); and Australasia (Sydney). In each sample, predictive performance was assessed using measures of discrimination (C-statistic); calibration (calibration plots), and clinical usefulness (decision curve analysis), as recommended. Furthermore, we considered site-specific recalibration of the intercept and slope terms (i.e., logistic calibration) to tune PsyMetRiC to the individual populations.

Results: Analyses are ongoing and will be finalised prior to the Congress. However, in summary, we have found consistent evidence that PsyMetRiC maintains its predictive performance and potential clinical usefulness across borders. In each international setting, as expected due to population differences we found differing degrees of miscalibration. However, this was fully corrected following site-specific recalibration.

Conclusions: PsyMetRiC has the potential to be generalisable for use across international borders. Our findings can pave the way toward a future globally-useful bedside tool to encourage personalized treatment decisions with the aim of improving the long-term physical health of young people with psychotic disorders.

37.4. PSYCHOSOCIAL FACTORS ASSOCIATED WITH THE RISK OF DEVELOPING PSYCHOSIS IN A MEXICAN GENERAL POPULATION SAMPLE

Tecelli Dominguez*¹, Tamara Sheinbaum², Ana Fresán², Lourdes Nieto², Rebeca Robles², Steven R López³, César Celada², Mauricio Rosel², Ricardo Saracco², Neus Barrantes Vidal⁴

¹*Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"*, ²*National Institute of Psychiatry*, ³*University of Southern California*, ⁴*Universitat Autònoma de Barcelona, Spain*

Background: Epidemiological evidence has linked an array of sociodemographic and psychosocial factors with an increased risk of developing psychosis. However, there is a lack of research on samples from low- and middle-income countries, where early psychosis programs are still scarce. This study used a Mexican sample to explore (i) sociodemographic and psychosocial differences between individuals with and without a positive screen for Clinical High-Risk for psychosis (CHR), and (ii) sociodemographic and psychosocial factors associated with screening positive for CHR.

Methods: The sample consisted of 1519 individuals from the general population who completed an online survey. Of the participants, 18.8% (n = 286) met the CHR screening criteria. Participants were assigned to the CHR-positive group if they met the established cut-offs on both the Prodromal Questionnaire (PQ-B: GREATER THAN 6 item rated as positive and distress score ≥ 29) and Social Functioning Questionnaire (SFQ: score ≥ 10).

Results: Comparisons between those who screened positive (CHR-positive group) and those who did not (non-CHR group) showed that participants in the CHR-positive group were younger ($t=2.9$; $p=0.003$), had a lower educational level ($\chi^2=36.7$, p LESS THAN 0.001), and reported more mental health problems than the non-CHR group ($\chi^2=59.9$, p LESS THAN 0.001). In the Non-CHR group, there were more participants with a partner ($\chi^2=9.6$, $p=0.05$) and of upper-middle class ($\chi^2=11.0$, $p=0.004$) than in the CHR group ($\chi^2=11.0$, $p=0.004$). Furthermore, relative to the non-CHR group, the CHR-positive group had a greater prevalence of medium/high risk associated with cannabis use, a higher prevalence of adverse experiences (i.e. bullying, intimate partner violence, and experiencing a violent or unexpected death of a relative or friend), as well as higher levels of childhood maltreatment, poorer family functioning, and more distress associated with the COVID-19 pandemic. Finally, when examined in multivariate analyses, the variables associated with screening positive for CHR were: having an unhealthy family functioning (OR=2,75; IC 95%: 1,87-4,04; p LESS THAN 0.001), a higher risk associated with cannabis use (OR=2,45; IC 95%: 1,70-3,54; p LESS THAN 0.001), a lower level of education (OR=1,90; IC 95%: 1,42-2,55; p LESS THAN 0.001), having experienced a violent or unexpected death of a relative or friend (OR=1,36, IC 95%: 1,01-1,82; p LESS THAN 0.05), higher levels of childhood emotional abuse (OR= 2,25, IC 95%: 1,52-3,34; p LESS THAN 0.001), physical neglect (OR=1,53, IC 95%: 1,11-2,08; p LESS THAN 0.01), and physical abuse (OR=1,40, IC 95%: 1,03-1,92; p LESS THAN 0.05), bullying (OR=1,40, IC 95%: 1,02-1,93; p LESS THAN 0.05), and higher COVID-related distress (OR=1,13, IC 95%: 1,07-1,20).

Conclusions: Overall, the findings highlight the importance of examining potential psychosocial contributors to psychosis vulnerability across different sociocultural contexts to delineate risk and protective processes relevant to specific populations and better target preventive intervention efforts.

38. DOPAMINERGIC IMPAIRMENT IN SCHIZOPHRENIA: FROM MECHANISMS TO NEW THERAPEUTIC TARGETS

Dragos Inta, *University of Fribourg*

Overall Symposia Abstract: Converging evidence implicate dopaminergic impairment in the pathophysiology of schizophrenia (SCZ). However, both the underlying pathogenic mechanisms and the superior therapeutic action of several atypical antipsychotics related to dopamine are not yet understood, hampering the development of more efficient therapies. We aim to discuss new aspects of molecular and cellular factors associated with dopaminergic dysfunction in SCZ, including innovative models and technologies, such as the Monocyte-Derived-Neuronal-like cells (MDNCs) or PharmacoSTORM.

Dr. Bellon will present data about neurostructural effects of dopamine in MDNCs in SCZ. Excessive pruning is considered the cause of the most consistent finding in SCZ, namely decreased brain volume. However, obtaining developing neurons from living patients is not feasible. He used a new protocol to transdifferentiate human circulating monocytes into neuronal-like cells, MDNCs that structurally resemble developing human neurons, as model to study the effect of dopamine on pruning of neuronal extension. His results indicate that MDNCs from patients grow more extensively and prune more primary neurites when exposed to dopamine than that of controls.

Dr. Inta will talk about the development and role of the Islands of Calleja (ICj), a largely understudied new site of adult neurogenesis in the ventral striatum, expressing highest levels of dopamine D3 receptors (D3R) in the brain. Recent dating studies showed robust adult neurogenesis in the human striatum. He will present data about the occurrence of this process in rodents and primates and the ICj as preferential target for antipsychotics effective also against negative symptoms of SCZ (clozapine, cariprazine, xanomeline and emraclidine).

Dr. Prokop will present data obtained by using PharmacoSTORM, a novel fluorescent-ligand based framework that unifies advanced pharmacology and super-resolution anatomical studies and allows the exact receptor binding profile of drugs at nanoscale. She demonstrated that the majority of fluorescent cariprazine molecules bind to D3R in the ICj in the mouse brain. Moreover, her three-dimensional reconstruction of high-affinity drug binding sites unveiled that the ICj represent an unexpectedly large continuous network of granule cells. She further showed that they are densely innervated by dopaminergic fibers and that D3R are localized mostly extrasynaptically, suggesting that D3R play a key role in dopaminergic volume transmission.

Dr. Papaleo will present results regarding the astrocytic regulation of basal ganglia dopamine-dependent behaviors with relevance for SCZ. Astrocytic involvement in sensory processing and its role in SCZ are unknown. He will show data on the consequences of the disruption of the SCZ-associated dysbindin Dys1A, the only isoform expressed by astrocytes on motivation and sensorimotor gating deficits, as well as astrocytic dopamine D2 receptors and dopaminergic tone within basal ganglia. His results reveal the role of astrocytes in motivational and sensory processes through Dys1A/dopamine-dependent mechanisms within the basal ganglia, suggesting them as therapeutic target in SCZ.

38.1. INCREASED PRUNING IN RESPONSE TO DOPAMINE IN NEURONAL-LIKE CELLS FROM PATIENTS WITH SCHIZOPHRENIA

Alfredo Bellon*¹

¹*Penn State Hershey Medical Center*

Background: Dopamine, a neurotransmitter consistently associated with the pathophysiology of schizophrenia (SCZ), participates in several aspects of brain development including pruning of neuronal extensions. Excessive pruning is considered a plausible etiological factor of decrease brain volume in SCZ. Therefore, we hypothesize that patients with SCZ carry an increased susceptibility to dopamine's pruning effects and that this susceptibility would be more obvious in the early stages of neuronal development when dopamine pruning effects are more prominent.

Methods: Since obtaining developing neurons from living patients is not feasible, we used Monocyte-Derived-Neuronal-like Cells (MDNCs). These cells are obtained from a standard blood sample and can be generated in only 20 days. The characterization of MDNCs involved electrophysiology, flow cytometry, immunofluorescence, qPCR, single cell mRNA sequencing as well as other techniques including comparing its structure to that of human developing neurons (HDNs) in vitro. We have tested the reproducibility of MDNCs in two separate studies. We have tested our transdifferentiation protocol in over 100 individuals including males and females.

Results: MDNCs respond similar to HDNs when exposed to colchicine, an agent that elicits pruning of neuronal extensions. We then studied MDNCs from 12 controls and 13 patients with SCZ and we found that patients' MDNCs differentiate more efficiently, extend longer secondary neurites and grow more primary neurites. Moreover, MDNCs from medicated patients expresses less dopamine 1 receptor (D1R) and prune more primary neurites when exposed to dopamine. D1R participates in pruning of primary neurites in MDNCs. Haloperidol did not influence our results but the role of other antipsychotics could not be excluded and is currently under investigation.

Conclusions: MDNCs mimic the structure of HDN in vitro. MDNCs also reproduce the pruning of neuronal extensions found in HDN when exposed to colchicine. In addition, patients with SCZ show structural differences in MDNCs when compared to cells from controls, while a subpopulation of patients evidence increased pruning in response to dopamine.

38.2. ISLANDS OF CALLEJA: THE HIDDEN NEUROANATOMICAL SUBSTRATE IN THE MECHANISM OF CARIPRAZINE

Susanne Prokop^{*1}, Péter Ábrányi-Balogh², Benjámín Barti¹, Miklós Zöldi¹, Márton Vámosi³, Barna Dudok⁴, Gabriella Urbán³, László Barna³, Attila Egyed², Hui Deng⁵, Gian Marco Leggio⁶, András D. Tóth⁷, Mario van der Stelt⁸, László Hunyady⁷, György M. Keserű², István Katona³

¹*Institute of Experimental Medicine*, ²*Research Centre for Natural Sciences*, ⁴*Stanford University*, ⁵*Leiden University and Oncode Institute*, ⁶*University of Catania*, ⁷*Semmelweis University*, ⁸*Leiden University and Oncode Institute*,

Background: A comprehensive understanding of the mechanisms of existing clinical compounds is crucial to enhance the efficacy and minimize the side effects of future neuropsychiatric treatments. While in vitro pharmacological assays can provide the exact receptor binding profile of drugs, it is increasingly acknowledged that the same drug-target interaction can differently modulate complex neuronal networks in the brain, depending on its cell-type and subcellular compartment-specific localization. On the other hand, a significant gap exists in the availability of techniques capable of visualizing cell-type specific drug-target interactions within complex tissue specimens.

Methods: We've addressed this gap with the development of PharmacoSTORM, a novel fluorescent-ligand based framework that unifies advanced pharmacology and super-resolution anatomical studies. Our innovation is supported by robust computational drug design and

refined chemical methodologies, enabling the development of fluorescent analogues of drugs for multiscale anatomical studies, including Stochastic Optical Reconstruction Microscopy (STORM) super-resolution imaging.

Results: We presented our workflow by the investigation of cariprazine, a rapidly emerging new medication (Vraylar™/Reagila™). Cariprazine displays unique efficacy against the negative symptoms of schizophrenia and is approved for acute manic/mixed, or depressive episodes associated with bipolar I disorder. However, the neuroanatomical substance that mediates its unique therapeutic effectiveness remains elusive. We demonstrated that the majority of fluorescent cariprazine molecules bind to a largely understudied subregion of the ventral striatum, the Islands of Calleja (IoC) in the mouse brain. Moreover, our three-dimensional reconstruction of high-affinity drug binding sites unveiled that the IoC represents an unexpectedly large continuous network of granule cells. Cell-type specific nanoscale PharmacostORM imaging revealed that fluorescent cariprazine molecules bind D3 dopamine receptors (D3Rs) on the axons of granule cells, which represent the principal cell-type of this enigmatic brain region. We further showed that the IoC is densely innervated by dopaminergic fibers and found that D3Rs localized mostly extrasynaptically, suggesting that these receptors play a key role in dopaminergic volume transmission. Additionally, we demonstrated that the nanoscale binding sites of fluorescent compound in the IoC represent real in vivo targets of the original, unlabeled antipsychotic, cariprazine.

Conclusions: Our results highlight the potential importance of IoC granule cells in neuropsychiatric diseases and their enormous potential as future pharmacological targets.

38.3. POSTNATAL NEUROGENESIS IN THE STRIATUM: LINKING NEURODEVELOPMENTAL TO DOPAMINERGIC DYSFUNCTION IN SCHIZOPHRENIA WITH FOCUS ON THE ISLANDS OF CALLEJA

Dragos Inta*¹

¹*University of Fribourg*

Background: For long time, the hippocampal dentate gyrus was the only brain region in which adult neurogenesis had been demonstrated in humans. This situation recently changed due to radiocarbon-14 dating that provided evidence for robust neurogenesis of specific, mostly calretinin (CR)-positive GABAergic interneurons in the adult human striatum. Similar adult-generated interneurons were described as well in the striatum of other species; however, the main focus of research continues to be on adult neurogenesis in the olfactory bulb, which is most likely absent or occurring at very low level in the human brain. The extent and the significance of this process for neuropsychiatric disorders are still unknown.

Methods: Fate-mapping studies in wildtype mice and rats and transgenic 5-HT3-EGFP and D3-EGFP mice that allow the in vivo labelling of newborn neurons migrating from the subventricular zone (SVZ) into the striatum under physiological conditions and following treatment with antipsychotics or electroconvulsive seizure (ECS)

Results: At postnatal stages many SVZ neuroblasts migrate from the SVZ into subcortical areas, nucleus accumbens and ventral striatum. Postnatally-generated neurons belong to two classes of small-size GABAergic interneurons: CR-positive interneurons and CR-negative granule cells forming the Islands of Calleja (ICj). The ICj receive dense dopaminergic projections from the ventral tegmental area and substantia nigra, expressing high levels of dopamine D3 receptors. Moreover, they are preferentially targeted by efficient antipsychotics like clozapine, cariprazine and xanomelin/emraclidine. ECS massively stimulates neurogenesis in the SVZ and striatum resulting in similar newborn CR-positive interneurons. Most ECS-

triggered newborn interneurons were found in the medial striatum, which is part of the limbic circuitry, with afferents from the medial prefrontal and cingulate cortices.

Conclusions: The striatum represents a main, yet poorly investigated area of postnatal neurogenesis in the mammalian brain, the ICj a possible link between ongoing abnormal neurogenesis and striatal dopaminergic dysfunction. Rodents appear to represent a valid model for investigating postnatal/adult striatal neurogenesis, showing similar neuronal subtypes. ECS strongly stimulates neurogenesis in the adult striatum. The implications for striatal neuroplasticity and the dopamine system, as well as for schizophrenia are discussed.

38.4. ASTROCYTIC MODULATION OF DOPAMINE AND BASAL GANGLIA DEPENDENT BEHAVIORS RELEVANT TO SCHIZOPHRENIA

Francesco Papaleo*¹, Zisis Bimpisidis²

¹*Istituto Italiano Di Tecnologia*, ²*Istituto Italiano di Tecnologia*

Background: The mechanisms underlying the dichotomic cortical/basal ganglia dopaminergic abnormalities in schizophrenia are unclear. Astrocytes are important non-neuronal modulators of brain circuits, but their role in dopaminergic system remains poorly explored.

Methods: Microarray analyses, immunohistochemistry, fiber photometry, optogenetics, two-photon laser scanning microscopy, in vivo recordings and manipulations in mice.

Results: We revealed that Dys1 hypofunction increases the reactivity of astrocytes, which express only the Dys1A isoform. Notably, behavioral and electrochemical assessments in mice selectively lacking the Dys1A isoform unraveled a more prominent impact of Dys1A in behavioral and dopaminergic/D2 alterations related to basal ganglia, but not cortical functioning. Ex vivo electron microscopy and protein expression analyses indicated that selective Dys1A disruption might alter intra-cellular trafficking in astrocytes, but not in neurons. In agreement, Dys1A disruption only in astrocytes resulted in decreased motivation and sensorimotor gating deficits, increased astrocytic dopamine D2 receptors and decreased dopaminergic tone within basal ganglia. These processes might have clinical relevance because the caudate, but not the cortex, of patients with schizophrenia shows a reduction of the Dys1A isoform.

Conclusions: we started to show a hitherto unknown role for the Dys1A isoform in astrocytic-related modulation of basal ganglia behavioral and dopaminergic phenotypes, with relevance to schizophrenia.

39. RETHINKING RELAPSE: PREVENTION AND PREDICTION

Rob McCutcheon, *University of Oxford*

Overall Symposia Abstract: Most individuals with a psychotic disorder will experience a relapse and this is linked to poorer long-term outcomes. Relapse is associated with the discontinuation of antipsychotic medication, but many individuals with psychotic disorders would like to reduce or discontinue medication. To improve clinical outcomes we need to know how to minimise risk of relapse when reducing antipsychotic medication, and how to predict which individuals are likely to relapse. The current symposium will provide an overview of current research addressing these crucial issues.

Dr Hui will present results from a one year prospective follow up study demonstrating the ability of cognitive measures to predict relapse. Dr McCutcheon will present analyses of individual patient data from 5 relapse prevention clinical trials, investigating whether absolute receptor occupancy and rate of occupancy reduction are associated with the timing of relapse.

Dr Rubio will describe how both neuroimaging and clinical data may predict both breakthrough psychosis and relapse following antipsychotic discontinuation. Dr Brand will discuss how risk of relapse changes over the menopause and how hormone replacement therapy may reduce relapse risk. Prof Murray will act as discussant to synthesise these findings and consider what the next steps for the field are.

39.1. COGNITIVE DETERIORATION IN PREDICTING RELAPSE IN PSYCHOTIC DISORDERS

Christy Hui¹, Tiffany Junchen Tao¹, Yi Nam Suen¹, Edwin Ho Ming Lee¹, Sherry Kit Wa Chan¹, Wing Chung Chang¹, Eric Yu Hai Chen¹, Eric YH Chen^{*2}

¹The University of Hong Kong, ²Nanyang Technical University LKC School of Medicine

Background: Relapse is common after the first episode of psychosis and can have potentially irreversible consequences, yet it is poorly understood and difficult to predict. Examining changes in cognitive function preceding relapse may be useful in enriching our understanding towards the underlying mechanism of psychotic relapse. It is hypothesized that relapse in fully remitted psychosis patients was preceded by working memory deterioration.

Methods: This was a prospective 1-year follow-up study of 110 psychosis patients in full clinical remission. The primary outcome of relapse (recurrence of positive symptoms of psychosis), visual (Visual Patterns Test) and verbal (Letter-Number Span Test) working memory were assessed monthly. Other clinical, functioning and psychosocial predictors were also examined at baseline.

Results: The 1-year relapse rate was 16% (18 of 110). Multiple logistic regression analyses showed that relapse was predicted by verbal working memory deterioration 2 months prior to relapse ($p = 0.029$), worse medication adherence ($p = 0.018$), and poor resilience ($p = 0.014$). The model explained about 60% of the variance in the relapse outcome (Nagelkerke $R^2 = 0.582$).

Conclusions: Our finding in cognitive deterioration as an early sign of relapse echoes the previous literature that cognitive deficits are present even during the prodromal phase of the disorders, as well as associated with the conversion to full-blown psychosis. These testable and objective markers in cognitive function provide valuable information to inform timely intervention in relapse prevention.

39.2. DOES SLOW AND STEADY WIN THE RACE? ANTIPSYCHOTIC DISCONTINUATION AND PSYCHOTIC RELAPSE

Rob McCutcheon^{*1}, David Taylor², Jose Rubio³, Joseph Nour⁴, Robin Murray⁵, Sameer Jauhar⁵

¹University of Oxford, ²Maudsley Hospital, Denmark Hill, London and Institute of Pharmaceutical Science, King's College London, ³Northwell Health, ⁴East London NHS Foundation Trust, ⁵Institute of Psychiatry, King's College

Background: Antipsychotics are recommended for prevention of relapse in schizophrenia. It is unclear whether increased risk of relapse following antipsychotic discontinuation is predominantly associated with absolute magnitude of dose reduction or rate of antipsychotic reduction. Establishing the responsible mechanism is important, as prolonged withdrawal schedules have been suggested to reduce risk of relapse.

Methods: Individual patient data from antipsychotic discontinuation studies were obtained. We estimated occupancy of receptors over time using half-lives and ED50 values obtained from pharmacokinetic and receptor occupancy studies. Hazard ratios for relapse events were calculated using cox proportional hazards models to assess the influence of formulation (oral, 1-monthly, and 3-monthly injection). The change in hazard ratio over time was estimated, and the effect of time varying covariates was calculated including rate of occupancy reduction and absolute receptor occupancy.

Results: 5 studies including 1,388 participants with schizophrenia were identified (k=2: oral, k=2: 1-monthly injection, k=1: 3-monthly injection). Withdrawal of long-acting injectable medication did not lead to a lower hazard ratio compared to withdrawal of oral medication and this included the period immediately following randomisation. Hazard ratios were not associated with the rate of decline of receptor occupancy however they were associated with reduced absolute occupancy in trials of long-acting injections (p=0.038).

Conclusions: Antipsychotic discontinuation is associated with an increased risk of psychotic relapse, related to receptor occupancy. While relapse does not appear to be related to the rate of discontinuation, gradual discontinuation strategies may allow for easier antipsychotic reinstatement in case of symptomatic worsening.

39.3. INDIVIDUAL ESTIMATION OF RELAPSE RISK IN INDIVIDUALS WITH SCHIZOPHRENIA

Jose Rubio*¹

¹*Northwell Health*

Background: Over 80% of individuals with schizophrenia will have multiple episodes of acute psychosis over their lifetime. Relapses may have irreversible consequences, such as decreasing responsiveness to antipsychotic drugs, and may be dangerous to self/others. Most often relapses occur in the context of treatment interruption, however some individuals will still relapse despite ongoing relapse-prevention treatment. Whether relapses occur after treatment interruption or despite treatment exposure has important therapeutic and neurobiological consequences, but this distinction is often uncertain since non-adherence is common but difficult to predict. To study the neurobiology of relapse without the confounding of non-adherence, we work with individuals who are treated with long-acting injectable (LAI) antipsychotics, for whom adherence at the time of relapse can be easily confirmed.

Methods: We scanned individuals with a psychotic disorder who had been treated with a LAI for at least 3 months. The fMRI scan consisted in 2 runs of 594 volumes each at TR=0.72, amounting to approximately 15 minutes of resting state. We used the resting state scan to calculate individual Striatal Connectivity Indices, a biomarker that summarizes functional connections of the striatum associated with treatment response. In validation studies, lower SCI scores have been correlated with treatment responsiveness. After the baseline scans, individuals were followed up monthly for up to 1 year (or until dropout or LAI discontinuation), assessing symptom severity measured with BPRS, and whether relapse criteria (psychosis BPRS subscore worsening GREATER THAN 25% since baseline and CGI-I GREATER THAN =6) were met. Participants who relapsed were scanned again at that time, and non-relapsing participants matched for sex, age and duration since baseline scan were scanned as well as a control condition. Individual symptom trajectories were calculated as the random slope of the psychosis BPRS subscore over time in a mixed model. For the analyses, we studied the effect of baseline SCI scores on time to meeting relapse criteria using a Cox regression, and whether changes in SCI scores correlate with symptom trajectory in LAI treated individuals.

Results: Out of 56 individuals for whom we did obtain baseline MRI scans, we had longitudinal MRI data for 28, out of whom 11 met relapse criteria despite guaranteed antipsychotic treatment. In our sample, 34 (61.8%) participants were men, mean age was 32.01 (SD=10.31) years old, and race was non-white for 44 (74.5%) individuals. Baseline scans were not predictive of time to relapse (HR=1.17, 95%CI=0.87-1.44), and similarly, they did not predict symptom trajectory ($r = -0.18$, 95%CI= -0.45 – 0.12). However, the individual symptom trajectory was significantly correlated with the longitudinal changes in SCI scores ($r = 0.41$, 95%CI=0.02-0.70).

Conclusions: A biomarker of treatment response obtained after treatment stabilization was not able to accurately predict subsequent risk of relapse despite ongoing treatment, suggesting that at least for this biomarker, relapse risk was not identifiable as a ‘trait’ at baseline. However, the SCI tracked as a ‘state’ biomarker symptom trajectory during guaranteed treatment. As individuals worsen despite treatment, their SCI score moves from lower values (typical of treatment responders) to higher values (typical of non-responders). Therefore, these data suggest that relapse despite ongoing treatment may relate to a transition out of a ‘treatment responsiveness’ neurobiological state, closer to that of treatment resistance.

39.4. REAL-WORLD EFFECTIVENESS OF HORMONE REPLACEMENT THERAPY IN PREVENTING RELAPSE IN WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

Bodily Brand¹, Iris Sommer², Shiral Gangadin², Antti Tanskanen³, Jari Tiihonen³, Heidi Taipale⁴

¹University Medical Center Groningen, ²UMC Groningen, ³Karolinska Institutet,

⁴Niuvanniemi Hospital, University of Eastern Finland

Background: Antipsychotic effectiveness in preventing relapse declines around menopausal age in women with schizophrenia or schizoaffective disorder (SSD). It is not known whether menopausal systemic hormone replacement therapy (HRT) can help to prevent relapse.

Methods: We did a nationwide, register-based cohort study in Finland, in women with SSD who initiated HRT aged between 40-62 years. HRT effectiveness in preventing psychosis relapse was studied using within-individual analyses. Age- and psychotropic drug use adjusted hazard ratios (aHR) were calculated for psychosis relapse as main outcome and any psychiatric hospitalization as secondary outcome. Ethnicity data was not available.

Results: The study population comprised 3488 women using HRT between 1994 and 2017. Use of HRT was associated with a 16% lower relapse risk (aHR 0.84 [95% CI 0.78-0.90]) when compared to non-use. Stratified by age, HRT was associated with decreased relapse risks when initiated between age 40-49 (aHR 0.86 [95% CI 0.78-0.95]) and age 50-55 (aHR 0.74 [95% CI 0.66-0.83]), but not between age 56-62 (aHR 1.11 [95% CI 0.91-1.37]). Similar effectiveness was found for estrogen alone or combined with fixed or sequential progestogens (aHR 0.79-0.86), transdermal and oral formulations (aHR 0.75-0.87), and for most specific formulations (aHR 0.77-0.85), except for tibolone (aHR 1.04 [95% CI 0.75-1.44]) and estrogen combined with dydrogesterone (aHR 1.05 [95% CI 0.85-1.30]). Similar results were observed with any psychiatric hospitalization as an outcome measure.

Conclusions: Our findings underscore the potential value of HRT in preventing psychosis relapse among women with SSD of menopausal age. Age-stratified analysis suggests optimal benefits when HRT is initiated before the age of 56.

Plenary Session VII - Matcheri Keshavan: Refining the Nosology of Psychotic Disorders: Toward Cognitive Subtypes

8:30 a.m. - 9:30 a.m.

40. REFINING THE NOSOLOGY OF PSYCHOTIC DISORDERS: TOWARD COGNITIVE SUBTYPES

Iris Sommer, *UMC Groningen*

40.1. REFINING THE NOSOLOGY OF PSYCHOTIC DISORDERS: TOWARD COGNITIVE SUBTYPES

Matcheri Keshavan, *Harvard University*

Individual Abstract: Current approaches to classifying psychotic disorders are limited by substantive heterogeneity within, blurred boundaries between, as well as overlaps across the various disorders in outcome, treatment response, emerging evidence regarding pathophysiology and presumed etiology. While symptom-based classifications have improved our reliability, they may lack validity. Critical next steps include deconstruction of disease dimensions, and endophenotypes, reclustering such data across symptom-based diagnoses using modern phenotypic and biometric approaches, and validating such entities using etio-pathology, outcome and treatment-response measures.

Cognitive impairments, being pervasive, stable, heritable and linked to neurobiology, are core aspects of psychoses, and offer a unique opportunity to parse psychosis syndromes into biologically meaning entities. The Bipolar-schizophrenia Network for Intermediate Phenotypes (BSNIP) used an agnostic, K-means clustering approach in a large sample of psychosis probands; three subtypes (biotypes) were identified that differ in regard to cognitive and electrophysiological endophenotypes. The replicability, stability and external validity of these subgroups, as well as ongoing studies investigating the potential value of this classification to treatment selection and outcome prediction, will be discussed.

Concurrent Symposia

10:00 a.m. - 12:00 p.m.

41. GENE-ENVIRONMENT INTERACTION IN PSYCHOSIS: NEW INSIGHTS INTO ETIOLOGY, PREVENTION, AND MANAGEMENT

Sinan Guloksuz, *Maastricht University*

Overall Symposia Abstract: Schizophrenia spectrum disorder has considerable genetic component, now quantifiable using a polygenic risk score. However, GWAS account for only a fraction of the variance in psychosis liability. This suggests that factors beyond genetics, such as gene-environment interactions (GxE) may play a significant role. Therefore, investigating GxE in psychosis is vital but presents complex challenges: environment is dynamic in a changing world; there are multitude of exposures; biological mechanisms underlying GxE remain unexplored.

To respond these challenges, our symposium will feature novel—yet-to-be-published—studies investigating GxE in psychosis.

Dr. Ku will discuss long-term trajectories of distressing psychotic experiences and their associations with genetic risk and environmental protective factors. He will present unpublished findings from a large cohort, age-range of 9-10 years, the Adolescent Brain Cognitive Development. He found that social aspects of physical activities may buffer the impact of genetic liability on persistently distressing psychotic experiences. These findings highlight the opportunity for early identification and potential intervention strategies throughout this sensitive developmental period and encourage investigating risk and protective factors underlying trajectories toward the psychosis spectrum.

Dr. Fusar-Poli will focus on the interplay between autistic traits and subthreshold psychotic experiences in a non-clinical population. She will discuss how genetic (i.e., polygenic risk score) and environmental risk factors for schizophrenia could interact with autistic traits in predicting the psychosis expression by leveraging the TwinssCan, a longitudinal twin cohort of adolescents and young adults from the general population in Belgium. The results may be relevant to implement preventive strategies in populations at greater risk of developing psychotic disorders, such as people with autism or elevated autistic traits.

Dr. Prachason will present unpublished findings from a study that investigated the longitudinal effects of polygenic and exposomic risks for schizophrenia on subclinical psychosis expression in early adolescence. Findings show that the aggregated environmental risk exposure additively interacted with the polygenic risk in predicting subsequent distressing psychotic experiences. Environmental influence also tended to increase when the experiences were more persistent. These findings highlight the interplay between genetic and environmental risk factors for schizophrenia on the development of subclinical psychosis expression and the clinical significance of symptom persistence in the general youth population.

Dr. Di Forti will present unpublished findings from the multisite EUGEI first episode psychosis study that investigated whether polygenic risk scores predicted age at first cannabis use and pattern of use (frequency/potency) and moderated the association between pattern of cannabis use and psychosis risk. Findings suggest that genetic load for psychosis and neurodevelopmental disorders but not for major depression might influence psychosis vulnerability among cannabis users. Moreover, engaging young adults with psychosis in an intervention for cannabis use can significantly improve illness outcome.

Prof. Murray will summarize and discuss the key findings, and implications of these findings for clinical translation and future studies of GxE in psychosis.

41.1. THE ASSOCIATIONS BETWEEN POLYGENIC LIABILITY, PHYSICAL ACTIVITIES, AND DISTRESSING PSYCHOTIC-LIKE EXPERIENCES OVER FOUR YEARS

Benson Ku^{*1}, Emerald Yuan², Angelo Arias-Magnasco³, Bochao Lin³, Elaine Walker⁴, Benjamin Druss⁵, Jiyuan Ren², Jim van Os⁶, Sinan Guloksuz³

¹Emory University School of Medicine, ²Emory, ³Maastricht University, ⁴Emory University,

⁵Emory University Rollins School of Public Health, ⁶Utrecht University Medical Centre

Background: Persistently distressing psychotic-like experiences (PLE) are associated with impaired functioning, mental health service utilization, cognitive deficits, and psychopathology. Physical activities (PA), particularly those that involve social engagement,

are potential protective factors for psychopathology among adolescents. However, the protective factor of PA against genetic risk on long-term outcomes of distressing PLE has not been examined. This study aims to assess whether the trajectories of distressing PLE are associated with a polygenic risk score for schizophrenia (PRS-SCZ), PA (including social and non-social activities), and their interaction.

Methods: This observational cohort study used four waves of data from the Adolescent Brain Cognitive Development Study 5.0. Data was collected between September 2016 and January 2022. The primary outcomes include the three distressing PLE groups (none, transiently, and persistently). PA was assessed at baseline by the average number of hours per week, further categorized into social activities (SA) and non-social activities (NSA). The PRS-SCZ was generated using the most recent GWAS of schizophrenia (freeze 3) - European subsample. Generalized linear mixed models adjusted for the following fixed effects (age, sex, parental education, income-to-needs ratio, family history of psychosis, body mass index, principal components for samples) and random effects (recruitment site, and family structure). Interaction term of PRS-SCZ-by-SA was then entered into the model to assess moderating effect of SA on the relationship between PRS-SCZ and distressing PLE.

Results; The study included 4736 adolescents of European ancestry ages 9 and 10 at baseline with 2507 (52.9%) males, and 930 (19.6%) and 670 (14.1%) had transiently and persistently distressing PLE, respectively. Greater PRS-SCZ and lower levels of PA were associated with a greater risk of persistently distressing PLE (adjusted relative risk ratio [RRR]=1.13, 95% CI=1.03 to 1.23, p LESS THAN 0.05 and adjusted RRR=0.87, 95%CI=0.79 to 0.97, p LESS THAN 0.05, respectively). Lower levels of SA were associated with a greater risk of distressing PLE (adjusted RRR= 0.81, 95% CI=0.73 to 0.90, p LESS THAN 0.05). The interaction of PRS-SCZ-by-SA was significantly associated with persistently distressing PLE such that the relationship between PRS-SCZ and distressing PLE was weaker as participants had greater levels of participation in team-based sports (adjusted RRR=0.87, 95% CI=0.73 to 0.90, p LESS THAN 0.05).

Conclusions: These findings demonstrate that the interaction between genetic liability and social-physical activities is associated with trajectories of distressing PLE. Further research is needed to understand which aspects of social activities may be protective against psychosis.

41.2. THE MODERATING ROLE OF GENETIC AND ENVIRONMENTAL RISK FACTORS FOR SCHIZOPHRENIA ON THE ASSOCIATION BETWEEN AUTISTIC TRAITS AND PSYCHOSIS EXPRESSION IN A GENERAL POPULATION TWIN SAMPLE

Laura Fusar-Poli^{*1}, Melike Karaçam Doğan², Thanavadee Prachason³, Bochao Lin⁴, Claudia Menne-Lothmann⁴, Jeroen Decoster⁵, Ruud van Winkel⁴, Dina Collip⁴, Philippe Delespaul⁴, Marc De Hert⁶, Catherine Derom⁷, Evert Thiery⁷, Nele Jacobs⁴, Jim van Os⁴, Bart Rutten⁴, Sinan Guloksuz⁴

¹University of Pavia, ²Karadeniz Ereğli State Hospital, ³Mahidol University, ⁴Maastricht University, ⁵Psychiatric Care Sint-Kamillus, ⁶Katholieke Universiteit Leuven, ⁷Ghent University

Background: The existence of subclinical psychotic experiences (PE), as well as subthreshold AT, in the general population suggests a continuum. Research has shown that people with increased autistic traits (AT) are more prone to psychotic experiences (PE). Compared with the general population, environmental risk factors for psychosis such as childhood trauma, bullying, and obstetric complications are more frequent in people with autism spectrum disorder (ASD). Additionally, genetic studies have identified several direct and indirect

associations between ASD and psychosis, further supporting the link between these phenotypes. Therefore, we have hypothesized that genetic and environmental risk for psychotic disorders could moderate the relationship between AT and PE in the general population.

Methods: We conducted analyses using the TwinssCan, a longitudinal general population twin cohort. Analyses were conducted in 794 participants aged between 18 and 35 years old. AT were evaluated using the Autism Spectrum Quotient (AQ). The frequency of PE was assessed with the Community Assessment of Psychic Experience (CAPE). Multilevel regression analyses, adjusted for age and sex, were used to evaluate the moderating role of polygenic risk score for schizophrenia (PRS-SCZ), environmental risk factors for psychosis (i.e., childhood adversities, bullying, obstetric complications) on the association between the total scores of AQ and CAPE. Childhood adversities were measured using the Childhood Trauma Questionnaire-Short Form (CTQ-SF), in the domains of physical, emotional, and sexual abuse, as well as physical and emotional neglect. Bullying was evaluated using the Retrospective Bullying Questionnaire (RBQ). Measures of environmental risk were dichotomized based on previously validated methods.

Results: AQ total scores were positively and significantly associated with CAPE total scores ($B=0.12$, 95% CI 0.10 to 0.14). We did not find any significant interaction between AQ total scores and PRS-SCZ on CAPE total scores ($B=-0.01$, 95% CI -0.03 to 0.005). As for childhood adversities, we found positive significant interactions between AQ total and emotional abuse ($B=0.08$, 95% CI 0.05 to 0.11), physical abuse ($B=0.11$, 95% CI 0.05 to 0.18), sexual abuse ($B=0.09$, 95% CI 0.03 to 0.15), emotional neglect ($B=0.04$, 95% CI 0.01 to 0.07), physical neglect ($B=0.06$, 95% CI 0.03 to 0.10) on CAPE total. No significant interactions were found between AQ total and bullying ($B=0.02$, 95% CI -0.01 to 0.05) or between AQ total and obstetric complications ($B=0.003$, 95% CI -0.002 to 0.01) on CAPE total scores.

Conclusions: Findings indicate that childhood adversities and life events may moderate the association between AT and PE in the general population. Prevention of risk factors for psychosis may be particularly relevant for reducing psychopathological symptoms in people with elevated AT

41.3. EXAMINING THE INDEPENDENT AND JOINT EFFECTS OF GENOMIC AND EXPOSOMIC LIABILITY FOR SCHIZOPHRENIA ON SUBCLINICAL PSYCHOSIS EXPRESSION IN EARLY ADOLESCENCE

Thanavadee Prachason^{*1}, Matteo Di Vincenzo², Gaia Sampogna², Angelo Arias-Magnasco³, Bochao D. Lin³, Lotta-Katrin Pries³, Jim van Os⁴, YOUTH-GEMs Investigators⁵, Bart P.F. Rutten³, Sinan Guloksuz⁶

¹ Ramathibodi Hospital, Mahidol University, ²University of Campania "Luigi Vanvitelli",

³School for Mental Health and Neuroscience, Maastricht University Medical Centre,

⁴University Medical Center Utrecht Brain Center, Utrecht, the Netherlands; Institute of Psychiatry, King's College London, ⁵YOUTH-GEMs Investigators, ⁶School for Mental Health and Neuroscience, Maastricht University Medical Centre, Yale University School of Medicine

Background: Psychotic experiences (PE) are reported by up to 10% of children and adolescents and are associated with an increased risk of developing both psychotic and non-psychotic disorders, particularly when accompanied by distress. Although research has identified shared genetic and environmental risk factors with psychotic disorders, their combined influence on subclinical PE in young populations remains unexplored. In this study, we conducted a longitudinal analysis using the Adolescent Brain and Cognitive Development

(ABCD) Study data to investigate the independent and joint effects of genomic and exposomic liability for schizophrenia on distressing PE during early adolescence.

Methods: The ABCD release 4.0 dataset was used in the primary analyses, which included 5,057 participants of European ancestry who had genetic data and underwent annual assessments until the 2-year follow-up. Subclinical PEs were assessed annually from baseline (ages 9 – 10) using the Prodromal Questionnaire-Brief Child Version. We classified participants with at least one PE accompanied by a distress score of ≥ 3 on a 5-point scale as having distressing PE. The primary outcome was past-month distressing PE reported at the 2-year follow-up (ages 11 – 12), with secondary outcomes including lifetime distressing PE and recurring distressing PEs with varying degrees of persistence across the 3 waves of assessment. Polygenic risk score for schizophrenia (PRS-SCZ) was calculated. Conforming to our previous study, exposome score for schizophrenia (ES-SCZ) was calculated using lifetime exposure to childhood adversity domains, cannabis use, winter birth, hearing impairment, and bullying reported up to the 1-year follow-up (ages 10 – 11). The main effects of PRS-SCZ and ES-SCZ on distressing PE were tested separately using multilevel logistic regression analysis. The additive interaction between PRS-SCZ and ES-SCZ was indicated by the relative excess risk due to interaction (RERI). Age and sex were covariates in all models, and sensitivity analyses included adjustments for baseline family income and parental education. As confirmatory analyses, all the analyses were repeated based on the ABCD release 5.0 dataset, using ES-SCZ calculated from lifetime exposure up to the 2-year follow-up and distressing PEs at the 3-year follow-up as the outcomes.

Results: In primary analyses, PRS-SCZ was significantly associated with past-month distressing PE at the 2-year follow-up (OR 1.13 [95% CI 1.01, 1.26], $P = .031$). Similar main effects of PRS-SCZ were observed for lifetime distressing PE (OR 1.14 [95% CI 1.06, 1.23], $P < .001$) and recurring distressing PEs (recurring ≥ 2 waves: OR 1.16 [95% CI 1.04, 1.29], $P = .007$; recurring in all 3 waves: OR 1.22 [95% CI 1.02, 1.47], $P = .034$). ES-SCZ was similarly associated with distressing PEs of all definitions, and its influence tended to increase with more persistence of experiences (past-month distressing PE: OR 1.60 [95% CI 1.43, 1.78]; lifetime distressing PE: OR 1.60 [95% CI 1.48, 1.74]; recurring ≥ 2 waves: OR 1.72 [95% CI 1.54, 1.93]; recurring in all 3 waves: OR 2.03 [95% CI 1.68, 2.45], all $P < .001$). Significant additive interactions between PRS-SCZ and ES-SCZ were observed for past-month distressing PE (RERI 0.22 [95% CI 0.02, 0.41], $P = .028$) and lifetime distressing PE (RERI 0.20 [95% CI 0.05, 0.35], $p = .010$), but not for recurring distressing PEs at the 2-year follow-up. Sensitivity and confirmatory analyses generally aligned with results derived from the primary analyses.

Conclusions: Genomic and exposomic liability for schizophrenia were independently and jointly associated with distressing PE in early adolescence. Notably, the association of ES-SCZ with PE tended to be stronger with increasing PE persistence. These findings underscore the interplay between genomic and exposomic risk for schizophrenia in subclinical psychosis expression in the general youth population.

41.4. FROM PREDICTING ONSET OF CANNABIS-ASSOCIATED PSYCHOSIS TO IMPROVING THE OUTCOME OF THE DISORDER

Marta Di Forti¹, Edoardo Spinazzola², Isabelle Austin-Zimmerman³, Giulia Trotta⁴, Craig Morgan⁵, Jim van Os⁶, Zhikun Li⁷, Evangelos Vassos⁸, Diego Quattrone⁹, Robin Murray¹⁰

¹SGDP, Institute of Psychiatry, ²King's College London, IoPPN, ³King's College London,

⁴Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁵Centre for Society and Mental Health, King's College London, ⁶Utrecht University Medical Centre,

⁷*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁸*SGDP, Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁹*MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London*, ¹⁰*Institute of Psychiatry, King's College, London*

Background: Heavy cannabis use is the most modifiable risk factor for the onset of psychotic disorder and for its clinical and functional outcome. Some but not all studies have suggested that genetic load for schizophrenia determines cannabis use behaviour and or interacts with cannabis use to increase the risk of developing a psychotic disorder. Nevertheless, it is unclear if and how the genetic load for other psychiatric phenotypes might influence a) cannabis use and b) later risk of psychotic disorder. The first half of this presentation will clarify these issues. A further problem is that young people with a cannabis-associated psychotic disorder often fall between Addiction Services and those for psychosis, with consequent bad outcome. The second half of this presentation will describe a new specialist clinic which offers young adults who develop a psychotic disorder an intervention to support them with reducing/stopping their cannabis use.

Methods: 1) Using genetic and cannabis use data from the multisite EUGEI first episode psychosis case-control study we calculated Polygenic Risk scores (PRS) for Major Depression and Psychosis to test a) if they predicted pattern of cannabis use and b) if they explained a greater proportion of the variance for case-control status than exposure to cannabis use alone. All analyses were controlled for the main sociodemographic, tobacco smoking and Principal Components. 2) We analysed changes between baseline and end of treatment, of the outcome measures (Cannabis Dependence, Pattern of use, psychopathology, level of functioning) from the first young adults with psychotic disorders, who completed their cannabis use reduction/cessation intervention with the Cannabis Clinic for Psychosis (CCP).

Results: In the First episode Psychosis Cases N=684, Controls=970 from the EUGEI study, neither the PRS for Major depression nor a General Psychosis-PRS predicted cannabis use. However, adding a General Psychosis-PRS to measures of cannabis use increased the variance explained for the onset of psychosis.

Data from the CCP show that 80% of the 40 young adults, who completed their cannabis use reduction/cessation intervention, stopped their cannabis use and 20% reduced their use from daily to once a week or less. Stopping cannabis use was associated with a) a significant reduction in delusions and in distress associated with hallucinations b) improvement in functioning c) sleep and d) attention scores.

Conclusions: Data from the EUGEI study suggest that genetic load for Psychosis, but not for major depression, influence individual vulnerability to psychosis among cannabis users. Moreover, data from the CCP indicate that engaging young adults with psychosis in an intervention to reduce/stop their cannabis can significantly improve their illness outcome.

42. NEW DEVELOPMENTS IN PSYCHOLOGICAL TREATMENTS FOR PATIENTS WITH NEGATIVE SYMPTOMS OF SCHIZOPHRENIA. CONSUMER ORIENTED ADAPTATIONS, TRANSLATIONAL APPROACHES AND ROUTINE CARE IMPLEMENTATION

Matthias Pillny, *Universität Hamburg*

Overall Symposia Abstract: The negative symptoms of schizophrenia comprise diminished motivation and blunted emotional expression. Particularly, diminished motivation has been

found to relate to profound impairment in long-term functioning and quality of life. However, while psychopharmacology and psychological interventions can effectively alleviate the positive symptoms of schizophrenia (i.e., delusions and hallucinations), diminished motivation and functional impairments are still often considered a feature of schizophrenia that generally is resistant to intervention. This symposium will challenge this assumption by showcasing the latest findings of recent clinical trials testing novel and translational psychological interventions as well as innovative combinations of already established and efficacious approaches and their adaptations across diverse settings.

Matthias Pillny (Universität Hamburg, Germany) will present findings from a randomized controlled effectiveness trial with ecological momentary assessment of outcomes testing whether Cognitive Behavioral Social Skills Training can improve the effectiveness of routine care on daily life functioning.

Felice Reddy (University of North Carolina, USA) will present findings from two randomized controlled trials examining the efficacy of Motivational Interviewing combined with Cognitive Behavior Therapy on diminished motivation and functional outcomes. She will discuss specific adaptations for special settings such as chronically homeless consumers and virtual delivery of their intervention.

Inez Myin-Germeys (KU Leuven, Belgium) will focus on a blended care approach including Acceptance and Commitment Therapy delivered in an ecological momentary intervention. She will discuss findings of her randomized controlled trial testing the benefits of this approach for daily life functioning and negative symptoms.

Clementine Edwards (King's College London, UK) adapts a translational perspective on diminished motivation and will present preliminary evidence suggesting that a mental imagery focused autobiographical memory training can improve diminished motivation and cognitive functioning in patients with schizophrenia.

Edo Jaya (Universitas Indonesia, Indonesia) will encourage a critical reflection of the evidence presented in this symposium and facilitate a discussion about the clinical implications to improve the routine care for people with negative symptoms of schizophrenia.

42.1. IMPROVING DAILY-LIFE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA WITH COGNITIVE BEHAVIORAL SOCIAL SKILL TRAINING: A RANDOMIZED-CONTROLLED EFFECTIVENESS TRIAL WITH ECOLOGICAL MOMENTARY ASSESSMENT OF OUTCOMES

Matthias Pillny*¹, Jason Holden², Kim Mueser³, Greg Aarons², David Sommerfeld², Dimitri Perivoliotis², Eric Granholm²

¹Universität Hamburg, ²University of California, San Diego, ³Center for Psychiatric Rehab, Boston University, USA

Background: Negative Symptoms of schizophrenia cause profound impairments in everyday functioning. Medications can effectively alleviate positive symptoms and prevent relapses, but they do not meaningfully improve long-term daily life functioning. By contrast, psychological interventions, such as Cognitive Behavioral Social Skills Training (CBSST), showed moderate effects on functional outcomes in efficacy trials. However, it remains unclear to what extent improvements that have been observed using retrospective in-lab assessments of functional outcomes in previous trials translate to the patients' daily life experiences. Furthermore, it has

not yet been tested whether CBSST can be effectively delivered in routine practice settings such as Assertive Community Treatment (ACT) in the United States. This study therefore aims to test whether the combination of ACT+CBSST leads to greater improvements in daily life functioning of patients with schizophrenia than ACT alone.

Methods: We conducted a parallel-group randomized-controlled effectiveness trial in seven ACT teams from the community mental health system in San Diego, California. Participants were eligible if they met diagnostic criteria for schizophrenia or schizoaffective disorder, were GREATER THAN 18 years of age and received ACT services for at least three months. Eligible participants were randomized to either ACT+CBSST or ACT alone, stratified by ACT team and gender. Participants in both conditions continued to receive weekly ACT visits. For participants in the ACT+CBSST condition the study goal was to deliver at least 36 sessions of CBSST within 18 months in the context of their weekly ACT visits. Assessments were obtained at baseline, 9 months and 18 months. At each study visit, participants were prompted 10 times per day over the course of one week with ecological momentary assessment surveys asking them to indicate their current activity from a list of ‘productive’ (e.g., self-care, home-care, work/school, socializing, etc.) and ‘non-productive’ (e.g., watching television, resting, etc.) activities. Daily life functioning was defined as the number of ‘productive activities’ and the ratio of ‘productive-’ to ‘non-productive activities’. Hierarchical linear mixed models were used to test group differences in the change of daily life functioning across study visits.

Results: The intent-to-treat population included N=155 participants (nACT = 80, nCBSST = 75). The median number of CBSST sessions delivered was 13 sessions, indicating low therapy exposure. We found significant group x time interactions in the models predicting the number of productive activities and the ratio of productive and non-productive activities. These interactions were driven by significant large improvements in the ACT+CBSST group, whilst the change in productive activities in ACT alone was not significant.

Conclusions: Our findings suggest that integrating CBSST into ACT leads to greater improvements in daily life functioning than ACT alone. Notably, this effect was evident despite relatively low therapy exposure with CBSST. This indicates that CBSST appears to be a highly potent psychological intervention that, even with low implementation, leads to significant improvements in daily life functioning.

42.2. A NOVEL PSYCHOSOCIAL INTERVENTION FOR MOTIVATIONAL NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: COMBINED MOTIVATIONAL INTERVIEWING AND CBT

Felice Reddy^{*1}, Michael Green², Shirley Glynn³

¹University of North Carolina at Chapel Hill, ²VISN 22 MIRECC, VA Greater Los Angeles Healthcare System, UCLA Semel Institute for Neuroscience and Human Behavior, ³UCLA/VA Greater Los Angeles Healthcare System

Background: Negative symptoms significantly interfere with daily functioning among individuals with schizophrenia and are considered an unmet treatment need. Among the types of negative symptoms, experiential negative symptoms (amotivation and anhedonia) are the primary determinants of impaired functioning. We developed a novel recovery-oriented psychosocial intervention aimed at reducing motivational negative symptoms and improving community functioning in individuals with moderate to severe negative symptoms. The intervention combines two evidence-based practices, Motivational Interviewing and Cognitive Behavior Therapy (MI-CBT) and is delivered in 12 sessions that focus on personally meaningful goals for each participant. In recent years we have expanded the protocol to be applied in diverse settings including group and one-on-one sessions with different kinds of

providers, and for varying clinical diagnoses that are characterized by motivation deficits. This talk will present results from two randomized controlled trials that used MI-CBT to address motivational deficits. The first study applied MI-CBT to people with schizophrenia who had at least moderate levels of negative symptoms. The second study, still being completed, applied MI-CBT to improve motivational deficits in homeless-experienced Veterans.

Methods: The original study included seventy-nine participants with schizophrenia and moderate to severe negative symptoms in a randomized controlled trial comparing the 12-session MI-CBT treatment with a mindfulness control condition. Participants were assessed at three time points through the study period and a 3-month follow-up. The primary outcome measures were motivational negative symptoms and community functioning. In subsequent iterations, we have implemented the treatment with a virtual option, delivered in individual therapy sessions with monthly booster sessions following the 12-week intervention. Participants in this second RCT had deficits in motivation and functioning, a history of houselessness, and a variety of psychiatric diagnoses. We are completing data collection by Dec 2023 and will include the results in our presentation. Finally, we will present our adapted version, which incorporates social networking technology and Peer Support Specialists and is tailored specifically for people recovering from first episode psychosis with residual negative symptoms.

Results: We will present findings from two large RCTs. In the first, compared with the control group, participants in the MI-CBT group showed significantly greater improvements in motivational negative symptoms over the acute treatment period. Their gains relative to baseline were maintained at follow-up. There were nonsignificant effects toward improvements in community functioning and defeatist performance beliefs. In our subsequent study of persons who have experienced long-term houselessness and have deficits in motivation and functioning, preliminary analyses indicate significant improvements in motivational negative symptoms and defeatist beliefs, as well as gains in work and social functioning. Analyses from this study will look at the additive benefit of the booster sessions for treatment efficacy and durability and will also examine potential mediators including defeatist beliefs and motivational stages of change.

Conclusions: The results show that combining MI with CBT yields improvements in negative symptoms, a feature of schizophrenia generally thought of as resistant to intervention. In the first large study, motivational negative symptoms not only responded to the novel treatment, but the gains were maintained over the follow-up period. Our second study's interim results suggest the intervention can be adapted and disseminated. Implications for future studies and for improving the generalization of the negative symptom gains to daily functioning domains will be discussed.

42.3. REMEMBERING THE PAST TO LIVE BETTER IN THE FUTURE: A FEASIBILITY RANDOMISED CONTROLLED TRIAL OF MEMORY SPECIFICITY TRAINING FOR MOTIVATION IN PSYCHOSIS

Clementine Edwards^{*1}, Philippa Garety¹, Amy Hardy¹

¹*Institute of Psychiatry, Psychology and Neuroscience, Kings College London,*

Background: People with a diagnosis of psychosis often experience low motivation, loss of pleasure and reduced activity levels, these are described as experiential negative symptoms. These problems often persist beyond hallucinations and delusions and have a significant impact on quality of life (Starzer et al, 2023). They are also often identified as a priority for recovery by patients (Mortiz et al, 2016). Despite this, we currently have no effective targeted psychological or pharmacological interventions for these difficulties. Autobiographical

memory deficits have been identified in people with psychosis and this may limit the role of memory retrieval in supporting motivation. This pilot study adapted a recently developed protocol, Memflex, which aims to enhance autobiographical memory and has shown promise in depression (Hitchcock et al, 2018). Our single session intervention targets experiential negative symptoms of psychosis using supported autobiographical memory retrieval.

Methods: A sample of 31 participants with psychosis were recruited from inpatient and community settings and randomised in a 2:1 ratio to either an enhanced recall intervention or a basic recall control group. Participants completed a series of measures assessing experiential negative symptoms and related constructs i.e., working memory, self-efficacy beliefs, depression. Participants were then asked to generate positive autobiographical memories linked to activities they wish to repeat in the future. The enhanced recall condition described these memories to the researcher and received additional prompts from the Memflex protocol, these prompts included details of the event, experience of the five senses during the event, identity, positive themes, generalisation of positive themes to other experiences and future planning. The basic recall condition recalled and described the memories but received no additional prompts.

Results: The measures completed showed that depressive and experiential negative symptoms were linked to ratings of the memory during the intervention, as well as to measures of cognition, but not self-efficacy beliefs. The intervention delivered was acceptable (rated GREATER THAN 80%) and feasible (94% adherence) to those who took part. Participants were able to generate positive autobiographical memories linked to their goals and experienced appropriate emotions linked to these. The controlled preliminary effect sizes (0.2-0.34) showed encouraging signals for self-efficacy, motivation, positive mood, and a reduction in negative mood.

Conclusions: The measure of depression symptoms (BDI) and experiential negative symptoms (CAINS) show potential utility as outcome measures for further studies targeting low motivation in psychosis as they demonstrated relationships with key constructs. The findings suggest that guided autobiographical memory retrieval, even delivered in a brief form, is feasible and acceptable and may be an effective tool for targeting motivation in people with psychosis.

42.4. THE INTERACT STUDY: FEASIBILITY AND EFFICACY OF ACCEPTANCE AND COMMITMENT THERAPY IN DAILY LIFE IN EARLY PSYCHOSIS

Inez Myin-Germeys^{*1}, Evelynne van Aubel¹, Thomas Vaessen¹, Henrietta Steinhart¹, Annelie Klippel¹, Tim Batink², Ruud van Winkel³, Mark Van der Gaag⁴, Machteld Marcelis⁵, Therese Van Amelsvoort⁶, Frederike Schirmbeck⁷, Lieuwe de Haan⁸, Ulrich Reininghaus⁹

¹KU Leuven, Center for Contextual Psychiatry, ²Open University, The Netherlands,

³University Psychiatric Center, KU Leuven, ⁴VU University Amsterdam Clinical Psychology,

⁵Maastricht University Medical Center, ⁶Maastricht University, ⁷AMC, University of

Amsterdam, ⁸AMC, Arkin, ⁹Central Institute of Mental Health, University of Heidelberg

Background: This study aimed to investigate the usability, acceptability and efficacy of a blended care intervention - Acceptance and Commitment Therapy in Daily Life (ACT-DL) in people in the early phases of psychosis. ACT-DL combines face-to-face therapy with an Ecological Momentary Intervention (EMI), in addition to treatment as usual (TAU). The INTERACT study is a multi-center RCT comparing ACT-DL+TAU with TAU only.

Methods: Individuals aged 15-65 years with clinically established Ultra-high risk (UHR) or First Episode of Psychosis (FEP) were randomly assigned to TAU or ACT-DL+TAU. ACT-DL+TAU consisted of 8 ACT-sessions augmented with an EMI-app, delivering ACT skills and

techniques in daily life. The primary outcome was psychotic distress assessed with the Comprehensive Assessment Scale of At Risk Mental State (CAARMS) at post-intervention, 6- and 12-month follow-up. Secondary outcomes were functioning, symptom severity, and momentary psychotic distress. We performed multivariate mixed models according to intent-to-treat principles. We also collected data on treatment adherence and acceptability of ACT-DL.

Results: Between June 1, 2015 and December 31, 2018, 668 participants were referred, of whom 148 were randomized to ACT-DL+TAU (n=71) or TAU (n=77). ACT-DL+TAU participants (n=71) completed a mean of 6 (SD=3) face-to-face sessions, with 59% (n=42) of participants completing all sessions. App adherence data (n=58) shows that, on a weekly basis, participants used the app 13 times and were compliant with 6 out of 24 (25%) notifications. Distribution plots of debriefing scores (n=46) showed that 85%-96% of participants reported usefulness on all acceptability items to at least some extent, and that 91% reported perceived burden by number and length of notifications. In total, 115 (78%) participants provided primary outcome data at least at one follow-up assessment. There was no evidence of greater reduction in the primary outcome measure CAARMS distress in ACT-DL+TAU compared to TAU ($\chi^2(3)=2.36$; $p=0.50$). However, out of the tested secondary outcomes, global functioning ($\chi^2(3)=9.05$; $p=0.033$), and negative symptoms ($\chi^2(3)=19.91$; $p \text{ LESS THAN } .001$) improved in ACT-DL+TAU compared to TAU, as did momentary psychotic distress ($\chi^2(3)=21.56$; $p \text{ LESS THAN } 0.001$).

Conclusions: Our results corroborate good treatment adherence to and acceptability of ACT-DL in early psychosis. INTERACT did not support a significant effect of ACT-DL over TAU on the primary outcome measure of psychotic distress as assessed with the CAARMS. However, we found significant effects on negative symptoms and global functioning, two of the hardest-to-treat symptoms in psychosis. Although we need further replication studies to confirm the strength and specificity of these effects, the findings indicate that ACT-DL may provide an exciting new avenue for the early treatment of negative symptoms.

43. NOVEL PERSONALIZED NEUROMODULATION APPROACHES TO TREAT CORE DEFICITS AND COMORBIDITIES IN SCHIZOPHRENIA

Aristotle Voineskos, *Centre for Addiction and Mental Health*

Overall Symposia Abstract: Non-invasive neuromodulation techniques represent novel and innovative treatment approaches that can be used to target neural circuits and have been amply applied and tremendously successful in the treatment of depression. Much less neuromodulation work has been done in schizophrenia, despite the demonstration of circuit deficits associated with particular core symptoms and dysconnectivity models. More recently, research in this area is increasing, and advances in individualized targeting approaches and predictive models are starting to be applied to address variable response rates to neuromodulation. In the current symposium, we present findings on the use of novel targeted and personalized neuromodulation approaches to treat core deficits and comorbidities in individuals with schizophrenia, including negative symptoms, neurocognition, social cognition, and nicotine dependence.

Dr. Voineskos (Centre for Addiction and Mental Health (CAMH)/University of Toronto) will introduce the topic of our symposium, providing a historical context, insights from his ongoing neurostimulation research, and incorporating his clinical perspective on the utility of novel neuromodulation approaches in the treatment of individuals with schizophrenia. Dr. Hasan (University of Augsburg) will present findings regarding improving response prediction to

repetitive transcranial magnetic stimulation (rTMS) in schizophrenia with a focus on negative symptoms, moving from large-scale clinical data to multimodal predictive models. Dr. Valiengo (University of Sao Paulo) will share results from a clinical trial examining the effects of a novel form of neuromodulation called photobiomodulation on magnetic resonance spectroscopy and negative symptoms in schizophrenia. Dr. Oliver (CAMH/Toronto) will discuss results from a multi-centre study of personalized rTMS to the dorsomedial prefrontal cortex in individuals with schizophrenia, demonstrating changes in social cognitive network functional connectivity. Dr. Ward (Vanderbilt University Medical Center) will present data that identifies a schizophrenia-specific circuit of nicotine dependence, validates this network with a pharmacologic intervention, and then uses an individualized, network-targeted rTMS intervention to modulate nicotine craving in schizophrenia. The panel will conclude with a discussion and question period led by Dr. Brady (Harvard Medical School), incorporating his ongoing research on the use of accelerated neuronavigated intermittent theta burst stimulation (iTBS) in schizophrenia. Taken together, the presented studies provide evidence for the promise and efficacy of neuromodulation approaches in targeting core symptoms and comorbidities in individuals with schizophrenia. Our results also highlight the need for approaches such as individual-level prediction of treatment response or stratification and/or personalized brain mapping to identify individualized brain stimulation targets for specific symptoms to ideally allocate critical resources to maximize treatment response and improve functional outcomes for patients.

43.1. EFFECTS OF INDIVIDUALIZED TRANSCRANIAL MAGNETIC STIMULATION ON SOCIAL COGNITIVE NETWORK FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA SPECTRUM DISORDERS

Lindsay Oliver^{*1}, Daniel M. Blumberger², Colin Hawco², Erin Dickie², Jerrold Jeyachandra¹, Zhi-De Deng³, James Gold⁴, George Foussias², Miklos Argyelan⁵, Zafiris J Daskalakis⁶, Robert Buchanan⁴, Anil Malhotra⁵, Aristotle Voineskos²

¹*Centre for Addiction and Mental Health*, ²*Centre for Addiction and Mental Health, University of Toronto*, ³*National Institute of Mental Health, Duke University School of Medicine*, ⁴*Maryland Psychiatric Research Center*, ⁵*Zucker Hillside Hospital, Feinstein Institute for Medical Research*, ⁶*University of California San Diego*

Background: Individuals with schizophrenia spectrum disorders (SSDs) often experience social cognitive impairments, which are associated with poor functional outcome. There are currently no approved treatment options for these debilitating deficits in SSDs or other brain disorders. Social processes affected in SSDs are thought to rely on a frontoparietal ‘simulation network’ and a cortical midline/lateral temporal ‘mentalizing network’, which may be amenable to modulation using neurostimulation. The present feasibility study applied a personalized targeting method to examine, for the first time, the effect of individually-targeted repetitive transcranial magnetic stimulation (rTMS) to the dorsomedial prefrontal cortex (DMPFC) on social cognitive network functional connectivity in individuals with SSDs. We examined the comparative efficacy on functional connectivity within and between social cognitive networks of conventional 10 Hz rTMS and intermittent theta burst stimulation (iTBS) to sham stimulation and examined the comparative tolerability of the different treatments.

Methods: We conducted a two-week, double-blind, sham-controlled, randomized clinical trial comparing 10 Hz rTMS and iTBS, a more time-efficient rTMS paradigm, applied to the DMPFC in clinically stable adults with SSDs across three sites. Our primary outcome measure was change in within mentalizing network connectivity. Our secondary outcome measure was tolerability. We also explored connectivity changes between the mentalizing and simulation networks. Participants completed pre- and post-treatment magnetic resonance imaging (MRI) scans, including the social processing Empathic Accuracy task which engages the simulation and mentalizing networks. Neurostimulation (10 Hz rTMS, iTBS, or sham) was individually targeted by combining electric field mapping, which accounts for anatomical brain surface variability, and functional connectivity mapping to localize each individual's point of maximal DMPFC-mentalizing network functional connectivity. Following MRI preprocessing, within-mentalizing and between mentalizing-simulation network functional connectivity metrics during the Empathic Accuracy task were calculated both pre- and post-rTMS. Given that this was a feasibility study designed to determine effect sizes and tolerability, Cohen's d effect sizes were calculated between each active treatment condition and sham to identify potential differences in the magnitude of changes.

Results: Of the 51 randomized participants, 46 completed treatment and 43 (10 Hz rTMS N = 15, iTBS N = 15, sham N = 13) were included in the imaging analyses following quality control. There was a greater increase in mentalizing network connectivity following iTBS compared to sham ($d = 0.53$). Negligible differences were observed in changes in mentalizing network connectivity following 10 Hz rTMS when compared to sham ($d = 0.07$). Little change was seen in mentalizing-simulation between-network connectivity, with negligible effect sizes when comparing iTBS to sham and 10 Hz rTMS to sham. Pain scores were low in all groups (mean LESS THAN 5 across arms) and there was no difference in drop-out rate among the three groups, suggesting good tolerability.

Conclusions: This study marks the first investigation of rTMS effects on social cognitive circuitry in SSDs, incorporating individualized targeting approaches and inclusion of both a 10 Hz rTMS and a more time-efficient iTBS arm. Our results suggest that iTBS can change mentalizing network connectivity with medium effect size. We are now embarking on a larger clinical trial using iTBS versus sham stimulation to assess changes in social cognitive performance.

43.2. NON-INVASIVE BRAIN STIMULATION TO TREAT NEGATIVE SYMPTOMS – FROM LARGE-SCALE CLINICAL DATA TO PREDICTIVE MODELS

Alkomiet Hasan^{*1}, Nikolaos Koutsouleris²

¹Universtiy of Augsburg, ²Ludwig-Maximilian-University

Background: The treatment of cognitive and negative symptoms of schizophrenia is still challenging. Non-invasive brain stimulation has been investigated as potential treatment option for this difficult-to-treat symptom domains with variable results. The response variability may be explained by several individual and methodological factors. In 2015, we were the first to publish the results of a randomized multi-centre trial applying 10 Hz rTMS to the left DLPFC in 157 patients with schizophrenia and predominant negative symptoms. The primary outcome was negative. This trial changed guideline recommendations and the results are contrary to the findings from small single-centre trials that inform current meta-analyses.

Methods: We applied a multi-modal approach to improve response rates of non-invasive brain stimulation for the treatment of cognitive and negative symptoms and schizophrenia. We hypothesized that it appears to be more likely that the response variability to brain stimulation will be targeted using more individualized predictors and predictive models or models to define

response-subtypes rather than refining stimulation paradigms and methods. We combined clinical data, imaging and genetic data to develop predictors for the response to rTMS. Moreover, we used IPD meta-analyses to evaluate whether rTMS is an effective option for ultra-treatment resistance.

Results: We will present results from classical and individual patient data meta-analysis, from subgroup analyses (e.g. treatment-resistant patients), from imaging-based predictive analyses and from multimodal predictive analyses combining imaging data, with genetic data and clinical parameters.

Conclusions: Our research track allows to conclude that the future of non-invasive brain stimulation for the management of schizophrenia symptoms is more likely to be influenced by selecting the right patient for a given intervention rather than trying to improve stimulation methods following the classic “one stimulation fits all” paradigm that has failed in the past.

43.3. A DISEASE-INFORMED, NETWORK-TARGETED NEUROMODULATION INTERVENTION AFFECTS CRAVING IN INDIVIDUALS WITH SCHIZOPHRENIA AND NICOTINE DEPENDENCE

Heather Ward*¹, Gulcan Yildiz², Jing Xie², Adam Beermann², Amy Janes³, Lauren Moran⁴, Mark Halko⁵, Roscoe Brady⁶

¹Vanderbilt University Medical Center, ²Beth Israel Deaconess Medical Center, ³National Institute on Drug Abuse, ⁴Harvard Medical School/ McLean Hospital, ⁵Harvard Medical School/McLean Hospital, ⁶Beth Israel Deaconess Medical Center, Harvard Medical School

Background: The prevalence of tobacco use in schizophrenia (SZ) is 3-times that of the general population. Yet, treatments for nicotine dependence are significantly less effective for SZ and do not target SZ-specific pathophysiology. We sought to identify and test a neuromodulation intervention on a SZ-specific circuit of nicotine dependence.

Methods: This study consisted of 3 phases: Network Discovery, Network Validation, and Network-Targeted Intervention. In Network Discovery, we used a data-driven, multi-variate pattern analysis of whole-connectome data from 35 smokers (18 SZ, 17 controls) to identify the strongest links between daily cigarette use and functional connectivity. In Network Validation, 24 participants (12 SZ, 12 control) participated in a placebo-controlled crossover study of nicotine patch with fMRI. Based on Network Discovery results, we correlated default mode network (DMN) connectivity change with nicotine patch dose. In Network-Targeted Intervention, 10 people with SZ and nicotine dependence participated in a crossover study of individualized, DMN-targeted repetitive transcranial magnetic stimulation (rTMS) with fMRI and craving assessment immediately before and after each rTMS session. rTMS was targeted to the left parietal node of an individual-specific DMN map for 3 sessions: intermittent theta burst stimulation (iTBS), continuous theta burst stimulation (cTBS), sham. We compared craving change between each rTMS type using a mixed ANOVA.

Results: In Network Discovery, the strongest ($p < .001$) correlate between functional connectivity and daily cigarette use was driven by individual variation in DMN topography specific to SZ. With higher cigarette use in SZ, the DMN spatial extent was pathologically expanded. In Network Validation, nicotine administration reversed DMN hyperconnectivity in SZ in a dose-dependent relationship ($R = -0.50$, 95% CI -0.75 to -0.12 , $p < .05$). In Network-Targeted Intervention, we observed a treatment $\times$ time effect ($p = .017$) where craving was increased by iTBS but not by cTBS or sham.

Conclusions: We identified a SZ-specific network of nicotine dependence (i.e., DMN), validated the effect of acute nicotine on that network, then applied an individualized, neuromodulation intervention to that network that affected craving in SZ. This is the first

evidence for a circuit-based intervention for substance use in SZ that was empirically derived, unique to SZ, and affected clinical outcomes.

43.4. CEREBRAL PHOTOBIMODULATION FOR THE TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: DOUBLE-BLIND, SHAM-CONTROLLED, RANDOMIZED CLINICAL TRIAL WITH MAGNETIC RESONANCE SPECTROSCOPY

Leandro Valiengo^{*1}, Bianca Pinto², Andre Brunoni¹

¹University of Sao Paulo, ²Instituto de Psiquiatria, University of São Paulo Medical School – São Paulo, Brazil

Background: Negative symptoms of schizophrenia are associated with poor clinical outcomes. They tend to increase over time in severity and prognostic weight and usually persist with antipsychotic medication treatment. Studies have suggested that the dorsolateral prefrontal cortex (DLPFC) is involved in the pathophysiology of negative symptoms in schizophrenic patients, with reduced levels of metabolism in the prefrontal cortex and an inverse correlation between the severity of negative symptoms and cerebral blood flow in the prefrontal cortex. Recent clinical trials demonstrated a possible role of non-invasive neuromodulation (targeting the DLPFC) as TMS and tDCS for the treatment of these symptoms. A new form of neuromodulation is emerging, called photobiomodulation (PBM), that uses infrared light to activate mitochondria, which in turn stimulates second messenger systems, DNA transcription, and growth factors. Studies have demonstrated that PBM can change magnetic resonance spectroscopy. This treatment has not been used in schizophrenia until now.

Methods: 30 adults (18-55 years) with schizophrenia (minimum of 20 points in PANSS – positive and negative symptom score) and stable antipsychotic medications (at least six weeks with the same dosage) were recruited at the Clinical Hospital of the Medical School of University of São Paulo. We excluded drugs that can interfere with negative symptoms, neuropsychiatric conditions, contra-indications to PBM (as metallic plaques in the skull), or severe clinical conditions. Participants were randomly allocated to active or sham stimulation and received 10 sessions of PBM in 10 consecutive days, and after that, they inverted groups (who was sham went to active group and vice versa). They were evaluated at weeks 0, 1, 2, 3, 4, 6 and 12 for clinical outcomes. The operator of the PBM, the evaluators, the participants and the staff were blinded. For sham, the device has a similar electrode that does not generate the light field. A blinding scale was applied to evaluators, applicators, and volunteers to see if blinding had been effective. trained psychiatrists evaluated the participants. The PANSS scale was applied at weeks 0 (baseline), 1, 2, 3, 4 (endpoint), 6 and 12. The SANS (scale for the assessment of negative symptoms) and BPSS (brief negative symptom scale) were used as secondary outcomes. Adverse effects were assessed using a standardized questionnaire. The primary analysis was a repeated-measures analysis of variance with PBM (2 levels: active and sham) as the between independent variable and time (4 levels: week 0, 1, 2 and 4) as the within independent variable negative subscale of PANSS scores is the dependent variable. We used the command anova for crossover of Stata. Treatments was administered daily over a period of 2 weeks with a Light-Aid (Bright Photomedicine, SP, Brazil), continuous wave, 300 LED wavelength (850 nm) over the bilateral prefrontal cortex or with a placebo probe of the same appearance and display. The irradiation parameters created were based on the disease, pain intensity, and skin phototype. The Proton Magnetic Resonance Imaging and Spectroscopy was performed using the spectrum of four signals: choline, creatine, N-acetyl-aspartate and the lactate double peak in anterior cingulate gyros at baseline, week 2 and at the end of the PBM sessions (week 4).

Results: We did not have any dropouts from the study. Both groups were similar regarding clinical and demographical measures. The group that started with active stimulation had differences (more decrease in the scales of negative symptoms) with the other group after 2 weeks and maintained the effects. All the scales of negative symptoms had differences between groups and time, and without carry-on effects, the p values of intrasubjects effects on period, treatment and carryover are the following: negative PANSS (LESS THAN 0.00, .04 and 0.66), SANSS (LESS THAN 0.00, .04 and 0.68) and BNSS (0.03, 0.18 and 0.63), benefiting the active group. The positive or total PANSS and Calgary scale (depression) did not show differences between groups.

Conclusions: The group that started with the active group had a decrease of negative symptoms with statistical significance after 2 weeks. It seems that the effect of PBM started only after the 10 sessions of stimulation. We did not find differences between the levels of lactate in spectroscopy MRI in the ACC. These positive results should be better explored in further trials.

44. PROTECTIVE MECHANISMS AGAINST PSYCHOTIC EXPERIENCES

Larisa Morosan, *UMCG*

Overall Symposia Abstract: Psychotic disorders develop through subsequent stages of illness severity, from subclinical to clinical psychotic experiences. Research focused on the risk factors for psychotic experiences, but factors that may reduce symptom progression or even prevent onset of psychosis remain poorly understood. Understanding these protective mechanisms may improve early stage-specific interventions promoting resilience and preventing the disorder progression. The presentations in this symposium examine different protective mechanisms that buffer against psychotic experiences, focusing on different time-scales (i.e. daily, months, years) and on different populations (i.e., different age groups and nationalities) across the psychosis continuum (i.e. both general and clinical populations).

Sara van der Tuin, PhD candidate will present work on the daily associations between positive affect and psychotic experiences. For this purpose, she used daily diary data from the Mapping Individual Routes of Risk and Resilience (MIRORR) study. The results showed that positive affect and psychotic experiences were associated bidirectionally and that individuals at ultra-high risk (UHR) for psychosis presented a stronger negative association between daily positive affect and psychotic experiences. This highlights the protective role of positive affect against psychotic experiences, which might be stronger for UHR individuals.

Larisa Morosan, PhD will present work on the effect of daily social support on the association between daily hassles and daily suspiciousness. She also used the MIRORR daily diary. The results suggest that when people felt more supported, the association between the daily negative events and suspiciousness was weaker compared to days when they felt less supported, but only for participants with moderate psychotic symptoms without being UHR. This suggests the buffering effect of daily social support on daily suspiciousness differs depending on the clinical stage.

Neus Vidal Barrantes, PhD will present work investigating the Differential Susceptibility model, which suggests that genetic variants that increase the negative effects of adverse experience, also enhance the beneficial effects of positive experiences. The model was tested in nonclinical young adults and adults sampled for schizotypy. The presence of high genetic sensitivity moderated the effect of childhood adversity and the effect of daily negative and positive contexts on psychotic experiences, positive schizotypy, and depression. The results

highlight the role of genetic sensitivity in the psychotic and affective reactivity in daily life and the transdiagnostic protective role of positive experiences.

Daniel Nuñez, PhD will present results from a randomized controlled trial study aiming to test the effectiveness of a blended cognitive-behavioral intervention (CBT) to reduce mental health problems and to improve emotion regulation in adolescents. Participants allocated to the intervention group were presented with 12 sessions CBT sessions and the control group received treatment as usual. The program reduced psychotic experiences, depression symptoms, suicide ideation and improved cognitive and emotional skills. This shows that CBT based interventions delivered in school settings could be suitable to reinforce protective mechanisms against psychotic experiences and psychopathology during adolescence.

44.1. THE DAILY ASSOCIATION BETWEEN POSITIVE AFFECT AND PSYCHOTIC EXPERIENCES IN INDIVIDUALS ALONG THE EARLY STAGES OF PSYCHOSIS CONTINUUM

Sara van der Tuin^{*1}, Lorna Staines², Larisa Morosan¹, Esdras Raposo de Almeida¹, David van den Berg³, Sanne Booij¹, Albertine Oldehinkel¹, Johanna Wigman⁴

¹UMCG, ²Royal College of Surgeons in Ireland, ³Parnassia Psychiatric Institute, The Hague | ⁴VU University, Amsterdam, ⁴University Medical Center Groningen

Background: Psychosis often develops gradually along a continuum of severity. Little is known about the role of protective factors as positive affect (PA) in the development of psychotic experiences

(PEs). This study investigated (i) the temporal (between-day) and contemporaneous (within-day) daily associations between PA and PEs in individuals at different early clinical stages for psychosis and (ii) whether these associations differed per clinical stage.

Methods: Daily diary data of 90 days came from 96 individuals at risk for psychosis, distributed over four subgroups defined according to the clinical staging model (stages 0-1b). Multilevel models were constructed with PA as predictor of PEs and vice versa. We investigated within- and between-person temporal and contemporaneous associations, and tested whether these associations differed among early stages with multilevel moderation analyses.

Results: We found no within-person temporal effects between PA and PEs in either direction. Contemporaneously, current day PA predicted current day PEs ($B = -0.14$, p and $lt;0.001$) and vice versa ($B = -0.61$, p and $lt;0.001$). Between persons, more 90-day PA predicted less PEs in the temporal model ($B = -0.14$, $p = 0.03$). In addition, more 90-day PEs predicted PA in the temporal ($B = -0.26$, p and $lt;0.001$) and contemporaneous ($B = -0.36$, p and $lt;0.001$) model. The contemporaneous association between PA and PEs was stronger in individuals at ultra-high risk (UHR) for psychosis than in earlier stages.

Conclusions: Our study supported a significant within-day, bi-directional relationship between PA and PEs. This suggests that a focus on PA and methods to improve PA might be an important addition to early intervention practices, particularly in those at UHR for psychosis.

44.2. THE IMPACT OF DAILY SOCIAL SUPPORT ON THE ASSOCIATIONS BETWEEN DAILY NEGATIVE EVENTS AND DAILY SUSPICIOUSNESS ACROSS DIFFERENT CLINICAL STAGES OF PSYCHOSIS

Larisa Morosan^{*1}, Esdras Raposo de Almeida¹, Sara van der Tuin¹, David van den Berg², Sanne Booij³, Johanna Wigman⁴

¹UMCG, ²Parnassia Psychiatric Institute, The Hague | VU University, Amsterdam,

³Groningen University, ⁴University Medical Center Groningen

Background: Psychosis mostly develops gradually, from mild to more severe manifestations. Research focused mostly on risk factors predicting illness progression, but little attention is paid to the daily factors decreasing this risk. The current study aimed to investigate: i) the impact of daily negative events on daily suspiciousness and ii) the potential buffering effect of daily social support on the association between daily negative events and daily suspiciousness and whether this effect differs across clinical stages for psychosis.

Methods: Diary data from the Mapping Individual Routes of Risk and Resilience study were used. Participants (N=96, 76% females, aged 18-35 years old) were assigned into four subgroups representing clinical stages, from the general population to Ultra High Risk (UHR) for psychosis. For 90 days, participants reported on the unpleasantness of negative events, social support and suspiciousness. Multilevel models were fitted to test the contemporaneous (i.e. same day) and lagged (i.e. from one day to another) relations hypothesized in both research questions.

Results: On days when participants reported more unpleasant negative events, they also reported more suspiciousness. On days with more social support, the association between the unpleasantness of negative events and suspiciousness was weaker than during the days when social support was lower, but only for participants presenting moderate psychotic symptoms, without being UHR. The lagged effects were not statistically significant.

Conclusions: These results may improve the theoretical understanding of psychosis and guide the development of stage-specific interventions and prevention strategies enhancing and targeting social support in specific at-risk populations.

44.3. GENETIC SENSITIVITY TO THE ENVIRONMENT MODERATES BOTH THE RISK- AND RESILIENCE-INDUCING EFFECTS OF CHILDHOOD EXPERIENCES ON PSYCHOTIC, DEPRESSIVE AND ANXIETY DIMENSIONS

Neus Barrantes-Vidal^{*1}

¹Universitat Autònoma De Barcelona

Background: Gene-by-environment (GxE) studies in psychosis have exclusively focused on negative exposures. However, emerging evidence supports the resilience-enhancing effect of positive factors on psychosis outcome. The Differential Susceptibility (DS) model proposes that common genetic variants may confer not only disproportionate responsiveness to negative environments, but also greater sensitivity to positive, resilience-enhancing conditions. This study is the first to apply the DS model to the expression of subclinical psychosis, employing polygenic risk scores of environmental sensitivity (PRS-ES). PRS-ES were hypothesized to moderate, in a DS manner, associations between childhood adversity and psychosis, affective, and anxiety dimensions in young adults. An exploratory goal examined whether PRS for psychotic-like experiences (PRS-PLE) also showed DS patterns.

Methods: PRS, schizotypy, PLE, depression, anxiety, and childhood adversity ratings were obtained for 197 nonclinical young adults. LEGIT software for testing competitive-confirmatory GxE models was employed.

Results: Results largely supported DS: Individuals high on PRS-ES showed increased subclinical psychosis, depression and anxiety if they had experienced elevated childhood adversity, and lower symptoms if exposed to low levels of adversity as compared to those with low PRS-ES. Similarly, PRS-PLE moderated the effect of adversity on PLE, positive schizotypy, and depression following the DS model, but only PRS-ES moderation on PLE survived statistical correction.

Conclusions: Our results suggest that genetic DS to the environment is relevant to psychosis, depression, and anxiety. Current debates on reconceptualization of genetic ‘risk’ and resilience may benefit from this insight that support optimistic views on preventative efforts for early detection and intervention.

44.4. THE EFFECT OF A PILOT CBT BLENDED INTERVENTION ON PSYCHOTIC EXPERIENCES, DEPRESSIVE SYMPTOMS, SUICIDAL IDEATION AND COGNITIVE-EMOTIONAL REGULATION SKILLS IN ADOLESCENTS FROM CHILE

Daniel Nunez¹, Jorge Gaete², Daniela Meza³, Javiera Andaur³, Jo Robinson⁴, Lorna Staines*⁵

¹Universidad de Talca, Chile, ²Universidad de los Andes, Chile, ³Universidad de Talca,

⁴University of Melbourne, Australia, ⁵Royal College of Surgeons in Ireland

Background: Under the common mental disorder perspective, psychotic experiences, depressive and anxiety symptoms are prevalent in adolescents and could be manifestations of a latent continuum of common mental distress, which in turn is associated with suicidal ideation in this population. Prior evidence suggests that cognitive-behavioral skills and emotional regulatory process could be protective factors against these phenomena during the adolescence. We conducted a pilot randomized controlled trial (RCT) study to test the effectiveness of a blended cognitive-behavioral intervention (BCBT) to reduce mental health symptoms and suicide ideation, and to improve cognitive-behavioral skills and emotion regulation strategies in adolescents from high schools in Chile.

Methods: We assessed psychotic experiences (CAPE-P15), depressive symptoms (PHQ-9), anxiety symptoms (GAD-7), suicidal ideation (SIQ-JR), social -problem skills (SPSI-RS), cognitive-behavioral skills (CBTQ) and emotion regulation (ERQ-CA). After a cluster randomization (3 intervention schools and 3 control schools), participants allocated to the intervention group were presented with 12 sessions (8 online, 4 face-to-face sessions) delivered in school settings. Participants allocated to the control group received the treatment as usual in primary care centers. We used linear mixed-effects model analysis to compare the intervention and control groups regarding the change in outcome measures from baseline to post-intervention. Schools were included as a random factor for each outcome measure to account for possible school effects.

Results: At post-intervention, in the intervention group (N=30, Mean age=15.40 (SD=0.97)), we found significant reductions in depressive symptoms ($\beta=-3.5$; -5.0 to -2.0, $p < 0.001$), suicide ideation ($\beta=-15.3$; 95% CI-19.1 to -11.4, $p < 0.001$) and psychotic experiences ($\beta=-6.7$; -10.5 to -2.8, $p < 0.001$). Moreover, we found improvements in social-problem skills ($\beta=1.2$; 0.1 to 2.4, $p < 0.001$), behavioral activation ($\beta=2.4$; .4 to 3.4, $p < 0.001$) and cognitive reappraisal ($\beta= 3.9$; 0.9 to 6.7, $p < 0.001$).

Conclusions: The program was effective to reduce symptoms, including psychotic experiences and suicidal ideation, and to improve cognitive and emotional skills. This supports that CBT based interventions delivered in school settings could be suitable to reinforce resilience

mechanisms against common mental symptoms during adolescence. We expect to confirm these preliminary results through the RCT study being conducted during 2023.

45. CARDIOMETABOLIC CO-MORBIDITY IN SCHIZOPHRENIA SPECTRUM DISORDERS - UNRAVELING THE MIND-BODY INTERACTION

Wiepke Cahn, *University Medical Center Utrecht*

Overall Symposia Abstract: Patients with schizophrenia spectrum disorders (SSDs) demonstrate evidence of metabolic abnormalities at the earliest stages of illness. These precede treatment with antipsychotic (AP) medications, which through well-documented metabolic adverse effects exacerbate the problem. Individuals with SSDs subsequently lose 15-25 years of life to premature cardiovascular disease. Beyond the medical sequelae of these comorbidities, AP- metabolic adverse effects contribute to medication non-adherence, low self-esteem, decreased quality of life, and worse cognitive functioning. Obesity and other cardiometabolic abnormalities are also associated with brain alterations and add to the burden of brain changes in SSD. Together, this suggests that targeting metabolic comorbidity can have a meaningful effect on cardiometabolic, mental health, and brain outcomes.

This symposium, chaired by Dr. Wiepke Cahn (UMC, Utrecht, NL), takes a translational approach to dissect an emerging and complex topic: the underlying causes of metabolic comorbidity in SSDs and the potential impact of effectively managing metabolic comorbidity in relation to physical and mental health. Building on previous findings demonstrating that APs inhibit central insulin action, Dr. Margaret Hahn (University of Toronto, ON, Canada) will present novel preclinical data demonstrating that APs – across low and high metabolic liability medications, interfere with brain nutrient sensing including glucose (the key fuel source of the brain) and fatty acids, resulting in whole body insulin resistance, contributing to risk of diabetes. Dr. Tomas Hajek (National Institute of Mental Health, Klecany, Czech Republic) will present findings from a large cohort of individuals hospitalized for their first episode of psychosis in networks of hospitals in Czech Republic, which examined risk factors for weight gain/metabolic alterations including prospectively collected trajectories of daily medication use. Dr. Mahavir Agarwal (Centre for Addiction and Mental health, Toronto, Canada) will present data from a combined analysis of 3 weight loss intervention randomized controlled trials (Denmark and Canada), demonstrating that reductions in BMI are associated with reductions in brain age. Finally, Dr. Toby Pillinger (Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK) will discuss new clinical data investigating metabolic dysregulation and cardiac abnormalities in children and young people with first-episode psychosis. Additionally, Dr. Pillinger will discuss the development of initiatives to facilitate metabolically-minded prescription practices including app development to reduce incidence of metabolic comorbidity. Dr. Belinda Lennox (Oxford University, UK) will act as discussant, to review the complexities of cardiometabolic disorders and their treatment in SSDs, as well as perspectives to move the field forward.

Collectively, this symposium provides new insights into central and peripheral mechanisms of metabolic dysfunction produced by APs, including risk factors in the earliest phases of illness. Moreover, we provide evidence that effective management of metabolic comorbidities can have a significant impact on brain health, and we discuss development of novel technologies to prevent and manage metabolic comorbidities across the lifespan of individuals with SSDs.

45.1. ANTIPSYCHOTICS DISRUPT BRAIN FATTY ACID SENSING RESULTING IN WHOLE BODY GLUCOSE DYSREGULATION

Emily Au¹, Sandra Pereira², Sally Wu³, Raghunath Singh⁴, Kristoffer Panganiban⁵, Sri Mahavir Agarwal², Margaret Hahn*¹

¹*Center for Addiction and Mental Health*, ²*Centre for Addiction and Mental Health*, ³*Institute of Medical Science, University of Toronto*, ⁴*Centre for Addiction and Mental Health (CAMH), Toronto*, ⁵*Centre for Addiction and Mental Health, University of Toronto*

Background: Antipsychotics (APs) are the cornerstone treatment for schizophrenia and are widely prescribed for other conditions. However, APs are associated with adverse metabolic effects, increasing the risk for type 2 diabetes in a population suffering from early cardiovascular mortality. APs can directly perturb whole body glucose metabolism independently from changes in body weight, and this occurs in part through actions on the central nervous system (CNS). We have previously shown that olanzapine impairs CNS insulin and glucose sensing, resulting in whole body insulin resistance. In addition to key metabolic regulatory functions of insulin and glucose in the brain, post meal increases in circulating free fatty acids (FFAs) signalling “nutrient abundance”, can also strongly regulate food intake and whole body glucose homeostasis. In the current study, we set out to examine the effects of the APs olanzapine and haloperidol on central sensing of the fatty acid oleic acid and subsequent regulation of peripheral glucose metabolism.

Methods: Gold standard pancreatic euglycemic clamps were used to assess changes in glucose kinetics in response to a primed, continuous intracerebroventricular (ICV) infusion of oleic acid or vehicle solution (1.71 mM, 5 μ L/hour, into the third ventricle). Male rats were co-treated with a subcutaneous injection of olanzapine (Ola) (3 mg/kg), haloperidol (Hal) (0.25 mg/kg), or vehicle. Groups included (central–peripheral) Veh–Veh (n=11), Ole–Veh (n=9), Ole–Ola (n=5), Veh–Ola (n=5), Ole–Hal (n=6), and Veh–Hal (n=8). A radioactive tracer (3-³H-glucose) infusion throughout the clamp procedure was used to assess glucose kinetics, including hepatic glucose production and peripheral glucose uptake.

Results: Intracerebroventricular (ICV) oleic acid infusion caused an increase in peripheral glucose infusion rate (mg/kg/min) compared to ICV vehicle (Ole-Veh 7.82 $\pm$ 0.47 vs Veh-Veh 2.44 $\pm$ 0.52, p LESS THAN 0.001). This effect was inhibited by co-treatment with olanzapine (Ole-Ola 1.99 $\pm$ 0.46 vs Veh-Veh, p GREATER THAN 0.05) or haloperidol (Ole-Hal 2.25 $\pm$ 0.58 vs Veh-Veh, p GREATER THAN 0.05). ICV oleic acid also suppressed hepatic glucose production (clamp relative to basal: Ole-Veh 79% $\pm$ 11.93 vs Veh-Veh 25.23% $\pm$ 6.19, p LESS THAN 0.001) and this effect was prevented by co-treatment with olanzapine (Ole-Ola 28.86% $\pm$ 6.64 vs Veh-Veh, p GREATER THAN 0.05) or haloperidol (Ole-Hal 22.18% $\pm$ 7.75 vs Veh-Veh, p GREATER THAN 0.05). ICV oleic acid increased glucose utilization which was not observed in the antipsychotic co-treatment groups.

Conclusions: Olanzapine and haloperidol disrupt the ability of central oleic acid to regulate peripheral glucose kinetics, resulting in impaired whole-body glucose metabolism. Impairments in brain nutrient sensing can have detrimental metabolic effects and have been observed in type 2 diabetes. Our findings suggest that impairments in central lipid sensing represent a mechanism by which APs mediate metabolic adverse effects. We also confirm that weight gain independent effects on glucose homeostasis can occur across AP classes, including “lower” metabolic risk agents like haloperidol.

45.2. TRAJECTORIES OF DAILY ANTIPSYCHOTIC USE AND WEIGHT GAIN/METABOLIC CHANGES IN PEOPLE HOSPITALIZED FOR FIRST EPISODE OF PSYCHOSIS

Tomas Hajek*¹, Kristyna Vochoskova², Marian Kolenic³, Sean McWhinney⁴, Filip Spaniel⁵

¹National Institute of Mental Health, Klecany, ²National Institute of Mental Health, Czech Republic, ³National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic., ⁴Dalhousie University, Halifax, NS, Canada, ⁵National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic

Background: Most people with schizophrenia die from cardiovascular disorders closely related to metabolic syndrome/obesity. While there are other causes, antipsychotic medications are a key contributor to weight gain/metabolic dysregulation in schizophrenia. It is also the one factor, which is mostly under the control of the psychiatrist. Yet, we know very little about how medication switches and combinations of medications impact weight.

Methods: We recruited participants with first episode psychosis (FEP, N=173) during their first psychiatric hospitalization in a network of collaborating hospitals in Czech Republic. We prospectively collected weight, body mass index, metabolic markers and daily medication exposure at admission and during hospitalization.

Results: One third of people with FEP remained on monotherapy. Almost half of individuals (43%) experienced an escalation of medications, mostly a switch to a medication with a worse metabolic profile than their initial treatment. Only 23.7% of individuals moved from a metabolically more to a metabolically less problematic medication. Individuals with FEP gained on average 0.97+/-2.26 BMI points or 3.46+/-7.81 kg of weight after an average of 44.6 days of their first inpatient treatment. Greater antipsychotic exposure was associated with greater BMI increase, but only in people with normal/low baseline BMI, who were treated with clozapine, olanzapine, sertindole, or quetiapine. Patterns of medication changes were not related to weight gain and would not be even with thousands of individuals. Antipsychotic treatment was not directly linked to metabolic markers, but higher BMI was associated with higher TGC, TSH, and lower HDL.

Conclusions: Clinicians should be especially cautious in prescribing metabolically more problematic antipsychotics to people with a normal to low baseline BMI. Weight was the best predictor of metabolic alterations, thus emphasizing regular weight monitoring during antipsychotic treatment.

45.3. THE EFFECT OF WEIGHT LOSS ON BRAIN AGE IN SCHIZOPHRENIA

Mahavir Agarwal*¹, Vittal Korann², Nicolette Stogios³, Bjorn Ebdrup⁴, Filip K Knop⁵, Margaret Hahn⁶

¹University of Toronto, ²Centre for Addiction and Mental Health, University of Toronto, ³Institute of Medical Science, University of Toronto, Centre for Addiction and Mental Health, ⁴University of Copenhagen, ⁵Gentofte Hospital, University of Copenhagen, , ⁶University of Toronto, Centre for Addiction and Mental Health (CAMH)

Background: Individuals with schizophrenia often have metabolic comorbidities, such as type 2 diabetes, and experience a reduced life expectancy due to cardiovascular diseases. Obesity, a common comorbidity in schizophrenia, can negatively affect brain health. However, there is limited understanding of how metabolic disorders impact brain structure in individuals with schizophrenia, and the effects of weight changes following pharmacological interventions have not been explored. In this study, we will investigate changes in brain morphology, specifically

brain-age, in overweight or obese individuals with or without diabetes who have been diagnosed with schizophrenia. We will assess these changes before and after a 12-week period of pharmacological treatment targeting metabolic dysfunction. We hypothesized that 1) a change in BMI will be positively associated with the change in brain age between baseline and endpoint; 2) there will be no significant difference in the strength of the correlation between the medication and placebo groups. As exploratory analyses, we also looked at the association between brain age and cognition and metabolic parameters.

Methods: This analysis includes 48 participants, aged 18 to 65, from three double-blind studies investigating interventions for antipsychotic-induced metabolic dysfunction: TAO study (NCT01794429, 9 on medication and 8 on placebo), Metformin for prediabetes/diabetes study (NCT02167620, 11 on medication and 8 on placebo), and Topiramate in clozapine study (NCT02808533, 12 on medication). In brief, inclusion criteria include patients with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder, metabolic comorbidity of prediabetes or type 2 diabetes, and BMI of above 25 kg/m². We collected brain structural MRI, metabolic measures, cognition data, and body mass index at baseline and week 12. We utilized a convolution neural network-based classifier that was trained and tested to estimate the brain age of each participant using high-quality brain anatomical T1 image. The study aims to examine the changes in BMI and estimated brain age scores using baseline and endpoint data.

Results: BMI change was found to be statistically significant in the whole sample ($p < 0.001$), as well as in the medication group ($p = 0.005$) and placebo group ($p = 0.008$). Likewise, significant changes were found only in total and HDL (high-density lipoprotein) cholesterol levels across all three groups in terms of metabolic parameters. However, none of the groups exhibited any substantial changes in psychopathological scores or cognitive data between the baseline and endpoint assessments. Multiple regression analysis revealed a positive correlation between BMI change and alterations in brain age for the whole sample ($\beta = 0.263$; $t = 1.85$; $p = 0.05$) and the medicated group ($\beta = 0.372$; $t = 2.12$; $p = 0.04$), but not in the placebo group ($\beta = -0.106$; $t = -0.40$; $p = 0.69$). However, no significant difference in the correlation strength was observed between the medication and placebo groups ($p = 0.12$). Furthermore, there was no significant association between changes in brain age and metabolic indicators such as total and HDL cholesterol. Lastly, no significant correlation was found between brain age and cognition.

Conclusions: our study showed a link between brain health (as assessed by delta brain age) and significant weight loss by anti-diabetic medication in patients with SCZ and comorbid obesity. These findings imply that large and extended weight loss, together with general improvements in cardiometabolic alterations, can prevent obesity-related abnormalities in brain health.

45.4. PHYSIOLOGICAL EFFECTS OF ANTIPSYCHOTICS ACROSS THE AGE SPECTRUM: CURRENT UNDERSTANDING AND IMPLICATIONS FOR PRECISION MEDICINE

Toby Pillinger^{*1}, Maria Rogdaki², Christoph Correll³, Stefan Leucht⁴, Oliver Howes⁵, Orestis Efthimiou⁶, Robert McCutcheon⁷

¹*Institute of Psychiatry, King's College London*, ²*King's College London, Institute of Psychiatry*, ³*The Zucker Hillside Hospital*, ⁴*Klinikum Rechts der Isar, Technical University of Munich*, ⁵*King's College/ Clinical Sciences Centre*, ⁶*Institute of Social and Preventive Medicine, University of Bern, Switzerland*, ⁷*Institute of Psychiatry, Psychology and Neuroscience*

Background: Antipsychotics are associated with physiological disturbance, with clear differences observed between drugs in adults. However, the degree to which these alterations occur in children and adolescents is unclear. Furthermore, although clinical guidelines recommend discussing side-effects with patients when making treatment decisions, considering all side-effects of all treatments is a complex, multidimensional process. Therefore, we aimed to compare and rank antipsychotics based on their physiological effects in children and young people using network meta-analysis. We aimed to use these side-effect data within a digital tool that facilitates evidence-based and personalized prescribing.

Methods: First, we first conducted a systematic review, searching MEDLINE, EMBASE and PsychINFO from inception until 31 September 2023. We included clinical trials that compared acute treatment with 13 antipsychotics and placebo in individuals aged LESS THAN 18 years. We performed frequentist random-effects network meta-analyses to investigate treatment-induced changes in body weight, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, prolactin, heart rate, blood pressure, and QTc interval. Second, these data were then incorporated into a digital tool, termed the Psymatik Treatment Optimizer. This combines the side-effect data with side-effect concerns of an individual user, to enable users to select side-effects of concern and the relative degree of concern for each side-effect. Concern weightings and the side-effect databases are synthesised via a multicriteria decision analysis method (technique for order of preference by similarity to ideal situation, or TOPSIS).

Results: Of 6697 citations, we included 40 RCTs (median duration=6 weeks (IQR 6-12), comprising 6007 patients (mean age=15.13±0.94 years). 13 antipsychotics were included in the study. Estimated mean differences for change in weight compared with placebo ranged from -2.01kg (95% confidence interval: -3.61 to -0.41) for molindone to 4.68kg (0.63 to 8.66) for clozapine; and for BMI from -0.70kg/m² (-1.21 to -0.19) for molindone to 2.03kg/m² (0.51 to 3.55) for quetiapine. The majority of antipsychotics were associated with increased triglycerides, with an increase of up to 0.52mmol/L (-0.02 to 1.06) observed with clozapine. Risperidone/paliperidone was associated with the largest increase in prolactin levels, with an increase of 26.40ng/mL (21.13 to 31.67). Quetiapine was associated with the largest increase in heart rate of +12.42bpm (3.83 to 21.01) and systolic blood pressure of +10.04 (5.56 to 14.51). The Psymatik Treatment Optimizer synthesises these side-effect data with individual user-defined concern weights. Psymatik ranks antipsychotics in order of preference for the individual user, with the output presented in a heatmap.

Conclusions: We found strong evidence of clinically significant differences between antipsychotics in physiological side-effects when used in children and adolescents. For cardiometabolic changes, olanzapine, quetiapine, risperidone, paliperidone, and clozapine exhibited the worst profiles, and aripiprazole, blonanserin, ziprasidone, lurasidone, and molindone the more benign profiles. For alterations in prolactin, risperidone/paliperidone performed the worst and aripiprazole the best. Incorporation of these data into the Psymatik Digital Optimizer facilitates collaborative, personalised, and evidence-based prescribing decisions.

46. DISTURBED MYELIN PLASTICITY IN SCHIZOPHRENIA: FROM RISK FACTORS TO TREATMENT

Andrea Schmitt, *LMU*

Overall Symposia Abstract: Despite the critical role of cognitive deficits in schizophrenia, we neither understand their pathophysiology nor have a psychopharmacological treatment for them. Evidence from diffusion-weighted magnetic resonance imaging studies show impaired structural connectivity, reduced fractional anisotropy and white matter microstructure (WM)

across the lifespan in schizophrenia. These findings are interpreted as indicators of decreased myelination. In post-mortem brain regions such as the hippocampus, prefrontal cortex and cingulum, decreased numbers of oligodendrocytes, which are responsible for myelination, have been reported in schizophrenia. J Seitz-Holland combined multi-site cognitive, imaging, and clinical data to characterize cognitive deficits across the schizophrenia lifespan and assessed the association between cognitive deficits, clinical symptoms, and WM. WM mediated the association between schizophrenia and language/processing speed/working memory/non-verbal memory. In addition, processing speed mediated the influence of diagnosis and WM on the other cognitive domains. Oligodendrocyte-related risk variants are not among the top associations in genome-wide association studies (GWASs). However, in an enrichment analysis study of cell type-specific gene expression, oligodendrocytes and oligodendrocyte precursor cells (OPCs) showed enrichment in genes associated with schizophrenia. S Papiol evaluated the modulatory role of cell type-specific schizophrenia polygenic risk scores (PRS) on volume changes after three months aerobic exercise in hippocampal subfields. The analyses shows that the PRS associated with OPCs significantly influenced the volume changes in the CA4/DG subfield in schizophrenia patients. A higher OPC-associated genetic risk burden was associated with a less pronounced volume increase during the exercise intervention. Results are discussed in the light of recent animal studies showing that exercise promotes OPC differentiation. M Wegner analyzed the role of Tcf4 in oligodendroglial cells and studied Tcf4-deficient as well as the double heterozygous Tcf4/Olig2 null mutant mice. In this work, the GWAS-based schizophrenia risk gene Transcription Factor 4 (Tcf4) was shown to be the preferred heterodimerization partner for the Oligodendrocyte Transcription Factor 2 (Olig2) in oligodendrocytes and is required for differentiation of OPCs. These mice have oligodendroglial deficits and display reduced numbers of oligodendrocytes. The mouse models are suitable to investigate effects of oligodendrocyte-related pathophysiology on schizophrenia-related behavior with the aim to develop new treatment strategies. J Liu administered clemastine, an antimuscarinic compound that has been shown to enhance oligodendrocyte differentiation and myelination in vitro, and in adult mice following social isolation as a mouse model with schizophrenia-related behavioural deficits. Clemastine successfully reversed social avoidance behavior in mice undergoing prolonged social isolation. Impaired myelination was rescued by oral clemastine treatment, and was associated with enhanced OPC differentiation and epigenetic changes. This symposium highlights the need for new treatment strategies targeting deficits in myelination-related pathological processes. Because OPCs are capable of remyelination, triggering their differentiation could rescue deficits of white matter structures, thereby promoting connectivity and improving cognitive symptoms in schizophrenia.

46.1. THE ASSOCIATION BETWEEN WHITE MATTER MICROSTRUCTURE AND COGNITION IN PSYCHOSIS

Johanna Seitz-Holland^{*1}, Cornelius Berberich¹, Joanne D. Wojcik², Suheyla Cetin Karayumak¹, Alan Breier³, Martha Shenton¹, Marek Kubicki¹

¹Brigham and Women's Hospital, Harvard Medical School, ²Beth Israel Deaconess Medical Centre, Harvard Medical School, ³Indiana University School of Medicine

Background: Several neuroimaging studies highlighted the role of white matter microstructure in the psychopathology of psychosis. Specifically, diffusion magnetic resonance imaging studies utilized the fractional anisotropy (FA) measure and frequently interpreted reduced FA findings in psychosis as indicators of compromised white matter (e.g., myelination). Smaller studies reported a link between FA and cognitive deficits in individuals with psychosis.

However, other studies fail to find these associations, suggesting time, domain, or diagnosis-specific effects. Here, we present our recent findings from studies utilizing state-of-the-art imaging methods to explore the association between white matter microstructure and cognition across the psychosis spectrum.

Methods: We will present the results of two studies. While the first study focuses on the overall association, the second introduces a transdiagnostic multi-dimensional approach to examine white matter microstructure and cognitive functioning in the early phases of psychosis.

In the first study, we examined data from a multisite study of 900 individuals diagnosed with schizophrenia. We harmonized imaging and cognitive data and examined eight cognitive domains (language, processing speed, vigilance, working memory, verbal memory, non-verbal memory, motor function, and executive function). We compared cognitive function between individuals with schizophrenia and healthy individuals using t-tests and Cohen's d-effect sizes. Next, we applied regression and mediation analyses to examine the association between a diagnosis of schizophrenia, whole-brain FA, and cognition.

In the second study, we examined data from 203 individuals diagnosed with psychosis collected as part of the Human Connectome Project for Early Psychosis (HCP-EP). We used harmonization and novel processing methods and clustered individuals based on their cognitive performance. We compared general functioning, Perceived Stress, Life Satisfaction, Meaning and Purpose, Self-Efficacy, and voxel-wise cellular and extracellular white matter structure between the cognitive clusters.

Results: The first study demonstrated cognitive deficits in all domains ($p < 0.006$) and an association between white matter microstructure and language, processing speed, working memory, and non-verbal memory in individuals with schizophrenia. Processing speed mediated the influence of diagnosis and WM microstructure on the other cognitive domains. In the second study, we found two clusters with good stability and prediction strength based on cognitive measures: cluster 1 with lower ($n = 82$) and cluster 2 with higher performance ($n = 100$). There were more individuals with affective psychosis in cognitive cluster 2 ($\chi^2(1) = 5.70$, $V = 0.19$, $p = 0.017$), and cluster 2 was associated with lower Meaning and Purpose ($T(176) = 3.38$, $d = 0.51$, $p < 0.01$), better Social Functioning ($T(179) = -2.06$, $d = 0.31$, $p = 0.041$) and Self Efficacy ($T(180) = -2.23$, $d = 0.33$, $p = 0.027$), but not white matter microstructure.

Conclusions: Together, the studies highlight the critical role of cognitive deficits across the psychosis spectrum. Importantly, cognition seems to be related to measures of Efficacy, Meaning, and Purpose, all relevant to the quality of life but traditionally neglected in psychosis research. In addition, they emphasize that white matter microstructure is crucial in explaining the association between psychosis and cognition, specifically in later, more severe stages of the disorder. The findings also suggest the potential of early neuroprotective treatment for individuals with impaired cognition.

46.2. RISK GENES ASSOCIATED TO MYELIN PATHOLOGY IN SCHIZOPHRENIA

Sergi Papiol^{*1}, Isabel Maurus², Man-Hsin Chang², Thomas Schneider-Axmann³, Daniel Keeser³, Florian J. Raabe³, Andrea Schmitt³, Moritz J. Rossner³, Peter Falkai³

¹IPPG / LMU, ²University Hospital, LMU, ³Ludwig-Maximilians University 4⁴⁵

Background: Despite the compelling evidence of an oligodendroglial/myelin dysfunction in at least a subset of schizophrenia (SCZ) patients, genome-wide association studies (GWAS) in SCZ have not been able to identify a remarkable role of oligodendrocyte lineage-related genes

on the risk of this disorder. Compared to neuronal cell types, only discrete enrichment of SCZ risk loci has been reported in gene sets associated with oligodendroglial cells so far. However, these negative results may be the consequence of poorly-defined oligodendrocyte/myelin-related gene sets due to several technical and methodological reasons. In this presentation we will present gene set enrichment analyses based on novel data derived from human induced pluripotent stem cells (hiPSCs) to re-evaluate the oligodendroglial-specific impact on SCZ genetic burden.

Several studies have shown that physical exercise represents an effective intervention for patients with severe mental disorders such as schizophrenia. Recent findings have shown the specific effects of physical exercise on cognitive functions and brain structure in schizophrenia patients. However, little is known regarding the biological underpinnings of such an effect. In this presentation we provide novel evidence of the impact of schizophrenia polygenic risk related to oligodendrocyte lineage on the modulation of the effects of aerobic training on hippocampal brain structure in SCZ patients.

Methods: After an initial clustering analysis of hiPSC-differentiated neuronal cells including oligodendrocyte precursor cells (OPCs) and oligodendrocytes (OLs) with human postmortem brain cells based on single-cell RNA sequencing (scRNAseq), we performed a MAGMA gene set enrichment analysis leveraging the hiPSC-derived cell type-specific gene sets. Regarding the polygenic analyses, three different PRS were generated exclusively on the basis of the genetic variants in the genes (± 10 kb) that constitute the radial glia (PRS-Rad), OPCs (PRS-OPC), and mature oligodendrocyte (PRS-Oli) gene sets. Univariate linear regression was used to ascertain the role of such polygenic scores on hippocampus subfields volumes upon physical activity intervention, while correcting for the appropriate covariates.

Results: Genetic features of hiPSC-OLs were highly enriched in SCZ GWAS. Specifically, the enrichment was observed in the OL2 lineage, corresponding to a mature stage of oligodendrocyte development. In addition, polygenic analyses showed that the PRS-Rad and PRS-OPC were significantly associated with the volume changes in the CA4/DG hippocampus subfields in SCZ patients. A higher OPC/Radial glia-associated genetic risk burden was associated with a less pronounced volume increase (an potentially a lesser degree of beneficial effects) after the exercise intervention.

Conclusions: Our enrichment analyses results suggest that oligodendrocyte genes, especially in the stage of more mature differentiation (OL2), could actually have an outstanding contribution to the polygenic architecture of SCZ. Likewise, we provide further evidence of the interest of oligodendrocyte-related genes to understand the heterogeneity in the response to a physical activity intervention. Taken together, our results suggest intriguing links between genetic risk for SCZ associated to the oligodendrocyte lineage and plastic processes in the brain in these patients with therapeutic potential.

46.3. THE SCHIZOPHRENIA RISK GENE TCF4 DOES NOT ONLY AFFECT NEURONAL DEVELOPMENT, BUT HAS ADDITIONAL FUNCTIONS IN OLIGODENDROCYTES AND MYELINATION

Michael Wegner*¹

¹*FAU Erlangen-Nürnberg*

Background: Several genes that are linked to schizophrenia by GWAS or similar studies are not only expressed in neurons, but at similar levels in the macroglial cells of the central nervous system, including the myelin-forming oligodendrocytes. Their mutation, inactivation or malfunction may therefore not only contribute to schizophrenia because of their role in neurons

but also because of their function in oligodendrocytes. TCF4 is such a gene and it codes for a class I basic helix-loop-helix (bHLH) type transcription factor. Haploinsufficiency of TCF4 also causes the neurodevelopmental disorder Pitt–Hopkins syndrome.

Methods: To study the role of TCF4 in oligodendrocytes, we analyzed oligodendroglial development in knockout mice and complemented our study by TCF4 gain- and loss-of-function approaches in cultured mouse and human oligodendrocytes.

Results: Our results consistently showed that TCF4 is required cell-autonomously for proper terminal differentiation and myelination. In the absence of TCF4, oligodendrocytes differentiate in lower numbers and fewer myelin sheaths are formed. These phenotypes may also contribute to the severe impairment of commissure development observed in TCF4 knockout mice. Considering that class I bHLH proteins usually function as heterodimerization partners and functional modulators of class II bHLH proteins and that OLIG2 is a highly expressed and functionally important class II bHLH protein in oligodendrocytes, we also investigated the possibility of a functional link between TCF4 and OLIG2. Indeed we established that TCF4 is the preferential heterodimerization partner of OLIG2 and that both proteins together influence myelin gene expression. In line with biochemical results mice with combined heterozygous loss of TCF4 and OLIG2 show clear deficits in oligodendrocyte differentiation and myelination that are not observed in the single heterozygous mice.

Conclusions: In summary, our findings establish a role of TCF4 in oligodendrocytes and point to the possibility that part of the consequences of TCF4 malfunction in neuropsychiatric disorders such as schizophrenia is due to altered oligodendroglial rather than neuronal function.

46.4. TREATING DISTURBED MYELINATION IN SCHIZOPHRENIA: REPURPOSING A WAY AHEAD?

Jia Liu*¹

¹*City University of New York, Advanced Science Research Center*

Background: Emerging evidence shows that oligodendrogenesis and myelination are highly responsive to behavioral experience, including physical activity and social experience. Transcriptional, translational and ultrastructural changes in the oligodendrocyte and subsequent myelin have been identified and represent powerful mechanisms to regulate neuronal circuit function. Our laboratory has demonstrated that various traumatic social experience has a significant impact on myelination and oligodendrocyte, the myelin-forming cells. Impaired myelination preceded depressive-like behavior in socially isolated mice and was associated with aberrant epigenetic modifications in the oligodendrocytes.

Methods: Through oral administration of clemastine, an antimuscarinic compound that has been shown to enhance oligodendrocyte differentiation and myelination in vitro, we showed here it successfully reversed social avoidance behavior in mice undergoing prolonged social isolation and was associated with enhanced oligodendrocyte progenitor differentiation and epigenetic changes.

Results: Clemastine induced higher levels of repressive histone methylation (H3K9me3), a marker for heterochromatin, in oligodendrocytes, but not neurons, of the PFC. This was consistent with the capability of clemastine in elevating H3K9 histone methyltransferases activity in cultured primary mouse oligodendrocytes, an effect that could be antagonized by co-treatment with muscarine.

Conclusions: Our data suggest promoting adult myelination as a potential strategy to reverse depressive-like social behavior.

Oral Session: Biological Mechanisms

1. THE MEDIATING ROLE OF INFLAMMATION ON ASSOCIATIONS BETWEEN MARKERS OF METABOLIC DYSFUNCTION AND DEFICITS IN MOTIVATION AND PLEASURE IN PATIENTS WITH SCHIZOPHRENIA

David Goldsmith*¹, Courtney S. Ning¹, Robin E. Gross¹, Benson Ku¹, Evanthia Wommack¹, Elaine Walker², Michael T. Treadway², Jennifer Felger¹, Andrew Miller¹

¹Emory University School of Medicine, ²Emory University

Background: Bidirectional relationships between inflammation and metabolic dysfunction may contribute to the pathophysiology of psychiatric illness, including patients with schizophrenia. Obesity and other metabolic disturbances drive systemic inflammation via activation of macrophages in adipocytes, and in turn, increased inflammation contributes to further metabolic dysfunction, such as insulin resistance. In patients with schizophrenia, inflammatory markers such as C-reactive protein (CRP) have been shown to be associated with deficits in motivation and pleasure, but it is unknown whether markers of metabolic dysfunction may also contribute to these debilitating symptoms that are difficult to treat. Herein, we hypothesize that markers of metabolic dysfunction would also be associated with deficits in motivation and pleasure, but not negative symptoms related to deficits in expressivity. Moreover, we hypothesize that the association between metabolic dysfunction and deficits in motivation and pleasure would be mediated by increased inflammation, as measured by CRP.

Methods: 57 medically healthy patients with schizophrenia were recruited from Grady Memorial Hospital in Atlanta, Georgia (USA). Negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS), from which individual items can be examined and domain scores can be calculated for the two domains of Deficits in Motivation and Pleasure (MAP) and Deficits in Expressivity (EXP). Fasting blood was collected between 8AM -10AM and stored at -80C for later batched analysis. Plasma markers related to glucose metabolism, including glucose, insulin, resistin, adiponectin, and leptin were measured and a composite was calculated from the sum of Z-scores of all markers to examine the shared contribution of all circulating metabolic markers to negative symptoms. High sensitivity CRP was measured using an immunoturbidimetric assay. Associations between symptoms and metabolic markers were assessed using correlation (Spearman) and in linear regression models including age and sex. Finally, mediation models were used to examine the mediating role of CRP on observed relationships between metabolic markers and negative symptoms. Bootstrapping was used to examine the indirect effects. All analyses were conducted using SPSS version 27, including the PROCESS version 4.2 macro for the mediation analyses. We assessed significance at a p LESS THAN 0.05, uncorrected.

Results: There was a significant correlation between the metabolic composite score and the MAP Domain ($r=0.277$) as well as the anhedonia subscale ($r=0.273$, both p LESS THAN 0.05). Only resistin showed a significant relationship with avolition ($r=0.3$, $p=0.02$). Trend level associations (all p LESS THAN 0.1) were found between resistin and MAP and total BNSS score, leptin and total BNSS and anhedonia, as well as the composite score and avolition. No relationships were found with the EXP domain score or individual items. In regression models, there was a significant association between the composite score and MAP ($\beta=0.292$, $p=0.041$), as well as resistin and avolition ($\beta=0.277$, $p=0.039$). In the mediation analyses, the indirect effect of the metabolic composite score on MAP through CRP was $\beta=0.2937$, bootstrapped SE=0.1945, and bootstrapped 95% CI (0.0024, 0.7499). The direct effect of the

metabolic composite score on MAP was $\beta=0.6987$, $SE=0.4232$, $p=0.1045$ (95% CI, -0.1497, 1.5471). The direct effect of CRP on MAP was $\beta=1.8288$, $SE=0.8516$, $p=0.0363$ (95% CI, 0.1213, 3.5362).

Discussion: These results provide preliminary evidence that metabolic dysfunction contributes to negative symptoms related to deficits in motivation and pleasure, and not deficits in expressivity, similar to what has previously been shown with CRP. The results of the mediation analyses suggest that the impact of metabolic dysfunction on these negative symptoms are mediated by the influence of inflammation. Of the metabolic markers that contributed to the composite score, resistin and leptin were most strongly associated with these negative symptoms. Resistin has been shown to induce production of inflammatory cytokines and could serve as a link between disturbances in metabolism and inflammatory processes that may impact the brain and subsequent behavior. Leptin is a protein made by adipose cells and controls appetite and satiety in order to regulate energy balance. Relevant to negative symptoms, it may function as a way to limit motivated behaviors in order to conserve energy stores. Future studies will need to elucidate the relative contributions of metabolic dysfunction and inflammation, which may provide insights into novel treatment approaches to address deficits in motivation and pleasure. Furthermore, this work has the potential to support precision medicine approaches to identify those patients who may benefit from targeting these metabolic and inflammatory pathways.

2. GROUP III METABOTROPIC GLUTAMATE RECEPTOR ALTERATIONS IN THE NUCLEUS ACCUMBENS IN SCHIZOPHRENIA

Samara Walpole*¹, Jeremy S. Lum¹, Rose Chesworth Vieyra², Tim Karl², Cynthia Shannon Weickert³, Kelly A. Newell¹

¹University of Wollongong, ²Western Sydney University, ³Neuroscience Research Australia; Upstate Medical University

Background: Group III metabotropic glutamate receptors (mGluRs) (consisting of mGluR4, 7 and 8) are of increasing interest in the pathophysiology and treatment of schizophrenia. These receptors largely sit on presynaptic terminals where they regulate neurotransmitter release. The nucleus accumbens (NAc) is a brain area critical for reward learning and motivated behaviour known to be altered in schizophrenia and involved in current antipsychotic treatment. Group III mGluRs can regulate the activity of medium spiny neurons within the NAc, through tight control of cortical glutamate and local dopamine release. Therefore, due to their intricate involvement with both the glutamatergic and dopaminergic systems, group III mGluRs are a promising target for novel antipsychotics. However, little is known about their expression levels in the NAc in schizophrenia.

Methods: To investigate group III mGluR mRNA and protein levels in the nucleus accumbens (NAc), frozen postmortem NAc tissue from 30 individuals who had schizophrenia and 30 matched controls was obtained from the NSW Brain Tissue Resource Centre, Sydney. Gene expression of the individual group III mGluRs, GRM4, GRM7 and GRM8 was measured via qRT-PCR. Protein expression of mGluR4 and mGluR7 was assessed via western blot. We used t-tests or ANCOVAs to uncover differences between schizophrenia and control cases. Exploratory subgroup analyses were performed to examine the impact of sex and suicide on glutamate receptor levels.

Results: Gene and protein expression of the group III mGluRs in the NAc was not changed between schizophrenia and control subjects (all p GREATER THAN 0.05). However, subgroup analyses, revealed that females with schizophrenia had increased mGluR7 protein

levels (+33%, $p=0.014$) and a trend towards increased mGluR4 protein levels (+36%, $p=0.067$) compared to female controls. In contrast, males with schizophrenia showed decreased mGluR7 protein levels in comparison to male controls (-20%, $p=0.040$). mGluR7 protein expression was significantly elevated in schizophrenia subjects that died by suicide compared to schizophrenia subjects that died from other causes (groups that were matched for sex) (+46%, $p=0.017$). There were no changes in GRM4, GRM7, or GRM8 gene expression according to sex or suicide (all p GREATER THAN 0.05).

Discussion: Overall, we detected sex-specific alterations of mGluR7 in the NAc in schizophrenia, suggesting that alterations in mGluR7 protein levels are consequently altered or potentially underlie the disrupted glutamate regulation within the ventral striatum. Since the glutamate receptor pathology is not found at the mRNA level in the NAc, this also supports that the mGluR protein changes may be localized on glutamate or dopamine axon terminals. A strategy used to normalize mGluR7 within the NAc may differ in males and females with schizophrenia, implicating that sex-specific drugs/treatment may need to be developed. Our results support that group III mGluRs are involved in the pathophysiology of schizophrenia, and that further investigation of mGluR7 changes in terms of cellular localization and regulation of ventral striatal signalling is warranted.

3. HEPATITIS C VIRUS INFECTION OF THE CHOROID PLEXUS IS ASSOCIATED WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

Maree J. Webster¹, Ou Chen², Sarven Sabunciya*²

¹Stanley Medical Research Institute, ²Johns Hopkins University School of Medicine

Background: Many epidemiological studies have shown an association between infectious agents, particularly viruses, and psychiatric disorders including schizophrenia. However, evidence of a viral infection has not been found in the brain of people with schizophrenia. To further investigate the possible association between viral infections and psychiatric disorders, we performed next generation sequencing in the choroid plexus, combined with sequence enrichment technology targeting 3153 different viruses.

Methods: We enriched for viral sequences and performed RNA sequencing in postmortem choroid plexus isolated from 84 schizophrenia (SCZ), 73 bipolar disorder (BPD), 23 major depression (MDD) cases and 76 unaffected controls (CNT) from the Stanley Medical Research Institute brain collection. We reanalyzed previously generated RNA sequencing data in the hippocampus to determine if hepatitis C infection of the choroid plexus could alter the brain transcriptome and we used the TriNetX electronic health record database to determine the rate of chronic hepatitis C in a population of 285 million patients, including SCZ, BPD, MDD and controls.

Results: We found multiple viruses in the choroid plexus, including the Hepatitis C Virus (HCV) that was present in 6 SCZ and 4 BPD at relatively high levels but absent in control and MDD samples. We validated this finding with quantitative PCR and verified that not everyone with a history of HCV infection has the virus in their choroid plexus. Analysis of hippocampus RNA sequencing data generated on the same subjects revealed that although the virus was absent in this tissue, HCV infection of the choroid plexus was associated with consistent transcriptional changes in the hippocampus that were related to the innate immune response. Analysis of the electronic medical records revealed that the rate of chronic HCV was 3.6 and 3.9 percent respectively in the SCZ and BPD populations which was almost double that observed for MDD (1.8%) and approximately 7-fold higher than the control population (0.5%).

Discussion: Our data suggest that viral infection of the choroid plexus, instead of the brain itself, may be associated with psychiatric disorders. We discovered an association between

HCV infection of the choroid plexus and SCZ and BPD. Our results are consistent with the observation that nearly 50% of HCV patients suffer cognitive or psychiatric symptoms and that the prevalence of HCV infection is increased in SCZ and BPD populations. Our finding that the prevalence of HCV in MDD is half the rate of SCZ and BPD suggests that the HCV infection may be associated with disease pathology rather than behaviors such as intravenous drug injection, since these behaviors are present in all three disorders. Finally, we were able to demonstrate that the infection of the choroid plexus alone may be able to alter transcription in the hippocampus. Additional studies with larger sample sizes are required to replicate our results. Potentially, HCV screening of all SCZ and BPD patients followed by subsequent treatment of the infection may prove to be an effective therapy for this subset of the psychiatric population. Given that the estimates for SCZ is 1% and BPD is 3% of the population worldwide, these findings are worth exploring further as they could impact the lives of millions of patients.

4. HETEROGENEOUS MICROCIRCUIT PHENOTYPES DRIVE A COLLECTIVE DEFICIT IN THE 22Q11.2 DELETION IN CA1

Stephanie Herrlinger^{*1}, Bovey Rao¹, Anna Tuttman², Haroon Arain¹, Bert Vancura¹, Tristan Geiller¹, Joseph Gogos¹, Attila Losonczy¹

¹Columbia University, ²Mt. Sinai

Background: Individuals with the 22q11.2 deletion syndrome (22q11.2DS), one of the largest known genetic risk factors for schizophrenia, demonstrate cognitive impairments, including episodic memory (EM) dysfunction. Our group previously showed that EM and place cell stability in the hippocampus is impaired in a mouse model for the 22q11.2DS (Df(16)A+/-). Place cells are under strong inhibitory control by heterogeneous subtypes of GABAergic interneurons, several which are implicated in the pathophysiology of schizophrenia. In this study, we examined the unique contributions of hippocampal interneuron subtypes to local microcircuit dysfunction in CA1.

Methods: Wild-type and Df(16)A+/- mice performed a goal-oriented learning task on a cued belt while undergoing large-scale, unbiased 3D GCaMP-Ca2+ imaging of in vivo CA1 interneuron dynamics. Molecular identification of interneuron subtypes was performed post-hoc with immunohistochemistry. Interneuron subtype-specific activity was assessed through Pearson cross-correlations with velocity, peristimulus time histograms around behavioral indicators, spatial bin occupancy, and a linear classifier support vector machine to decode position.

Results: Fewer interneurons exhibit place preference in Df(16)A+/- mice (n=5ea, p=0.014), and interneuron activity decodes space more poorly than controls (n=5ea, p=0.0001). Interneuron-selective interneurons (ISI2/3-types) exhibit altered velocity-correlated (n=4ea, p=0.03/0.001) and less predictable activity (n=4ea, p=0.01). Somatostatin expressing interneurons exhibit a failure to extinguish old reward location enrichment activity when a reward zone is translocated (n=5ea, p=0.0001), while parvalbumin basket cells exhibit an aberrant reward modulation not observed in controls (n=5ea, p=0.006).

Discussion: We identify heterogeneous subtype-specific alterations in interneuron dynamics in the hippocampus during reward extinction, suggesting a dysfunctional microcircuit causing impaired learning in Df(16)A+/- mice.

5. INTESTINAL PERMEABILITY BIOMARKERS IN PATIENTS WITH SCHIZOPHRENIA: ARE THEY ASSOCIATED WITH PSYCHOPATHOLOGY AND COGNITIVE FUNCTION?

Leticia González-Blanco^{*1}, Francesco Dal Santo², M. Paz García-Portilla³, Miquel Alfonso⁴, Carla Hernández⁴, Mónica Sánchez-Autet⁴, Gerard Anmella⁵, Silvia Amoretti⁶, Gemma Safont⁷, Stefanie Malan-Müller⁸, David Martín-Hernández⁸, Miquel Bernardo⁹, Belen Arranz⁴

¹*Servicio de Salud del Principado de Asturias, University of Oviedo - CIBERSAM*, ²*Servicio de Salud del Principado de Asturias, University of Oviedo*, ³*University of Oviedo - CIBERSAM - INEUROPA - ISPA - Servicio de Salud del Principado de Asturias, Oviedo, Spain*, ⁴*Hospital Parc Sanitari Sant Joan de Déu*, ⁵*Barcelona Clinic Schizophrenia Unit, Institute of Neurosciences, University of Barcelona, IDIBAPS, CIBERSAM. Barcelona*, ⁶*Barcelona Clinic Schizophrenia Unit (BCSU). Bipolar and Depressive Disorders Unit. Hospital Clinic of Barcelona. University of Barcelona. IDIBAPS, CIBERSAM*, ⁷*Hospital Universitari Mutua Terrassa*, ⁸*Complutense de Madrid*, ⁹*Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clinic Barcelona. Universitat Barcelona. IDIBAPS. CIBERSAM*

Background: There is emerging evidence that increased intestinal permeability, along with the dysbiosis of gut microbiome, could be implicated in the pathophysiology of schizophrenia (SZ) (Caso et al., 2016). It involves the translocation of lipopolysaccharides (LPS), endotoxins found on the membrane of gram-negative bacteria, from the gut into the peripheral circulation, triggering a pro-inflammatory cascade (Ghosh et al., 2020).

The study aims to: (1) describe intestinal permeability in a cohort of SZ patients through plasma parameters of bacterial translocation: LPS, LPS binding protein (LBP), and intestinal fatty acid binding protein (I-FABP); (2) to investigate its association with the clinical severity of schizophrenia across the main symptomatic domains including positive, negative symptoms, and cognitive impairment.

Methods: The sample consisted of 242 adult patients with confirmed diagnosis of SZ (DSM-5) from an observational, cross-sectional and multicentric study including 4 centers in Spain (Anmella et al., 2023): mean age = 44.09 ± 12.63 , range = 18-76; males = 63.3%.

Assessment:

- a) Sociodemographic variables, years of illness, toxic habits, psychopharmacological treatment, body mass index (BMI), Mediterranean Diet Adherence Scale (MEDAS) and the Short Scale of Physical Activity (IPAQ).
- b) The PANSS to evaluate clinical severity and the Screen for Cognitive Impairment in Psychiatry (SCIP) to assess cognitive performance (immediate and delayed verbal learning, working memory, verbal fluency, processing speed).
- c) Plasma C-reactive protein (CRP), LBP, LPS and I-FABP levels.

Statistical analyses: U-Mann Whitney test, Spearman correlation and partial correlation analyses.

Results: Mean $\pm$ SD plasma concentrations of LBP, LPS and I-FABP were 17.93 ± 7.53 $\mu\text{g/mL}$, 0.76 ± 2.43 EU/mL and 0.23 ± 0.44 ng/mL respectively, and 62% of patients presented increased intestinal permeability (LBP GREATER THAN 15).

Correlations were found between LBP and age ($r=0.162$, $p=0.012$), BMI ($r=0.182$, $p=0.004$), CRP ($r=0.387$, p LESS THAN 0.001), between LPS and BMI ($r=0.194$, $p=0.003$), CRP ($r=0.298$, p LESS THAN 0.001), and between I-FABP and CRP ($r=0.227$, $p=0.001$). No

differences by sex were detected. Regarding lifestyle habits, only I-FABP showed significant correlation with MEDAS score ($r=-0.149$, $p=0.030$), and cigarettes per day with LPS ($r=0.285$, $p < 0.001$) and I-FABP ($r=0.178$, $p=0.007$).

Clinical severity: I-FABP showed a weak correlation with PANSS-Total ($r=0.185$, $p=0.004$), and both LPS ($r=0.145$, $p=0.026$) and I-FABP ($r=0.179$, $p=0.006$) with PANSS-Negative subscore.

Cognitive function: Only LBP showed inverse relationship with delayed verbal learning ($r=-0.198$, $p=0.011$).

However, when adjusted for age and BMI (partial correlation analyses), correlations of intestinal permeability parameters with clinical scores were no longer statistically significant.

Discussion: Plasma levels of intestinal permeability biomarkers were positively related to systemic inflammation, obesity and lower adherence to the Mediterranean diet in our sample of patients with SZ. However, like previous studies (Gokulakrishnan et al., 2022; Scheurink et al., 2023), we do not identify any association with clinical severity or cognitive impairment once confounding factors were controlled.

6. MICROGLIAL CANNABINOID RECEPTOR TYPE 1 MEDIATES SOCIAL MEMORY DEFICITS IN MICE PRODUCED BY ADOLESCENT THC EXPOSURE AND 16P11.2 DUPLICATION

Yuto Hasegawa^{*1}, Juhyun Kim², Gianluca Ursini³, Yan Jouroukhin⁴, Xiaolei Zhu¹, Yu Miyahara¹, Feiyi Xiong¹, Samskruthi Madireddy¹, Mizuho Obayashi¹, Beat Lutz⁵, Akira Sawa¹, Solange Brown⁶, Mikhail Pletnikov⁴, Atsushi Kamiya¹

¹Johns Hopkins University School of Medicine, ²Korea Brain Research Institute, ³Lieber Institute for Brain Development, ⁴Jacobs School of Medicine and Biomedical Sciences SUNY, University at Buffalo, ⁵Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University, ⁶Solomon H. Snyder

Background: Given recent marijuana legalization in the US, heightened attention has been the deleterious effect of cannabis use during adolescence, a critical period for prefrontal cortex (PFC) maturation, as a risk factor for psychiatric disorders such as schizophrenia. Notably, most cannabis users do not develop psychiatric symptoms, implying that cannabis exposure might act as an environmental risk factor for individuals with a genetic predisposition to psychiatric disorders. The cannabinoid receptor type 1 (Cnr1) is not only expressed in neurons and astrocytes, but also in microglia, which play a role in shaping neural connections during adolescence. However, the specific involvement of microglia in mediating the adverse effect of cannabis remains unexplored. In this study, we investigate the impact of adolescent delta-9-tetrahydrocannabinol (THC) exposure on microglia of which disturbance may be exacerbated by a genetic risk factor for psychiatric disorders, leading to aberrant PFC maturation and producing adult pathophysiology. Of particular interest is the interplay between THC exposure and 16p11.2 duplication (16p11dup), a major Copy number variation (CNV) risk associated with schizophrenia.

Methods: 16p11dup and control mice (both male and female) were chronically exposed to THC (8mg/kg) during adolescence by single daily subcutaneous injections. Subsequently, we conducted a series of molecular, histochemical, biochemical, electrophysiological, and behavioral assays to reveal the convergent effect of THC and 16p11dup on microglial function, resulting in disturbance of medial PFC (mPFC) neuronal function and cognition in adulthood.

Results: Adolescent THC treatment induced mPFC-specific microglial molecular and morphological changes via *Cnr1*-mediated mechanisms ($p=0.0001$, $t=10.97$, $df=10$). We also found that these microglia changes were exacerbated by 16p11dup, leading to neuronal subtype-specific deficits in intrinsic excitability of mPFC pyramidal neurons and resultant social memory deficits (THC x 16p11dup interaction [$F_{1,30}=5.665$, $p=0.0239$]). By performing microglia-specific RNA-seq experiments, we identified specific genes which may mediate these phenotypes induced by the convergent action of adolescent THC treatment and 16p11dup.

Discussion: Our findings highlight the unexplored impact of adolescent THC exposure on microglial function. In particular, we identified the role of *Cnr1* expressed in microglia for mediating its gene-environment effect on adolescent mPFC maturation and adult social memory in 16p11dup mice. We are currently investigating molecular mechanisms of how adolescent THC treatment impair microglia-mediated mPFC maturation in a neuronal subtype-specific manner.

7. PHARMACOLOGICAL INHIBITION OF HISTONE DEMETHYLASE LSD1 CORRECTS SCHIZOPHRENIA-RELATED DYSFUNCTIONS IN A MOUSE MODEL OF HUMAN ENDOGENOUS RETROVIRUS EXPRESSION

Felisa Herrero^{*1}, Michelle Meier¹, Ulrike Weber-Stadlbauer¹, Urs Meyer¹

¹*University of Zurich*

Background: Endogenous retroviruses (ERVs) are remnants of germline infections that took place several million years ago and represent approximately 8% of the human genome. Accumulating evidence implicates increased ERV expression in the spectrum of psychotic disorders, including schizophrenia and bipolar disorder. Thus far, however, the link between increased ERV expression and psychotic disorders remains largely circumstantial. To gain mechanistic insights into the neurobiological disease pathways affected by ERVs, we recently characterized a novel mouse model that mimics the expression of the human-specific ERV type-W envelope protein (HERV-Wenv). Compared to wild-type (WT) littermates, HERV-Wenv transgenic (TG) mice show schizophrenia-related behavioral and cognitive abnormalities, including deficits in prepulse inhibition (PPI) of the acoustic startle reflex and social recognition memory. In addition, HERV-Wenv TG mice display reduced expression of the schizophrenia risk gene *Setd1a*, a histone methyltransferase that produces mono-, di-, and trimethylated histone H3 at the lys4 residue (H3K4). The reduction in *Setd1a* expression was further associated with increased activity of histone demethylase LSD1, indicating widespread changes in the molecular machinery regulating histone methylation in HERV-Wenv TG mice. Therefore, the present study was designed to investigate whether pharmacological inhibition of LSD1 corrects schizophrenia-related abnormalities in HERV-Wenv TG mice.

Methods: Mice with transgenic HERV-Wenv expression were generated by inserting the multiple sclerosis-derived retrovirus (MSRV)-pvl4env sequence, featuring the HERV-W envelope open reading frame (ORF) and 3' long terminal repeat (3'LTR) under the CAG promoter, into the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. Adult male HERV-Wenv TG mice and WT littermates were treated orally with the LSD1 inhibitor, ORY-1001 (0.01 mg/Kg per day) or were subjected to vehicle treatment only. Behavioral and cognitive testing commenced after two weeks of drug or vehicle treatment. After completion of testing, brain samples were collected for molecular analyses of histone methylation and gene expression in hippocampal tissue.

Results: ORY-1001 fully mitigated the deficits in social recognition memory and PPI in HERV-Wenv TG mice without affecting these behavioral functions in WT mice. In addition,

the pharmacological treatment increased the expression of Setd1a and other histone methyltransferase genes, including, Kmt2a, Kmt2b, Kmt2d, and Setdb1. Additional molecular analyses are currently ongoing and will also be presented.

Discussion: Our preclinical data provide causal evidence for a role of HERV-W in disrupting schizophrenia-related behavioral and cognitive functions and epigenetic changes involving histone methylation. Moreover, our findings obtained in this preclinical model suggest that the inhibition of histone demethylase LSD1 may be an effective pharmacological approach for ameliorating schizophrenia-related dysfunctions, at least under conditions of abnormal HERV-W expression.

Oral Session: Neurophysiological Markers, Functional MRI and Neuromodulation

8. FUNCTIONAL NEUROIMAGING ANALYSIS OF ALTERED BRAIN METABOLIC PATTERNS IN SCHIZOPHRENIA: A COMPARATIVE HEAD-TO-HEAD TREATMENT-RESISTANT VS. TREATMENT-RESPONSIVE SCHIZOPHRENIA PATIENTS VS. CONTROLS

Mariateresa Ciccarelli^{*1}, Felice Iasevoli¹, Annarita Barone¹, Licia Vellucci¹, Giuseppe De Simone¹, Benedetta Mazza¹, Luigi D'Ambrosio¹, Valeria Gaudieri¹, Alberto Cuocolo¹, Sabina Pappatà², Andrea de Bartolomeis¹

¹University of Naples "Federico", ²Biostructure and Bioimaging Institute, CNR, Naples

Background: Antipsychotics represent the first-line therapy for schizophrenia, however a third of patients suffer from a treatment-resistant schizophrenia (TRS) condition characterized by more frequent brain structural and functional alterations. In this context, TRS shows putative unique neuroimaging correlates compared to treatment-responsive schizophrenia (nTRS), probably related to specific functional disconnection patterns. The present functional neuroimaging study aims at identifying significant differences in brain glucose metabolism of TRS vs. nTRS patients and healthy controls (HC) to be used as metabolic biomarkers to address clinical response in schizophrenia. The object of this study is to identify a functional metabolic alteration that may predict the response to antipsychotics in schizophrenia.

Methods: The study enrolled 70 subjects: 28 nTRS patients (15 males, 13 females; mean age 37.3 ± 10.1 ; disease duration 13.7 ± 8.1 ; chlorpromazine equivalents 333.6 ± 211.4 ; education years 12.6 ± 3.9), 26 TRS patients (23 males, 3 females; mean age 38.5 ± 10.5 ; disease duration 13.7 ± 8.1 ; chlorpromazine equivalents 604 ± 392.7 ; education years 11.6 ± 2.8), and 16 HC matched in age and sex. The clinical features were evaluated using the PANSS 5-factor model, and a t-test was performed using SPSS (p LESS THAN 0.01). The images were acquired with ¹⁸(F)FDG PET and analyzed using PMOD. The PET datasets were anatomically parcellated into 71 volumes of interests (VOIs) according to the AAL-merged atlas. The averaged VOI uptake values were normalized to the global GM matter average values. TRS, nTRS, and HC groups were compared using the one-way ANOVA statistical model ($p \leq 0.01$). Post hoc analyses were conducted with Bonferroni correction for multiple comparisons ($p \leq 0.00075$) and Tukey's test in all pairwise comparisons between groups ($p \leq 0.05$).

Results: 1. TRS patients compared to nTRS and HC showed a significant gradual frontal relative hypometabolism in the Left and Right Superior Frontal Gyri, Left and Right Middle Frontal Gyri, Left and Right Inferior Frontal Gyri (p LESS THAN 0.000).

2. TRS patients compared to HC showed significant relative hypometabolism in the Left Rectus Frontal Gyrus (p LESS THAN 0.000).

3. TRS patients compared to nTRS and HC showed a significant gradual relative hypermetabolism in the Right Calcarine Sulcus and Right Lingual Gyrus ($p < 0.000$).

4. TRS patients compared to HC showed significant relative hypermetabolism in the Left Calcarine Sulcus, Left Lingual Gyrus, Right Fusiform Gyrus, Vermis, Left and Right Cerebellum ($p < 0.000$).

Discussion: The results confirm that a more severe hypometabolism in the frontal cortex is one of the neurobiological underpinnings of TRS. These data suggest that the gradually altered brain metabolism in TRS patients compared to nTRS and HC potentially indicates a progressive more severe aberrant functional brain network associated with the resistance to antipsychotics.

9. DIMINISHED PAIRED CLICK RESPONSES IN PATIENTS WITH SCHIZOPHRENIA ASSOCIATED WITH IMPAIRED EXCITATORY-INHIBITORY CONNECTIVITY: INSIGHTS FROM THE BSNIP DATABASE

Hope Oloye^{*1}, Daniel J. Hauke², Julia Rodriguez-Sanchez¹, Vishal Thakkar³, David Parker⁴, Brett Clementz⁴, Carol Tamminga³, Karl Friston¹, Rick Adams⁵

¹University College London, ²Centre for Medical Image Computing, University College London, ³University of Texas Southwestern Medical Center, ⁴University of Georgia, ⁵University College London - Institute of Cognitive Neuroscience and Division of Psychiatry

Background: The paired click paradigm provides a simple, and reliable measure of early sensory processing (Boutros et al., 2004; Lijffijt et al., 2009; Wan et al., 2009). However, when paired with electroencephalography (EEG) patients with schizophrenia show a reduced response to both stimuli (Clementz et al., 1997; Mathiak et al., 2011; Sanchez-Morla et al., 2008; Rentzsch et al., 2008; Oranje et al., 2013). Theories of schizophrenia attribute these impaired responses to (1) a loss of pyramidal cell excitability via NMDA receptor dysfunction, (2) disinhibition due to interneuron dysfunction, or (3) a global loss of pyramidal cell inputs into interneurons (Dienel and Lewis, 2018). Here, we use dynamic causal modelling (DCM) of EEG-paired click paradigm data from the BSNIP dataset, to infer excitatory and inhibitory cell function in schizophrenia.

Methods: EEG data from people with a schizophrenia diagnosis (Scz, $n = 212$) and controls ($n = 277$) were grand averaged and source-localised, yielding a network comprised of bilateral primary auditory cortex (A1), insula, and middle frontal gyrus. We then modelled EEG responses to each of two clicks in the paired click paradigm, with a microcircuit consisting of superficial and deep pyramidal cells, spiny stellate cells, and inhibitory interneurons for all modelled regions.

Results: Diminished EEG responses (N100 and P200) to the clicks in patients with schizophrenia were explained by a reduced local excitability in bilateral A1 in patients and by reduced global excitatory pyramidal to inhibitory interneuron connectivity. Conductance-based modelling further revealed that this global reduction in excitatory-inhibitory connectivity was likely AMPA receptor-mediated.

Discussion: Our findings indicate that reduced N100 and P200 elicited through the paired click paradigm in people with a schizophrenia diagnosis is potentially due to impaired A1 excitability and global changes in AMPA-mediated pyramidal inputs to interneurons. Our results support theories that postulate a loss of both pyramidal cell excitability and their inputs to interneurons in schizophrenia. This modelling approach could potentially be employed as a

computational assay to probe AMPA-mediated receptor function and identify individuals who will benefit from glutamatergic pharmacological interventions.

10. CORTICAL REACTIVITY AND PLASTICITY AS TREATMENT BIOMARKERS OF SCHIZOPHRENIA: A PERTURBATION BASED STUDY

Sohini Chakraborty*¹, Urvakhsh Mehta¹, Jagadisha Thirthalli¹, Vanteemar Sreeraj¹, Rakshathi Basavaraju¹

¹*National Institute of Mental Health and Neurosciences*

Background: One of the most complex severe mental illnesses with a chronic course is schizophrenia. The age of onset in, most cases, is adolescence to early adulthood; ambushing individuals at a period when they are trying to be independent. However, around 20-30% do not respond to medication. Till the current year, we are searching for methods to reliably predict who will respond better to treatment with antipsychotic agents.

In this scenario, biomarkers like diminished cortical plasticity rose to prominence. This is especially significant since schizophrenia has evolved as a conceptual archetype of excitation/inhibition imbalance in the brain as a result of gene-environment interaction. Non-invasive biomarkers have gained much attention like TMS or transcranial magnetic stimulation. TMS is a neuro-psychiatric tool for measuring cortical activity using Faraday's law of electromagnetic conduction. This study aims to build on the previously conducted research to ascertain the degree to which treatment response with antipsychotics can be associated with cortical reactivity and plasticity, along with the speed of response, and the hypothesis proposed was higher cortical plasticity would be associated with better and faster treatment response.

Methods: A longitudinal study design was implemented where a total of 70, either medication-free or minimally treated, consenting adults of any gender, who were diagnosed with schizophrenia, psychosis NOS, or schizoaffective disorder based on ICD 10 were to be recruited. Participants with co-morbid substance use (except nicotine use), seizure disorder, intellectual disability, neurological disorder, head injury, gravid or post-partum females, or with metallic brain implants were excluded from the study.

Baseline psychopathology was determined using relevant scales: SAPS, SANS, BPRS, and CGI-SCH. The cortical reactivity parameters of 1-mV motor evoked potential (MT1), 120% of resting motor threshold (120% RMT), Short-interval intracortical inhibition (SICI), Long-interval intracortical inhibition (LICI), and Intracortical facilitation (ICF) along with cortical plasticity measures of MT1 and 120 RMT at 5 and 10 minutes post-intermittent Theta Burst protocol were recorded using TMS procedure.

The follow-up period for each patient was 4-8 weeks after starting antipsychotic treatment. This is an interim analysis of 40 patients recruited so far who have been successfully followed up weekly using CGI-SCH via either in-person or teleconsultation, with SAPS, SANS, and BPRS applied in the last follow-up.

Results: Equal male and female participants were recruited. Age of onset (39.4 years) and duration of illness (54 months) were highest for widowed females, while it appeared urban and rural residents had similar ages of onset of illness, 28.7 and 28.6 years respectively. The duration of education in years received by the individuals was negatively correlated with the age of onset of illness. Most of them belonged to Upper Lower socio-economic status and did not have an earlier age of onset of psychosis when compared with other socioeconomic groups. The duration of untreated illness appeared to be around one year, significantly lower than other

studies done in the Indian population. Only 10% of participants had a comorbid psychiatric illness and 60% had an additional medical illness, the most common being over-weight.

The interquartile range of baseline MT1 was higher for females than males while mean baseline MT1 and 120% RMT were lower for treatment-naïve individuals and those who had a history of prodrome. Participants with a family history of psychosis and who had poor pre-morbid functioning show facilitation instead of short-interval cortical inhibition. Average cortical plasticity at MT1 showed a wider variation in males (IQR=1.44) as compared to females (IQR=0.419), with overall cortical plasticity higher in those with a prodrome of psychosis.

In the follow-up, it was noted that treatment response was correlated with only the baseline LICl i.e., the higher the cortical inhibition better the treatment response in terms of positive symptoms rating scale SAPS and BPRS, a novel finding. Other factors like ICF, SICl, and cortical plasticity did not show a significant link with treatment response, which shall be re-examined further once recruitment is completed.

Discussion: The study aimed to determine if cortical reactivity or plasticity is associated with treatment response, which would in turn allow its use as a predictive biomarker. In this regard, the only stand out of the study is LICl. This is as per previous TMS and post-mortem-based findings where there are GABAergic inhibitory deficits in patients of schizophrenia. LICl, which is a paired-pulse TMS parameter utilizing a suprathreshold conditioning pulse 50–200 msec before the test pulse helps us understand GABA-B interneuron activity. This can be theorized as the stronger the activity of the inhibitory system in the brain, positive symptoms mediated by dopamine are more favourably controlled by additional dopamine-blocking effects of antipsychotics. However, we acknowledge there might be changes associated with prior medication use, even though 2 months of a drug-free period is considered critical for the inclusion of participants.

11. ALPHA-BAND EEG DESYNCHRONIZATION IN A VISUAL ODDBALL TASK PREDICTS CLINICAL OUTCOMES IN THE PSYCHOSIS RISK SYNDROME

Wendy Zhang^{*1}, Sarah Chang¹, Holly Hamilton², Sullivan Salone¹, Rui Ma¹, Charles Schleifer¹, Gregory Light³, Jean Addington⁴, Kristin Cadenhead³, Tyrone Cannon⁵, Barbara Cornblatt⁶, Matcheri Keshavan⁷, Diana Perkins⁸, William Stone⁹, Ming Tsuang³, Elaine Walker¹⁰, Scott Woods⁵, Carrie Bearden¹, Daniel Mathalon¹¹

¹University of California, Los Angeles, ²University of California, San Francisco; San Francisco VA Health Care System, ³University of California, San Diego, ⁴University of Calgary, ⁵Yale University, ⁶The Zucker Hillside Hospital, ⁷Harvard University, ⁸University of North Carolina At Chapel Hill, ⁹Harvard Medical School / Beth Israel Deaconess Medical Center, ¹⁰Emory University, ¹¹University of California, San Francisco

Background: Event-related desynchronization (ERD) of posterior alpha-band (8-12 Hz) oscillations following the presentation of task-relevant visual stimuli has been proposed as a key neural mechanism underlying visual perception and attentional control in service of ongoing goals. While attenuated posterior alpha ERD has been observed in individuals with schizophrenia and linked to visual attention impairment in this population, it remains unclear whether this neural deficit is readily evident among individuals at clinical high risk for psychosis (CHR-P) and predictive of clinical outcomes.

Methods: Electroencephalography (EEG) data were collected as part of the North American Prodrome Longitudinal Study (NAPLS-2) study. Individuals with CHR-P syndrome (n=492) and healthy control participants (HC; n=207) completed at baseline a visual oddball task in

which they were instructed to press a button in response to infrequently presented target visual stimuli while withholding responses to standard and distractor stimuli. Alpha ERD was measured as the change in alpha power at posterior electrode sites following target stimulus presentation relative to the pre-stimulus interval. The magnitude of alpha ERD was compared between CHR-P participants who developed psychosis before 24-month follow-up ($n=63$), those who remained symptomatic ($n=138$) or remitted from CHR-P ($n=52$) at follow-up, and HCs.

Results: Alpha ERD was attenuated in CHR-P individuals compared to controls ($d = 0.24$). Baseline magnitude of alpha ERD was significantly reduced in those who later converted to psychosis compared to non-converters ($d = 0.31$). CHR-P participants who remitted showed similar degrees of baseline alpha ERD to that of control participants and significantly greater alpha ERD than those who remained symptomatic ($d = 0.23$) and converted to psychosis ($d = 0.48$).

Discussion: Modulation of posterior alpha oscillations in response to task-relevant visual stimuli, a neural index of visuospatial attention, was associated with clinical outcomes in individuals at clinical high risk for psychosis. Impairment in alpha ERD was only observed at baseline for at-risk individuals who later developed psychosis and, to a lesser degree, those who continued to be symptomatic at follow-up, but not for those with subsequent symptom remission. The study demonstrates a promising neural marker of psychosis risk that may contribute to ongoing efforts to improve outcome prediction in CHR-P.

12. FUNCTIONAL CONNECTIVITY GRADIENTS AND THOUGHT-PATTERNS IN SCHIZOPHRENIA - NEGATIVE SYMPTOMS

Tal Geffen^{*1}, Samyogita Hardikar², Jonathan Smallwood³, Mariia Kaliuzhna⁴, Fabien Carruzzo⁴, Teresa Katthagen⁵, Stephan Kaiser⁶, Florian Schlagenhauf⁵

¹*Campus Charité Mitte, Charité - Universitätsmedizin, Berlin*, ²*Max Planck Institute for Human Cognitive and Brain Sciences*, ³*Queen's University*, ⁴*University of Geneva, Clinical and Experimental Psychopathology Laboratory, Faculty of Medicine*, ⁵*Campus Charité Mitte, Charité - Universitätsmedizin, Berlin*, ⁶*Geneva University Hospital, Adult Psychiatry Division*

Background: In schizophrenia patients (SZP) with predominantly negative symptoms, we investigated Thought-Patterns (TP) and their links with macroscale neural connectivity patterns known as ‘gradients’. The first gradient (G1) reveals a change in connectivity pattern from the unimodal Visual network to the multimodal Default Mode Network (DMN). The second gradient (G2) reflects a change between two sensorial networks: the Somatomotor (SomMot) and Visual (Margulis et al., 2016). We compared the results to healthy controls (HC).

Methods: 77 SZP and 66 HC participants underwent a 9.8-minute resting-state fMRI scan at two study centers in Berlin and Geneva. Post-scan, they reported thoughts using the Multi-Dimensional-Experience-Sampling (MDES: Gorgolewski et al., 2014). TP were summarized using Principal Component Analysis (PCA) and (A) compared between groups, controlling for center. We generated cortical connectivity gradients using PCA in the BrainSpace toolbox (Vos de Wael et al., 2020), using Schaefer-400 parcellation and incorporating 7 Yeo networks. (B) Gradients were compared between groups at both parcel and network levels. We used 400 parcels from the first three gradients (1200 General Linear Models; GLM) and seven network scores from the first three gradients (21 GLMs in total) as independent variables, controlling for center and motion. Results were corrected for False Discovery Rate (FDR) and additional Bonferroni correction for multiple comparisons. (C) Using significant parcels and TPs from analyses A and B, we regressed, parcel connectivity values against group and TP, and

corrected all results for multiple comparisons. (D) Finally, within the SZP group, we calculated partial Spearman correlation, controlling for motion, between the TP and parcels that were significantly different between groups.

Results: SZP had lower Abstract-Spontaneous TP values [$t(140) = -2.68$, $P_{\text{bonf6}} = 0.048$] and higher Intrusive-Negative TP values than controls [$t(140) = 3.49$, $P_{\text{bonf6}} = 0.003$]. (B) Network Gradient analyses revealed that SZP exhibit greater dissociation between attentional-related networks (Control and Dorsal Attentional Network: DAN) and the DMN and more similarity of the attentional networks to sensorial networks in G1 and G2 [G1-DAN: $t(139) = 3.42$, $P_{\text{bonf21}} = 0.01$; G2-Control: $t(139) = 3.33$, $P_{\text{bonf21}} = 0.021$]. An important finding was a shorter G2 in SZP, [G2-visual: $t(139) = 3.34$, $P_{\text{bonf21}} = 0.021$], i.e., less segregation between the two dissociate networks on G2, the SomMot and the Visual. Three parcels differed significantly between the groups, replicating some of the network-level findings. (C) Furthermore, the parcel score of G2_SomMot/ Temporal-Parietal-right was predicted based on the group and the Abstract-Spontaneous TP [$t(136) = 2.63$, $P_{\text{bonf3}} = 0.02$]. (D) In addition, a positive Spearman correlation was found in SZP between Intrusive-Negative TP and parcel score of G3_DAN/Post-central-gyrus-right (POSTc_r) [$r(74) = 0.25$, $p = 0.02$].

Discussion: MDES effectively assesses TP and differentiates HC and SZP. Gradient analyses in SZP showed increased similarity between attention and sensorial networks and dissociation of the DMN from the attentional networks. SZP display a shorter G2, indicating reduced segregation between SomMot and visual networks, aligning with previous findings in SZ (Holmes et al., 2023). We could predict gradient parcel score based on TP. Additionally, in SZP, Intrusive-Negative TP correlates positively with G3_DAN/POSTc_r score, suggesting increased DMN dissociation and Control network similarity of that parcel, associated with more intrusive-negative TP. A similar finding was noted in HC with Specific-Intrusive TP (Hardikar et al., 2022).

13. NETWORK-INFORMED BRAINAGE PREDICTION IN EARLY PSYCHOSIS

Shalaila Haas^{*1}, Yuetong Yu², Hao-Qi Cui², Faye New¹, Ruiyang Ge², Sophia Frangou²

¹*Icahn School of Medicine at Mount Sinai*, ²*University of British Columbia*

Background: Extensive research has established the difference between neuroimaging-predicted and actual chronological age (brainAGE), as a robust and biologically meaningful measure of brain health. This has been convincingly demonstrated by the ENIGMA Schizophrenia Working Group which found an average acceleration of brain aging of ~4 years using brain morphometric data obtained from 2803 patients (Constantinides et al. 2023). However, brainAGE is generally computed as a global index of age-related brain changes, disregarding information about spatial variation. To address this gap, we developed brainAGE models for various brain networks in healthy individuals that were applied to patients with affective and non-affective early psychosis.

Methods: The T1w structural images were processed using Freesurfer v7.1 in 9473 healthy individuals (aged 3-92 years; N [%] female = 5126 [54.11%]) across 9 datasets. Subsequently, the Schaefer atlas was used to generate parcels (200, 400, 600, 800, 1000) of cortical thickness and cortical surface area, each assigned to one of the 7 Yeo networks. Sex-specific pooled datasets were split into a training (80%) and testing (20%) subsets. Model performance was assessed by mean-absolute-error (MAE) and the correlation between predicted and chronological age in the test set after age-related bias adjustment. The parcellation with the lowest MAE was subsequently applied to 93 non-affective psychosis (mean [SD] age = 22.19 [3.36]; 28 [41.79%] female), 28 affective psychosis (mean [SD] age = 24.46 [4.26]; 19 [28.36%] female), and 57 healthy individuals (mean [SD] age = 24.79 [4.12]; 20 [29.85%])

female) from the Human Connectome Project for Early Psychosis, and compared with respect to brainAGE.

Results: For all networks except the visual network, the mean-absolute-error reduced with increasing number of parcels (ranges across all: visual=6.00-6.70; somatomotor=5.00-5.67; dorsal-attention=6.91-7.32; salience=5.31-5.92; limbic=5.82-6.65; control=5.46-6.20; default=4.89-5.51). Correlation between predicted and chronological age was high across all networks (mean correlation across networks = 0.93) and varied by maximally 0.02 with increasing parcels. Correspondence between males and females for mean-absolute-error across networks was high (GREATER THAN 0.97). Network-brainAGE was highest across networks in patients with non-affective psychosis (mean brainAGE = 5.42), then affective psychosis (mean brainAGE = 3.57), and healthy individuals (mean brainAGE = 1.42). In patients with non-affective psychosis, brainAGE was greatest in sensory networks including the visual (mean [SD] = 6.25 [9.76]) and somatomotor networks (mean [SD] = 8.13 [8.03]). In patients with affective psychosis, brainAGE was greatest in somatomotor (mean [SD] = 6.64 [7.58]) and salience/ventral attention networks (mean [SD] = 5.31 [8.33]).

Discussion: This study introduces novel network-specific brainAGE models that offer spatially distinct insights into aging patterns in clinical samples, including patients with early psychosis. These network-informed measures might demonstrate stronger associations with cognitive deficits, psychopathology, and risk factors.

14. THE EEG MULTIVERSE OF SCHIZOPHRENIA

Dario Gordillo*¹, Janir Ramos da Cruz², Eka Chkonia³, Wei-Hsiang Lin¹, Ophélie Favrod¹, Andreas Brand¹, Patrícia Figueiredo⁴, Maya Roinishvili⁵, Michael H Herzog¹

¹EPFL, ²EPFL, *Universidade de Lisboa*, ³Tbilisi State Medical University, *Free University of Tbilisi*, ⁴Universidade de Lisboa, ⁵Free University of Tbilisi, *Beritashvili Centre of Experimental Biomedicine*

Background: Studies in patients with schizophrenia typically use a single experimental paradigm. The results often show a clear-cut difference in patients compared to healthy controls. Subsequent studies then try to understand the underlying cognitive, neural, and genetic abnormal mechanisms. This approach rests on the implicit assumption that the paradigms tap into a key abnormality of schizophrenia. If true, the different paradigms should strongly correlate with each other. Here, we explicitly tested this assumption by examining whether different features from resting-state electroencephalogram (EEG) are correlated in patients with schizophrenia.

Methods: We recorded resting-state EEG from 121 patients with schizophrenia and 75 healthy controls and extracted 194 EEG features, including EEG microstates, source and sensor connectivity, and spectral features, which have long been well-established in schizophrenia research. We identified the EEG features with significant differences between patients and healthy controls. We recorded the EEG from 38 patients with schizophrenia and 27 healthy controls after approximately 5 years to investigate the stability of our results.

Results: We found that 69 of the 194 EEG features showed significant group differences between patients and healthy controls with medium to large effect sizes (Cohen d ranged from 0.46 to 1.04), indicating that important mechanisms are targeted. Surprisingly, the correlations between these 69 EEG features were very weak in the patient population, suggesting that different EEG features target different mechanisms. As such, they may be less representative of schizophrenia than initially thought. Importantly, we show that most of these EEG features show very good long-term reliability, i.e., the results are stable.

Discussion: Our findings raise several questions about the specific nature and interpretation of significant results in schizophrenia research. We propose that analyzing the relationship between several features from a multiple of paradigms and analysis methods may help to identify the most representative paradigms and mechanisms of schizophrenia. We argue that representing schizophrenia within a high-dimensional space holds promise as an approach to address the heterogeneity of the disorder.

15. COMPUTATIONAL MODELLING OF P300 RESPONSES TO PROBE INHIBITORY AND EXCITATORY CELL FUNCTION IN PATIENTS WITH SCHIZOPHRENIA AND ACROSS TRANSDIAGNOSTIC BIOTYPES: INSIGHTS FROM THE BSNIP STUDY

Daniel J. Hauke^{*1}, Hope Oloye¹, Julia Rodriguez-Sanchez¹, Vishal Thakkar², David Parker³, Brett Clementz³, Carol Tamminga², Rick Adams¹

¹University College London, ²University of Texas Southwestern Medical Center, ³University of Georgia

Background: The P300 is a brain response that is elicited when individuals detect a behaviorally relevant change in the environment and is reduced in schizophrenia. Impaired responses have been attributed to (1) a loss of pyramidal cell excitability via NMDA receptor dysfunction, (2) disinhibition due to interneuron dysfunction or (3) a global loss of pyramidal cell inputs into interneurons (Dienel and Lewis, 2018). Recent efforts to identify transdiagnostic biotypes across schizophrenia, bipolar disorder and schizoaffective disorder further suggest that P300 responses may be differentially impaired in different biotypes (Clementz et al., 2016). Here, we modelled P300 responses in schizophrenia patients and previously derived biotypes to determine how inhibitory and excitatory circuit function is changed across these groups.

Methods: Electroencephalography (EEG) data was recorded during an auditory oddball paradigm from healthy controls (n=284), patients with schizophrenia (n=231) and three transdiagnostic biotypes that included patients with schizophrenia, bipolar and schizoaffective disorder diagnoses (biotype 1: n=167, biotype 2: n=163 and biotype 3: n=169; Clementz et al., 2016). We modelled circuit function in a network of regions comprising the dorsal attention network including bilateral inferior frontal junction (IFJ), intraparietal sulcus (IPS) and primary auditory cortex (A1) as an auditory input region. Each region was modelled as a microcircuit comprising spiny stellate cells, inhibitory interneurons and superficial and deep pyramidal cells.

Results: Our results suggest that impaired P300 responses in individuals with a schizophrenia diagnosis are associated with a loss of local excitability in IPL (group-by-condition interaction, $p < 0.05$). Interestingly, biotype 1 exhibited a more severe loss of excitability in IPL, but also net disinhibition of pyramidal cells due to loss of pyramidal inputs to interneurons and disinhibition due to loss of interneuron function (all $p < 0.05$). Biotype 2 showed a loss of local excitability in IPL (similar to biotype 1, but less severe) accompanied by globally reduced excitatory inputs to pyramidal cells (all $p < 0.05$). Lastly, biotype 3 showed no loss of excitability but was rather characterized by a net disinhibition of pyramidal cells due to loss of pyramidal inputs to interneurons (all $p < 0.05$).

Discussion: Our findings support aetiological theories that postulate that schizophrenia is characterized by disturbances in regulating the excitation/inhibition balance. They also suggest that transdiagnostic biotype 1, showing the most severe impairments, may map onto all three postulated dysfunctions: (1) loss of pyramidal cell excitability, (2) interneuron function and (3)

pyramidal cell inputs into interneurons. Conversely, biotype 2 and biotype 3 were better explained by only (1) a loss of pyramidal cell excitability or (3) a loss of pyramidal cell inputs into interneurons, respectively. This modelling approach could be used to probe different cell functions non-invasively in the future and identify new drug targets for individualized pharmacological interventions to restore excitation/inhibition balance and alleviate psychotic symptoms.

Oral Session: Clinical Trajectories

16. INTEGRITY OF AUDITORY SENSORY PROCESSING AT FIRST-EPISODE PSYCHOSIS PREDICTS SYMPTOM RECOVERY: EVIDENCE FROM MEG AND EEG USING A SINGLE-TONE PARADIGM

Francisco José López Caballero*¹, Mark Curtis¹, Brian Coffman¹, Dean Salisbury¹

¹*University of Pittsburgh School of Medicine*

Background: Predicting the course of symptoms in individuals experiencing their First Episode of Psychosis (FEP) is essential for tailoring precise treatment strategies and enhancing clinical outcomes. Recent findings highlight the role of temporal lobe function, specifically assessed through biomarkers like N100, in predicting the progression of psychotic symptoms and its association with the consequences of untreated psychosis. Our laboratory's recent report supported that Magnetoencephalographic (MEG) M100 responses to tones in an oddball paradigm predicted the longitudinal recovery of positive symptoms in FEP individuals, as evaluated by the Positive and Negative Syndrome Scale (PANSS). Additionally, the Duration of Untreated Active Psychosis (DAP), a metric of untreated psychosis based on the onset of clinician-recognized symptoms, predicted symptom change through its influence on M100. In this study, our objective was to extend these findings by 1) using a simpler single-tone paradigm, easier to incorporate in routine clinical practice; 2) incorporating both MEG and EEG methodologies; and 3) examining associations across PANSS dimensions (Positive, Negative, General).

Methods: We recorded MEG (M100) and EEG (N100) in 29 FEP individuals, assessing symptom severity at baseline and approximately seven months later. Sequential Regression analyses predicted overall symptom change (Δ PANSS Total) from DAP and baseline M100 source-localized in bilateral auditory cortex, controlling for baseline symptoms. Identical regressions were performed for each PANSS subscale. Parallel regression analyses were conducted in a subsample of participants with usable EEG ($n = 24$), measuring N100 at FCz.

Results: Results revealed that a smaller baseline M100 predicted poorer overall symptom recovery at follow-up, independently of baseline symptom severity. Longer DAP showed a similar prognostic relationship, with this association being fully mediated by M100. Regression analyses with PANSS factors indicated that M100 predictions were primarily associated with the general psychopathology factor, rather than specific positive or negative symptoms. Parallel results were observed when measuring N100 with EEG.

Discussion: Our findings underscore the significance of temporal lobe dysfunction, particularly compromised auditory sensory processing, as an indicator of a more challenging recovery trajectory in general psychopathology during the initial months post-disease onset. Prolonged untreated psychosis exacerbates temporal lobe dysfunction, further predicting a worsened disease progression. Notably, utilizing N100 measured with EEG and a single-tone task emerges as a cost-effective and easily implementable tool for informing clinicians about

the likely progression of overall psychotic symptomatology, thereby guiding resource allocation, closer monitoring, or intensified pharmacological intervention.

17. CHILDHOOD TRAUMA TYPES AND ANTIPSYCHOTIC EFFECTIVENESS IN PSYCHOSIS: A PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL

Nina Mørkved*¹, Erik Johnsen², Rune A. Kroken³, Christoffer A. Bartz-Johannessen⁴, Else-Marie Løberg⁵

¹*Mosjoen District Psychiatric Centre, Helgeland Hospital*, ²*Division of Psychiatry, Haukeland University Hospital; University of Bergen*, ³*Division of Psychiatry, Haukeland University Hospital; NORMENT Center of Excellence, University of Oslo; Department of Clinical Medicine (K1), University of Bergen*, ⁴*Division of Psychiatry, Haukeland University Hospital; NORMENT Center of Excellence, University of Oslo*, ⁵*Faculty of Psychology, University of Bergen; Division of Psychiatry, Haukeland University Hospital*

Background: Treatment with antipsychotics (APs) for schizophrenia spectrum disorders (SSDs) is generally effective, however, a significant proportion does not respond favorably to first-line APs. Factors influencing effectiveness may include exposure to childhood trauma (CT), including subtypes such as physical, sexual, and emotional abuse, and physical and emotional neglect. There is a paucity of research on CT in relation to treatment with APs in SSDs. Some studies find CT to be associated with less treatment effect, others fail to find this association. Possibly, the variation and heterogeneity in treatment response could be explained by different subtype profiles of CT.

Methods: The Bergen-Stavanger-Trondheim-Innsbruck (BeSt InTro) study is a pragmatic, single-blinded, randomized controlled drug trial. Participants (n = 98) with diagnoses within the schizophrenia spectrum (F20-29 in the International Classification of Diseases – 10th Revision) were randomized to receive one of the first-line atypical APs amisulpride, aripiprazole or olanzapine. The present study examined the relation of CT subtypes on the level of psychosis symptoms as measured by the PANSS after 52 weeks of antipsychotic treatment. The Childhood Trauma Questionnaire Short-Form (CTQ-SF) was used to assess subtypes of trauma; sexual, physical, and emotional abuse, and physical and emotional neglect. We used multiple linear regression analyses, and included relevant confounders: baseline psychosis symptoms, onset age, duration of untreated psychosis, years of education, dosage of antipsychotic medication, and previous exposure to antipsychotics.

Results: Regression analyses showed statistically significant effects for the CT subtypes on PANSS total scores, $F(13, 14) = 4.69$, $p = .004$, adjusted R^2 (R^2a) = .64, mainly driven by CT subtype sexual abuse ($p = 0.042$). CT subtypes significantly predicted PANSS general psychopathology subscale scores, $F(13, 14) = 10.18$, $p < .001$, $R^2a = .82$, which was also mainly driven by sexual abuse ($p = 0.014$). While the regression models on CT subtypes predicting PANSS positive and negative subscale scores were not statistically significant, there was a possible relation between emotional neglect and positive psychosis symptoms ($p = 0.18$), although those models overall showed poor fit.

Discussion: CT subtypes, especially childhood sexual abuse, predicted psychosis symptom levels and antipsychotic effectiveness in SSDs. The present results point to CT subtypes influencing AP effectiveness, and is consistent with the extant but scarce available body of research on the association of CT subtypes, especially sexual abuse, and clinical features in SSDs. Limitations of the present study concern the failure of comparing different groups of patients, such as first-episode compared to more chronic cases, and we were not able to examine potential clinical mediators such as dissociation and trauma symptoms. The data on

CT were retrospectively reported, which is associated with concerns related to validity of the data. We did however have prospectively gathered data on AP effectiveness from real-life clinical practice, and a relatively long follow-up period. The present results support clinical guidelines recommending assessment and treatment of trauma in SSDs.

18. TIME TO ANTIPSYCHOTIC DISCONTINUATION AND ASSOCIATION WITH CLINICIAN-RECORDED SIDE EFFECTS IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

Rashmi Patel^{*1}, Aimee Brinn¹, Jessica Irving¹, Jaya Chaturvedi¹, Shanmukha Gudiseva², Christoph U. Correll³, Paolo Fusar-poli¹, Philip McGuire⁴

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*BRC Nucleus, South London and Maudsley NHS Foundation Trust*, ³*The Zucker Hillside Hospital; The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell*; *Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health*, ⁴*University of Oxford*

Background: In people with first episode psychosis (FEP), antipsychotics are effective in improving symptoms and reducing the risk of subsequent relapse. However, many patients discontinue antipsychotic medications during the first year of treatment due to a lack of efficacy or side effects. Antipsychotic medications have varying side effect profiles based on their pharmacological properties but among individuals with FEP, little is known about the associations of side effects with subsequent antipsychotic discontinuation in real-world clinical practice. We investigated the associations of side effects recorded by clinicians in electronic health records (EHRs) with antipsychotic discontinuation in a large sample of patients receiving treatment for FEP. We hypothesised that recorded side effects are associated with greater rates of antipsychotic discontinuation.

Methods: De-identified EHR data were assembled from the South London and Maudsley (SLaM) NHS Trust Biomedical Research Centre (BRC) case register using the Clinical Record Interactive Search tool (CRIS). SLaM provides mental healthcare for people with FEP through Early Intervention Services (EIS) covering a catchment area of four South London boroughs. Data were obtained from patients who received antipsychotic treatment from a SLaM EIS between 1st April 2008 and 31st March 2019. Follow-up data were obtained up to 31st March 2021 from the index date, defined as the date of acceptance to a SLaM EIS. Structured clinical and demographic data were assembled including age, gender, ethnicity, psychotic disorder diagnosis and EIS team. Data on prescribed antipsychotic, prescription setting (inpatient vs outpatient), start and end dates of antipsychotic treatment, and clinician-recorded side effects (sedation, weight gain, extrapyramidal side effects (EPSEs), sexual side effects or hyperprolactinemia) were obtained from unstructured, free text clinical records through manual review. Multivariable Cox regression analyses were performed to investigate the associations of (i) prescribed antipsychotic and (ii) clinician-recorded side effects with time to antipsychotic discontinuation.

Results: Data from 2,309 patients (64.6% male) were analysed with a mean age of 26.7 years and a total follow-up duration of 6,380.8 person years. The three most frequently prescribed antipsychotics during the first treatment episode were olanzapine (n=1,013), risperidone (n=571) and aripiprazole (n=460). A total of 1,551 patients (67.4%) discontinued the first antipsychotic prescribed during the follow-up period. At least one side effect was recorded in 1,136 (49.2%) patients and more than one side effect was recorded in 365 (15.8%) patients. Among male patients, 476 (31.9%) experienced sedation, 249 (16.7%) weight gain, 136 (9.1%)

EPSEs, 56 (3.8%) sexual side effects, and 48 (3.2%) hyperprolactinaemia. Among female patients, 265 (32.4%) experienced sedation, 181 (22.2%) weight gain, 60 (7.3%) EPSEs, 42 (5.1%) sexual side effects, and 59 (7.2%) hyperprolactinaemia. Female patients discontinued antipsychotics faster than male patients (hazard ratio (HR)=1.23, 95%CI=1.11-1.37). The median time to discontinuation was 9.4 months for olanzapine, 8.8 months for risperidone, and 12.9 months for aripiprazole. Compared to olanzapine, haloperidol (n=18, median time to discontinuation: 1.2 months; HR=2.78, 95%CI=1.69-4.60) and quetiapine (n=145, median time to discontinuation: 4.7 months; HR=1.43, 95%CI=1.16-1.80) were discontinued significantly earlier. Sexual side effects (HR=1.59, 95%CI=1.03-2.46) and EPSEs (HR=1.33, 95%CI=1.08-1.64) were associated with significantly faster discontinuation.

Discussion: Most patients discontinued the first prescribed antipsychotic following presentation with FEP. EPSEs and sexual side effects were associated with a substantially increased discontinuation rate indicating that these side effects are particularly likely to lead to discontinuation of antipsychotic treatment. Haloperidol was discontinued at a substantially higher rate than olanzapine which may reflect the high risk of EPSEs associated with its use. Only 98 (4.2%) patients had recorded sexual side effects suggesting that these are under-recognised or poorly documented in clinical records. Antipsychotic discontinuation is strongly associated with increased risk of relapse. When considering treatment options for FEP, the potential impact of side effects on treatment discontinuation should be taken into account.

19. SEASONAL MODULATION OF NEUROCOGNITION AND ELECTROPHYSIOLOGICAL BRAIN FUNCTIONING IN INDIVIDUALS WITH SCHIZOPHRENIA

David Kimhy*¹, Sloane A. Miller¹, Abraham Reichenberg¹, Luz H. Ospina¹, Chloé Ifrah¹, René Kahn¹, Keith H. Nuechterlein², COGS Investigators³

¹*Icahn School of Medicine at Mount Sinai*, ²*University of California, Los Angeles*, ³*COGS investigators*

Background: People with schizophrenia (SZ) display substantial deficits in neurocognitive functioning that are major predictors of poor functioning and disability. These deficits have traditionally been regarded as stable. However, evidence from pre-clinical and clinical studies (e.g., Alzheimer's disease) point to seasonal variability in humans' neurocognition and related neuroplasticity. Yet, this putative variability has not been investigated in SZ. To address this gap, we aimed to examine: 1) Do neurocognition and related electrophysiological brain functioning in people with SZ vary across seasons? and 2) Are there differences in seasonal variability of neurocognition and electrophysiological functioning between people with SZ and healthy controls (HC)?

Methods: We conducted a secondary analysis of cross-sectional data from a cohort of 2249 individuals (SZ: n=1239, HC: n=1010) who completed neurocognitive and electrophysiological brain functioning measures as part of the assessment of Phase 2 of the Consortium on the Genetics of Schizophrenia (COGS) project, a multi-site NIMH-sponsored investigation of the genetic basis of neurocognitive endophenotypes. Participants were recruited from five geographically diverse United States sites in New York City, Philadelphia, Seattle, Los Angeles, and San Diego. The neurocognitive and electrophysiological phenotyping dates were first transformed to weeks of the year (e.g., January 1-7: Week 1, January 8-14: Week 2, etc.) and then aggregated to meteorological seasons based on maximum/minimum seasonal daylight (e.g., yearly solstices and equinoxes).

Results: The participants with SZ displayed significantly poorer neurocognitive performance during the summer as indexed by the Degraded-Stimulus Continuous Performance Task (DS-CPT; $F=2.72$, $p=.04$), along with trends for worse performances on the Penn Face Memory Test ($F=2.04$, $p=.10$) and Mismatch Negativity (MMN; $F=2.48$, $p=.06$). Similarly, the P300 amplitude was significantly lower during the fall ($F=4.21$, $p < .01$). Examination of group differences indicated there was a significant group by season interaction for P300 ($F=3.08$, $p=.03$), with the largest differences between the SZ and HC groups observed during the fall (SZ group performed worse).

Notably, analyses of data from the three most northern sites (New York, Philadelphia, Seattle; SZ: $n=689$, HC: $n=585$), which experience greater seasonal variation in daylight, suggested greater seasonal impact. The participants with SZ displayed significantly poorer neurocognitive performance during the summer as indexed by the Continuous Performance Task-Identical Pairs (CPT-IP; $F=3.41$, $p=.02$), DS-CPT ($F=3.04$, $p=.03$), Penn Verbal memory task ($F=2.97$, $p=.03$), and MMN ($F=4.74$, $p < .01$). Significantly poorer performance was observed in the fall on the California Verbal Learning Test ($F=3.21$, $p=.02$), with a trend for P300 ($F=2.54$, $p=.06$). Group comparisons indicated a significant group by season interaction for CPT-IP ($F=3.01$, $p=.03$; largest difference in the summer), along with trends for DS-CPT and the Penn verbal memory task ($F=2.41$, $p=.06$ and $F=2.06$, $p=.10$, respectively; SZ group performed worse on all).

Discussion: This is the first report describing the links between seasons, neurocognition, and electrophysiological brain functioning in people with SZ. Our Results: identify a novel source of variabilities in these targets, highlighting the significant impact of seasons on neurocognition and electrophysiological functioning in this population. We discuss the translational and therapeutic implications of the findings, including the impact on the design and analyses of data from clinical trials targeting enhancement of neurocognition in people with SZ.

20. LONG TERM RECOVERY AND TREATMENT RESISTANCE IN FIRST-EPISODE PSYCHOSIS: A 10-YEAR FOLLOW-UP STUDY

Kristin Wold^{*1}, Isabel Kreis², Gina Åsbø¹, Carmen Simonsen³, Ingrid Melle⁴

¹NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, ²NORMENT, Institute of Clinical Medicine, University of Oslo, ³NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Early Intervention in Psychosis Advisory Unit for South East Norway, Oslo University Hospital, ⁴NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo

Background: There are several possible illness trajectories for patients experiencing first-episode psychosis (FEP) with considerable variation in symptoms and functional levels over time and between patient groups. This underlines the importance of stratification in treatment studies and having tools to identify patients in need of different treatment approaches. Data from previous studies indicate that early course parameters are among the most significant predictors of long-term outcome, but to identify early predictors affecting long-term course, we need longitudinal data of FEP cohorts.

We aimed to use longitudinal data to investigate the prevalence of clinical recovery (CR) and treatment resistance (TR) at 10-year follow-up (10Y FU), and to investigate clinical, demographic and pre-illness predictors of long-term outcomes.

Methods: 102 participants with FEP DSM-IV Schizophrenia spectrum disorders who were recruited to the “Thematically Organized Psychosis” (TOP) research study within their first year of treatment was eligible to this naturalistic observational 10Y FU study. The SCID-I for DSM-IV was used for diagnosis, symptoms were measured with the SCI-PANSS. Treatment history was gathered through interviews and medical charts. TR was defined by the Treatment Response and Resistance in Psychosis Working Group (TRRIP) criteria and Clinical Recovery was defined by most recent used criteria. After initial analyses, we conducted binary and multinomial logistic regression analyses to identify predictors of long-term outcome.

Results: Out of 102 participants, 29 (29%) could be classified as in CR and 32 (31%) as TR at 10Y FU. We also identified a larger middle group (n=41, 40%) consisting of both participants with partial recovery, remitting/relapsing patterns, and participants not meeting the TR criteria due to lack of treatment trials but with the same clinical outcome as the TR group. Insidious onset (OR=4,16) and disorganized symptoms at baseline (OR=2,96) were independently significantly associated with increased odds of developing TR, and acute onset (OR=3.94) were independently significantly associated with increased odds of CR. At 10Y FU only 7 (7%) of all the participants had tried Clozapine.

Discussion: Using recent consensus definitions we identified three long-term outcome groups: CR (28%), TR (31%) and a middle heterogeneous group (40%). The prevalence of CR and TR corresponds with earlier findings. However, identified predictors of 10-year outcome is not completely in line with earlier findings. We identify the potential important predictive value of assessing baseline disorganized symptoms and further target disorganized symptoms in early intervention treatments, as well as to monitor more closely patients with insidious onset.

21. 30-YEAR FOLLOW-UP OF THE CANTABRIA FIRST-EPIISODE-SCHIZOPHRENIA STUDY, FROM EARLY INTERVENTION TO CHRONICITY

Javier Vázquez-Bourgon*¹, María Jesús Cuesta², Ismael Lastra Martínez², Adriá Palau Miguel², Sara Herrera Castanedo², Álvaro De Santiago-Sánchez², Rocío Pérez-Iglesias²

¹University Hospital Marques de Valdecilla -IDIVAL; University of Cantabria; CIBERSAM,

²University Hospital Marqués de Valdecilla - Instituto de Investigación Marqués de Valdecilla (IDIVAL)

Background: Early intervention psychosis (EIP) programs are effective in treating subjects with a first episode psychosis ensuring a better outcome during the most critical period, the first 3-5 years after the psychosis breakout. However, there is little evidence on the long-term progression of those patients after being discharged from EIP to standard community treatment. We aim to report on the long-term outcome of those individuals treated 30 years earlier, in the Cantabria First-Episode-Schizophrenia study (Vazquez-Barquero et al., 1999, 1995).

Methods: We designed a cross-sectional observational study. We collected sociodemographic, clinical and functioning data from the patients' clinical records. A total of 88 patients were included in the current analyses.

Results: At the time of the medical records review, at 30-years follow-up, 56 patients (63.6%) had a diagnosis of non-affective psychosis, mainly schizophrenia (n=46, 52.3%), while 10.2% (n=9) had a diagnosis of bipolar disorder. While 67% (n=59) had a recognized disability, 20 were currently working and 5 were retired.

Only 42 (47.7%) patients continued treatment in a community mental health team while 10 patients had been discharged or abandoned treatment. Only 63.6% of patients were on psychopharmacological treatment; most of them (n=43, 76.7%) were on just one antipsychotic,

although 8 (14.8%) were on two or more antipsychotics. Nearly 20% (N=11) were on mood stabilizers. And, 16 (28.5%) were having antidepressants.

Among those treated with antipsychotics (n=51), 19.6% received long-acting injectable: 6 paliperidone palmitate, 1 aripiprazole maintenance, 1 risperidone, and 2 zuclopenthixol decanoate. The most frequently prescribed oral antipsychotic was olanzapine (n=15, 29.4%), with a mean dose of 13.5mg. 9 patients were on clozapine (17.6%, mean dose 334.4mg), 4 aripiprazole (mean dose 13.75mg), 4 risperidone (mean dose 3.5mg), 3 paliperidone (mean dose 6mg), and 5 perphenazine (mean dose 7.2 mg). Mean chlorpromazine equivalent dose for all the patients on antipsychotics was 546.7 (median 450.0).

A total of 41 patients (46.6%) required hospital admission to psychiatric ward during the 30-years follow-up, with a mean number of 8 psychiatric hospitalizations.

According to clinical records, only 3% patients were tobacco smokers and none of them had consumed illegal substances in the previous year. However, there was an important lack of information in this regard (missing data for 60 patients, 67%).

Regarding medical co-morbidities, 29.5% were obese, 30.7 had dyslipidemia, and 25% hypertension. Thirteen (15.9%) patients had died during the course of the last 30 years, with a mean age at the time of death of 52.5 years. Of these, four (28.5%) had died from suicide: three occurred within the first 5 years after the first hospitalization. The average age of those who died by suicide was 29.7 years, and all of them were men.

Seven deaths (50%) were from natural causes, with a mean age of 56.7 years. The two most prevalent causes of natural deaths were respiratory and cardiologic.

Discussion: The results showed that, despite having been treated in an specialized EIP program during their first 3 years of their psychosis, these patients present later in life high rates of premature mortality. The number of readmissions, polypharmacy and medical co-morbidities are also high. And most of patients present indirect indicators of a poor functioning.

These results suggest that the clinical improvements achieved in EIP might be lost after discharged from EIP, leading to a standard “chronification” of the condition. Thus, a major effort must be put in place in treating more effectively those patients throughout their long-term.

22. RISK OF RELAPSE DURING CONTINUOUS DOPAMINE D2 RECEPTOR BLOCKADE IN FIRST-EPISODE SCHIZOPHRENIA

Jari Tiihonen¹, Antti Tanskanen¹, Heidi Taipale*²

¹Karolinska Institutet, ²Niuvanniemi Hospital, University of Eastern Finland

Background: Concerning the neurobiology of schizophrenia, it is not known how large proportion of patients with first-episode schizophrenia relapse despite of continuous dopamine 2 (D2) receptor blockade. It has also remained controversial whether long-term use of D2-blocking antipsychotics increases the risk of relapse due dopamine hypersensitivity, since no study has investigated this during several years of assured antipsychotic treatment. We aimed to compare the risk of relapse in continuous use of long-acting antipsychotics (LAIs) to those not using LAIs among persons with first-episode schizophrenia over 5 years of follow-up.

Methods: Persons with first-episode schizophrenia, aged ≤ 45 years, were identified from Finnish nationwide register of inpatient care during years 1996-2014. During the first 30 days after first diagnosis, patients were categorized as LAI users versus non-LAI users (using oral

antipsychotic or not using any antipsychotic). Outcome was severe relapse defined as readmission to hospital due to psychosis relapse. During the follow-up, those categorized as LAI users were censored if they discontinued LAI. The follow-up was 5 years or until the first relapse.

Results: Of the entire cohort of 5367 patients (64.2% men, mean age 29.5 years, SD 7.8), 3058 (57%) had a relapse. Among those patients who were not re-admitted to hospital within the first 30 days of follow-up (N=4788), 305 initiated LAI use and 4483 did not. Among continuous LAI users, 21.6% relapsed (95% CI 17.1-26.7%; N=66) compared with 34.2% of the other patients not on LAI (95%CI 32.8-35.8%, N=1534). The relapse rate among patients using LAI continuously was 47/305 (15.4%) during year 1, 8/139 (5.7%) during year 2, 6/98 (6.1%) during year 3, 3/73 (4.1%) during year 4, and 2/47 (4.3%) during year 5 (difference between year 1 vs. year 4, $p = 0.02$, Fisher exact test).

Discussion: Up to one quarter of patients with first-episode schizophrenia relapse despite of continuous D2-blockade which may be attributable to neurobiological heterogeneity in the pathophysiology of the illness. The relapse risk decreased as a function of assured cumulative D2-antagonist use during the first 4 years, after which it plateaued, indicating that cumulative exposure to dopamine D2 receptor blockade is associated with decreased, rather than increased risk of breakthrough psychosis. A large proportion of relapses could be prevented by continuous LAI use.

23. THE CLINICAL AND FUNCTIONAL OUTCOMES OF A LARGE NATURALISTIC COHORT OF YOUNG PEOPLE ACCESSING NATIONAL EARLY PSYCHOSIS SERVICES

Andrew Thompson^{*1}, Caroline Gao¹, Georgia Williams¹, Debra Rickwood², Nic Telford², Cerissa Papanastasiou³, Patrick D McGorry¹, Eleanor Brown¹

¹Orygen, ²Headspace

Background: Services for individuals with a first episode of psychosis or at ultra-high risk of psychosis have become a treatment model of choice in mental health care. The longitudinal changes in clinical and functional outcomes as a result of real-world treatment remain under-reported in large datasets.

Methods: We analysed routine outcome data from first episode of psychosis and ultra-high risk services delivered across the whole of Australian primary youth mental health care services known as headspace between 19 June 2017 and 30 September 2019. Additional data up to September 2023 will be available making this the largest real world early psychosis longitudinal dataset. Outcome measures were completed and entered into a minimum dataset every 90 days a participant was receiving treatment and included psychiatric symptomatology (Brief Psychiatric Rating Scale and psychological distress, K10) and psychosocial functioning (Social and Occupational Functioning Assessment Scale and My Life Tracker). Linear mixed-effects models were used to evaluate changes in outcome over time.

Results: Outcome data from a total of 1252 young people were evaluated (643 first episode of psychosis, 609 ultra-high risk). Of those who entered ultra-high risk services, 11.8% transitioned to first episode of psychosis services. Overall, substantial improvement in clinical (Brief Psychiatric Rating Scale, K10) and functional (Social and Occupational Functioning Assessment Scale, My Life Tracker) outcomes were seen across groups and outcomes. Ultra-high risk patients showed a greater reduction in distress symptoms, while first episode of psychosis patients experienced a greater reduction

in positive psychosis symptoms. Although clinical outcomes showed a plateau effect after approximately 3 months of care, improvement in functional outcomes (Social and Occupational Functioning Assessment Scale, My Life Tracker) continued later in treatment. We will be able to supplement and contrast these results with an additional 3 1/2 years of data (September 2019- July 2023) and an anticipated n of over 4000 young people with first episode psychosis or ultra high risk.

Discussion: These findings support the use of real-time, real-world and low-cost administrative data to rigorously

evaluate symptomatic and functional outcomes in early psychosis treatment settings. Findings that functional outcomes improve past the remittance of clinical outcomes also support the functional recovery focus of early psychosis services and remaining high levels of distress suggest the need for ultra-high risk services to extend beyond 6 months of care. Information on important sub-groups will also be available with the substantially larger dataset (over 4000 individuals).

Oral Session: Development

24. THE IMPACT OF ESTRADIOL LEVELS AND PUBERTY TIMING ON PSYCHOTIC EXPERIENCES IN THE CONTEXT OF EXPOSOMIC VULNERABILITY FOR SCHIZOPHRENIA: AN ABCD STUDY

Lotta-Katrin Pries*¹, Thanavadee Prachason², Angelo Arias-Magnasco³, Bochao D. Lin³, Bart P. F. Rutten³, Sinan Guloksuz⁴

¹*School for Mental Health and Neuroscience, Maastricht University Medical Centre*, ²*Faculty of Medicine Ramathibodi Hospital, Mahidol University*, ³*School for Mental Health and Neuroscience, Maastricht University Medical Centre*, ⁴*School for Mental Health and Neuroscience, Maastricht University Medical Centre; University School of Medicine*

Background: Sex (biological) and gender (social/cultural) effects contribute to the diversity in the onset, progression, prognosis, and etiology of psychotic spectrum disorders (PSD). Especially during critical developmental phases, such as puberty, sex- and gender-specific processes play a pivotal role in shaping distinct symptom profiles. Although puberty timing is associated with internalizing and externalizing symptoms, research on puberty markers and PSD is limited and conflicting. Furthermore, the etiology of PSD is marked by different environmental factors. This study aims to explore whether puberty status and hormone (estradiol) levels during puberty can potentially moderate the impact of exposomic (environmental) vulnerabilities for schizophrenia on psychosis experiences (PEs) in young female individuals.

Methods: This study utilized data from 5682 female children and adolescents in the Adolescent Brain Cognitive Development (ABCD) Study, assessing them at baseline and with 3-year follow-ups. Binary significantly distressing PEs were assessed using the Prodromal Psychosis Scale. Puberty status (prepubertal, early pubertal, midpubertal, late pubertal, postpubertal) was assessed with the Pubertal Development Scale, covering changes in height, body hair, skin, breast development, and menarche (first period). Salivary samples were taken to measure estradiol levels. Exposomic vulnerability for schizophrenia (ES-SCZ) was assessed through an aggregated weighted sum score, including factors like cannabis use, hearing impairment, winter birth, and childhood adversities. ES-SCZ was dichotomized at the 75th percentile.

Multilevel mixed regression analyses, taking into account the nested structure of study site and family membership were applied to test the interaction of puberty status and estradiol levels with ES-SCZ, in association with psychosis expression in female participants at the first follow-up assessment. Furthermore, analyses were conducted to test the interaction between age of menarche and ES-SCZ on PEs at the third follow-up assessment. Analyses were adjusted for BMI, parental education, family income, ethnicity, and age. Hormonal analyses were controlled for variables that could bias salivary hormone levels.

Results: Elevated standardized estradiol levels were associated with an increased probability of reporting PEs at trend level (OR = 1.09, 95% CI = 0.99 to 1.19), while a later age of menarche was associated with a reduced likelihood of reporting PEs (OR = 0.83, 95% CI = 0.74 to 0.94). Analysis with puberty status showed significant differences between the prepubertal (reference) group and those in midpubertal (OR=1.72, 95% CI = 1.29 to 2.30) and late pubertal (OR = 2.13, 95% CI = 1.45 to 3.12) stages. Furthermore, ES-SCZ was associated with an elevated likelihood of experiencing PEs at the first (OR = 1.81, 95% CI = 1.49 to 2.19) and the third follow-up assessment (OR = 1.59, 95% CI = 1.28 to 1.98). We found a significant interaction between ES-SCZ and puberty status, comparing the prepubertal to the late pubertal stage (OR = 0.42, 95% CI = 0.19 to 0.90). No other significant interaction was detected.

Discussion: This study examines the interplay between exposomic vulnerability for schizophrenia and physical as well as hormonal puberty markers in young female participants. The study underscores the critical role of puberty, revealing it as a period of significant biological and socio-cultural changes directly tied to psychosis expression. Puberty may trigger processes impacting neurodevelopment, influencing psychosis expression. The absence of interaction effects may be attributed to the age range of the cohort. Further research during follow-ups, when clinically relevant phenotypes emerge, is essential.

25. AN ANALYSIS OF CHILDHOOD TRAUMA AND ITS RELATION TO LIMBIC STRUCTURES IN A LARGE TRANSDIAGNOSTIC SAMPLE

Varun Thvar*¹, Elisabetta C. del Re², Brett Clementz³, Elliot Gershon⁴, Sarah Keedy⁴, Godfrey Pearlson⁵, Carol A. Tamminga⁶, Matcheri S. Keshavan²

¹*Beth Israel Deaconess Medical Center, Harvard Medical School*, ²*Beth Israel Deaconess Medical Center, Harvard Medical School*, ³*University of Georgia*, ⁴*University of Chicago*, ⁵*Yale University School of Medicine*, ⁶*University of Texas Southwestern Medical Center*

Background: Childhood trauma is significantly associated with risk for regulation disorders, psychotic disorders, cognitive impairment, and suicidal behavior. Previous research has focused on investigating childhood trauma's relationship to single brain structures in clinical and non-clinical populations. To expand the understanding of how childhood trauma affects multiple brain regions, we examined the association between childhood trauma and the volume, area, cortical thickness, and local gyrification index (LGI) of limbic and associated brain structures. We also explored the relationship between childhood trauma and cognition and suicidal thoughts. We hypothesized that a) total childhood trauma score would be negatively correlated with limbic regional volume, area, LGI, and cortical thickness and b) effects of childhood trauma on cognition and suicide would be mediated at least partially through the limbic structure.

Methods: The study included 1079 participants, consisting of 672 probands and 407 controls. Childhood trauma and limbic measure associations were examined using a large, deeply phenotyped, trans-diagnostic adult sample from the BSNIP-2 database. Participants received a 3 T-MPRAGE MRI scan based on the Alzheimer's Disease Neuroimaging Initiative (ADNI)

protocol, and limbic region atlases were used to parcellate and extract data. We investigated relationships between the total score of the Childhood Trauma Questionnaire (CTQ) and several clinical measures and brain morphology of the following limbic and associated structures, individually and as a whole: the Parahippocampus, Insula, Amygdala, Hippocampus, Thalamus, Hypothalamus, and Cingulate. Demographic information for HC and PRO was analyzed using univariate analyses (ANCOVA) and χ^2/F tests. Analyses were performed with Student's t-tests, MANOVA, regressions, and Spearman correlations.

Results: Thirty-three out of 36 limbic measures showed statistically significant differences (p LESS THAN 0.001) between childhood trauma-exposed ($n = 453$) and non-exposed participants ($n = 626$). Regressions between CTQ and total limbic volume yielded significant correlation ($t = -7.28$), significantly stronger in probands. Childhood trauma-exposed probands had lower hippocampus and amygdala volumes compared to non-trauma-exposed controls, such as in the Right Anterior Hippocampus (Cohen's $d = -0.34$). FDR-corrected Spearman correlations indicated statistically significant positive relationships between childhood trauma and clinical measures, such as Depression (p LESS THAN 0.001), Anxiety (p LESS THAN 0.001), and Suicidal Thoughts ($p = 0.00345$), as well as negative relationships with Social Functioning (p LESS THAN 0.001) and Cognition ($p = 0.00562$).

Discussion: Our data indicate that childhood trauma affects the structure of several limbic and associated system regions. These observations have strong implications for early detection of risk for trauma-related psychopathology and for biopsychosocial interventions.

26. EARLY LIFE ADVERSITIES AND ADOLESCENT PSYCHOTIC EXPERIENCES: THE MEDIATING EFFECT OF PLANT-BASED DIETARY PATTERNS

Xuemei Ma^{*1}, Rebecca Pollard¹, Pei-Jung Chen¹, Svenja Kretzer², Nare Amasi-Hartoonian¹, Maryam Matter¹, Andrew J. Lawrence¹, Corentin Vallée¹, Olivia Johnson-Trewick¹, Craig Morgan¹, Seeromanie Harding³, Gunter Schumann¹, Carmine Pariante¹, Mitul Mehta¹, Giovanni Montana⁴, Ana Rodriguez-Mateos⁵, Chiara Nosarti¹, Paola Dazzan¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*King's College London; Agency for Science, Technology and Research (A*STAR), Singapore*, ³*Division of Diabetes and Nutritional Sciences, King's College London*, ⁴*University of Warwick*, ⁵*Faculty of Life Sciences and Medicine, King's College London*

Background: Due to the importance of adolescence as period of risk for the emergence of psychopathology, the role of early life adversities (ELAs) in adolescence in relation to psychopathology has received more attention recently. ELAs have also been associated with a less healthy dietary pattern, which in turn is associated with more mental health disorders. However, to date no study has investigated whether different healthy dietary patterns are also associated with psychotic experiences in adolescents, and whether a healthy dietary pattern could buffer the relationship between ELAs and psychotic experiences. This study evaluated the relationship between different plant-rich dietary patterns and psychotic experiences in an adolescent cohort, testing the mediating effect of dietary patterns in between.

Methods: A total of $n=199$ school young adolescents (mean age: 12.94 ± 0.93 years) were included in this study. Individual-level ELAs were assessed by interview, and included maltreatment, household fragmentation, bullying, discrimination, and adverse life events. Area-level ELA was indicated by living in 1st to 3rd deciles of the UK Indices of Multiple Deprivation (IMD). Psychotic experiences were assessed with the adolescent psychotic-like symptom screen (APSS). Dietary patterns were estimated using food consumption data

obtained from the Food Frequency Questionnaires (FFQ) and included the Plant-based Diet Index (PDI), Dietary Approaches to Stop Hypertension Diet (DASH), Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND), Original Mediterranean Diet (oMED), Alternate Mediterranean Diet (aMED) and (poly)phenol-rich diet score (PPS). Multivariate linear regression models were used to test the direct effect of ELAs and dietary patterns on psychotic experiences. Hayes PROCESS macro was used to test the role of dietary pattern in the relationship between ELAs and psychotic experiences.

Results: The multivariate model showed a positive association between number of individual-level ELAs and psychotic experiences ($B=0.195$, $p < 0.001$) and a negative association between the DASH diet score and psychotic experiences ($B=-0.061$, $p=0.039$). Since the DASH score was also negatively correlated with the number of individual-level ELAs ($r=-0.215$, $p=0.002$), we explored the role of DASH as a mediator in the relationship between ELAs and psychotic experiences. When adjusted for age, energy intake and area-level ELA, the DASH score was a significant mediator in the association between number of individual-level ELAs and psychotic experiences (standardised indirect effects being 0.030 (95%CI: 0.004, 0.059)), accounting for 8.1% of the total effect. Considering each dietary component of the DASH score, we found that higher intake of nuts and legumes was particularly significant in explaining the potential positive role of DASH on psychotic experiences ($B=-0.005$, $p=0.035$).

Discussion: We confirmed that exposure to ELAs is associated with more psychotic experiences in adolescence and found that diet might contribute to understand this link. Compared to other diets, the DASH diet uniquely limits intake of saturated fats, added sugars and sodium, which are all linked to immune activation, suggesting that the anti-inflammatory potential of DASH might be the mechanism that explains its potential beneficial contribution to mental health. However, future studies will need to confirm the precise biological mechanisms underlying dietary contributions.

27. PERSISTENT CHILDHOOD INFLAMMATION AND RISK OF DEVELOPING PSYCHOSIS AND OTHER MENTAL AND PHYSICAL HEALTH PROBLEMS IN ADULTHOOD: A LONGITUDINAL BIRTH COHORT STUDY

Edward Palmer^{*1}, Isabel Morales-Muñoz², Benjamin Perry³, Jack Rogers¹, Ella Warwick¹, Steven Marwaha⁴, Rachel Upthegrove¹

¹University of Birmingham, ²University of Birmingham, Finnish Institute for Health and Welfare (THL), Helsinki³University of Cambridge, ⁴University of Birmingham, Specialist Mood Disorders Clinic, Zinnia Centre

Background: There is a growing body of evidence showing that inflammation or changes in the immune system play a key role in certain mental health disorders. The evidence is particularly strong for psychosis and depression. However, a potential causal link between inflammation and psychosis is yet to be proven, and less is known about the trajectories, nature and degree of inflammation that might have an impact on mental health. The aim of this study was to characterize the inflammatory trajectories within a large general population across childhood and adolescence, and how these trajectories would associate with a range of mental and cardiometabolic health conditions in young adulthood. This would help identify which mental health disorders and other cardiometabolic health outcomes in young adulthood are linked with early life inflammation. We hypothesized that there would be sub-group of young people who have different and raised levels of inflammation, and that this group would be at highest risk of developing certain mental health conditions, namely psychosis and depression,

as well as related cardio-metabolic psychological health conditions such as diabetes and associated insulin resistance.

Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) study, which has data from over 14,000 individuals at birth. Groups of inflammatory trajectories across childhood and adolescence were identified using latent class growth analysis (LCGA). Inflammation was assessed via blood samples of CRP measures at ages 9, 15 and 17. Scores above 10 were excluded to rule out the impact of acute infection, with all CRP-measures z-transformed and LCGA carried out on the z scores adjusted for BMI at each time point to provide classes of different inflammatory trajectories across childhood and adolescence.

We also investigated the prospective associations between inflammatory trajectories identified by LCGA, and different mental health (including psychosis, various severities of depression, hypomania, generalised anxiety disorder, social phobia, panic disorder, mild depression, alcohol abuse or cannabis misuse) and cardiometabolic health (including diabetes, and insulin resistance) outcomes at age 24. As well as predefined outcomes, we also calculated the Homeostatic Model Assessment for Insulin Resistance (HOMA score) at age 24 from recorded insulin and glucose measures. We used regression analyses across binary (e.g. diagnosis) and continuous (e.g. HOMA scores) outcome measures. Further, we controlled for gender, preterm, family diversity index score, ethnicity, and child health age 8 and 13. To deal with missingness, we applied inverse probability weighting.

Results: LCGA results

We identified 3 trajectories of inflammation across childhood and adolescence. Class 1 had persistently low levels of CRP (Low Group - 93% of cohort), which was used as the comparison group in the subsequent logistic regression analyses. Further, there were two divergent groups, both with persistently raised levels of CRP. Class 2 had a persistently raised level of CRP with a peak earlier at age 9 (Early Peak - 5% of cohort) and Class 3 had persistently raised CRP levels and a peak later at age 17 (Late Peak - 4% of cohort).

Regressions results

Logistic regressions were used to compare odds ratio (OR) of outcomes between the Early Peak and Late Peak groups and the comparison group (Low Group). The Early Peak was 4 times more likely to develop psychotic disorder at age 24 (OR = 4.39, 95% CI 1.73-11.13, $p=0.002$), twice as likely to develop psychotic-like symptoms at age 24 (OR = 2.31, 95% CI 1.34-3.99, $p=0.003$), over 4 times more likely to develop severe depression at age 24 (OR = 4.54, 95% CI 1.69-12.20, $p=0.003$) and more than twice as likely to develop moderate depression (OR = 2.13, 95% CI 1.14-3.97, $p=0.01$) than the Low Group. Neither group showed any significant results for hypomania, generalised anxiety disorder, social phobia, panic disorder, mild depression, alcohol abuse or cannabis misuse.

in regards to cardiometabolic outcomes, the Early Peak group (class 2) was significantly associated with an increased risk of insulin resistance (HOMA score GREATER THAN 2.9) at age 24 (OR 2.48, 95% CI 1.52-4.02, $p=$ LESS THAN 0.001) and using linear regressions, we found a significant association between the Early Peak group and higher levels of HOMA scores at age 24.

Discussion: Our findings from a large population cohort show that specific trajectories of low grade systemic inflammation across childhood and adolescence are related to later onset of mental health disorders, particularly psychosis and depression, with early rather than later inflammation potentially holding importance. Our results also show specificity in the development of psychosis and depression, and not all or other mental health disorders. Finally,

our results show that the same early peak group is also at higher risk of developing certain cardio-metabolic disorders such as insulin resistance. This study adds new information about the chronicity and timing of inflammation predating illness, and provides insight into the co-occurrence of related cardio-metabolic disorder that may be useful in developing targeted preventive interventions.

28. BULLYING VICTIMIZATION'S IMPACT ON GUT MICROBIOTA AND ADOLESCENT PSYCHOTIC SYMPTOMS: A LONGITUDINAL COHORT STUDY

Syudo Yamasaki^{*1}, Shuntaro Ando², Mitsuhiro Miyashita³, Eiji Miyauchi⁴, Kazuya Toriumi⁵, Satoshi Yamaguchi³, Makoto Arai⁵, Mariko Hiraiwa-Hasegawa³, Takefumi Kikusui⁶, Kiyoto Kasai⁷, Atsushi Nishida¹

¹*Research Center for Social Science and Medicine, Tokyo Metropolitan Institute of Medical Science,* ²*Graduate School of Medicine, The University of Tokyo,* ³*Research Center for Social Science and Medicine, Tokyo Metropolitan Institute of Medical Science,* ⁴*Laboratory of Mucosal Ecosystem Design, Institute for Molecular and Cellular Regulation, Gunma University,* ⁵*Tokyo Metropolitan Institute of Medical Science, Schizophrenia Research Project,* ⁶*Laboratory of Human-Animal interaction and Reciprocity, Azabu University,* ⁷*Graduate School of Medicine, The University of Tokyo; Tokyo Center for Integrative Science of Human Behaviour (CiSHuB), The University of Tokyo; The International Research Center for Neurointelligence (WPI-IRCN) at The University of Tokyo Institutes for Advanced Study (UTIAS), The University of Tokyo*

Background: Longitudinal cohort studies consistently support the adverse impact of adolescent bullying victimization on mental health, particularly through increased psychotic symptom risk. However, the biological pathways linking bullying to psychotic symptoms remain unclear. The gut microbiota, referred to as the "second genome," plays a crucial role in physical and mental health (Herd 2018 Nat Hum Behav), offering a promising intervention target for mitigating social stress and psychotic symptoms due to its susceptibility to environmental factors (Sherwin 2019 Science). Despite its potential, current studies are limited to animal models and cross-sectional human studies with small samples. This study aims to investigate the longitudinal relationship among bullying victimization, gut microbiota, and psychotic symptoms using a large cohort of randomly selected adolescents.

Methods: Data from 345 adolescents in the population-based biomarker subsample study of the Tokyo Teen Cohort Study (pb-TTC) were analyzed (mean age [SD] = 13.5 [0.6] years). The pb-TTC subsample was followed up after one year, with 282 participants (82%) completing the follow-up survey. Bullying victimization was measured by self-report and caregiver's report at age 12, a year before the pb-TTC baseline survey. Gut microbiota were evaluated from fecal samples using a terminal restriction fragment length polymorphism (T-RFLP) method to determine the structure and dynamics of the microbial gut community. Psychotic symptoms and other mental health problems were assessed at age 16 using the Adolescent Psychotic Symptoms Screener (APSS) and the Child Behavior Checklist (CBCL).

Results: Cluster analysis at age 13 identified five distinct gut microbiota groups, with one group exhibiting *Prevotella* genus occupancy 160 times higher, and 25% of children in this group reported bullying within the past year. Frequency of bullying victimization at age 12 significantly correlated with *Prevotella* occupancy at ages 13-14 ($r=0.31$, $p < .001$), and *Prevotella* occupancy increased by 20-fold in the group bullied at least once a week compared to the non-bullied group ($p < .001$). Path analysis revealed a longitudinal relationship: bullying victimization (age 12) increased *Prevotella* occupancy (age 13-14),

subsequently worsening mental health at age 16. Prevotella occupancy was associated with psychotic symptoms ($\beta=0.18$, $p=.0008$) and CBCL thought problems as a psychosis risk ($\beta=0.20$, $p=.0002$), and was strongly correlated with delinquent behavior, physical complaints, and self-injurious behavior ($\beta=0.28$, 0.27 , 0.23 , respectively, all $p < .001$), indicating a link between gut microbiota and adolescent psychotic symptoms, physical health, and impulsivity.

Discussion: Prevotella spp. are linked to inflammatory diseases, suggesting an association with inflammation, oxidative stress, and glycation stress (Tett 2021 Nat Rev Microbiol). Future investigations will explore the causal relationship through longitudinal analyses, including inflammation markers and glycation stress, to elucidate the process by which bullying-induced damage increases Prevotella spp. and therefore identify potential intervention targets.

29. LINKING EARLY LIFE ADVERSITY AND MENTAL HEALTH OUTCOMES WITH DISTINCTIVE INTERHEMISPHERIC FUNCTIONAL CONNECTIVITY PATTERNS

Corentin Vallée^{*1}, Xuemei Ma¹, Rebecca Pollard¹, Andrew Lawrence¹, Svenja Kretzer¹, Pei-Jung Cheng², Craig Morgan³, Seeromanie Harding¹, Giovanni Montana⁴, Ana Rodriguez-Mateos⁵, Gunther Schumann¹, Carmine Pariante⁶, Chiara Nosarti⁷, Mitul Mehta⁸, Paola Dazzan⁶

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London*, ²*Institute of Psychiatry, Psychology, and Neuroscience, King's College London; Chang Gung Memorial Hospital, Taoyuan*, ³*Institute of Psychiatry, Psychology, and Neuroscience, King's College London; SRC Centre for Society and Mental Health, King's College London*, ⁴*University of Warwick, Coventry, United Kingdom*, ⁵*Faculty of Life Sciences and Medicine, King's College London, London*, ⁶*Institute of Psychiatry, Psychology, and Neuroscience, King's College London; National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London*, ⁷*Institute of Psychiatry, Psychology, and Neuroscience, King's College London; School of Biomedical Engineering and Imaging Sciences, King's College London*, ⁸*National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London*

Background: Early life adversity (ELA) is the range of detrimental circumstances that an individual encounters during their formative years, typically encompassing childhood and adolescence. ELA can manifest in various forms, including abuse, neglect, disadvantageous socio-economic factors or exposure to violence. The consequences of ELA on mental health are manifold in particular regarding psychopathology: depression, anxiety, psychosis, or behavioral trouble. Current research indicates functional resting-state connectivity, as key feature in understanding the effect of ELA on the brain, and the subsequent development of MH outcomes. In the present study, we have explored interhemispheric functional connectivity (IHFC) in relation with history of ELA and MH problems.

Methods: A total of 230 adolescents aged from 11.2 to 14.9 were recruited from schools in Southeast London.

We evaluated Early Life Adversity with The Difficult and Harmful Life Event questionnaire, along with the England Index of Multiple Deprivation to address area-level adversity.

Participants were categorized as negative for ELA if they: 1) faced a maximum of two events from the Difficult and Harmful Life Event questionnaire (on 28 possible) along with lowest severity, lowest frequency, no distress nor injury for these maximum two events, and 2) resided in areas not classified as deprived by the Index of Multiple Deprivation.

We evaluated mental health of participants using four questionnaires: the Generalized Anxiety Disorder 7 for anxiety, the Short Mood and Feelings Questionnaire for depression, the Adolescent Psychotic-like Symptom Screener for psychosis, and the Strengths and Difficulties Questionnaire for overall well-being and behavioral traits.

Participants were categorized as positive for MH problems if they were screened positive by at least one of these questionnaires.

The participants were then divided into three groups: 1) with ELA but without MH problems (Group 1, $n=81$); 2) with both ELA and MH problems (Group 2, $n=71$); and 3) a control group without ELA and without MH problems (Control group, $n=29$). The group sizes are given after excluding participants with incomplete questionnaires and after fMRI quality control.

Resting-state BOLD fMRI data were collected using a 3T GE scanner. The imaging data were processed using fMRIPrep default pipeline and further denoised with CONN using the confounders calculated by fMRIPrep. We defined functional connectivity as linear correlation, specifically between BOLD signal of contralateral voxel signals for IHFC. Our group-level analysis utilized a general linear model with group classifications as predictors of connectivity. We conducted voxel-level hypothesis testing using multivariate parametric statistics with random-effects modeling. Our inferences were based on individual cluster evaluations, using non-parametric permutation testing (1000 iterations). Our results were determined using a dual-threshold approach, with a voxel-level threshold set at 1% (α_{voxel}) and a cluster-mass threshold adjusted for the false discovery rate at 5% (α_{cluster}).

Results: We investigated IHFC differences between the three groups. The size of cluster are given in number of voxels, which size is 2mm³ isotropic.

1) Control group vs group 1: We found one cluster (1316 voxels, $p=0.000127$, $p_{\text{FDR}}=0.025708$) where control group had higher IHFC. The cluster is located in posterior areas of the brain, mostly in the middle occipital and precuneus cortex.

2) Control group vs group 2: We found one cluster (2585 voxels, $p=0.000283$, $p_{\text{FDR}}=0.027140$) where control group had higher IHFC. This cluster covers similar area than the latter case (774 voxels in common), and is more extended toward the hippocampus and amygdala. We found a second cluster located in the cerebellum (2378 voxels, $p=0.000269$, $p_{\text{FDR}}=0.027140$) where Control group has a lower IHFC than group 2.

3) Group 1 vs Group 2: Only one cluster was found in the cerebellum (2816 voxels, $p=0.000165$, $p_{\text{FDR}}=0.032742$), where Group 1 IHFC is lower than Group 2. This cluster has a good overlap with the latter case cerebellum cluster (1438 voxels in common).

As in case 3) both groups are positive for ELA and only group 2 is positive for MH problems, results suggest the cerebellum IHFC increase is specific of the co-occurrence of ELA and MH problems, while the posterior IFHC decrease is specific of ELA alone.

Discussion: Our findings suggest that the ELA is associated with different alterations of interhemispheric functional connectivity depending on the co-occurrence of MH problems. These changes in IHFC might be the consequence of structural modifications in the corpus callosum, as diffusion MRI experiment found a decreased fractional anisotropy in the corpus callosum of individuals with ELA, hinting at potential myelin deterioration or localized

neuroinflammation. Additionally, the unique involvement of the cerebellum in cases where ELA and MH problems coexist could be a key factor in the development of symptoms or a sign of diminished resilience. This aspect deserves further investigation through a longitudinal approach.

30. MOTOR SKILLS, LINGUISTIC ABILITY, AND RELATED DISORDERS IN 7-YEAR-OLD CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

Marta Schiavon*¹, Birgitte Klee Burton², Nicoline Hemager³, Aja Greve⁴, Katrine S. Spang⁵, Ditte Ellersgaard³, Kerstin Jessica Plessen⁶, Jens Richardt Møllegaard Jepsen⁷, Anne Amalie Elgaard Thorup⁸, Thomas Werge⁹, Merete Nordentoft¹⁰, Ron Nudel¹¹

¹CORE - Copenhagen Research Centre for Mental Health, ²iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ³CORE - Copenhagen Research Centre for Mental Health and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ⁴Research Department P, Aarhus University Hospital, Risskov, Denmark and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ⁵Research Unit at Child and Adolescent Mental Health Center, Capital Region of Denmark and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ⁶CORE - Copenhagen Research Centre for Mental Health and Service of Child and Adolescent Psychiatry, University Medical Center, University of Lausanne, ⁷Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Mental Health Services - Capital Region of Denmark, Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, ⁸Faculty of Health and Medical Sciences, University of Copenhagen, and CORE - Copenhagen Research Center for Mental Health; iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research; Child and Adolescent Mental Health Center, University of Copenhagen, ⁹Faculty of Health and Medical Sciences, University of Copenhagen, ¹⁰CORE - Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, University of Copenhagen – Faculty of Health and Medical Services 4 The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ¹¹CORE - Copenhagen Research Centre for Mental Health, Mental Health Centre Copenhagen and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research

Background: Developmental disorders affecting motor function and linguistic ability such as Specific Language Impairment (SLI) and Developmental Coordination Disorder (DCD) tend to co-occur in developing children and may indicate underlying aberrant neurodevelopmental processes. Although schizophrenia (SZ) and bipolar disorder (BP) are seldom diagnosed during childhood, they may be preceded by early language and motor deficits. In fact, children at familial high-risk of SZ present significantly impaired motor skills and linguistic ability compared with population-based controls (PBC) and children with definite motor problems are more likely to perceive psychotic-like experiences.

Based on these findings, we have investigated the co-occurrence of SLI and DCD in 7-year-old children at familial high-risk of SZ, at familial high-risk of BP, and PBC. Moreover, we assessed how the children's familial high-risk status and their SLI or DCD status impacted their motor skills and linguistic ability.

Methods: We leveraged data from the Danish High Risk and Resilience Study (the VIA 7 study), a cohort of 522 7-year-old children born to parents with SZ (FHR-SZ, N=202) or BP (FHR-BP, N=120) or neither of these disorders (PBC, N=200). Motor skills were tested using the Movement Assessment Battery for Children-2 (MABC-2), while linguistic ability (in the form of receptive language and verbal intelligence) was assessed using the Test for Reception of Grammar-2 (TROG-2) and the Reynolds Intellectual Screening Test (RIST) – Guess What. The relationship between motor skills and linguistic ability was investigated using correlation and linear regression. DCD and SLI status were defined based on the children’s MABC-2 and TROG-2 scores. To determine the impact of the children’s familial high-risk status on their motor skills and linguistic ability, we performed linear regressions of the quantitative linguistic or motor scores on respectively DCD or SLI status (i.e., having the disorder affecting the other domain) together with familial high-risk status and sex. We also calculated the prevalence of concomitant DCD and SLI among children in each group (FHR-SZ, FHR-BP, and PBC).

Results: We found significant correlations between most measures of linguistic ability and motor skills, and an association between DCD and SLI (OR=8.22, $P=2.28 \times 10^{-7}$). Familial high-risk of SZ had a significant negative effect on all linguistic and motor outcomes, apart from the “aiming and catching” subdomain of the MABC-2, while adjusting for DCD or SLI status and sex. Familial high-risk of BP had no effect on either linguistic or motor outcomes. Most DCD and SLI cases were found in the FHR-SZ group. The prevalence of concomitant DCD and SLI was 6.9% in the FHR-SZ group, 2.5% in the FHR-BP group, and 1.7% among PBC.

Discussion: Our results confirm an overlap between DCD and SLI. In fact, motor and language development have been reported to mutually influence each other, though other factors may also be at play. The higher prevalence of both DCD and SLI among children in the FHR-SZ group and their overall poorer performance in linguistic and motor tests may indicate the presence of group-specific factors affecting neurodevelopmental processes. Further research should focus on identifying modifiable, environmental factors on which to intervene to ensure optimal neurodevelopment in children of parents with SZ, and potentially increase their resilience to psychosis.

31. ASSOCIATION BETWEEN CHILDHOOD ADVERSITIES AND THE RISK OF PSYCHOSIS: A META-ANALYTIC UPDATE AND EXTENSION OF THE EVIDENCE

Lan Zhou^{*1}, Pengyuan Yang², Jim van Os³, Iris Sommer¹, Marieke Begemann¹

¹University Medical Center of Groningen, ²Ghent University, ³Utrecht University Medical Centre

Background: Research on the association between childhood adversity and psychosis has rapidly accumulated during the past decade, presumably in response to the first large-scale meta-analysis by Varese et al. in 2012, showing that patients with psychosis were 2.72 times more likely to have been exposed to childhood adversity than controls (41 studies). Current meta-analysis provides an update by adding studies published since 2012 and extends the evidence by investigating the effect of ten specific trauma subtypes, examining potential gender differences and evaluating the age of onset of psychosis between exposed and non-exposed individuals.

Methods: An electronic search was performed using PubMed, EMBASE, PsychINFO, Web of Science, Wanfang, and China National Knowledge Internet, with a search cutoff date of February 28, 2023. We included case-control studies comparing either the prevalence of adversity between psychotic patients and controls or the prevalence of psychotic symptoms

between adversity exposed and nonexposed subjects, as well as cross-sectional studies and cohort studies exploring the association between childhood adversity and psychotic symptoms/illness, using dichotomous or continuous measures.

Results: The main analysis included 183 unique study samples (N = 344,678), of which 120 with a case-control design (15,339 cases and 14,975 controls), 51 cross-sectional studies (total participants: 299,256), and 12 cohort studies (total participants: 15,108). Significant associations between childhood adversity and psychosis were observed across all study designs, yielding an overall effect size of OR = 2.79 (95% CI 2.15 - 3.61). When evaluating specific study designs, the largest effect size in magnitude was observed for the case-control studies with OR = 3.49 (95% CI = 3.06 - 3.98, p LESS THAN .001; 95% PI = 0.88 – 13.84), as compared to an OR of 2.37 for both cross-sectional studies (95% CI = 2.09 - 2.69, p LESS THAN .001; 95% PI = 0.92 – 6.11) and cohort studies (95% CI = 1.80 - 3.11, p LESS THAN .001; 95% PI = 0.69 – 8.13). Secondary analyses revealed statistically significant associations between all types of childhood adversity (i.e., physical abuse, physical neglect, emotional abuse, emotional neglect, sexual abuse, bullying victimization, parental death, parental separation, abuse, and neglect) and psychosis, with emotional abuse exhibiting the highest odds ratio (OR = 3.61 [95% CI: 3.10, 4.20]), and parental death displaying the lowest odds ratio (OR = 1.39 [95% CI: 1.06, 1.80]). In addition, we found that the association between childhood adversity and psychosis was similar between males (OR 2.45, 95% CI: 1.73 - 3.48) and females (OR 2.55, 95% CI: 1.96 - 3.33). We did observe that age of onset was a significant factor, as individuals exposed to childhood adversity exhibited an earlier age of onset of psychotic symptoms compared to unexposed individuals, with a mean difference of -0.79 (95% CI = -1.47 to -0.12, p LESS THAN 0.05).

Discussion: To our knowledge, this study represents the largest meta-analysis to date on childhood adversity and psychosis, including 183 studies with a total of 344,678 individuals. Our findings replicate the Odds ratio provided by Varese et al. in 2012 between childhood adversity and an increased risk of psychosis. Secondary analyses indicated that this association appears to be similar for males and females, while signifying that the age of onset of psychosis or psychotic symptoms may be earlier in adversity-exposed individuals versus those unexposed to early adversity.

Oral Session: Cognition and Symptom Profiles

32. COGNITIVE FUNCTION AND COGNITIVE HETEROGENEITY IN ANTI-PSYCHOTIC DRUG-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS - AN UPDATED META-ANALYSIS

Maria Lee^{*1}, Martin Cernvall², Jacqueline Borg³, Pontus Plavén-Sigra⁴, Cornelia Larsson³, Sophie Erhardt⁵, Carl M. Sellgren⁵, Helena Fatouros Bergman³, Simon Cervenka³

¹Karolinska Institute, Clinical Neuroscience, ²Uppsala University, ³Center for Psychiatry Research, Karolinska Institutet, ⁴Center for Psychiatry Research, Karolinska Institutet and Stockholm County Council; Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet, ⁵Karolinska Institutet

Background: Cognitive dysfunction in psychotic disorders contributes significantly to clinical outcome and level of function. These impairments are present already at psychosis onset, however the extent of heterogeneity in cognitive function among patients has not been systematically investigated. Our objective was to quantify the level of cognitive impairment at

psychosis onset, before patients receive potentially confounding antipsychotic treatment, and to investigate within-group variability in cognitive function compared to healthy controls.

Methods: To perform a meta-analysis of mean differences and within-group variability, PubMed database was searched up to September 15th 2022, with a focus on original studies reporting data on cognitive function in antipsychotic drug-naïve first episode psychosis patients (FEP).

Data Extraction and Synthesis:

Data was independently extracted by two researchers. Cognitive tasks were clustered according to six domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the domain of executive function. Random-effect model meta-analyses of mean differences and coefficient of variation ratios (CVR) were performed, as well as meta-regressions, assessment of study quality and publication bias.

Main Outcomes and Measures:

The main outcome measure was Hedges' g for mean differences in cognition, and CVR for within-group variability.

Results: Fifty studies were included with a total of 2625 individuals with FEP (mean age 25.2 [SD 3.6], 40% female) and 2917 healthy controls (mean age 26.0 [SD 4.6], 45% female). In all cognitive domains, the FEP group displayed a significant impairment compared to controls (Speed of processing $g = -1.16$ [95% CI: -1.35, -0.98]; Verbal learning $g = -1.08$ [95% CI: -1.28, -0.88]; Visual learning $g = -1.05$ [95% CI: -1.27, -0.82]; Working memory $g = -1.04$ [95% CI: -1.35, -0.73]; Attention $g = -1.03$ [95% CI: -1.24, -0.82]; Reasoning/problem solving $g = -0.90$ [95% CI: -1.12, -0.68] and Executive function $g = -0.88$ [95% CI: -1.07, -0.69]). Individuals with FEP also exhibited a larger variability across all domains (CVR ranged from 1.34 to 1.94).

Discussion: This meta-analysis confirms cognitive impairment in FEP before the initiation of antipsychotic treatment, with large effect sizes. The high variability within the FEP group indicates the need to identify those individuals with more severe cognitive problems who risk worse outcome and could benefit the most from cognitive remediation.

33. THE ARCHITECTURE OF PARANOIA IN THE GENERAL POPULATION: A SELF-REPORT AND ECOLOGICAL MOMENTARY ASSESSMENT STUDY

Maja Neidhart^{*1}, Sebastian Mohnke², Bob O. Vogel¹, Henrik Walter¹

¹Charite University Medical Center Berlin, ²Practice for Psychotherapy Praxis

Background: Delusions are fixed beliefs that are not amenable to change in light of conflicting evidence (APA, 2013; DSM-5). They represent a core symptom of psychotic disorders, which are among the most cost-intensive and burdensome illnesses worldwide (Bebbington et al., 2013; Rössler et al., 2005; Schneider et al., 2019). Paranoia is a prevalent type of delusion in adolescents and adults in the general population and follows a continuum, where at least 10-15% experience paranoid symptoms regularly (Bird et al., 2019; DeRosse and Karlsgodt, 2015; Freeman, 2007; Garety et al., 2013; Pechey and Halligan, 2011). Bebbington et al. (2013) conceptualized paranoia within the general population as a hierarchical, dimensional continuum. They suggested four categories, representing increasing levels of paranoia: interpersonal sensitivity, mistrust, ideas of reference and persecution ideas. In alignment with the cognitive model of persecutory delusions (Freeman et al., 2002), clinically relevant paranoia is on the extreme end of a dimensional spectrum that is built on typical and adaptive emotional concerns like worrying. What is currently lacking and could provide insights into

etiology is a comprehensive clinical characterization of the lower end of the paranoia spectrum, psychological domains that are associated with symptom severity, and how paranoia and its structure fluctuate over time.

Methods: This study was a cross-sectional and longitudinal survey. 802 people from the general German population completed self-report questionnaires assessing paranoia and general psychopathology. Furthermore, data was collected through Ecological Momentary Assessment (EMA) (N = 515). Our study aimed to reproduce and extend existing research on paranoia in the general population. First, we examined the hierarchy and structure of paranoia in a large German sample to reproduce findings from Bebbington et al. (2013) using questionnaires and EMA. We hypothesized that our data would cluster into the suggested four paranoia-subgroups. We also explored subgroup differences in psychological factors including psychopathology, emotions and coping styles. Finally, we explored the temporal dynamics of paranoia using a short EMA battery for real-time-self-reports and potential predictors of overall paranoia. To address our research questions, we employed (1) confirmatory factor analysis to examine the structure of the items from the Bebbington Questionnaire in N = 802 participants, (2) latent class analysis to determine group membership, and other statistical tests including ANOVA to investigate group differences, and (3) mixed modelling analyses in N = 515 to examine the temporal dynamics of paranoia and time associations with interpersonal sensitivity and persecutory ideation.

Results: Paranoia was common in the general population. Prevalence of the overall paranoia score in the general German population ranged from 0-15, mean score was 2.79 (SD = 2.95). It followed an exponential distribution, with many people with a low and few people with a high paranoia score. For examination of the dimensionality and hierarchical structure of paranoia, results from CFA showed that 4-factor second order model showed the best fit with high factor loadings (0.22-0.66). LCA results also showed, that subjects clustered into four paranoia severity subgroups: interpersonal sensitivity, mistrust, ideas of reference, and persecutory ideas. Significant associations existed between severity groups and various psychological domains, including increased psychiatric symptoms and maladaptive coping. ANOVA results indicate highly significant differences ($p < .001$) among paranoia severity and psychological domains. Results from mixed modelling showed that paranoia fluctuate over time in all four severity subgroups but the hierarchical subgrouping was stable. Both persecutory ideations and interpersonal sensitivity were significant predictors of paranoia ($p < .001$).

Discussion: Our study investigated the prevalence and structure of paranoia in the German general population. Results suggest that paranoia is a relatively common phenomenon in the general population which occurs along a continuum of increasing severity. We were able to identify paranoia severity subgroups, therefore subjects clustered into four groups: interpersonal sensitivity, mistrust, ideas of reference, and persecutory ideas. Here, we provide evidence that severity subgroups differ on a variety of psychological domains, which was previously unknown. Individuals with higher levels of paranoia were generally more anxious, more depressed and had higher levels of maladaptive coping strategies. Additionally, we employed EMA to assess paranoia over time and its predictors. Paranoia fluctuates, depending on time of day and severity subgroup. Both interpersonal sensitivity and persecutory ideas were significant predictors of overall paranoia, with persecutory ideation having the strongest effect. This provides further evidence for the proposed structure of paranoia in the general population.

34. REVEALING PSYCHOTIC SYMPTOM PATTERNS IN SCHIZOPHRENIA AND BIPOLAR I DISORDER: INSIGHTS FROM SYMPTOM PATTERN INVESTIGATION

Younghoon Kim^{*1}, Jinhyeok Jang¹, Nuree Kang¹, Jae Hoon Jeong¹, Jayoun Kim¹, Yong Min Ahn², Yong Sik Kim³, Se Hyun Kim⁴

¹*Seoul National University Hospital*, ²*Seoul National University*, ³*Nowon Eulji University Hospital*, ⁴*Seoul National University College of Medicine*

Background: The field of psychiatry has encountered ongoing challenges in understanding the intricate nature of psychotic symptoms, particularly when they manifest in individuals diagnosed with either bipolar disorder or schizophrenia. The overlapping characteristics and underlying neurobiology of schizophrenia and bipolar spectrum disorders, particularly bipolar I disorder, have presented difficulties in differentiation. Through an exploration of symptom patterns and their clinical significance, we aim to gain a more profound insight into these intricate disorders. Our goal is to enhance our comprehension and approach to managing these demanding psychiatric conditions by prioritizing symptom patterns over rigid diagnostic classifications.

Methods: We investigate our hypothesis regarding potential differences in the occurrence patterns of symptoms between schizophrenia and bipolar I disorder through the use of manifold and network analyses in this study. The present analysis relies on a dataset including 555 participants, consisting of 282 individuals diagnosed with schizophrenia-related disorders and 273 individuals diagnosed with bipolar I disorder. The U-MAP is employed as an initial approach for manifold analysis in order to visually represent and examine the distribution of eighteen symptoms associated with psychosis and anxiety. In addition, support vector machine analysis is utilized to examine the distinctive patterns identified by U-MAP. In the context of network analysis, the eLasso method is used to investigate the interconnections and dynamics among symptoms within the network framework. In order to evaluate the clinical implications of symptom dimensions, we used the chi-square test to compare the clinical outcomes between groups with and without specific symptom dimensions.

Results: In the context of schizophrenia, negative symptoms, particularly avolition, play a significant role in shaping the range of symptoms observed in affected individuals. The U-MAP manifold space effectively captures the significance of negative symptoms in schizophrenia by demonstrating how the manifold distributes individuals based on the overall number of negative symptoms. Furthermore, this distribution is found to be correlated with the total number of psychotic symptoms. The results obtained from the analysis of networks offer additional evidence to support the concept that avolition displays a significant level of centrality. Avolition is a phenomenon of clinical significance that has been observed to exhibit associations with the administration of clozapine, patterns of deterioration, tendencies towards remission, and the severity of the illness. On the other hand, bipolar I disorder demonstrates identifiable patterns in which positive symptoms play a significant role in network analysis. The utilization of manifold analysis unveils an unforeseen segregation of patients into two distinct clusters. In summary, it can be concluded that schizophrenia and bipolar I disorder, despite having common psychotic symptoms, demonstrate discernible patterns of co-occurrence. Schizophrenia places emphasis on negative symptoms, while bipolar I disorder places emphasis on positive symptoms. The strength of associations between these symptoms varies, with bipolar I disorder exhibiting stronger connections to psychotic symptoms.

Discussion: Negative symptoms have long been recognized as a central aspect of schizophrenia, a notion reinforced by our manifold analysis. A consistent upward trend was observed in the cumulative count of psychotic symptoms in individuals diagnosed with schizophrenia, exhibiting a positive correlation with the number of negative symptoms. This observation implies that the existence of negative symptoms in individuals with schizophrenia may be indicative of a more pronounced symptomatology. Within network analysis, negative symptoms grouped together, with aversion being the most central in a number of measures

(Katz, betweenness, and closeness). On the other hand, bipolar I disorder exhibited a greater prominence of positive symptoms. The strong intra-connectivity between symptoms and their frequent co-occurrence with positive symptoms suggest a "all-or-nothing" pattern in bipolar I disorder symptomatology. The observed clustering pattern is consistent with the DSM-5 specifier that differentiates between bipolar I disorder with and without psychotic features. In summary, our research highlights the significant impact of negative symptoms on the manifestation of symptoms in individuals with schizophrenia, emphasizing their fundamental influence. On the other hand, bipolar I disorder demonstrates a greater prevalence of positive symptoms and strong connections among psychotic symptoms. Although our study has limitations by the limited sample size, conducting future research with larger datasets could potentially yield additional insights. The present study makes a substantial contribution to the field by emphasizing the intricacy of these disorders and the significance of symptom patterns in enhancing comprehension and treatment, thereby challenging the limitations of rigid diagnostic classifications.

35. COMPREHENSIVE TRANSDIAGNOSTIC ANALYSIS OF VERBAL FLUENCY IN SCHIZOPHRENIA AND AUTISM SPECTRUM DISORDER, COMPARING WITH NEUROTYPICAL CONTROLS

Kinga Farkas*¹, Eszter Zarka¹, Orsolya Pesthy²

¹*Semmelweis University*, ²*ELTE, Eötvös Loránd University*

Background: Verbal fluency, a cognitive function that reflects executive functions and the rapid retrieval of pertinent information from memory, has yielded inconsistent findings in previous research on autism spectrum disorder (ASD), however in schizophrenia (SCH) semantic fluency exhibits a more pronounced impairment compared to letter fluency. In this study we aim to comprehensively investigate verbal fluency in ASD, SCH, and neurotypical healthy control individuals (NTP). The primary objective is to investigate disparities in novel response generation, specifically between the ASD, SCH and NTP groups, using phonemic and semantic fluency tasks. Three central inquiries guide our research: (1) whether differences between groups (ASD, SCH, and NTP) can be identified in word productivity, clustering, errors, and perseverations; (2) whether participants with ASD and SCH exhibit different word production with elevated imageability and concreteness values; and (3) if individuals with ASD and schizophrenia demonstrate reduced productivity during the earlier phases of fluency tasks.

Methods: Forty participants with ASD (12 female, 24 male, 4 other, mean age: 30.5), 39 with SCH (10 female, 28 male, 1 other, mean age: 34.7) and 41 NTP (13 female, 28 male, mean age: 31.0) were recruited from the outpatient units of the Department of Psychiatry and Psychotherapy, Semmelweis University. Participants were requested to list as many words as they could on two phonemic and two semantic category conditions. Audio recordings were later transcribed. To assess concreteness and imageability, we employed a seven-point scale and recruited independent external raters to evaluate a total of 1481 words.

Results: Preliminary results indicate that the three study groups did not differ significantly in phonemic fluency ($F(2, 119) = 0.983, p=0.377$), during either time period. However, a significant difference was observed in semantic fluency ($F(2, 119) = 6.531, p=0.002$). Post-hoc tests (Tukey corrected) revealed that this difference stemmed from impaired performance in the SCH group. Participants with schizophrenia (SCH) exhibited reduced semantic word productivity compared to both neurotypical (NTP) individuals and participants with ASD. However, there were no significant differences between participants with ASD and NTP individuals. In terms of concreteness and imageability, schizophrenic patients listed less concrete (tendency, $p=0.064$) and lower imageable ($p=0.037$) words during the phonemic

fluency task. However, contrary to our expectations, participants with autism, did not show significant differences. At the same time, individuals with autism produced significantly more neologisms (non-existent words) and rare words, than the other two groups.

Discussion: Our study investigated the characteristics of verbal fluency in a transdiagnostic approach. While phonemic fluency did not reveal significant differences among the three groups, our analysis of semantic fluency unveiled a distinction. Specifically, individuals with schizophrenia exhibited impaired semantic word productivity. Furthermore, schizophrenic group used more abstract words, and words with lower imageability during phonemic fluency task. Our study highlights the complex nature of verbal fluency impairments in different conditions and the importance of considering more nuanced methods when assessing cognitive functions.

36. OUT OF CONTEXT: A “HYPER-RECENCY” BIAS IN MEMORY CHARACTERIZES BOTH PSYCHOTICISM AND DÉJÀ VU EXPERIENCES

William Koller*¹, Joan Danielle K. Ongchoco², Michael V. Bronstein³, Brian Scholl¹, Tyrone D. Cannon¹

¹*Yale University*, ²*University of British Columbia*, ³*University of Minnesota*

Background: Psychosis is characterized by salient conflicts between reality and one’s experience of it, but the cognitive processes involved are not fully understood. A relatively more common experience – déjà vu – seems to imply similar conflicts, in that the feeling that one has lived through the present situation before is highly salient despite not being able to pinpoint why or knowing that this cannot be true. Here, we hypothesized that both psychosis-like symptoms and déjà vu experiences might be related to a breakdown in memory for when events occurred in time.

Methods: Across two preregistered studies, 500 subjects completed a novel timeline-based recognition memory task. During encoding, subjects viewed a stream of images depicting everyday objects. During recognition, in addition to being tested on what they remembered (i.e., “Old or New?”), subjects used a “timeline” slider to indicate when they remembered recognized items as having occurred during encoding. This enabled a precise measure of temporal displacement reflecting whether temporal judgments were overly recent or overly distal relative to an item’s original position. In Study 1 and 2, we measured paranoia (Revised Green Paranoid Thoughts Scale) and schizotypy (Multidimensional Schizotypy Scale Brief; including positive, negative, and disorganized symptoms); in Study 2, we measured intensity of déjà vu experiences. Mixed-effects linear regressions assessed whether psychoticism (i.e., a composite of paranoia, positive symptoms, and disorganized symptoms) and déjà vu were associated with temporal displacement, over and above negative symptoms.

Results: Results indicated that those higher in psychoticism performed more poorly on the timeline task. Yet, instead of a pattern of general disorganization, psychoticism was associated with a tendency to misjudge recognized items as having occurred more recently than they actually did. This manifested as a main effect of psychoticism on temporal displacement in Study 1, $t(226.68)=6.31$, $p < .001$, $\eta^2=0.15$, 95% CI [0.07, 0.24], which was replicated in Study 2, $t(227.08)=5.57$, $p < .001$, $\eta^2=0.12$, 95% CI [0.05, 0.20]. A parallel effect was seen for recognition “false alarms” in both Study 1, $t(195.33)=6.77$, $p < .001$, $\eta^2=0.19$, 95% CI [0.10, 0.29], and Study 2, $t(237.78)=6.36$, $p < .001$, $\eta^2=0.15$, 95% CI [0.07, 0.23]. Notably, Study 2 revealed that déjà vu was similarly associated with hyper-recency of both correct recognitions $t(231.03)=5.51$, $p < .001$, $\eta^2=0.12$, 95% CI [0.05, 0.20], and false alarms, $t(230.71)=5.82$, $p < .001$,

$\eta^2=0.13$, 95% CI [0.06, 0.21]. Finally, across studies, negative schizotypy showed no such patterns (ps ranging from .09 to .75; with any trends leaning towards hypo-recency).

Discussion: Across two preregistered studies, psychoticism and déjà vu (but not negative schizotypy) were associated with the tendency to remember recognized items as having occurred more recently than they actually did. This “hyper-recency” bias was seen for both correct and false recognitions, was robust to alternate explanations (e.g., low attention), and replicated in an independent sample. Together, these results indicate that aberrant temporal memory may be related to challenges with reality monitoring across a continuum, creating conflicts between reality and one’s experience of it wherein remotely encountered stimuli currently in mind are perceived to have happened just recently.

37. THE EFFECT OF ANTIPSYCHOTIC DRUGS ON SOCIAL COGNITION IN SCHIZOPHRENIA – A RETROSPECTIVE COHORT STUDY

Makarand Pantoji*¹, Rakshathi Basavaraju¹, Anuradha Rao¹, Urvakhsh M Mehta¹

¹*National Institute of Mental Health and Neurosciences, Bengaluru*

Background: Social cognition is an important determinant of real-world functional outcomes in schizophrenia, and hence an important treatment target (Hajdúk et al., 2021). The effect of antipsychotic drugs on social cognition has been studied in the recent past. Most of the studies failed to show any significant difference with antipsychotic treatment (Haime et al., 2021). This could be because social cognition impairments are stable trait like impairments and are unaffected by antipsychotic drugs. This can be proven by comparing social cognition functioning with and without antipsychotic drugs using tests of equivalence, as lack of a statistically significant difference does not imply equivalence.

Hence, we aimed to examine equivalence in social cognition between two groups – treatment group: patients with schizophrenia who are on a stable dose of any antipsychotic drug, control group: individuals with schizophrenia who are not on any antipsychotic drug.

Methods: 60 patients with schizophrenia were recruited in the treatment group, and 81 were recruited in the control group. Participants in both groups were assessed at a single time point. The assessments included – socio-demographic details, illness and treatment related details, positive and negative symptoms (using PANSS), and social cognition (using SOCRATIS and TRENDS). Social cognition was examined under five domains – first and second-order theory of mind (ToM), faux pas recognition, social cue perception, emotion recognition and attribution bias. The two groups were compared with respect to the social cognition domains using two one-sided t-tests (TOST) for equivalence, with equivalence bounds for effect size (Hedge’s g) set as (-0.2 to 0.2). Correlation between social cognition, and positive and negative symptoms was examined using Pearson’s correlation coefficient.

Results: The two groups were comparable with respect to the age and severity of negative symptoms. The treatment group had a lesser proportion of females (24% vs. 56%), fewer positive symptoms (PANSS – positive score: 6.6 vs. 33) and a longer mean duration of illness (9.7 years vs. 2.9 years). Duration of illness showed no significant correlation with any social cognition domain. The two groups showed equivalence with respect to first-order ToM (TOST upper: p LESS THAN 0.001; TOST lower: p LESS THAN 0.001), second-order ToM (TOST upper: $p=0.003$; TOST lower: p LESS THAN 0.001), faux pas recognition (TOST upper: p LESS THAN 0.001; TOST lower: p LESS THAN 0.001), emotion recognition (TOST upper: p LESS THAN 0.001; TOST lower: p LESS THAN 0.001) and social cue perception (TOST upper: p LESS THAN 0.001; TOST lower: p LESS THAN 0.001). The treatment group had more personalizing bias ($p=0.01$) and lesser externalizing bias ($p=0.04$) than the control group.

In both groups, deficits in social cue perception had a negative correlation with negative symptoms (treatment group: $r = -0.469$, $p = 0.001$; control group: $r = -0.345$, $p = 0.027$). In the control group, deficits in second-order ToM showed a negative correlation with positive symptoms ($r = -0.45$, $p < 0.001$).

Discussion: Social cognition deficits are linked to positive and negative symptoms. Antipsychotic drugs though effective in reducing positive and negative symptoms, had no effect on four out of five domains of social cognition.

The treatment group had a lesser externalizing bias. Treatment with antipsychotic drugs may reduce persecutory delusions, and this may be linked to the lower externalizing bias.

None of the social cognition domains showed any significant correlation with the duration of illness, implying these could be stable trait-like impairments.

In both groups, patients with more severe negative symptoms had poorer performance in social cue perception. Poor social cue perception may be contributing to the negative symptoms of passive social withdrawal and poor rapport.

We conclude that most of the social cognition deficits remain stable and are unaffected by antipsychotic treatment. We need to further explore our understanding of the relation between social cognition deficits and positive and negative symptoms.

38. IMPAIRED REWARD REPRESENTATIONS IN SCHIZOPHRENIA AND DEPRESSION: RE-EVALUATING THE UNDERPINNINGS OF ANHEDONIA FROM A TRANSDIAGNOSTIC PERSPECTIVE

Zheng Xia^{*1}, Han-shan Jiang¹, Lan Zhou², Ling-ling Wang³, Zheng-hui Yi⁴, Su-hong Wang⁵, Chao Yan¹

¹East China Normal University, ²University of Groningen, ³Shanghai Normal University, ⁴Shanghai Mental Health Center, ⁵The First People's Hospital of Changzhou

Background: Anticipatory anhedonia, characterized by the inability to experience pleasure in anticipation, is a transdiagnostic symptom observed in both schizophrenia (SCZ) and major depressive disorder (MDD). Despite its prevalence, the underlying mechanisms remain unclear, and it is uncertain whether there are differences in anticipatory anhedonia between SCZ and MDD. This study aims to explore the activation and maintenance capacity of reward representation and its influence on anticipatory pleasure in patients with SCZ and MDD, respectively.

Methods: We recruited 63 patients meeting the DSM-5 criteria for SCZ and 60 patients meeting the criteria for MDD. An additional 77 healthy controls (HC) were enrolled from the community, with age and sex ratios matched. The Reward Representation and Maintenance Task (RRMT) was designed to measure the ability of reward representation activation and maintenance, as well as subsequent anticipatory experience. Initially, participants were presented with symbols indicating different levels of monetary reward (i.e., 1, 5, or 10 RMB). They were then required to maintain representations for varying lengths (i.e., short maintenance vs. long maintenance), and a second symbol was presented. Participants had to judge whether these two symbols representing the reward value were the same or different. The mismatch rate was calculated to reflect the ability of reward representation activation (short length) and maintenance (long length). During the anticipation phase, they were asked to press the space bar to express how much they would like to see the rewarding symbol again, with more key presses indicating a higher level of anticipatory pleasure.

Results: The interaction effect of group and maintenance level was marginally significant between the SCZ and HC groups ($F(1,135) = 2.78, p = .098$) and was significantly present between the MDD and HC groups ($F(1,136) = 3.88, p = .049$), with a larger between-group discrepancy in mismatch rate during long maintenance trials than that during short trials. Further analysis revealed that both SCZ ($F(1,135) = 27.16, p \text{ LESS THAN } .001$) and MDD ($F(1,136) = 5.63, p \text{ LESS THAN } .05$) patients were more likely to mismatch during short maintenance tasks compared to HCs, implying the dysfunction of activation of SCZ and MDD patients. Additionally, a significant group effect of mismatch rate between SCZ and MDD group was observed ($F(1, 119) = 9.07, p \text{ LESS THAN } .01$), with SCZ patients exhibiting higher mismatch rate than MDD patients.

In the anticipatory phase, a significant interaction between group and reward amount was observed between SCZ and HC groups ($F(2,270) = 17.50, p \text{ LESS THAN } .001$). The number of button presses by SCZ patients decreased as rewards increased, with a significant drop for larger rewards (10 RMB, $p \text{ LESS THAN } .001$) and an increase for smaller rewards (1 RMB, $p = .014$) compared to HCs. We did not observe a significant interaction of group and maintenance level, suggesting that impairment patterns persisted across both maintenance conditions. In contrast, MDD patients showed fewer button presses than HCs for all rewards, particularly for larger rewards ($F(1,140) = 12.65, p \text{ LESS THAN } .001$), suggesting a generally reduced anticipatory response for rewards. Moreover, SCZ patients pressed the button significantly more often than MDD patients ($F(1,119) = 11.33, p \text{ LESS THAN } .001$).

Discussion: Our research not only replicated previous observations of reduced anticipatory pleasure in both schizophrenia (SCZ) and major depressive disorder (MDD) patients but also revealed nuances in the nature of these deficits between the two groups. Additionally, both SCZ and MDD patients exhibit impairments in the activation and maintenance of reward representations, with SCZ patients displaying more pronounced difficulties. Our findings suggest that the distinct mechanisms underlying activation and maintenance contribute to the varied patterns of anticipatory pleasure in SCZ and MDD patients. These insights advance our comprehension of the cognitive foundations of anticipatory anhedonia and lay the groundwork for a transdiagnostic approach to comprehend and address anhedonia effectively.

39. DYNAMICS OF HALLUCINATION AND DELUSION EMERGENCE SUPPORT A SECONDARY ACCOUNT OF HALLUCINOGENESIS

Catalina Mourgues-Codern¹, David Benrimoh², Jay Gandhi¹, Emily Farina³, Tihare Zamorano², Deven Perekh², Jean Addington⁴, Carrie Bearden⁵, Kristin Cadenhead⁶, Ming Tsuang⁶, Barbara Cornblatt⁷, Matcheri Keshavan⁸, William Stone⁹, Daniel Mathalon¹⁰, Diana Perkins¹¹, Elaine Walker¹², Tyrone Cannon¹, Scott Woods¹, Jai Shah², Albert Powers^{*3}

¹Yale University, ²McGill University, ³Yale University School of Medicine, ⁴University of Calgary, ⁵University of California, Los Angeles, ⁶University of California, San Diego, ⁷The Zucker Hillside Hospital, ⁸Harvard University, ⁹Harvard Medical School / Beth Israel Deaconess Medical Center, ¹⁰University of California, San Francisco, ¹¹University of North Carolina At Chapel Hill, ¹²Emory University

Background: Hallucinations and delusions are commonly grouped together as the positive symptoms of psychosis, but recent evidence suggests that they may be driven by different and perhaps opposing computational mechanisms. However, most studies examining the computational underpinnings of hallucinations and delusions do so in fully-formed symptoms, which may obscure important information about the causal relationships between these

symptoms' underpinnings. By appealing to the relative timing of hallucination and delusion emergence, we may uncover dynamics informative for understanding their coexistence.

Methods: Participants at Clinical High Risk for Psychosis enrolled in the second (N = 719) and third iterations (N = 699) of the North American Prodrome Longitudinal Study were assessed for timing of CHR-P-level delusion and hallucination onset, defined as SIPS scores greater than 2 and less than 6 on SOPS P1/P2 and P4, respectively. Timing of symptom onset in first-episode psychosis patients from the Prevention and Early Intervention Program for Psychosis (PEPP-Montréal; N = 695) was assessed using the Circumstances of Onset and Relapse Schedule (CORS). Neural correlates of bottom-up and top-down information flow were examined using Dynamic Causal Modeling (DCM) for fMRI and EEG applied to resting-state fMRI data and EEG data gathered during an oddball task.

Results: In all three samples, participants were markedly more likely to report the onset of delusions prior to that of hallucinations (NAPLS 2: odds ratio (OR) = 4.09; NAPLS 3 OR = 4.14; PEPP OR = 4.04) and to present with only delusions than only hallucinations (NAPLS 2: OR = 5.6; NAPLS 3: OR = 11.11; PEPP: OR = 86.42). Across the time followed, transition from having no CHR-P-level symptoms to only delusions was much more likely than transition to having only hallucinations (NAPLS 2: Z = 2.920, P = 0.003; NAPLS 3 Z = 2.683, P = 0.007). The reverse was also true: hallucination resolution was more likely than delusion resolution from a state of having both CHR-P-level delusions and hallucinations (NAPLS 2: Z = 8.557, P LESS THAN 0.001; NAPLS 3: Z = 7.843, P LESS THAN 0.001). Hallucinations were also more volatile over the CHR-P period than delusions, with markedly higher standard deviations (NAPLS 2: T39 = 2.04, P = 0.048; NAPLS 3: T39 = 2.941, P = 0.005) and higher Lempel-Ziv complexity (NAPLS 2: T399 = 2.099, P = 0.036; NAPLS 3: T308 = 2.445, P LESS THAN 0.001). Critically, In the CHR-P samples, hallucination onset was found to be preceded by a period of high delusional intensity, which fell significantly following hallucination onset (T59 = 2.78, P = 0.007). This pattern was observed in both remitters and non-remitters.

A Bayesian model positing a causal relationship between the states underlying delusion severity and hallucination performed well and significantly explained the data observed. Preliminary results from fMRI and EEG analysis demonstrate a switch from bottom-up information flow to top-down dominance in individuals who have delusions at baseline assessment and subsequently develop hallucinations.

Discussion: Development of hallucinations follows that of delusions in most people in the earliest phases of psychosis. High delusion intensity leading up to hallucination onset that then drops after hallucination onset may support a secondary account of hallucinogenesis in which mechanisms driving hallucination onset are an attempt to compensate for the factors driving delusion formation.

Oral Session: Genetics, Genomics and Proteomics

40. EXPLORING THE LINK BETWEEN POLYGENIC RISK SCORES AND CORTICAL STRUCTURE IN YOUTH AT FAMILIAL RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Irene Martínez Serrano^{*1}, Elena De la Serna², María Ortuño³, Daniel Ilzarbe⁴, Patricia Camprodón-Boadas³, Mireia Rosa², Adriana Fortea⁵, Àlex González-Segura⁶, Natalia Rodríguez⁶, Sergi Mas⁶, Inmaculada Baeza⁷, Josefina Castro-Fornieles⁷, Gisela Sugranyes⁸

¹University of Barcelona, Hospital Clinic, ²Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM, ³Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), ⁴Institute of Neuroscience, Hospital Clinic de Barcelona, ⁵Hospital Clinic / Fundació Clínic per la Recerca Biomèdica (FCRB) / Universitat de Barcelona, ⁶University of Barcelona, ⁷2017SGR881, Neurosciences Institute, Hospital Clinic de Barcelona, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi Sunyer), CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), ⁸Institute of Neuroscience, Hospital Clinic of Barcelona Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS)

Background: The etiology of schizophrenia and bipolar disorder involves a complex interplay of genetic, environmental and neurobiological factors (Jauhar et al. 2022). Given their polygenic nature, the polygenic risk score (PRS) method has been developed to capture the genetic liability of these disorders at the individual level. Additionally, brain magnetic resonance imaging (MRI) has revealed structural brain abnormalities among individuals with these disorders (Jalbrzikowski et al. 2019), an alteration that is also found, with smaller effect sizes, in first-degree relatives (de Zwarte SMC et al. 2019). Our aim is to examine the association between brain imaging measures and the polygenic burden of various psychopathological illnesses and cognitive phenotypes in children and adolescents at familial risk for psychosis.

Methods: One hundred and ninety participants, including 34 offspring of patients with schizophrenia (SzO), 74 offspring of patients with bipolar disorder (BpO), and 66 offspring of healthy controls (HcO), aged 6 to 17 years at intake, were assessed using clinical, genetic and neuroimaging methods. PRS for schizophrenia (PRS_SZ), bipolar disorder (PRS_BD), major depression disorder (PRS_MDD), general intelligence (PRS_IQ), educational attainment (PRS_EA) and cognitive performance (PRS_CP) were computed based on the latest available summary statistics from each one. The scores were constructed using a Bayesian Regression method with the PRS-Continuous Shrinkage (PRS-CS) tool. MRI was performed on a 3Tesla scanner; cortical surface reconstruction was applied to measure cortical thickness, surface area and grey matter volume on lobar brain regions. Linear mixed-effects models were used to assess the association between MRI measures and PRS, considering family as a random effect and correcting for the 5 first components of the genetic principal component analysis (PCA), age, sex and intracranial volume. Analyses were stratified by group, given the previously observed differences in SzO compared to other groups (Sugranyes et al. 2015).

Results: There was an effect of group on PRS_SZ, with SzO showing a significantly higher PRS_SZ than both HcO and BdO ($\beta = 0.69$, $\text{padj} = 0.01$; $\beta = 0.62$, $\text{padj} = 0.01$). We identified group-specific patterns of significant associations between PRS and MRI measures, specifically within the SzO group. PRS_SZ demonstrated a significant negative association with the gray matter volume of the left insula ($\beta = -0.35$, $\text{padj} \text{ LESS THAN } 0.01$), while PRS_BD was significantly positively associated with the gray matter volume of the right temporal lobe ($\beta = 0.30$, $\text{padj} = 0.04$). PRS_MDD showed a significant positive association with the surface area of the left occipital lobe ($\beta = 0.46$, $\text{padj} = 0.05$). Both PRS_IQ and PRS_CP were significantly negatively linked to the surface area and gray matter volume of the left cingulate lobe ($\beta = -0.24$, $\text{padj} \text{ LESS THAN } 0.01$; $\beta = -0.24$, $\text{padj} \text{ LESS THAN } 0.01$; $\beta = -0.30$, $\text{padj} \text{ LESS THAN } 0.01$; $\beta = -0.30$, $\text{padj} \text{ LESS THAN } 0.01$). No differences were observed between BdO and HcO across MRI measures within lobar brain regions.

Discussion: Our findings suggest a potential association between brain structure and the genetic burden of psychiatric disorders and cognitive phenotypes within SzO group. The lack of association between PRS and MRI measures in the BdO and HcO groups aligns with previous literature suggesting no overall effect of PRS on brain structure in the general

population (Van der Auwera et al., 2015) and a different brain signature of BdO versus SzO (Sugranyes et al. 2015). Future steps of this research include exploring how these factors contribute to clinical and cognitive outcomes.

This study has been funded by Instituto de Salud Carlos III co-funded by the EU (PI1800976, PI2100330, PI2100519), and by the European Union grant ID 101057529 and the Alicia Koplowitz Foundation, CIBERSAM and 2021 SGR 01319.

41. CHANGE IN POLYGENIC SCORES FOR PSYCHIATRIC DISORDERS FOR COHORTS BORN BETWEEN 1981-2008

Mette Lise Lousdal¹, Sonia Labianca², Andrew Schork², Esben Agerbo¹, John McGrath³, Bjarni Vilhjálmsson¹, Oleguer Plana-Ripoll^{*1}

¹Aarhus University, ²Institute for Biological Psychiatry, ³University of Queensland

Background: The incidence of several clinically diagnosed psychiatric disorders has increased over the last decades. This may be due to environmental risk factors or other factors (e.g., widening of diagnostic criteria, increased public and professional awareness, and changes in capacity and referrals). To describe patient characteristics over time, we propose to explore how polygenic scores (PGS) for psychiatric disorders have changed according to birth cohort. If diagnostic criteria have widened over time, we would expect PGS distributions in patients to shift toward lower values (due to the inclusion of milder cases) while the PGS distribution in the general population would be more stable. We aimed to explore changes in PGS in the general population and individuals diagnosed with specific psychiatric disorders in cohorts born in Denmark from 1981 to 2008.

Methods: iPSYCH is a population-based case-cohort sample selected from a study base consisting of all singleton births in Denmark between May 1, 1981 and December 31, 2008 (n=1,657,449). Individuals were linked to the Danish Psychiatric Central Research Register to obtain information on diagnoses of schizophrenia spectrum disorder (SSD) (ICD-10 codes: F20-F29), major depressive disorder (MDD) (F32-F33), autism spectrum disorder (ASD) (F84.0, F84.1, F84.5, F84.8, F84.9), or attention deficit hyperactivity disorder (ADHD) (F90.0). In addition to all cases of these disorders, the sample includes a subcohort that was randomly selected disregarding any diagnostic information. PGS were generated using LDpred2 based on external GWAS summary statistics (excluding the iPSYCH sample). After excluding genetic outliers, we examined the distributions of disorder-specific PGS comparing birth cohorts graphically and through linear regression models (for diagnosed individuals, we adjusted for age at diagnosis) and we used Cox regression models to estimate hazard ratios (HRs) for psychiatric disorders based on PGS, birth year, and their interaction.

Results: We included 40,501 controls and the following number of patients: SSD (10,701), MDD (28,216), ASD (15,758), and ADHD (16,686). Distributions according to birth cohorts showed no shift over time, neither in the random subcohort nor in patient cohorts. In the random subcohort, PGS showed no linear trend according to birth date, except for SSD with an average 10-year change of -0.013 (-0.025; -0.002). In individuals with a diagnosis, the average change in PGS over 10 years was: SSD (-0.083 [-0.132; -0.034]), MDD (-0.046 [-0.078; -0.013]), ASD (-0.033 [-0.076; 0.011]), and ADHD (-0.003 [-0.049; 0.043]). We found an elevated risk of diagnosed psychiatric disorders for higher PGS and more recent birth cohorts, but the association between PGS and risk of psychiatric disorders did not change according to birth year, except for SSD with a reduction of 9% (3%; 14%) and 11% (4%; 18%) in the HRs for birth years 1990-1995 and 1996-2001, respectively, as compared to 1984-1989.

Discussion: PGS were stable in the random subcohort. For individuals diagnosed with SSD and MDD, the mean PGS decreased for later birth cohorts. For ASD and ADHD, the mean was stable, but the GWAS summary statistics were based on a small sample (after excluding the iPSYCH sample). The association between PGS and the risk of psychiatric disorders did decrease according to birth year for SSD, as we would expect if milder cases were included, but we observed no differences for the other psychiatric disorders. PGS are imprecise instruments, far from fully capturing heritability. Nonetheless, studying time trends in PGS may be relevant for validating studies using all cases and disregarding potential changes over time.

42. METHYLATION IN HOXA5, HTR2A AND PRR5 GENES PREDICTS RESPONSE TO AMISULPRIDE AND IS PARTIALLY CONTROLLED BY GENETIC FACTORS IN THE OPTIMISE COHORT

Ana Lokmer*¹, Réjane Troudet¹, Delphine Bacq-Daian², Anne Boland-Auge², Caroline Barau³, OPTiMiSE Study group⁴, Jean-François Deleuze², Marion Leboyer⁵, Jamain Stéphane¹

¹Univ Paris Est Créteil, INSERM, IMRB, Translational Neuropsychiatry; Fondation FondaMental, ²Centre National de Recherche en Génomique Humaine (CNRGH), Institut de Biologie François Jacob, CEA, Université Paris-Saclay, ³AP-HP, Hôpital H. Mondor – A. Chenevier, Plateforme de Ressources Biologiques, ⁴International sites, ⁵Univ Paris Est Créteil, INSERM, IMRB, Translational Neuropsychiatry; Fondation FondaMental; AP-HP, Hôpitaux Universitaires H. Mondor, DMU IMPACT

Background: Replacing the time-consuming, trial-and-error based, antipsychotic (AP) switching in the process of schizophrenia (SCZ) therapy adjustment by personalized approach using predictive biomarkers would strongly benefit both the patients and health systems. Epigenetic variation represents a potentially interesting source of biomarkers, as it reflects genetic and environmental factors, while being more stable than gene expression. Here we present one of the first EWAS prospective studies designed to search for epigenetic biomarkers in the blood of patients with a first-episode psychosis and aiming to shed light on the link between genetic and epigenetic mechanisms of AP response.

Methods: We analyzed 232 blood methylomes of 116 first-episode psychosis patients from the OPTiMiSE cohort, mostly of European origin. Patients have been sampled before starting the amisulpride therapy and 4 weeks later during the follow-up visit in order to identify stable as well as treatment-induced epigenetic differences between good and bad responders. Good response to treatment was defined as at least 20% total PANSS reduction. Following the identification and functional characterization of the genomic regions differentially methylated between the good and bad responders by univariate analysis, and their correlation with gene expression, we proceeded to predictive modelling of amisulpride response using the baseline methylation values of those regions as candidates. We further examined the extent of cis-genetic control over the selected co-methylated regions, by searching for mQTLs (methylation quantitative trait loci) in a 2Mbp window. Finally, we integrated our results with publicly available data to improve our understanding of the mechanisms involved in AP response.

Results: We identified 67 regions differentially methylated between the good (N=83) and bad (N=33) responders and 197 regions with response-specific temporal dynamics. Whereas the former were primarily associated with the processes involved in synapse assembly, cell signalling (including neurotransmission) and morphogenesis, the latter were dominated by immune system functioning, inflammation, signalling and developmental processes.

Correlation with the expression revealed over-representation of the genes whose expression had been previously linked to SCZ. Baseline methylation values of three regions, within the HOXA5, HTR2A and PRR5 genes, were selected as good predictors of amisulpride response (MCC = 0.81). While we detected only two mQTLs affecting a single CpG in the PRR5 region, the majority of CpGs in the HTR2A region were influenced by dozens of SNPs, including rs6313, previously linked to AP response. Finally, we identified multiple mQTLs in the HOXA5 region, whose effect was, however, mostly constrained to two CpGs. None of the identified mQTLs or linked SNPs (R^2 GREATER THAN = 0.8) has been previously linked to SCZ according to the LDlink database, but we observed enrichment in traits related to blood cell count, weight, lipid metabolism and eyesight. Whereas most of the correlations between the gene expression and methylation of the selected regions were temporally inconsistent, HOXA5 was stably negatively correlated with the SKAP2 expression, involved in Src signalling.

Discussion: Our results indicate that AP response is shaped by interaction of genetic and epigenetic factors, many of which previously linked to SCZ or similar disorders and neurodevelopment. Prospective design, well-described cohort and focus on a single AP enabled us to identify a number of co-methylated regions associated with AP response, including three with a good predictive power and to provide promising directions for future research.

43. GENETIC VARIANTS IN ESTROGEN RECEPTOR 1 GENE AND COMT GENE PREDICT TREATMENT RESPONSE TO RALOXIFENE AUGMENTATION IN MEN AND WOMEN WITH SCHIZOPHRENIA

Bodyl Brand*¹, Anne Jetske de Boer², Janna de Boer¹, Kim Morris³, Kiyomet Bozaoglu⁴, Susan Rossell⁵, Iris Sommer²

¹University Medical Center Groningen, ²UMC Groningen, ³Swinburne University of Technology, ⁴Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Melbourne; University of Melbourne, ⁵Swinburne University

Background: Sex differences in schizophrenia manifest in distinct symptom profiles and treatment responses. Premenopausal women show a less severe disease course than men, which has been attributed to the protective effects of estrogens. While estrogens are unsuitable for long-term augmentation therapy, the addition of raloxifene, a selective estrogen receptor modulator (SERM), has been considered a safe alternative. Raloxifene has estrogen-like influences on brain tissue, without the increased risk of breast and uterine cancer. While studies have demonstrated beneficial effects of raloxifene on symptoms in women with schizophrenia, research on men is scarce, and existing results are inconsistent. Previous studies have indicated that genetic variations in the estrogen receptor gene (ESR1) and the UDP-glucuronosyltransferase 1A8 (UGT1A8) gene may influence the response to raloxifene. Moreover, studies suggest that activity of the enzyme Catechol-O-methyltransferase (COMT) can be influenced by estrogen receptor activation, affecting dopamine neurotransmission. The current study aimed to examine whether genetic variants in the ESR1, UGT1A8, and COMT gene can predict treatment response to raloxifene augmentation in individuals with schizophrenia.

Methods: This study seeks to explore whether genetic variations in single nucleotide polymorphisms (SNPs) of the ESR1, UGT1A8, and COMT genes can predict treatment response to 12 weeks of raloxifene augmentation in patients with schizophrenia. We utilized a sub-sample from a parallel, randomized, double-blind, placebo-controlled trial that included adult individuals diagnosed with schizophrenia spectrum disorders (SSD) across the

Netherlands and Belgium. Participants were stratified based on age, sex, and global functioning and were randomly assigned in a 1:1 ratio to either receive a 12-week add-on of raloxifene (120 mg/day) or a placebo. Symptom severity was assessed using the Positive and Negative Syndrome Scale at baseline, after 6 weeks, and after 12 weeks (end of treatment). DNA was collected from saliva during the baseline visit using GenoTek Oragene DNA OG 500 kits. Genotyping was performed for 3 SNPs of the ESR1 gene (rs2234693, rs2144025, rs9340799), 1 SNP of the UGT1A8 gene (UGT_rs1042597), and 4 SNPs of the COMT gene (rs165599, rs737865, rs4680, rs4818).

Analyses were performed using linear mixed-effect models for each SNP. These models included a random effect for patient, and fixed effects were time, treatment condition, sex, and SNP genotype. To examine whether the treatment effect was dependent on SNP genotype, we added a two-way interaction of genotype-by-treatment condition to the model and tested whether this led to a significant improvement of the overall model. Due to the limited number of women in our sample, sex-specific analyses were only conducted in men.

Results: The total group included 83 patients (28% women), which were equally distributed across the raloxifene (n=40) and placebo (n=43) group.

We found a significant effect of genotype-by-treatment for 1 out of 3 SNPs of the ESR1 gene and 2 out of 4 SNPs of the COMT gene, indicating that for these SNPs, a treatment response to raloxifene was found for specific genotypes. In TT carriers of the ESR1 SNP rs2234693, raloxifene had beneficial effects on general symptoms. In CG carriers of the COMT SNP rs4818, raloxifene had beneficial effects on positive symptoms, which was also reflected in our male-specific analysis. Furthermore, male-specific analyses revealed a beneficial effect of raloxifene on total symptom severity in CT carriers of COMT SNP rs737865.

Discussion: In summary, our findings suggest that genetic variants in the COMT and ESR1 genes can predict treatment response to raloxifene in patients with schizophrenia. We replicated and extrapolated earlier results regarding the ESR1 gene from postmenopausal women to a mixed group of patients with schizophrenia. Additionally, we have identified novel insights related to genetic variants of the COMT gene. These findings enhance our understanding of the mechanisms through which raloxifene may exert its effects on psychotic symptoms. They underscore the importance of continued research to explore personalized treatment approaches, taking into account genetic variations, to elucidate the predictive value for the effectiveness of raloxifene in men and women with schizophrenia.

44. GENE-ENVIRONMENT INTERACTION STUDY ON THE CORRELATES FOR PSYCHOTIC EXPERIENCES IN THE UK BIOBANK

Bochao Lin^{*1}, Lotta-Katrin Pries¹, Angelo Arias-Magnasco¹, Sinan Guloksuz¹

¹*School for Mental Health and Neuroscience, Maastricht University Medical Centre*

Background: The previous study has successfully identified 148 exposures associated with any psychotic experiences (PE) in UK-Biobank. In addition, the polygenic risk score for schizophrenia (PRS-SCZ) demonstrated a contributory role in the prognostication of psychosis. However, the interaction of identified these exposures with genetic underpinning for PE remains unknown.

Methods: To systematically investigate the Gene-environment interaction of PE through data-driven agnostic analyses. We conducted exposome-wide interaction studies using the logistic regression models and estimated the multiplicative and additive interaction of PRS-SCZ with

exposures on PE, with age and sex as covariates. We also investigated the correlations of PRS-SCZ with exposure with significant interaction.

Results: The study included 148 502 participants (83 830[56.5%] female; mean [SD] age, 55.95 [7.74] years). In the XWAS interaction model, we found a significant interaction between PRS-SCZ with 27 exposomes in categories of Lifestyle and environment (n=6), physical measures (n=5), psychosocial factors (n=4), Mental health (n=5), Local Environment (n=3), health and medical history (n=1), biological samples (n=1), sociodemographics (1) and population characteristics (n=1). Furthermore, minimal (r^2 LESS THAN 0.07) but significant correlations were estimated between PRS-SCZ with 13 variables, with the most significant correlation observed for townsend deprivation index at recruitment (f189, $r^2=0.07$, $P=2,6E-167$).

Discussion: These findings reveal preliminary evidence for gene-environment interaction in psychotic experiences and suggest that genetic vulnerability and exposures might represent intertwined pathways leading to psychosis.

45. EXPLORING PERIPHERAL BIOMARKERS OF WORKING MEMORY DYSFUNCTION IN EARLY PSYCHOSIS: INSIGHTS FROM PROTEOMIC ANALYSES

Javier Labad*¹, Itziar Montalvo², Meritxell Tost², Diego Palao², Antonio Armario³, Sergi Papiol⁴, Ángel Cabezas⁵, Martí Llaurador⁵, Lourdes Martorell⁵, Elisabet Vilella⁵

¹*Consorci Sanitari del Maresme, Mataró*, ²*Parc Taulí Hospital Universitari, I3PT, CIBERSAM. Sabadell*, ³*Animal Physiology Unit, Faculty of Biosciences, Universitat Autònoma de Barcelona, Spain*, ⁴*Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich*; *Max Planck Institute of Psychiatry*, ⁵*Hospital Universitari Institut Pere Mata, Institut d'Investigació Sanitària Pere Virgili (IISPV- CERCA), Universitat Rovira i Virgili, Reus*

Background: Working memory deficits, characterized by difficulties in temporary information storage and manipulation, are recognized as core features in psychosis spectrum disorders and are present at early stages of the illness. Understanding the molecular underpinnings of working memory dysfunction in early psychosis is essential for unravelling the complex interplay between neurobiology and cognitive deficits. Protein biomarker detection with proteomics has demonstrated associations between neurology-related proteins and general fluid cognitive ability in later life. We aimed to study peripheral biomarkers related working memory in a sample of people with clinical-high-risk (CHR) for psychosis, first episode psychosis (FEP) and healthy controls.

Methods: We studied 44 CHR and 116 FEP aged between 18 and 45 years old who were attending an Early Intervention Service and 49 healthy controls. Visuospatial working memory was assessed with the Wechsler memory scale—Third Edition Spatial span (WMS-III-SS). A fasting morning blood sample was obtained for obtaining plasma and measuring proteins. The high-multiplex immunoassay panel Olink Target 96 Neurology (based on the proximity extension assay technology with PCR amplification) was used for detecting and quantifying the protein expression of 92 proteins related to neurology processes. Statistical analyses were conducted in R and SPSS v 25.0 (IBM Corp, USA). First, the glmnet package in R was used to conduct a Lasso Regression in all participants (N= 206) for identifying proteins associated with the studied outcome (WMS-III-SS scores), considering as significant associations those with a coefficient GREATER THAN 0.1. Second, we used multiple linear regression analyses

to explore the relationship between the identified proteins and working memory while adjusting for covariates (age, sex, education status, CHR and FEP diagnoses). Interactions between sex and diagnoses and each biomarker were tested. Significance was defined as $p \leq 0.05$. We did not correct p values for multiple comparisons as our analyses were exploratory in nature.

Results: Of all 92 proteins, the Lasso Regression identified 11 proteins that had a significant association with working memory and a coefficient GREATER THAN 0.1. Multiple linear regression analyses adjusted for age, sex, education status yielded 7 significant proteins associated with working memory: 1) P15311 (Ezrin; Beta= -0.197, $p = 0.006$); 2) P41217 (OX-2 membrane glycoprotein [CD200]; Beta= -0.228, $p = 0.001$); 3) P09919 (Granulocyte Colony-Stimulating Factor [G-CSF]; Beta= -0.151; $p = 0.035$); 4) O43157 (Plexin-B1 (PLXNB1); Beta= -0.312, $p = 0.070$, with significant interactions O43157 x FEP [Beta= 1.064, $p = 0.020$] and O43157 x CHR [Beta= 1.475, $p = 0.002$] diagnoses); 5) Q8TDQ1 (CMRF35-like molecule 1 [CLM-1]; Beta= -0.222, $p = 0.020$; with a significant interaction Q8TDQ1 x FEP: Beta= 2.111, $p = 0.001$); 6) Q08629 (Testican-1 [SPOCK1]; Beta= -0.205, $p = 0.004$); 7) Q16719 (Kynureninase [KYNU]; Beta= -0.179, $p = 0.018$).

Discussion: The identification of specific peripheral biomarkers associated with working memory in early psychosis unveils novel insights into the neurobiological basis of cognitive dysfunction at the onset of psychosis. Proteins such as Ezrin, CD200, G-CSF, SPOCK1 and KYNU emerged as significant peripheral markers related to working memory deficits, suggesting potential targets for future interventions. Intriguingly, interactions between PLXNB1 and CLM-1 with diagnostic categories (FEP and CHR) underscore the complex interplay between these proteins and the evolving stages of psychosis, warranting further exploration. These findings represent a crucial step toward the development of targeted therapeutic strategies aimed at ameliorating cognitive impairments in early psychosis.

46. USING AI TO UNCOVER GENETIC AND ENVIRONMENTAL RISK FACTORS FOR ANTIPSYCHOTIC-INDUCED METABOLIC ADVERSE EFFECTS IN THE MILLION VETERAN PROGRAM

Ayman Fanous^{*1}, Philip Harvey², Julie Kreyenbuhl³, Stephen Marder⁴, Silviu-Alin Bacanu⁵, Benjamin McMahon⁶, Sutanay Choudhury⁷, Hamed Abbaszadegan⁸, Khushbu Agarwal⁷

¹University of Arizona College of Medicine - Phoenix, ²University of Miami Miller School of Medicine, ³University of Maryland/Baltimore VAMC, ⁴University of California, Los Angeles/Los Angeles VAMC, ⁵Virginia Commonwealth University, ⁶Los Alamos National Laboratory, ⁷Pacific Northwest National Laboratory, ⁸Phoenix VA Health Care System

Background: Antipsychotic drugs are widely used to treat psychiatric disorders such as schizophrenia and bipolar disorder. However, they are known to have important adverse effects related to

metabolic syndrome (MS), which significantly impacts their effectiveness. Quantifying this effect is complicated because the temporal patterns of both antipsychotic medication usage and MS-related outcomes vary across patients. To minimize deleterious effects on patients, it is of the utmost importance to characterize and predict MS effects using genetic and non-genetic information available in electronic medical record (EMR) datasets.

Methods: In this work, we identify phenotypes and genotypes associated with adverse metabolic effects, which we characterize with, i) body mass index (BMI), ii) low density lipoproteins (LDL), and iii) hemoglobin A1c (HbA1c). Our cohort was selected on the basis of antipsychotic medication usage and completeness of the characterization of our MS outcomes,

from all 25 million patients with records in the VA EMR system, in use between 2000 to 2023. This results in a combined 12,303,200 patient-quarters of observation among 135,200 unique patients who have had at least one hundred measurements of weight and ten antipsychotic prescription fills.

For our initial analysis, we aggregate patient's EMR data into three-month intervals, and perform model selection and linear regression to identify important covariates such as age, sex, comorbid medical conditions, oral hypoglycemic, statin, and metformin usage, and hospitalization. We further develop a longitudinal deep learning model that uses high dimensional EMR data to predict MSvar trajectories and utilize SHAP (Shapely additive explanations) values to identify both temporal and polypharmacy-related patterns, predictive of adverse metabolic effects.

In addition, we utilize highly-predictive phenotypes developed on the full cohort of VA patients to perform GWAS for the rate of change in MS outcomes as a function of SNP genotype in the MVP population (currently 658,582 patients with genomic profiles) and antipsychotic type, while adjusting for 20 ancestry principal components and other biologically relevant covariates. Subsequently, we use summary statistics from GWAS to perform transcriptome/proteome/

Results: To be discussed.

Discussion: To be discussed.

47. PREDICTING NEGATIVE SYMPTOMS OF SCHIZOPHRENIA BY DISORDER SPECIFIC AND SHARED GENETIC LIABILITIES FOR SCHIZOPHRENIA, BIPOLAR DISORDER AND MAJOR DEPRESSIVE DISORDER

Ezgi Ince Guliyev*¹, EUGEI investigators², Bart Rutten³, Jim van Os⁴, Alp Ucok⁵, Sinan Guloksuz⁶

¹*Istanbul University Faculty of Medicine*, ²*EUGEI WP6*, ³*University of Maastricht, Netherlands*, ⁴*School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands*, ⁵*Istanbul University Faculty of Medicine, Istanbul, Turkey*, ⁶ *University Medical Centre; Department of Psychiatry, Yale School of Medicine*

Background: Negative Symptoms (NS) are core components of schizophrenia, significantly impacting functioning but also a trans-diagnostically observed phenomenon. Currently, there is a widespread recognition of the heterogeneity seen within the NS dimension, usually partitioned as diminished expressions and as motivation-pleasure deficit domains. Understanding the neurobiological underpinnings of these domains is crucial for tailored interventions, as personalized approaches that address the specific array of NS experienced by each individual can significantly improve their quality of life and functional outcomes. This study aimed to investigate whether distinct and shared liabilities for different psychiatric disorders, as well as environmental liability for schizophrenia, predict NS and two NS subdomains of schizophrenia.

Methods: The sample comprised 949 patients from the EUGEI study, with NS severity assessed using the Schedule for Deficit Syndrome (SDS). Polygenic risk scores (PRSs) were calculated using Genome-Wide Association Study (GWAS) results for Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Schizophrenia from the Psychiatric Genomics Consortium (PGC). PRSs were also derived from shared genetic variants among the three disorders, serving as an indicator of shared liability. Additionally, exposome scores, employed in prior studies, were computed within the EUGEI dataset. A series of linear regression

analyses were performed. Initially, the relationship between the total SDS score and PRSs for MDD, BD, schizophrenia, and the shared liability score was compared, adjusting for age, sex, country, ten principal component scores, and exposome scores. Subsequently, experiential deficits (ED) and motivation-pleasure deficit (MAP) subgroups of negative symptoms were analyzed separately, investigating their associations with PRSs for MDD, BD, schizophrenia, and the shared liability score, utilizing identical adjustments.

Results: Among the 949 patients, 359 (37.8%) were female, with a mean age of 32.54 (8.73) years. Total SDS score was predicted by the shared liability components ($B=0.117$; $p=0.009$), BD ($B=-0.092$; $p=0.036$), and exposome score for schizophrenia ($B=0.135$; $p=0.002$), but not with the liabilities that differentiate schizophrenia ($B=0.071$; $p=0.104$) and MDD ($B=-0.020$; $p=0.639$). After dividing negative symptoms into ED and MAP subgroups, we found that while ED severity was predicted by distinct liability components for schizophrenia ($B=0.102$; $p=0.019$) and bipolar disorder ($B=-0.114$; $p=0.009$), MAP severity was predicted by the shared liability component ($B=0.130$; $p=0.003$) and exposome score for schizophrenia ($B=0.159$; $p < 0.001$).

Discussion: The findings suggest a closer association between ED and schizophrenia genotype, while MAP appears to have a transdiagnostic relevance and may be influenced by environmental factors. Understanding the nature of this heterogeneity will be critical for identifying the different pathophysiological processes underlying NS and developing precision therapeutics.

Oral Session: Pharmacological Interventions: Novel Insights on New and Old Compounds

48. ADD ON TREATMENT WITH EVENAMIDE IN SCHIZOPHRENIC PATIENTS NOT RESPONDING ADEQUATELY TO THEIR CURRENT ANTIPSYCHOTIC: RESULTS OF A POTENTIALLY PIVOTAL, PHASE 2/3, INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

Ravi Anand^{*1}, Alessio Turolla², Francesca Sansi², Giovanni Chinellato², Rodolfo Giuliani², Richard Hartman³

¹Anand Pharma Consulting, ²Newron Pharmaceuticals SpA, ³NeurWrite LLC

Background: A major cause of concern in schizophrenia is the large proportion (30-60%) of patients failing to adequately benefit from antipsychotic (AP) treatment, and up to one-third showing no response (Solanki et al., 2009; Lieberman et al., 2005). As a result, hospitalization rates, morbidity and suicidality are increased, and lifespan reduced in patients who do not benefit from AP. (Laursen et al., 2013; Pompili et al., 2017) Growing evidence supports an important role of the glutamatergic neurotransmitter system, which is not targeted by 5HT₂/D₂-blocking APs and therefore represents a promising therapeutic strategy. (Moghaddam et al., 2012; Demjaha et al., 2014; Mouchlianitis et al., 2016) Evenamide, a selective inhibitor of voltage-gated sodium channels, devoid of activity at GREATER THAN 130 CNS targets (Anand et al., 2018), has proved to reduce aberrant neuronal firing, normalizing excessive glutamate release without any effect on basal glutamate. In animal models of psychosis, the combination of ineffective doses of APs and evenamide was associated with significant benefit, suggesting synergistic mechanisms that would benefit

patients with inadequate response to APs. Preliminary evidence of efficacy of evenamide added on to an AP (except clozapine) was demonstrated in phase II trials: a placebo-controlled study in non-TRS patients (Anand et al., 2017) as well as in an open-label, long-term trial in TRS patients. (Anand et al., 2023)

Methods: Study 008A is a phase 2/3 international, randomized, double-blind, placebo-controlled, 4-week trial designed to assess the efficacy and safety of evenamide 30 mg bid as add-on in patients not adequately benefiting from their atypical AP. Patients with a diagnosis of schizophrenia (DSM-5) are eligible for the study, provided they are symptomatic despite treatment with an atypical AP for an adequate period at a therapeutic dose. Adherence to the background AP is assessed through determination of blood levels. Psychiatric inclusion criteria require that patients are moderately to severely ill (CGI-S 4-6), with a PANSS total score of 70-85 and predominant positive symptoms (core symptoms total score ≥ 20). Efficacy ratings for PANSS and CGI-S/C are performed by two different trained psychiatrists. Changes from baseline to endpoint (Day 29) for the key efficacy outcome measures (PANSS, CGI-S, LOF, MSQ) will be compared between evenamide and placebo groups using a Mixed Model Repeated Measures (MMRM) analysis. Moreover, the proportion of patients reaching a clinically important level of improvement will be compared between groups using a logistic regression model (chi-square test).

Results: Approximately 430 patients have been screened and ~270 patients have been randomized to evenamide or placebo to date. The low attrition rate (LESS THAN 4%) during the randomized treatment period and high compliance to the study medication and procedures suggest that evenamide is well tolerated. Routine interim safety analyses reviewed by an ISMB did not detect any evidence of toxicity. The mean age of the patients is ~40 years, ~75% are males, with a mean PANSS total score at baseline of 78, and mean duration of illness of ~11 years. The most common background APs are risperidone (~40%), olanzapine (~20%), and clozapine (~15%); mean duration of treatment with current AP is GREATER THAN 1-year. Although many patients (55%) had not responded adequately to multiple medications in the past, they did not meet the TRRIP criteria for TRS. Final, unblinded efficacy and safety results will be presented at the Congress.

Discussion: Study 008A represents the first placebo-controlled, double-blind trial of evenamide 30 mg bid as add-on to an AP in patients with schizophrenia. Positive results could change the treatment paradigm of patients with chronic schizophrenia and expedite the initiation of a potentially pivotal phase 3 study designed for the evaluation of evenamide add-on in the TRS population.

49. REVISITING THE BALANCE BETWEEN RISK AND PROTECTIVE EFFECTS OF CLOZAPINE ON MORTALITY: EVIDENCE FROM 2003 – 2019 CHILEAN COHORT

Camila Diaz¹, Cristián Mena^{*2}, Gabriel Cavada³, Alfonso Gonzalez-Valderrama⁴

¹*Clozapine Pharmacovigilance Program, Instituto Psiquiátrico Dr. J. Horwitz Barak. Santiago, Chile.*, ²*Early Intervention in Psychosis Program at J. Horwitz Psychiatric Institute, Santiago; Finis Terrae University,* ³*School of Medicine, Universidad Finis Terrae. Santiago, Chile,* ⁴*Early Intervention in Psychosis Program at J. Horwitz Psychiatric Institute, Santiago, Chile and Finis Tearrae University*

Background: Clozapine has robust clinical efficacy in the management of treatment-resistant schizophrenia (TRS). Despite this, severe side effects – neutropenia, myocarditis, pneumonia, and others – have been extensively described with an underutilization of this medication as a

worldwide consequence. Clozapine has been also superior for prevention of all-cause mortality, especially in suicide. This protective effect is relevant considering well documented mortality gap between general population and people with diagnosis of TRS. The balance between risk and protective effects of clozapine must be better understood with clinical and population studies. Considering this, we analysed Clozapine's Chilean national cohort to explore: the mortality gap between clozapine users and general population; the main causes of death in a clozapine population in comparison with general population; and the impact on mortality of continued /discontinued pattern of clozapine treatment.

Methods: A retrospective analysis of individuals aged 15 years or older registered in the National Clozapine Pharmacovigilance Program between January 1, 2003, and June 30, 2019, was developed. Database contains relevant information, including gender, diagnosis, age of clozapine initiation, exposure time to clozapine, discontinuation date (defined by more than 30 days without blood count), age/causes of death (from death certificates). General population (GP) characteristics were obtained from Chilean National Institute of Statistics and the Chilean Ministry of Health. Causes of death were categorized as natural (ICD 10: A00- Q99), external (ICD 10: S00-Z99) and other causes (ICD 10: R00 – R99). A sub analysis for accident/assault and suicide (ICD 10: X64-X84) was performed. We estimated crude overall mortality incidence rates per 1000 person-years and 95% confidence intervals (CIs) by sociodemographic characteristics, cause of death and over time. Next, we used negative binomial regression to report mortality incidence rate ratios (IRR) for multivariable analysis.

Results: The clozapine cohort included 6063 individuals. Most of them were male (n=3905; 64.4%). Age of clozapine initiation was 34.6 + 12 years. We identified 642 deaths in the clozapine population (CP) during 58697 person-years between 2003 and 2019, corresponding to a crude mortality rate of 10.9 per 1000 person-years, in comparison with 1597378 deaths in GP during 228897703 person-years with a crude mortality rate of 7 per 1000 person-years. Pneumonia was the main cause of death in CP (17%), higher than GP (4%); malignant neoplasms was the main cause of death in GP (24% v/s 9% in CP). Adjusted by biological gender, age and time, global mortality IRR excess was 3.45 (95% CI 3.15-3.78, p LESS THAN 0.0001) in CP in comparison with GP. Between both populations, mortality IRR excess was 3.52 (CI 95%: 3.21-3.87, p LESS THAN 0.0001) for natural causes; 3.74 (CI 95%:3.09-4.53, p LESS THAN 0.0001) for external causes; and 11.58 (CI 95%: 8.71-15.42, p LESS THAN 0.0001) for other causes in CP in comparison with GP. Mortality IRR's between CP with continued use and GP decreased for global mortality (IRR: 1.83; 95% CI: 1.59-2.11; p LESS THAN 0.001), natural causes (IRR: 2.20; 95% CI:1.90-2.55, p LESS THAN 0.001) and other causes (IRR: 6.38; 95% CI 4.01-10.13, p LESS THAN 0.001); the excess of risk disappeared for external causes (IRR:0.96; 95% CI:0.62-1.47, p=0.87). In terms of suicide, there was no difference between CP with continued use and GP (IRR:0.58; 95% CI:0.21-1.54, p=0.27) increasing the risk for population with a discontinued use of clozapine (IRR:11.37; CI 95%: 8.01-16.13, p LESS THAN 0.001).

Discussion: Our findings have evidenced an important mortality gap between clozapine users and one Latin American general population, in a similar way to previous reports from the Global North. Considering pneumonia as the main cause of mortality in CP, a call to action is urgent for prevention and adequate management of respiratory infections. Differences in IRR observed remarks the importance of continued use of clozapine to reach the maximal benefits in mortality protection for this group.

50. EFFICACY AND EFFECTIVENESS OF ANTIPSYCHOTICS IN SCHIZOPHRENIA: COMBINING EVIDENCE FROM RANDOMISED CONTROLLED TRIALS AND REAL-WORLD DATA

Jurjen Luykx^{*1}, Orestis Efthimiou², Heidi Taipale³, Joaquim Radua⁴, Johannes Schneider-Thoma⁵, Justo Pinzon⁶, Jari Tiihonen⁷

¹University Medical Center Utrecht Rudolf Magnus Institute of Neuroscience, ²Institute of Social and Preventive Medicine, University of Bern, Switzerland, ³Niuvanniemi Hospital, University of Eastern Finland, ⁴Institute of Psychiatry, King's College, London, United Kingdom, ⁵School of Medicine, Technical University of Munich, ⁶Barcelona Clinic Schizophrenia Unit (BCSU), Neurosciences Institute, Hospital Clinic of Barcelona, ⁷Karolinska Institutet

Background: There is debate about the generalisability of results from randomised clinical trials (RCTs) to 'real-world' (RW) settings. Studying outcomes of treatments for schizophrenia can shed light on this issue and inform treatment guidelines. We therefore compared the efficacy (RCT) and effectiveness (RW) of antipsychotics for relapse prevention in schizophrenia and estimated overall treatment effects utilizing all available RCT and RW evidence in what we believe is the largest study examining effectiveness or efficacy of antipsychotics.

Methods: We conducted network meta-analyses (NMAs) using individual participant data from Swedish and Finnish national registries and aggregate data from RCTs. The target population was people with schizophrenia and schizoaffective disorder with stabilized symptoms. We analysed each registry separately to obtain hazard ratios (HRs) and 95% Confidence Interval (CI) for relapse within 6 months post-antipsychotic initiation as our main outcome. Interventions were antipsychotics, no antipsychotic use, and placebo. We compared HRs vs a reference drug (oral haloperidol) between registries, and between registry individuals who would be eligible and ineligible for RCTs, using the ratio of HRs (RHR). We synthesized evidence using NMA and compared results from our RW-NMA with our RCT-NMA, including oral vs long-acting injectable (LAI) formulations. Finally, we conducted a joint RW/RCT-NMA.

Results: We included 90,469 individuals from the Swedish and Finnish registries (mean age 45.9 (SD 14.6) years; of whom N=43,025 (48%) were women) and 10,091 individuals from 30 RCTs (mean age 39.6 years (SD 11.7); N=3,724 (36.9%) women). Ethnicity data were unavailable in the registries. We found good agreement in effectiveness of antipsychotics between Swedish and Finnish registries (RHR 0.97, 95%CI [0.88; 1.08]). Drug effectiveness vs no antipsychotic was larger in RCT-eligible than RCT-ineligible individuals (RHR 1.40 [1.24; 1.59]). Efficacy vs placebo in RCTs was larger than effectiveness vs no antipsychotic in RW (RHR 2.58 [2.02; 3.30]). We found no evidence of differences between effectiveness and efficacy for between-drug comparisons (RHR vs haloperidol oral 1.17 [0.83; 1.65], where RHR GREATER THAN 1 means superior effectiveness in RW to RCTs), except for LAI vs oral comparisons (RHR 0.73 [0.53; 0.99], indicating superior effectiveness in RW relative to RCTs). The RW-NMA showed clozapine was most effective, followed by olanzapine LAI. The RCT-NMA exhibited heterogeneity and inconsistency. The RW/RCT-NMA identified olanzapine as the most efficacious antipsychotic amongst those present in both RCTs and RW.

Discussion: In analyzing over 100,000 study participants, LAI antipsychotics performed slightly better in RW than according to RCTs. Otherwise, RCT evidence was in line with RW evidence for most between-drug comparisons, but RCTs may overestimate effectiveness of antipsychotics observed in routine care settings. Our results further the understanding of the generalisability of RCT findings to clinical practice and may inform preferential prescribing guidelines.

51. DEVELOPMENT OF AN INDIVIDUALIZED RISK CALCULATOR OF TREATMENT RESISTANCE IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS (TRIPCAL) USING AUTOMATED MACHINE LEARNING: A 12-YEAR FOLLOW-UP STUDY

Ting-Yat Wong¹, Hao Luo¹, Jennifer Tang², Tyler Moore³, Ruben Gur³, Yi Nam Suen⁴, Christy Hui⁵, Ho Ming Edwin Lee⁶, Wing Chung Chang¹, Wai Ching Yan⁷, Eileena Chui⁸, Lap Tak Poon⁹, Alison Lo¹⁰, Koi Man Cheung¹¹, Chui Kwan Kan¹², Eric Yu Hai Chen¹, Sherry Kit Wa Chan^{*1}

¹The University of Hong Kong, ²The Chinese University of Hong Kong, ³University of Pennsylvania, ⁴University of Hong Kong, ⁵The University of Hong Kong, ⁶THE CHINESE UNIVERSITY OF HONG KONG, ⁷Kowloon Hospital, ⁸Queen Mary Hospital, ⁹United Christian Hospital, ¹⁰Kwai Chung Hospital, ¹¹Castle Peak Hospital, ¹²Pamela Youde Nethersole Eastern Hospital

Background: About 15-40% of patients with schizophrenia are treatment resistance (TR) and require clozapine. Identifying individuals who have higher risk of development of TR early in the course of illness is important to provide personalized intervention. Though multiple factors have been explored in prospective studies as possible predictors of TRS, only 12 studies have been identified in a recent systematic review and found early age of onset as the most consistent predictor reported. About half of the included studies had five years or less follow-up period. Use of integrated prediction models in TRS prediction has been advocated. However, there are only four studies attempting to develop a prognostic prediction model to predict TR development using machine learning (ML) methods with three being in patients with first-episode psychosis (FEP). Most studies used LASSO logistic regression or forced-entry models with area under curve (AUC) ranging from 0.59 to 0.67. These studies are initial attempts to establish a predictive model using ML approaches, and results suggest that more advanced ML models may be needed to improve prediction performance.

Methods: A total of 1400 patients with FEP enrolled in the early intervention for psychosis service or receiving the standard psychiatric service between July 1, 1998, and June 30, 2003, for the first time were included. Clozapine prescriptions until June 2015, as a proxy of treatment resistance (TR), were obtained. Premorbid information, baseline characteristics and monthly clinical information were retrieved systematically from the electronic clinical management system (CMS). Training and testing samples were established with random subsampling. An automated machine learning (autoML) approach was used to optimize the ML algorithm and hyperparameters selection to establish four probabilistic classification models (baseline, 12-month, 24-month and 36-month information) of TR development.

Results: This study found 191 FEP patients (13.7%) who had ever been prescribed clozapine over the follow-up periods. An automated machine learning (autoML) approach was implemented to automate the selection of ML algorithms and hyperparameters using the Tree-based Pipeline Optimization Tool (TPOT) package in Python. The ML pipelines identified with autoML had an area under the receiver operating characteristic curve ranging from 0.676 (baseline information) to 0.774 (36-month information) in predicting future TR. Features of baseline information, including schizophrenia diagnosis and age of onset, and longitudinal clinical information including symptoms variability, relapse and use of antipsychotics and anticholinergic medications were important predictors and were included in the risk calculator. Finally, the features were reduced to a reasonable number by refitting the data using the above procedures with top 10, 15 or 20 features and comparing their performance to determine an optimal number of features. A risk calculator was developed with the optimal number of features to calculate predicted probabilities of future clozapine use of FEP patients.

Discussion: Our study presented the development of a risk calculator of future clozapine use, a proxy of TR, in FEP patients (TRipCal) over 12-17 years, using both baseline and longitudinal clinical information in the first 36 months of treatment. This work demonstrated the importance of longitudinal clinical information in predicting development of future TR with acceptable accuracy using the AutoML approach and thus the possibility of establishing data-driven tools assisting clinicians for earlier detection of individuals with higher risk of future TR development. The individual calculator developed using the top 10 features identified in the current study could be used to personalize the interventions to prevent, postpone TR development and reduce the delay of clozapine use. Future validation studies in different populations and settings are required.

52. CEREBRAL BLOOD FLOW IN TREATMENT RESISTANT SCHIZOPHRENIA AND DURING CLOZAPINE TREATMENT

Junyu Sun^{*1}, Fernando Zelaya¹, Kyra-Verena Sendt¹, Grant McQueen¹, Amy Gillespie², Oliver Howes¹, Gareth J Barker¹, James MacCabe¹, Alice Egerton¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*University of Oxford*

Background: Treatment resistant schizophrenia (TRS) observed in approximately one-third of individuals diagnosed with schizophrenia 1, of which clozapine is the gold-standard treatment. Previous radiotracer studies indicate decreases in cerebral blood flow (CBF) in TRS that may be altered during clozapine treatment in relation to clinical response 2-5. However, this has not yet been examined with arterial spin labelling (ASL), a more recent and MRI-based method. To address this gap, we applied ASL to investigate regional CBF in TRS and during clozapine treatment.

Methods: CBF maps were acquired from healthy volunteers (HV, N=16) and participants with TRS before commencing clozapine ('baseline', N=36), and again in the TRS group 12 weeks after clozapine initiation ('week 12', N=24). Data were analysed using a region of interest (ROI) based approach (ROIs: anterior cingulate cortex (ACC), hippocampus, thalamus, and striatum) and whole-brain voxel-wise analysis. Symptom severities were assessed using the Positive and Negative Syndrome Scale (PANSS). For cross-sectional comparison of TRS at baseline vs. HV, CBF data were analysed with/without age and global CBF as covariates by univariate linear models (SPSS) and voxel-wise two-sample t-tests (SPM). For within-subjects comparison of TRS at baseline vs. after 12 weeks of clozapine, CBF data were ascertained with/without change in global CBF as a covariate using repeated measures ANOVA (SPSS), and voxel-wise paired t-tests (SPM). Relationships between change in CBF and symptom improvement over 12 weeks, and between baseline CBF and symptom improvement over 12 weeks, were assessed by partial correlation (SPSS), voxel-wise multiple regression (SPM) with/without covarying for change in global CBF. Statistical thresholds were set at a two-tailed significance level of $p \text{ LESS THAN } 0.05$, and significant clusters were assessed at the $p \text{ LESS THAN } 0.05$ family-wise error (FWE) threshold from a cluster forming threshold of $p \text{ LESS THAN } 0.001$.

Results: Global CBF was significantly lower in TRS than in healthy volunteers ($t(50)=-2.731$, $p=0.009$). After accounting for age and global CBF, the TRS group exhibited significantly lower CBF in frontal, temporal, and parietal regions than the HV group (all $p \text{ LESS THAN } 0.05$, FWE corrected). Over 12 weeks of clozapine treatment, CBF decreased in the ACC ($F(22)=11.177$, $p=0.003$; $p=0.001$ FWE) and increased in the left postcentral area ($p=0.017$ FWE). Reductions in CBF in the ACC and thalamus during clozapine treatment were

associated with less improvement in negative (ACC, $r=-0.493$, $df=21$, $p=0.017$), positive (thalamus, $r=-0.417$, $df=21$, $p=0.048$), and total (thalamus, $r=-0.494$, $df=21$, $p=0.017$) symptoms. Higher striatal CBF at baseline was associated with greater improvements in total ($r=0.394$, $df=24$, $p=0.046$) and general ($r=0.449$, $df=24$, $p=0.021$) symptoms, and higher hippocampus CBF at baseline was associated with greater improvements in total ($r=0.510$, $df=24$, $p=0.008$) and positive ($r=0.465$, $df=24$, $p=0.017$) symptoms.

Discussion: TRS is associated with widespread reductions in CBF, and CBF may be further reduced in the ACC during clozapine treatment. Higher regional CBF may facilitate symptom improvement during clozapine treatment. ASL may have potential as a biomarker for TRS and prediction of clozapine response.

53. GLP-1 ANALOGUES AND THEIR LONG-TERM EFFECTS ON PSYCHIATRIC AND METABOLIC PARAMETERS IN INDIVIDUALS WITH SEVERE MENTAL DISORDERS

Ayala Gerberg^{*1}, Noa Menkes-Caspi², Sharon Taub³, Ofer Rahamin³, Abraham Weizman⁴, Mark Weiser⁵, Amir Krivoy⁴

¹Geha Mental Health Institution, ²Geha Mental Health Center, Petach Tikva, ³Geha Mental Health Center, ⁴Geha Mental Health Center, Sackler Faculty of Medicine, Tel-Aviv University, ⁵Sheba Medical Centre, Tel Hashomer

Background: Patients with schizophrenia have a doubled prevalence of metabolic syndrome and are twice as likely to develop type 2 diabetes mellitus, resulting in a 15-20 year reduction in lifespan compared to the general population. GLP-1 analogues, a therapeutic class of antidiabetic drugs, have proven safe for individuals with severe mental illness. However, their long-term effects, both metabolically and mentally, remain understudied. Our study aimed to assess the long-term efficacy (over one year) of GLP-1 analogues compared to shorter usage durations among individuals with severe mental illness.

Methods: We conducted a community-based, historical retrospective cohort study among Clalit Health Services (CHS) members from 2010 to 2020. Data were obtained from all CHS members diagnosed with a schizophrenia-spectrum or bipolar affective disorder who had purchased at least one prescription of a GLP-1 analogue during this period. Further inclusion criteria involved a diagnosis of type 2 diabetes and/or obesity. Patients were categorized into three groups based on GLP-1 analogue usage duration. Cox proportional hazard models were employed to analyze the effects of demographic and clinical variable adjustments on mortality, metabolic and psychiatric outcomes.

Results: We identified 3,609 relevant patients. Significant metabolic outcomes included changes in BMI and HDL levels. Extended GLP-1 analogue use demonstrated a decrease in mortality (over 12 months, adjusted HR 0.52, 95% CI [0.36-0.76]) and a reduction in psychiatric hospital admission rates (use of over 7 months, adjusted HR 0.61, 95% CI [0.42-0.91] and HR 0.59, 95% CI [0.45-0.78] in groups 7-12 months and over 12 months, respectively) compared to short-term users.

Discussion: Long-term treatment with GLP-1 analogues yielded beneficial metabolic and psychiatric outcomes. The observed reduction in psychiatric hospital admissions and mortality suggests potential revisions to disease management strategies and policies regarding medication subsidization.

54. POPULATION PHARMACOKINETIC MODELING FOLLOWING ADMINISTRATION OF OLANZAPINE FOR EXTENDED-RELEASE INJECTABLE

SUSPENSION (TV-44749) FOR SUBCUTANEOUS USE TO SUPPORT DOSE SELECTION FOR PHASE 3 CLINICAL TRIAL (SOLARIS)

Itay Perlstein*¹, Roberto Gomeni², Raphael Bilgraer³, Irina Cherniakov³, Dikla Gutman³, Anna Elgart³, Laura Rabinovich-Guilatt³, Avia Merenlender Wagner³, Rajendra Singh³

¹*Magic Wand Research, LLC*, ²*Pharmacometrica*, ³*Teva Pharmaceutical Industries, Ltd.*

Background: TV-44749 (Teva) is a long-acting subcutaneous (sc) injectable (LASCA) formulation of olanzapine based upon a novel copolymer drug delivery technology that forms a depot under the skin that ensures a controlled release of olanzapine. TV-44749's formulation and sc route of administration were also designed to eliminate the causes of post-injection delirium sedation (PDSS). A phase 1 study evaluated TV-44749 in healthy volunteers (HV) and patients with schizophrenia or schizoaffective disorder. A population pharmacokinetic (Pop-PK) model was developed and dopamine D2 receptor occupancy (D2RO) levels estimated following oral olanzapine and TV-44749 administration. Simulations were performed to guide TV-44749 dosing for the phase 3 study (SOLARIS).

Methods: PK samples were collected from participants (n=91) who received oral olanzapine (2.5 and 5mg/day for HVs; 10mg, 15mg, and 20mg/day for patients) for 7 days followed by a washout, and then received either TV-44749 single sc injection of 70mg and 105mg for HVs; single 318mg, 425mg or 531mg, or three monthly sc injections of 283mg or 566mg for patients. Different structural PK models were evaluated and Pop- PK analyses of oral olanzapine and TV-44749 were used to identify comparability in exposure over a month at steady state between oral doses 10, 15 and 20 mg/d and TV-44749 doses. The comparison focused on 3 PK parameters C_{max}, C_{ave} and C_{trough} GREATER THAN 10ng/mL to assure plasma levels are maintained over the dosing interval. Additionally using a published plasma-D2RO model, the PopPK model was utilized to assure dosing regimen would provide D2RO between the 65-80% for most of the dosing interval, which is the recommended therapeutic window for optimal antipsychotic effect with minimal side effects.

Results: The olanzapine concentration-time profile observed following oral administration was best described using a two-compartment model. The olanzapine concentration-time profiles observed after TV-44749 sc injections showed complex kinetics characterized by a double Weibull input function representing two phases of drug release: a first phase associated with an initial immediate release of a fraction of the dose, and a second phase associated with a delayed and sustained release of a second fraction of the dose. Final Pop-PK model estimates suggests the immediate first phase, with initial release of 23.6% of the associated dose (FF) peaking (TD=63.2% release) at 5 days post-dose. The second phase is associated with a delayed and more sustained release peaking at 14 days post-dose (TD1=63.2% release) of the remaining fraction of administered TV-44749 dose (76.4%). Median exposure throughout the dosing interval (C_{avg}) was identified as the main pharmacokinetic parameters with potential impact on efficacy. The trough plasma drug concentration (C_{trough}) was used as the main anchor for dose selection to ensure drug levels maintained throughout the dosing interval were similar or above C_{trough} of oral treatment to and optimize the clinical outcome of patient stability following TV 44749 administration. C_{max} was identified as a pharmacokinetic parameter with potential impact on the safety profile of TV-44749. Simulated steady state TV-44749 of monthly doses of 318mg, 425mg, and 531mg most adequately met aforementioned criteria. These doses also demonstrated comparable exposure to daily oral olanzapine doses (10, 15 and 20mg) over one month interval, and resulted in simulated D2 receptor occupancy levels within the recommended D2RO range of 65–80%.

Discussion: Based on PopPk exposure estimates and simulated D2RO, once monthly doses of 318mg, 425mg, and 531mg q1m were selected to be tested in Phase 3 efficacy and safety study of TV-44749.

Oral Session: Psychosocial Interventions and Special Populations

55. PSYCHOSIS RISKS FOR LESBIANS, GAYS AND BISEXUALS: SYSTEMATIC REVIEW AND META-ANALYSIS

Jean-Paul Selten^{*1}, Hussam Alrashed², Hans Oh³, Gabriella MA Blokland⁴

¹University of Maastricht, ²King's College London, Faculty of Life Sciences and Medicine,

³University of Southern California, ⁴Maastricht University, Amsterdam

Background: The social defeat hypothesis of schizophrenia spectrum disorders posits that low status, repeated humiliation and poor homeostatic control of dopamine neurons in midbrain and dorsal striatum increase the risk for the disorders (Selten and Ormel, 2023). The purpose of this systematic review and meta-analysis is to test the hypothesis of an increased risk of psychotic disorder and psychotic experiences for people who are lesbian, gay or bisexual (LGB people)

Methods: PubMed and Psycinfo were searched from database inception until 31 July 2023. We selected studies that compared the risk of psychotic disorder or psychotic experiences for LGB people to that for heterosexuals. The study followed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) reporting guidelines. Two independent reviewers assessed the eligibility and quality of studies, extracted effect sizes and noted the results of mediation analyses. Separate analyses were conducted for psychotic disorder and for psychotic experiences. The main outcome measures were pooled Odds Ratios (ORs), based on unadjusted ORs and on ORs adjusted for a large variety of covariates, respectively.

Results: The search identified six studies of psychotic disorder and four of psychotic experiences. The quality of studies was generally high. One study reported about the sexual orientation of 582 patients with psychotic disorder; six studies were based on large, general population surveys. There was no significant heterogeneity across studies on psychotic disorder. Using a fixed effects model, both the unadjusted, pooled OR (2.04; 95% CI 1.55-2.70) and the covariate-adjusted, pooled OR of psychotic disorder (2.46; 95% CI 1.55-2.70) were increased for LGB individuals. Given the presence of significant heterogeneity across studies on psychotic experiences, we used a random effects model and found that the pooled ORs were increased (unadjusted, pooled OR= 2.07; 95% CI: 1.44-2.96; covariate-adjusted, pooled OR = 1.85; 95% CI: 1.50–2.28). Publication bias played a very small role; the pooled ORs remained significantly increased after correction for this type of bias. Two studies of psychotic experiences examined the mediating role of drug abuse and reported that the contribution of this variable was small compared to that of psychosocial stressors, like discrimination and childhood trauma.

Discussion: These findings suggest an increased psychosis risk for LGB people and support the social defeat hypothesis.

Reference: Selten JP, Ormel J (2023). Low status, humiliation, dopamine and risk of schizophrenia. *Psychological Medicine*, 53, 609-613.

56. FINDINGS FROM A MIXED METHOD FEASIBILITY STUDY ON AN AUTOMATED VR APPLICATION FOR ANXIOUS AVOIDANCE IN PEOPLE SUFFERING FROM SCHIZOPHRENIA

Andreas Seierstad*¹, June lystad², Olivia Schjøtt-Pedersen², Helen Bull², Jan Ivar Røssberg³

¹*Oslo University Hospital, Section for Early Psychosis Intervention*, ²*Oslo University Hospital,*

³*NORMENT KG Jebsen Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital*

Background: People with schizophrenia experience high levels of anxious avoidance with 2/3 of the patient group meet the criteria for comorbid agoraphobia. Anxious avoidance is in turn associated with higher levels of hallucinations, hallucinations, depression, and lower levels of quality of life and meaningful activity. Alleviating anxiety symptoms may therefore be key to improving subjective and objective outcomes in people suffering from schizophrenia.

The gameChange VR program (GC), developed at the University of Oxford is an automated virtual reality application intended for individuals with psychosis experiencing anxiety in everyday social situations. The application allows individuals to enter virtual reality simulations of situations they would normally avoid in order to test out their fears and experiment with alternative behavioral coping strategies. GC has been validated in a large randomized trial in the UK.

The aim of this feasibility trial was to investigate if GC could lead to changes in anxiety, avoidance, depression and hallucinations as well as improve quality of life and functioning in people with schizophrenia spectrum disorder in Norway.

Methods: 28 participants received GC, and quantitative assessments were carried out at baseline, at 6 and 26 weeks after inclusion. Qualitative interviews were conducted at 6 weeks after inclusion. Recruitment and retention rates were calculated.

Results: GC was perceived as a novel, fun and innovative approach to therapy. Participants described the virtual environment as artificial, yet realistic. One stated “I imagine it’s like partaking in a reality show. Even though you know it’s a TV-production, at some point: you forget that the cameras are there”. VR simulations triggered anxiety by effectively mimicking every day, fear-inducing situations like taking the bus or visiting a café. Participants who experienced strong anxious avoidance in real life also tended to report improved functioning after the intervention. Several pathways of change were described: GC provided exposure training, but also a safe environment to experiment with behavior and learn new skills. Some participants noted that GC had bolstered their social agency by enabling them to for example greet a neighbor or make eye contact with strangers when using public transport.

A total of 76 % of participants were satisfied or very satisfied with the intervention, 64% found it helpful in managing everyday situations. We found reductions in anxious avoidance, depression and small reductions in hallucinations, as well as improvements in quality of life and functioning, with strong recruitment and retention rates. Retention was also good between post-intervention and follow-up assessments.

Employing a mixed method design with both qualitative and quantitative and qualitative data sources allowed us to corroborate our findings.

Discussion: VR-therapy could be a powerful tool for improving clinical and functional outcomes in psychosis as well as making effective therapy more accessible to patients. However, developing new applications are costly, time consuming and require close collaboration between users, clinicians and developers. This small feasibility trial utilized a

VR-intervention developed and validated in the UK within a Norwegian treatment setting. High participant satisfaction, reductions in key symptomological outcomes, improvements in quality of life and function, as well as good recruitment/retention rates, suggest that expensive VR applications can be efficaciously shared across borders. Findings from this feasibility study supply valuable input for a future multicenter RCT.

57. MINDFULNESS ENHANCED REAL-TIME FMRI NEUROFEEDBACK REDUCES AUDITORY HALLUCINATIONS AND MODULATES ASSOCIATED BRAIN ACTIVITY AND CONNECTIVITY

Clemens Bauer^{*1}, Jiahe Zhang¹, Francesca Morfini¹, Ann K. Shinn², Emma Andrikidis³, Emma Tusuzian¹, Lena Stone², Chelsea C. Ajunwa¹, Keara D. Greene¹, Nicholas W. Ford¹, Jude Hammound¹, Yoon Ji Lee¹, Angelina Awad⁴, Emily Quin⁴, Mia Kriksciun⁴, Zoi Urban¹, Paul Nestor⁵, Susan Whitfield-Gabrieli¹, Margaret A. Niznikiewicz⁶

¹Northeastern University, ²McLean Hospital/Harvard Medical School, ³McLean Hospital, ⁴Veterans Affairs Boston Healthcare System, ⁵Laboratory of Neuroscience, Boston VA Healthcare System, Harvard Medical School, ⁶Harvard Medical School, Veterans Affairs Boston Healthcare System

Background: Auditory hallucinations (AH) are a major and debilitating symptom of schizophrenia (SZ). AH does not respond to medications in one-third of SZ patients; hence, an urgent need for alternative therapies exists. Mindfulness-based interventions have shown promise in this regard, yet learning mindfulness can be challenging for patients with schizophrenia since they often have attentional, emotion regulation, and self-awareness impairments, which are core mechanisms of mindfulness. This study aimed to test if mindfulness-based real-time functional magnetic resonance imaging (fMRI) neurofeedback (mbNF) can boost downregulation of superior temporal gyrus (STG) activation and reduce AH in medication-resistant schizophrenia.

Methods: In this sham-controlled, single-blinded, randomized study, 23 adults (19 males) with SZ and medication-resistant AH received one session of mbNF either from STG (n=10; active mbNF) or motor cortex (n=13; sham mbNF). During mbNF, participants were instructed to (1) attend to pre-recorded sentences read by the participant (self) or (2) ignore pre-recorded sentences read by unfamiliar voices (other). Participants were trained in mindfulness to ignore other voices. Activation was displayed in the form of a thermometer. Participants were asked to reduce brain activation when listening to the other voice by using mindfulness, and increase brain activation by attending to self voice. STG and motor cortex targets were identified using a localizer scan. AH were assessed using the Psychotic Symptom Rating Scale (PSYRATS). Before and after

Results: ANOVA test on AH change contrasting active and sham groups across pre- and post-TT showed only a significant main effect of time ($F(18)=2.62$, $p=.01$), but did not reveal a significant main effect of group or group-by-time interaction. Nonetheless, compared to sham mbNF, active mbNF reduced rMTG activation (p LESS THAN .005, Cohen's $f^2=.54$), and PPI connectivity was reduced between rMTG cluster and both right dorsolateral prefrontal cortex (rDLPFC) and anterior cingulate cortex (ACC) (p LESS THAN .001, Cohen's f^2 GREATER THAN 2). Change in rMTG-rDLPFC connectivity correlated with AH-score reduction in the active mbNF group ($n=10$, $r=.45$, $p=.09$); we observed no such relationship in the sham mbNF group ($n=12$, $r=-.24$, $p=.78$). A post hoc Fisher's Z test showed a trend at $p=.06$ between the two groups. We found no correlation between rMTG-ACC and AH-score for either group.

Discussion: Mindfulness enhanced by real-time fMRI neurofeedback helps patients with medication-resistant AH to engage in mindfulness successfully. Specifically, we demonstrate that neurofeedback from STG, a region implicated in the pathophysiology of AH, in conjunction with mindfulness, indeed leads to reductions in MTG activation, and farther modulates brain connectivity in a network associated with cognitive control regions, which in turn leads to AH reduction; sham neurofeedback from the motor cortex does not achieve it.

58. SHORT-TERM PSYCHOEDUCATION GROUP REDUCING BURDEN, ANXIOUS AND DEPRESSIVE SYMPTOMS IN CAREGIVERS OF FIRST-EPISEDE PSYCHOSIS PATIENTS

Walter Soares*¹, Amann da Lima¹, Debora Medeiros¹

¹*Onofre Lopes University Hospital - Federal University (HUOL-UFRN)*

Background: The first-episode psychosis (FEP) is a life-changing experience for the patient and their family. The psychotic patient care is linked to anxious, depressive symptoms and objective/subjective burden. At the beginning of FEP, psychotherapeutic interventions for caregivers can bring more positive results than the patient approach. Psychoeducation of caregivers promotes knowledge about mental health, emotional support, reduction of burden, adherence to treatment and prevents relapses.

Methods: We recruited caregivers (N=14) for brief group psychoeducation. Each group involved 2–4 carers and had 3 sessions (90 minutes), 1 or 2 weeks apart. The discussions were guided by structure compute presentations about psychotic symptoms, diagnosis, treatment, prognosis, comorbidities, treatment adherence and relapse prevention. We assessed participants at baseline and 30 days after intervention for anxiety (GAD-7), for depression (PHQ-9), and for objective and subjective burden with the Family Burden Interview Scale for Relatives of Psychiatric Patients (FBIS-BR). The data was analysed using R software. We used Student test to compare the values of continuous variables (GAD-7, PHQ-9, FIBS-A, FIBS-B, FIBS-D and FIBS-E scores).

Results: Most of the participants were women (78.6%), was employed (71.5%), most of them formal jobs, 71.4% were one of the parents. Before the intervention of group psychoeducation sessions, family members had levels of anxious and depressive symptoms above the clinical threshold with a mean of 10.3 (GAD-7) and 9.0 (PHQ-9). Regarding the burden on family members, the FBIS-BR subscale that demonstrated the greatest commitment for caregivers was “worries about present and future life”(reaching 75% of the maximum score (MS) – mean 26.3), followed by the “impact on family routine” (59.3% of the MS – mean 21.4), “assistance in daily life” (56.7% of the MS – mean 46) and the least affected, “supervision of problematic behavior” (38% of the MS – mean 27.4). Even 30 days after the intervention, all scales means reduced. Both PHQ-9 (mean: 6.8, $p \leq 0.01$) and GAD-7 (mean: 8.3, $p \leq 0.05$) reached a level lower than or equal to the clinical threshold. Regarding the FBIS-BR subscales, the greatest reduction occurred in “worries about present and future life” (12.4% reduction – mean 21.9), followed by “supervision of problematic behavior” (7.9% reduction – 21.7), “assistance in daily life” (6.8% reduction – mean 40.4) and the “impact on family routine” (5.1% reduction – mean 19.6), $p \leq 0.01$.

Discussion: The literature demonstrates the positive impact of structured psychoeducational interventions for caregivers of patients experiencing FEP, both in terms of wellbeing and stigma reduction, as well as anxious and depressive clinical symptoms. Unlike other interventions proposed in the literature, we suggest a shorter one in small groups, which is better suited to our Brazilian reality of low availability of psychologists in the public service, especially for such specific service. However, we had qualitatively similar results, as both

depressive and anxious symptoms below clinical level. The burden on caregivers also reduced overall. As this is a first experience with a psychotic illness, less knowledge of this clinical condition is expected for caregivers. Psychoeducation work has a direct impact on knowledge about the condition, which may justify the largest proportional difference in the FBIS-BR subscale being in the “worries about present and future life” cluster. Our research reinforces the importance and short-term effectiveness of early approach to family members of FEP patients in reducing caregiver suffering at the onset of psychotic illness.

59. THE EFFECT OF MINDFULNESS-BASED GROUP THERAPY ON CORTISOL AND OXYTOCIN LEVELS AND PSYCHOLOGICAL STRESS PARAMETERS IN SCHIZOPHRENIA SPECTRUM DISORDERS

Marco Zierhut¹, Niklas Bergmann², Sarah Koop², Inge Hahne², Julia Kraft³, Alice Braun³, Josefa Wohlthan², Ingmar Conell², Thi Minh Tam Ta², Malek Bajbouj², Neil Thomas⁴, Paul Chadwick⁵, Ripke Stephan³, Eric Hahn², Kerem Böge²

¹Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, ²Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, ³Charité – Universitätsmedizin Berlin, Campus Mitte, ⁴Centre for Mental Health, Swinburne University of Technology, Melbourne, Australia, ⁵University of Bath

Background: Recent studies have shown positive effects of mindfulness-based interventions in healthy individuals and schizophrenia spectrum disorders (SSD). Positive effects in healthy individuals have been observed in healthy individuals for example in the area of stress reduction. In particular, individuals with an SSD have an increased stress level due to multiple factors. Oxytocin and cortisol levels in plasma and saliva can function as biological stress parameters according to the literature. The interplay between mindfulness, stress and the oxytocinergic system in SSD has yet to be investigated to date. Therefore, this exploratory study examined the impact of mindfulness-based group therapy (MBGT) on biological stress parameters as OXT plasma and saliva as well as cortisol saliva levels and changes in psychological stress parameters.

Methods: A blinded, randomized, and controlled study was conducted. Participants were assigned to either MBGT with four weekly sessions in addition to treatment as usual outpatient treatment (MBGT+TAU) or only treatment as usual (TAU). Venous blood and saliva samples were collected before and after the MBGT sessions to determine OXT and cortisol levels. Self-reported questionnaires measured stress via visual analogue scales before and after the MBGT sessions.

Results: In total, 48 outpatients with SSD received either MBGT+TAU (n=25) or TAU (n=23). Analyses revealed effects in form of a significant reduction in subjective stress levels during each MBGT session. After the MBGT sessions also a significant reduction in cortisol levels could be shown, which correlated significantly with the reduction in subjective stress experience. During the first session, oxytocin levels increased, particularly significantly in the saliva. In the last session, however, there was a significant decrease in oxytocin levels in both blood and saliva. In addition, the MBGT+TAU group showed a significantly lower OXT plasma level at the end of the intervention compared to TAU.

Discussion: The outcomes of this study provide insight into the potential effects of mindfulness on biological and psychological stress parameters in SSD. In line with recent research, we found strong effects on subjective stress as well as changes in oxytocin and cortisol levels in the course of the MBGT intervention. A fully powered trial is needed to determine the efficacy of current outcomes.

60. EXTENDING SUICIDE THEORY TO PSYCHOSIS RISK AMONG LGB+ AND HETEROSEXUAL BLACK AND LATINE NORTH AMERICAN ADULTS

Daisy Lopez^{*1}, Amy Weisman de Mamani², Carrie Bearden³

¹*UCLA*, ²*U. of Miami*, ³*University of California, Los Angeles*

Background: Black and Latine U.S. individuals are diagnosed with psychotic disorders at rates 3-4 times greater than White individuals (Schwartz and Blankenship, 2014). There is also recent evidence of greater rates of psychotic disorder diagnoses in LGB+ samples as compared to heterosexual samples (Jacob et al., 2019; Oh, 2021; Bolton and Sareen, 2011). LGBTQ+ ethno-racially marginalized individuals are more likely than people with only one marginalized identity to report more than one type of discrimination (Vargas, 2020). Therefore, Black and Latine LGB+ individuals are vulnerable to the combination of discrimination they face from sexual orientation and racial/ethnic background compared to Black and Latine heterosexual individuals, which is theorized to exacerbate mental health outcomes (Bowleg et al., 2003). The construct of social defeat has been implicated in both psychosis and suicide risk literatures (Selten et al., 2013; Pollak et al., 2021). Further, in suicide research the interpersonal theory of suicide (IPTS; Joiner, 2005; Chu et al., 2017) is widely cited, which posits the importance of two risk factors for suicide— thwarted belongingness (TB) and perceived burdensomeness (PB). Cohen and colleagues (2019) conducted a principal component analysis and found that TB, PB, and social defeat loaded onto a single “interpersonal” factor. However, the IPTS has not been extended to psychosis risk. Among Black and Latine individuals, the current study tested the hypotheses that 1) sexual orientation would be associated with psychosis and suicide risk such that LGB+ individuals would present with greater psychosis and suicide risk compared to heterosexual individuals and 2) greater TB, PB, and social defeat would be associated with both greater psychosis and suicide risk.

Methods: Hypotheses were tested among a sample of 211 Black and Latine LGB+ (n=105) and heterosexual (n=106) adults (M age in years=39.17, SD= 15.87) recruited from across the U.S. through Qualtrics XM who self-reported experiences in an online survey using the Suicidal Ideation Attributes Scale (SIDAS; van Spijker et al., 2014), Community Assessment of Psychic Experiences (CAPE; Koningset al., 2006), Interpersonal Needs Questionnaire (Van Orden et al., 2012), and Defeat and Entrapment Scale (Gilbert and Allan, 1998).

Results: Contrary to expectations, sexual orientation was not associated with risk for psychosis or suicidal behaviors (operationalized using the SIDAS’s cut-off score of a sum of 21 or greater and a cut-off score of 50 or greater on the sum of the CAPE’s positive symptom subscale). As hypothesized, when tested individually, greater TB, $\chi^2(8)=43.47$, $p < .001$, OR=1.05, $p < .01$, PB, $\chi^2(8)=53.70$, $p < .001$, OR=1.08, $p < .001$, and social defeat, $\chi^2(8)=47.04$, $p < .001$, OR=1.20, $p < .001$ were associated with greater risk for suicidal behaviors. Similarly, greater TB, $\chi^2(8)=19.37$, $p=.01$, OR=1.05, $p=.04$, PB, $\chi^2(2)=21.89$, $p < .01$, OR=1.06, $p < .01$, and social defeat, $\chi^2(8)=30.36$, $p < .001$, OR=1.30, $p < .001$ were associated with greater risk for psychosis.

Discussion: Results indicate that LGB+ identity may not be driving the risk of psychosis and suicide among this intersectional community and therefore requires further study. Further, TB, PB, and defeat are associated with both greater suicide and psychosis risk among LGB+ and heterosexual individuals, extending the IPTS to psychosis. Our results suggest that psychosis interventions might be enhanced by targeting TB and PB for both LGB+ and heterosexual individuals alike.

61. MOTIVATIONAL INTERVIEWING FOR LOVED ONES: RANDOMIZED CONTROLLED TRIAL OF BRIEF TRAINING FOR FIRST EPISODE PSYCHOSIS CAREGIVERS

Emily Kline^{*1}, Heather Thibeu², Beshoun Davis³, Bediha Ipekci⁴, Aliyah Simone Sanders⁵, Rachel Oblath¹, Shirley Yen⁶, Matcheri Keshavan⁷

¹*Boston University School of Medicine*, ²*Boston Medical Center*, ³*University of Maryland School of Medicine*, ⁴*Boston University*, ⁵*Georgia State University*, ⁶*Alpert Medical School, Brown University*, ⁷*Harvard Medical School*

Background: First episode psychosis (FEP) is characterized by the onset of symptoms such as hallucinations, delusions, and disorganized behavior, and often is the first stage of a more chronic illness such as schizophrenia or bipolar disorder. Typically occurring in adolescence or early adulthood, most FEP patients reside with parents and other family members. Research shows that family involvement in psychosis treatment leads to better patient outcomes. Interventions that involve and counsel family members may improve patient outcomes by addressing barriers to treatment adherence and lowering family expressed emotion, thereby creating a less stressful and more supportive home environment. Motivational interviewing is an evidence-based style of therapeutic communication used by clinical providers to support behavior change in patients. Learning to use motivational interviewing communication skills may help FEP caregivers to decrease conflict and expressed emotion and improve treatment adherence.

Methods: The current study is a pilot randomized controlled trial testing the impact of “Motivational Interviewing for Loved Ones” (MILO), a brief five-hour psychoeducational intervention for caregivers, in a sample of family members of individuals with early course psychosis (N = 40). Using a randomized crossover design, caregivers were randomized to either immediate MILO or a six-week waitlist control condition; all participants eventually received the intervention.

Results: Caregiver participants experienced large ($d = 1.08$ – 1.43) and significant improvements in caregiver

wellbeing, caregiver self-efficacy, family conflict, and expressed emotion. There was no change over time in caregiver-reported patient treatment adherence. Relative to waitlist, MILO had significant effects on family conflict and expressed emotion, a trending effect on perceived stress, and no detectable effect on parenting self-efficacy or treatment adherence at the six-week assessment.

Discussion: This randomized controlled trial demonstrates that brief motivational interviewing training for caregivers effectively targets important facets of family environment (expressed emotion and family conflict) that have been shown to predict psychosis outcomes. Longitudinal analyses also indicated that MILO may significantly impact caregiver wellness by decreasing stress and increasing self-efficacy. Observed effects on caregiver outcomes were larger than expected, which suggests that caregivers' own mental health and expressed emotion represent important treatment targets that may be overlooked in typical study designs that focus on symptom improvement in the individual with psychosis. The study also had excellent engagement and retention, likely due to our prioritization of feasibility in designing the intervention and our responsiveness to families' requests for a brief intervention that did not require participation of the individual with psychosis. Future research will confirm the impact of MILO in a larger population of caregiver while attending more carefully to outcomes relevant to the mental health and treatment participation of the individual with psychosis. We

hope to study whether caregiver involvement with MILO may indirectly impact psychosis treatment outcomes via improved treatment adherence and positive family climate.

62. SECONDARY PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Graham Blackman^{*1}, Ronan Byrne², Neha Gill², Jack Fanshawe¹, Vaughan Bell³, Cameron Watson², Nikolaos Koutsouleris⁴, Paolo Fusar-Poli², Thomas Pollak², Philip McGuire¹

¹University of Oxford, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London, ³University College London, ⁴Ludwig-Maximilian-University

Background: The detection of patients with psychosis due to an identifiable disease state or exogenous agent – commonly referred to as ‘secondary psychosis’ – is an essential, but challenging diagnostic task in psychiatry. Early identification is critical in ensuring appropriate care, which may include treatment for the underlying cause. Whilst it is recognized that psychosis can have a secondary basis, surprisingly little is known about the epidemiology of such cases. The proportion of patients presenting with secondary psychosis is currently unknown; we therefore sought to derive a meta-analytic estimate.

Methods: Electronic databases (MEDLINE, PsycINFO, and Global Health) were searched up to August 2022, alongside references of included articles and review articles. We selected studies that reported the number of patients with psychosis attributable to a secondary cause and calculated the meta-analytic proportion of patients with a secondary cause, along with a 95% confidence interval (CI) using a random-effects inverse variance method. We also estimated the number of patients who would need to be assessed to detect one case of secondary psychosis (numbers-needed-to-assess; NNA) and the proportion of specific types of secondary psychosis. Statistical significance was $p \leq 0.05$ for all analyses.

Results: Based on 34 independent studies ($N = 26,693$), 13% (95% CI 8% to 18%) of patients had a secondary cause, yielding an overall NNA of 8 (95% CI 6 to 12), with marked between-study heterogeneity ($I^2 = 99\%$). The proportion estimate was revised to 11% (95% CI 7% – 16%), excluding a statistical outlier. Among patients with a first episode of a psychotic disorder, 14% ($N = 4,341$, 95% CI 8% – 22%) had a secondary cause. Overall, the most common cause of secondary psychosis was drug-induced psychosis (12%; 95% CI 6 to 19%). An underlying medical cause accounted for 5% (95% CI 3% to 9%) of cases, with infection (1%; 95% CI 0% to 4%) and autoimmune disease (1%; 95% CI 0 to 2%) being the most common medical causes. Clinical setting was a significant moderator of study variability, with the proportion of secondary psychosis in a general hospital setting highest. Geographical area was also a significant moderator.

Discussion: Based on a pooled sample of over twenty-six thousand patients presenting with psychosis, an estimated 11% had a secondary cause for their symptoms. This corresponds to an average number needed to assess (NNA) to detect one case of secondary psychosis of approximately eight. This estimate increases to around 14% in patients presenting with first-episode psychosis. Estimates vary by clinical setting and geographical area. Drug-induced psychosis accounted for most cases of secondary psychosis, whilst psychosis secondary to an underlying medical condition (commonly termed “organic” psychosis) accounted for 5% of all patients.

Findings indicate that a substantial minority of patients with psychosis have a secondary cause, particularly those presenting with a first episode of psychosis, however, estimates vary substantially by context.

Oral Session: Multimorbidity, Unmet Needs and Service Development

63. THE RAPID-LEARNING HEALTH SYSTEM IN EARLY INTERVENTION SERVICES FOR PSYCHOSIS IN QUÉBEC, CANADA: QUALITATIVE EVALUATION OF BARRIERS AND FACILITATORS TO IMPLEMENTATION

Manuela Ferrari*¹, Srividya Iyer², Marc-André Roy³, Annie LeBlanc³, Amal Abdel-Baki⁴

¹McGill University and Douglas Mental Health Institute, ²McGill University and Douglas Hospital Research Institute, ³Université Laval Faculty of Medicine, ⁴Centre Hospitalier de l'Université de Montréal

Background: In 2019, SARPEP (Système Apprenant Rapide pour les Programmes de Premiers Épisodes Psychotiques), the first rapid learning health system (RLHS) for first-episode psychosis in Canada, was created. Bringing together 11 early intervention services (EIS) from urban, semi-rural, and rural areas, SARPEP aimed to determine the feasibility/acceptability of implementing a RLHS in EIS. Evaluation of the project used a mixed method design grounded in the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. Stakeholder involvement was strong, with all RLHS components successfully implemented. Meaningful indicators for EIS were selected by consensus among all the stakeholders, based on an external scan and internal survey. SARPEP developed user-friendly technologies for routine real-time data collection (REDCap platform), allowing team leaders to share program-level data. These included onsite “happy or not” digital terminals with a 3-question survey on satisfaction with services, and an in-depth questionnaire for service users and family members on satisfaction with care received that covered 9 recovery dimensions (e.g., health, quality of life). Collected data were aggregated and anonymized. The REDCap platform performed data analysis and provided real-time feedback on standards to participating programs via (graphical) data visualization with tailored practice recommendations. SARPEP offered community of practice activities, generating insights for building program capacity and aligning practices with provincial standards. This presentation describes the findings from the qualitative phase, presenting barriers and facilitators to implementation.

Methods: Six focus groups were conducted, two with service users, and one each with family members, psychiatrists, managers, and team leaders to ensure multistakeholder perspectives. Participants (n=24) were asked to share their experiences with the implementation of the RLHS over two years. The focus group questions were designed using Lessard’s five dimensions for a learning health system.

Results: Participants (n=24) confirmed the value of introducing a standardized, measurement-based, digital system through SARPEP for the routine collection and sharing of program-level data provincially. SARPEP capacity-building activities met with great success in creating a learning community. Participants viewed the key indicators selected by stakeholder consensus for the SARPEP project as both relevant and recovery-oriented. They considered the technologies developed to support data collection, analysis and data sharing as effective tools. SARPEP members greatly appreciated receiving periodic graphical feedback, using these performance evaluations to celebrate good results and set new objectives based on exchanges in the community of practice and other capacity-building activities. Yet, challenges were encountered in the implementation of user-rated outcomes and satisfaction questionnaires, whether on REDCap or the “happy or not” terminals. Digital tools were new for both providers and service users, and their integration into routine EIS care was challenging. Importantly,

stakeholders identified the provision of service user and family peer support as the crucial next step for the RLHS.

Discussion: Stakeholders agreed that a RLHS can promote evidence-based care in EIS. The RLHS created a sense of belonging in a community aiming to learn and improve. Overall, implementing SARPEP proved feasible and successful, reaching targeted EIS/participants, who adopted and maintained the RLHS, improving in key program indicators despite the pandemic, and provided a new Québec database of quality care indicators. Additional strategies, such as the establishment of peer support services, are needed to attain and maintain consistent standards.

64. UTILIZING QUALITATIVE METHODS TO REFINE THE IMPLEMENTATION OF NEW APPROACHES IN EARLY PSYCHOSIS CARE DELIVERY.

Mark Savill^{*1}, Lindsay Banks¹, Regina Gemignani¹, Valerie Tryon¹, Sabrina Ereshefsky¹, Kathleen Nye¹, Christopher K. Hakusui¹, Renata Botello¹, Viviana Padilla¹, Karina Muro¹, Laura M. Tully¹, Rachel Loewy², Tara Niendam¹

¹University of California, Davis, ²University of California, San Francisco

Background: Implementing new approaches in routine healthcare delivery can be a challenging process. A key feature of successful implementation is rooted in the perception of the innovation amongst relevant community partners, including its perceived benefit, complexity, and compatibility with existing values and needs. To address this, qualitative efforts have represented a central feature of the implementation of EPI-CAL, a statewide effort to support a learning healthcare network approach to early psychosis (EP) care.

Methods: During the design phase, focus groups held in English and Spanish were conducted to support a co-design approach to the development of the assessment battery, data sharing procedures, and the creation of the data collection and presentation application (Beehive). During the implementation phase, provider and service user interviews were conducted to identify barriers and facilitators to effective implementation, with findings iteratively fed back to the implementation team to inform program delivery.

Results: To date, 33 interviews and 40 focus groups including 284 providers, service users, and family members have been completed across 15 EP programs. In the outcomes focus groups functioning, quality of life, recovery, and symptoms of psychosis were identified as key domains to assess in EP care. Participants emphasized the clinical utility of predictors of outcomes, and the importance of concrete, client reported measures. In the focus groups concerning data sharing priorities, participants reported being receptive to data sharing, but exhibited concerns regarding third-party sharing, risk of breaches, and hidden motives in user legal agreements. Increased user-level control for data, and an understandable, transparent EULA was considered key to mitigating concerns. In focus groups supporting Beehive development, participants suggested adding program demographic visualizations, modifications to the registration process to reduce service user burden, and aesthetic changes to make the tool look less “clinical”. Interviews with EP program providers and service users identified multiple facilitators to EPI-CAL implementation, including the importance of leadership buy-in, program administrative staff support, and ongoing communication with research staff. Barriers included the challenge of integrating the project alongside existing administrative requirements, the lack of clarity on the clinical utility of the data, software bugs, and high staff turnover.

Discussion: Integrating qualitative approaches to better understand community partner needs and experiences during healthcare innovation initiatives can serve the dual purpose of

improving the initial implementation, while also producing generalizable knowledge to support the more widespread adoption of these innovations should they be effective. In EPI-CAL, ongoing and systematic feedback from partners has been critical to developing an outcomes battery that meets the needs and values of users, a usable data collection and presentation system that focuses on the clinical priorities of those delivering and receiving care, and a process whereby barriers to successful implementation can be identified and addressed as they emerge. While the integration of the Beehive application has been variable, the data collected throughout the process has led to substantive changes in the development and implementation of the process, re-orienting the project direction towards community partner needs. This approach has supported the successful implementation of EPI-CAL and may serve as a template to support the implementation of other innovations in healthcare delivery.

65. ASSOCIATION BETWEEN CANNABIS USE DISORDER AND SCHIZOPHRENIA STRONGER IN YOUNG MALES THAN IN FEMALES

Carsten Hjorthøj¹, Wilson Compton², Marie Starzer³, Dorte Nordholm⁴, Emily Einstein², Annette Erlangsen³, Merete Nordentoft⁵, Nora Volkow⁶, Beth Han², Merete Nordentoft*⁷

¹Copenhagen Research Center for Mental Health - CORE, ²National Institute on Drug Abuse (NIDA), ³Copenhagen University Hospital, Mental Health Center Copenhagen, Copenhagen Research Center for Mental Health - CORE, ⁴Copenhagen Research Center for Mental Health, ⁵Copenhagen Research Center for Mental Health-CORE; Mental Health Center Copenhagen, Copenhagen University Hospital, Denmark, ⁶National Institute on Drug Abuse, National Institutes of Health, ⁷Mental Health Centre Copenhagen

Background: Previous research suggests an increase in schizophrenia population attributable risk fraction (PARF) for cannabis use disorder (CUD). However, sex and age variations in CUD and schizophrenia suggest the importance of examining differences in PARFs in sex and age subgroups.

Methods: We conducted a nationwide Danish register-based cohort study including all individuals aged 16-49 at some point during 1972-2021. CUD and schizophrenia status was obtained from the registers. Hazard ratios (HR), incidence risk ratios (IRR), and PARFs were estimated. Joinpoint analyses were applied to sex-specific PARFs.

Results: We examined 6,907,859 individuals with 45,327 cases of incident schizophrenia during follow-up across 129,521,260 person-years. The overall adjusted HR (aHR) for CUD on schizophrenia was slightly higher among males (aHR=2.42, 95% CI=2.33-2.52) than females (aHR=2.02, 95% CI=1.89-2.17); however, among 16-20-year-olds, the adjusted IRR (aIRR) for males was more than twice that for females (males: aIRR=3.84, 95% CI=3.43-4.29; females: aIRR=1.81, 95% CI=1.53-2.15). During 1972-2021, the annual average percentage change in PARFs for CUD in schizophrenia incidence was 4.8 among males (95% CI=4.3-5.3; P LESS THAN 0.0001) and 3.2 among females (95% CI=2.5-3.8; P LESS THAN 0.0001). In 2021, among males, PARF was 15%; among females, it was around 4%.

Discussion: Young males might be particularly susceptible to the effects of cannabis on schizophrenia. At a population level, assuming causality, one-fifth of cases of schizophrenia among young males might be prevented by averting CUD. Results highlight the importance of early detection and treatment of CUD and policy decisions regarding cannabis use and access, particularly for 16-25-year-olds.

66. PATTERNS OF MULTIMORBIDITY, HEALTH CARE UTILIZATION, AND MORTALITY AMONG MID- TO LATE-LIFE ADULTS WITH SCHIZOPHRENIA

Alison Hwong*¹, Yixia Li², Michael Steinman¹, Christina Mangurian³, Donna Zulman⁴, Ruth Morin⁵, Amy Byers¹

¹UCSF and San Francisco VA Medical Center, ²Northern California Institute for Research and Education, ³UCSF, ⁴Stanford and Palo Alto VA Medical Center, ⁵Hoag Hospital

Background: As adults with schizophrenia are increasingly entering older age, there is a need to better understand their risk factors for accelerated aging and premature mortality. We identified patterns of multimorbidity and their relationship to health care utilization and cause-specific mortality among mid- to late-life adults with schizophrenia to characterize how multiple chronic conditions affect this population.

Methods: The study leveraged a national, longitudinal and population-based cohort of 5 million United States (U.S.) veterans aged GREATER THAN 50 years to create a representative subcohort called the “Aging Veterans with Schizophrenia Dataset” (N=82,858). The parent dataset has linked national VA and non-VA databases to provide diagnoses, encounters, pharmacy and cause-specific death data from 2012 to 2020. Individuals were identified as having schizophrenia if they had one inpatient or two outpatient encounters associated with a primary diagnosis of schizophrenia in the two years preceding the baseline cohort.

Forty-five major comorbid conditions were selected based on their applicability to an older population with schizophrenia. These conditions were measured across the entire study period and defined using algorithms from the U.S. Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse.

Latent class analysis (LCA) was used to identify latent profiles of comorbid conditions, with the best-fitting model determined by a combination of fit statistics, clinical acumen, and theoretical parsimony. Demographics, comorbidities, utilization, and mortality outcomes were assessed using means and standard deviations or frequencies and proportions, with statistical significance of differences between classes tested by F tests for continuous variables and chi-square tests for categorical variables.

Results: We identified three comorbidity profiles: Low Comorbidity (67.0% of cohort), High Medical Comorbidity and Depression (17.6%), and Substance Use Disorders and Related Conditions (SUDRC, 15.4%). The Low Comorbidity profile had low prevalence (LESS THAN 15%) of medical and psychiatric conditions. The High Medical Comorbidity and Depression profile had high prevalence (GREATER THAN 50%) of chronic obstructive pulmonary disease (COPD) and hypertension and moderate prevalence (25-50%) of diabetes, congestive heart failure, dementia, chronic kidney disease, sleep disorders, tobacco use disorder, and depression. The SUDRC profile was notable for high prevalence of alcohol use disorder, tobacco use disorder and other drug use disorder as well as COPD, hepatitis C, chronic pain, depression, and posttraumatic stress disorder.

The SUDRC profile had the highest rates of utilization of emergency, inpatient, and outpatient mental health services as well as the highest utilization rates of emergency and inpatient medical services. The Low Comorbidity and SUDRC profiles had similar utilization rates for outpatient primary care services (91.4% vs. 92.8% with a least 1 encounter, respectively).

The High Medical Comorbidity and Depression profile had the highest mortality rate (56.0%) over the study period. Primary causes of death were heart disease, cancer, chronic lower respiratory diseases, dementia, and diabetes. The SUDRC profile had the highest rates of death due to suicide, alcohol use, hepatitis and unintentional injuries.

Discussion: Older adults with schizophrenia are a heterogeneous population, consisting of profiles with distinct patterns of multimorbidity. High rates of suicide death and substance use-related deaths among those who are high utilizers of health care services may point to more opportunities for effective psychosocial and clinical intervention.

67. ESTIMATING THE PREVALENCE OF MULTIMORBIDITY IN PEOPLE WITH AND WITHOUT SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Sean Halstead¹, Chester Cao², Grimur Høgnason Mohr³, Bjørn H. Ebdrup⁴, Toby Pillinger⁵, Robert McCutcheon⁶, Joseph Firth⁷, Dan Siskind⁸, Nicola Warren⁹, Dan Siskind*¹⁰

¹*The University of Queensland*, ²*Royal Brisbane and Women's Hospital, Brisbane*, ³*Center for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen*, ⁴*Centre for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Centre Glostrup*, ⁵*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁶*Institute of Psychiatry, Psychology and Neuroscience, King's College London; University of Oxford*, ⁷*University of Manchester, Manchester, UK*, ⁸*School of Medicine, The University of Queensland, Brisbane, MIRT, Woolloongabba Community Health Centre, Addiction and Mental Health Services and MIRT*, ⁹*Metro South Addiction and Mental Health Services*, ¹⁰*Metro South Addiction and Mental Health Service*

Background: People living with severe mental illness (SMI), such as schizophrenia-spectrum disorder and bipolar disorder, experience significantly poorer health outcomes, such as a significantly reduced life expectancy. One major contributor to these outcomes are the multiple chronic conditions, or 'multimorbidity', that those living with SMI experience. This term can be categorised into both 'physical multimorbidity', denoting the coexistence of multiple chronic physical conditions, and 'psychiatric multimorbidity', corresponding to the coexistence of multiple psychiatric conditions. As multimorbidity is an emerging epidemiological concept, the overall prevalence of physical and psychiatric multimorbidity in people with SMI remains unknown, as does the ratio of prevalence of physical multimorbidity between those with and without SMI. We undertook a systematic review and meta-analysis to consequently estimate the prevalence of physical and psychiatric multimorbidity in people living with SMI.

Methods: We undertook a systematic database search in CINAHL, EMBASE, PubMed, and PsycINFO from inception until January 29, 2023 with our review protocol registered on PROSPERO. Our inclusion criteria comprised observational studies that had measured prevalence of multiple physical or multiple psychiatric conditions in people with SMI. Studies with control data from a comparable population without SMI were sought but not required. For studies with control data, we undertook a random-effects meta-analysis to compare the prevalence ratio of physical multimorbidity (≥ 2 physical conditions) between people with and without SMI. We also calculated the absolute prevalence of physical and psychiatric multimorbidity (≥ 3 psychiatric conditions, including the SMI) in people with SMI using a meta-analysis of proportion. We tested whether study factors (date of publication, country of study), population demographic factors (age, sex, ethnicity), illness factors (diagnostic composition), and methodological factors (case-control matching, study quality) had an influence on our results through a series of sensitivity and meta-regression analyses.

Results: Our systematic search identified 10,219 relevant citations which were screened by two authors at title, abstract, and full-text level. Of those, 79 studies were included which featured 1,620,420 individuals with SMI (mean age 47.8 ± 16.1 , sex ratio of 37% female: 63% male, insufficient data to report pooled ethnicity demographics), of whom 1,223,278

individuals had schizophrenia-spectrum disorder. 21 studies also featured data on people without SMI, with a pooled control population of 13,235,882 individuals. The ratio of physical multimorbidity (≥ 2 physical conditions) prevalence between people with and without SMI was 2.03 ($k = 11$, 95%CI: 1.43, 2.89, $p = 0.0012$). Sensitivity analysis that stratified studies by mean age revealed that younger cohorts with SMI (mean age ≤ 40 years) had a greater prevalence ratio of physical multimorbidity compared to controls (PR=2.90, 95%CI: 1.29, 6.49) compared to older cohorts (mean age GREATER THAN 40 years; PR=1.42, 95%CI: 0.94, 2.14, $p=0.0025$). Moreover, for those with SMI, meta-analysis estimated that 25% ($k = 28$, 95%CI: 0.19, 0.32) have physical multimorbidity and 15% (≥ 3 psychiatric conditions, $k = 19$, 95%CI: 0.09, 0.25) have psychiatric multimorbidity.

Discussion: This is the first meta-analysis to estimate both physical and psychiatric multimorbidity prevalence in people with SMI. Our findings highlight that for people with SMI physical multimorbidity is twice as prevalent compared to those without SMI. Further, this gap in multimorbidity burden appears widened in younger populations. Multimorbidity is common amongst people with SMI, with estimates that one in four have two or more physical conditions, and one in six have two or more other psychiatric conditions in addition to the SMI. These prevalence estimates highlight the relevance of studying multimorbidity in people living with schizophrenia in order to characterise the burden of chronic disease faced by this cohort. These findings clarify the need for healthcare services to provide integrated care models that address intertwined physical and psychiatric health needs and risk factors for those living with schizophrenia and SMI more broadly.

68. PSYCHOTROPIC DRUG EXPOSURES DURING PREGNANCY AND DEVELOPMENT OF OBSTETRIC COMPLICATIONS: A POPULATION-BASED STUDY IN HONG KONG

Perry Bok Man Leung^{*1}, Evangelos Vassos², Marta Di Forti², Robin M Murray², Hon-Cheong So³, Pak C Sham¹, Simon SY Lui¹

¹The University of Hong Kong, ²King's College London, ³The Chinese University of Hong Kong

Background: Psychotropic drug use in pregnant women has been associated with subsequent obstetric complications. However, psychiatric diagnosis and associated factor may confound this relationship. The analysis of population-based data using causal inference methods may clarify the association of psychotropic drug use during pregnancy with increased obstetric complications.

Methods: Data were gathered from the population-based electronic health records of the Hospital Authority (HA) which provides government-funded medical care to the entire population of Hong Kong. We identified all HA birth episodes from 2004 to 2022, then retrieved each mother's ICD-10 diagnosis and medication records in the two years before and one year after the delivery date, including prescriptions for psychotropic drugs, including antipsychotics, antidepressants, benzodiazepines, and mood stabilisers. We employed Firth's bias-reduced logistic regression to investigate the associations between different psychotropic drugs used during the pregnancy period and obstetric complications. In addition, negative control analysis was performed using mothers who were exposed to psychotropic medications before conception but not during pregnancy.

Results: We retrieved data on 585,409 birth episodes involving 421,578 mothers, in which 7,245 episodes (1.2%) had exposure to psychotropic drugs during their pregnancy period. We found significant associations between antipsychotics exposure and admission to neonatal

intensive care unit for at least 24 hours (NICU admission (≥ 24 hours)) (OR = 1.39; P-FDR = 0.0001); antidepressants and gestational diabetes (OR = 1.15; P-FDR = 0.014), gestational hypertension (OR = 1.16; P-FDR = 0.034), low birth weight (OR = 1.18; P-FDR = 0.014), NICU admission (≥ 24 hours) (OR = 1.49; P-FDR = 3×10^{-15}), and premature rupture of membranes (negatively: OR = 0.9; P-FDR = 0.028). Mood stabilisers were significantly associated with gestational hypertension (OR = 1.28; P-FDR = 0.014), emergency caesarean section (OR = 1.32; P-FDR = 1×10^{-5}), low birth weight (OR = 1.39; P-FDR = 0.0001), NICU admissions (≥ 24 hours) (OR = 1.58; P-FDR = 4×10^{-15}) and neonatal major infection (OR = 1.87; P-FDR = 0.004). Weaker associations between psychotropic drug exposure and many obstetric complications were observed in negative controls compared to pregnant women who used psychotropic drugs. Besides, after adjusted for exposures of multiple drug classes during pregnancy, emergency caesarean section (OR=1.37, P-FDR=0.0003), preterm birth (OR=1.44, P-FDR=0.001), NICU admissions (≥ 24 hours) (OR=1.56, P-FDR = 6×10^{-9}) and placental abnormalities (negatively: OR=0.5, P-FDR = 0.046) were associated with a diagnosis of schizophrenia spectrum disorders in the mother. Similarly, admission to NICU (≥ 24 hours) (OR=1.13, P-FDR = 0.028) was associated with depressive spectrum disorder in the mother.

Discussion: This population-based study provides evidence that psychotropic use during pregnancy is associated with increased risk of obstetric complications, after adjustment for underlying psychiatric diagnoses and the concurrent prescription of multiple psychotropic drugs (over half of the mothers who were prescribed antipsychotics were also prescribed antidepressants). Moreover, although some exposures or outcomes were relatively rare in our sample, the use of Firth's logistic regression reduced bias and allowed full use of available data. Our findings offer valuable insights for obstetricians and psychiatrists in caring for pregnant women with significant mental health issues.

69. SCHIZOPHRENIA RECOVERY: THE IMPACT OF COMMUNITY-BASED PSYCHIATRIC REHABILITATION PATHWAYS ON RE-HOSPITALIZATION TRAJECTORIES

Sharon Florentin¹, Yehuda Neumark², David Roe³, Paola Rosca⁴, Amir Krivoy⁵, Amir Krivoy*⁶

¹Hadassah Medical Center, Jerusalem, Israel; Faculty of Medicine, The Hebrew University of Jerusalem, ²Braun School of Public Health and Community Medicine, Faculty of Medicine, The Hebrew University of Jerusalem, ³University of Haifa, Israel; Aalborg University, ⁴Ministry of Health; The Hebrew University of Jerusalem, ⁵Geha Mental Health Center, Petach-Tikva, Israel; Sckalar Faculty of Medicine, Tel-Aviv University, Israel., ⁶Geha Mental Health Center, Petach Tikva

Background: Psychiatric rehabilitation is essential to the recovery process of individuals with schizophrenia. This study examined the impact of varied psychiatric rehabilitation services on the long-term clinical trajectory of schizophrenia patients.

Methods: We utilized data from 18,684 adults diagnosed with schizophrenia and schizoaffective disorder, derived from Israel's national rehabilitation and psychiatric hospitalization case registries. The data was divided into three periods: before the enactment of the national rehabilitation law in Israel (1991-2000), rehabilitation services availability (2001-2009), and readmission follow-up (2010-2017). The association between rehabilitation and readmission risk was tested using a Cox proportional hazard model. Associations between vocational and residential rehabilitation services subtypes and annual re-hospitalization days (ARHD), were analyzed using ANCOVA.

Results: The usage of rehabilitation services was significantly associated with a lower risk to readmission (p LESS THAN 0.0001, HR 1.20, 95%CI 1.14-1.26). Median [IQR] time-to-readmission was 752 days [1454 days] for the rehabilitation group and 381 days [1096 days] for the non-rehabilitation group. Combined residential and vocational rehabilitation resulted in a mean decrease of 20 ARHD, while either residential or vocational rehabilitation led to decreases of 2 and 5 ARHD, respectively. Absence of rehabilitation was associated with a mean increase of 9 ARHD. High levels of residential support were linked with reduced ARHD. Out of the vocational rehabilitation types, supported employment and sheltered workshops showed the greatest reductions in ARHD (17 days; p LESS THAN 0.0001).

Discussion: Community-based psychiatric rehabilitation effectively lessens admission rates and re-hospitalization days. Combined vocational and residential services may optimally reduce psychiatric exacerbations, as demonstrated by fewer hospital readmissions.

70. RESEARCH GAPS IN SUICIDE PREVENTION AMONG INDIVIDUALS WITH PSYCHOSIS: A CALL TO ACTION TO ADVANCE KNOWLEDGE AND INFORM PRACTICE

Samantha Chalker^{*1}, Roxanne Sicotte², Lindsay Bornheimer³, Emma M. Parrish⁴, Heather Wastler⁵, Blaire Erhet⁶, Jordan DeVlyder⁷, Collin A. Depp¹

¹VA San Diego Healthcare System, ²Research Center, Centre Hospitalier de l'Université de Montréal, ³University of Michigan, ⁴San Diego State University/University of California San Diego, ⁵Ohio State University Wexner Medical Center, ⁶Lyra Health, ⁷Fordham University

Background: Individuals with schizophrenia spectrum disorders have an increased risk of suicide of up to 20 times that the general population. It is estimated that 30 to 50% of those experiencing psychosis will have suicide ideation in their lifetime, 20 to 50% will attempt suicide and 4 to 13% will die by suicide. Given these alarmingly high rates, a better understanding of the intersection of psychosis and suicide is needed. The overarching goal of this call to action is to provide specific action steps to address research gaps in suicide prevention among individuals with psychosis, and thus, inform research and improve clinical practice.

Methods: A group of researchers working on different aspects of suicide in psychosis has been put formed to reflect on the main research gaps to be filled. For each gap identified, a review of the literature has been conducted and key findings highlighted. Informed by the literature, several action steps were outlined to help researchers and providers fill these gaps.

Results: Four major gaps have been identified: 1) lack of research design standards, 2) unknown reliability and validity of suicide risk screening and assessment tools in a psychosis population, 3) insufficient evidence of efficacious suicide-focused psychosocial interventions and therapies for those experiencing psychosis, and 4) limited training standards and opportunities for providers to build competencies in suicide prevention and psychosis.

First, research design standards considering the heterogeneity of both psychosis and suicide thoughts and behaviors are needed to support data aggregation. This implies the recruitment of diverse samples across the psychosis spectrum (e.g., varying levels of psychosis severity and diagnoses, variety of settings, include sexual and gender diverse individuals and persons from differing racial and ethnic backgrounds), conducting theory-driven longitudinal studies and largescale, multisite research that supports data sharing.

Second, in order to determine the reliability and validity of suicide risk screening and assessment tools in individuals with psychosis, studies testing the use of established suicide

risk screening and assessment in this population are needed. Furthermore, to determine whether tailored screening or assessment tools are necessary, is it essential to better understand how the risk of suicide in this person with psychosis may be influenced by 1) unique aspects of psychosis (e.g., experience of involuntary hospitalization, cognitive impairments, internalized stigma), 2) the effect of specific symptoms, 3) the mechanisms underlying the association between psychosis and suicide.

Third, the effectiveness of suicide-focused psychosocial interventions and treatments needs to be assessed across the psychosis spectrum, which includes testing the use of existing suicide prevention interventions and novel suicide prevention intervention adaptations.

Fourth, training to prepare providers with competency and effectiveness in treating suicide risk and psychosis needs to be implemented, including, but not limited to, augmenting suicide prevention training in service settings that are designed for people with psychosis, training suicide prevention professionals in core competencies for working with individuals with psychosis and developing specific training for clinicians working with persons with psychosis beyond broad- or general population-focused suicide prevention training.

Discussion: Suicide is a critical public health issue among individuals with psychosis. Despite substantial progress in research and clinical care for persons with psychosis at risk for suicide, important gaps remain. The action steps outlined in this call to action provide a framework for addressing these gaps and improving care and prognosis in persons with psychosis at risk for suicide.

Oral Session: Structural and Neurochemical Imaging

71. GABA, GLUTAMATE AND NEUROMELANIN IN FIRST-EPISODE PSYCHOSIS: A MULTIMODAL MRI STUDY

Francisco Reyes-Madrigal¹, Pablo León-Ortiz¹, Kenneth Wengler², Xiangling Mao³, Dikoma Shungu⁴, Guillermo Horga⁵, Camilo de la Fuente-Sandoval^{*6}

¹*Instituto Nacional de Neurología y Neurocirugía, Mexico City*, ²*New York State Psychiatric Institute, Columbia University Medical Center*, ³*Weill Cornell Medical College*, ⁴*Weill Cornell Medicine*, ⁵*Columbia University and New York State Psychiatric Institute*, ⁶*Instituto Nacional de Neurología y Neurocirugía*

Background: Abnormally elevated levels of gamma-aminobutyric acid (GABA) and of Glutamate + Glutamine (Glx) in the medial prefrontal cortex (mPFC) and the striatum have been reported in antipsychotic-free patients with schizophrenia. Additionally, neuromelanin is a promising marker in psychosis, since neuromelanin-sensitive magnetic resonance imaging (NM-MRI) is proxy measure of dopamine function. Here, we examined prefrontal and striatal GABAergic and Glutamatergic metabolites, and their associations with NM-MRI in a group of first-episode psychosis (FEP) patients.

Methods: Twenty-three antipsychotic-naïve patients with FEP and 22 age- and sex-matched healthy controls completed the study. All participants underwent a 3T MRI study in which NM-MRI of the substantia nigra (SN), and proton magnetic resonance spectroscopy (1H-MRS), targeting the mPFC and the dorsal striatum, were acquired within the same imaging session. Averaged NM-MRI contrast-to-noise ratio (CNR) values of the whole SN (SN-CNR) and 4 subregions of interest (SN pars compacta –SNpc-CNR–, SN pars reticularis –SNpr-CNR–, Ventral tegmental area –VTA-CNR–, and Parabrachial pigmented area –PBP-CNR–)

were calculated. GABA and Glx levels were analyzed using XsOSNMR software, referenced to water signal and corrected to account for the tissue composition of the voxel.

Results: Higher GABA levels were found both in the mPFC and in the dorsal caudate of patients with

FEP compared with healthy control subjects ($t=3.3$, $p=.002$; $t=3.1$, $p=.004$, respectively). Glx elevations were only seen in the dorsal striatum of the FEP group ($t=3.3$, $p=.002$). Preliminary correlations were shown between SNpr-CNR and mPFC GABA levels ($r=-.33$, $p=.04$), and SNpc-CNR and age ($r=.35$, $p=.02$) across all subjects. In the FEP group, duration of untreated psychosis correlated with both SNpc-CNR ($r=0.45$, $p=.04$) and mPFC Glx ($r=0.48$, $p=.04$).

Discussion: To the best of our knowledge, this study is the first to assess a proxy measure of dopamine function, GABAergic and Glutamatergic metabolites in drug-naïve patients with FEP. Longitudinal studies are required to establish if these combine markers are a suitable biomarker for predicting treatment response in schizophrenia.

72. DOPAMINE AND DEPRESSION ACROSS THE PSYCHOSIS SPECTRUM: AN 18F-DOPA PET STUDY

Sameer Jauhar^{*1}, Robert McCutcheon², Mattia Veronese³, Matthew Mq Noue⁴, Maria Rogdaki⁵, Thomas Whitehurst⁵, Ellis Onwordi⁵, Fedrico Turkheimer⁶, Allan H Young⁵, Oliver D Howews⁵

¹*Institute of Psychiatry, King's College*, ²*Oxford University*, ³*University of Padua*, ⁴*University College, London*, ⁵*Institute of Psychiatry, Psychology and Neuroscience*, ⁶*Institute of Psychiatry, Psychology and Neuroscience*

Background: Dopamine has played a central role in hypotheses regarding the patho-aetiology of schizophrenia, a tenet of which was response to D2 blocking antipsychotics, with in-vivo neuroreceptor imaging validating this. The treatment of psychotic symptoms across most psychotic disorders (eg bipolar disorder and delusional disorder) with antipsychotics is accepted, with a modest amount of biological data from in-vivo imaging supporting this. However, in disorders such as psychotic major depression (PMD) it is unclear if, and to what extent antipsychotics exert an effect. Whilst psychotic symptoms may respond to antipsychotics in this disorder, RCT evidence is not strong (suggesting a role for both antidepressants and antipsychotics), depression itself (in the absence of psychosis) being theoretically being linked to decreased dopamine function. Depression symptoms are seen trans-diagnostically in psychotic disorders, and often occur before illness onset (in the clinical high-risk state), as well as at first episode psychosis (FEP), and more established illness. We therefore wished to assess dopamine function (specifically dopamine synthesis capacity, DSC), in people across the psychotic spectrum, across diagnostic boundaries.

Methods: 18F-DOPA PET in people at clinical high risk of psychosis, psychotic major depression and first episode psychosis (FEP).

Inclusion criteria

People with and without positive psychotic symptoms, defined by PANSS P1, 3 or 6 GREATER THAN =4, meeting diagnostic criteria for MDD (defined by SCID, or screening using the Hamilton Depression Rating Scale (HDRS) cut-off GREATER THAN =14 or Hospital Anxiety Depression Scale (HADS). Mania/mixed defined by Young Mania Rating Scale (YMRS) GREATER THAN =12 (mania) and Montgomery Asberg Depression Rating Scale (MADRS) GREATER THAN =8 (mixed).

Multiple linear regression, controlling for age and sex, was used to examine if mood state was associated with striatal dopamine synthesis capacity in individual with psychosis spectrum disorder. Mood state was coded linearly (depressed -1, euthymic 0, manic/mixed 1). The same approach was used to determine if individuals with psychosis and depression differed from healthy controls.

Results: Total participants, N=184 (92 patients with current positive symptoms, (Clinical High Risk (CHR).N=31, First Episode Psychosis (FEP), N=47, established illness, N=14), 46 controls).

In individuals with psychosis spectrum and positive psychotic symptoms at time of scanning mood state was associated with striatal Ki, coef=0.05, SE=0.02, p=0.013), with elevation in those with manic/mixed state.

In individuals with psychosis spectrum diagnosis but no positive psychosis symptoms at time of scanning (N=46) mood state was not associated with striatal ki (N=46, coef =-0.002, se=0.03, p=0.96)

No significant mood*psychosis interaction in the model was seen in the full sample (N=184) Compared to controls (N=46), individuals with psychosis and depression (N=37) showed non-significantly lower Ki (coef=-0.03, Se=0.03, p=0.3).

Discussion: These findings suggest that, across the psychosis spectrum, in those people with current positive psychotic symptoms, mood state (presence of depression, euthymia or mania/mixed state) is related to dopamine synthesis capacity. This may have implications for targeted treatments of affective disorders across the psychosis spectrum.

73. PSYCHOSIS MRI SHARED DATA RESOURCE (PSY-SHARED): A GLOBAL MRI DATASET FOR ALL PSYCHOSIS RESEARCHERS

Mariana Zurita*¹, Matthew Kempton¹, Veena Kumari², Simon Evans³, Jack Rogers⁴, Rachel Upthegrove⁴, Urvakhsh Mehta⁵, Rubaida Easmin¹, Sara Bucci¹, Paul Allen¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*Brunel University London*, ³*University of Surrey*, ⁴*University of Birmingham*, ⁵*National Institute of Mental Health and Neuro Sciences (NIMHANS)*

Background: Magnetic Resonance Imaging (MRI) studies have significantly enhanced our understanding of the neuroanatomical basis of psychosis. However, persistent challenges, including underpowered datasets, recruitment difficulties, high costs, and limited diversity in patient populations, hinder progress. Furthermore, the majority of psychosis MRI research has been conducted in western populations. Multi-centre initiatives, though promising, often focus on only one or two illness or risk stages, can still feature small samples, and are generally conducted in western populations.

Here we introduce the Psychosis MRI Shared Data Resource (Psy-ShareD), a global repository that aims to address these challenges. Psy-ShareD provides curated data allowing diverse analytical approaches, including voxel-based morphometry, cortical thickness, surface area, and region of interest assessments. It also includes linked standardised clinical, demographic, and cognitive data and encompasses schizophrenia, bipolar disorder, first-episode psychosis, various at-risk cohorts, and control populations.

Methods: Psy-ShareD currently hosts 1,736 T1-weighted MRI images from 8 different sites across Europe and Asia. These datasets are expected to grow with contributions from additional

partner sites (incorporating South America) and future collaborators in China and Australia. Collaborators anonymise their data by using custom code provided by our team to de-face all structural images and create unique subject IDs (with keys only accessible by the original sites). We carefully curate the data to ensure that what will be available is of high quality. Additionally, we harmonise the data at the image and feature level to ensure reliability and consistency by reducing unwanted variation caused by differences in image acquisition. Image-level harmonisation is carried out using HACA3 (Zuo et al., 2023) and CycleGAN (Gao et al., 2019). Feature-level harmonisation is being conducted using ComBat (Fortin et al., 2018).

Clinical data is standardised using an ordinal system, regardless of the scale used. Cognitive data is standardised and harmonised across three domains: i) intellectual function, ii) working memory and executive function, and iii) verbal learning, by creating standardised z-scores and using data from respective control cohorts matched for age.

Results: Psy-ShareD's curated and harmonised T1 MRI data will be freely accessible and managed by the Psy-ShareD Partnership for researchers at all career stages. It is expected that the resource will be particularly useful for early career researchers and doctoral student projects, particularly those who would otherwise struggle to access MRI datasets in psychosis and psychosis cohorts. Therefore, the Psy-ShareD resource has the potential to significantly increase research capacity and provide opportunities for early-stage researchers to undertake MRI studies in clinical datasets that would not have previously been accessible. Furthermore, we will provide a number of tools and training materials for users to facilitate analyses.

Discussion: In conclusion, Psy-ShareD, a global MRI resource, is positioned to advance schizophrenia and psychosis research by overcoming challenges and enhancing accessibility. Data sharing not only improves reliability and reproducibility but also provides a global perspective on these conditions, emphasising the importance of cross-ethnic MRI datasets in understanding brain structure variations across diverse populations.

74. 7 T MRS REVEALS NEURAL METABOLIC DYSFUNCTION AND ASSOCIATION WITH SYMPTOMS IN PEOPLE WITH PSYCHOSIS

Caroline Demro*¹, Michael-Paul Schallmo¹, Kyle W. Killebrew¹, Małgorzata Marjańska¹, Scott Sponheim²

¹University of Minnesota, ²Minneapolis VA / University of Minnesota

Background: Altered brain chemistry contributes to distressing impairments in cognitive and perceptual functioning in people with psychosis (PwP). These alterations may extend to biological relatives, given the role of genetic factors in psychosis, but studies directly comparing PwP and relatives are sparse (1). Results of previous magnetic resonance spectroscopy (MRS) studies quantifying neurochemical concentrations in PwP are mixed, likely due to methodological differences (2,3). Previous meta-analyses in schizophrenia suggest widespread reduction of N-acetyl aspartate (NAA) (4), a marker of neuronal integrity that has been associated with neuroinflammation. Inflammatory biomarkers can be measured in blood serum and low-grade inflammation has been associated with psychosis. In this study, we addressed common methodological limitations and directly compared neurochemical concentrations and peripheral inflammatory biomarkers between PwP, their relatives, and controls.

Methods: We acquired MRS data at 7 tesla in occipital and prefrontal cortices from 43 controls, 42 first-degree biological relatives, and 64 PwP. MRS methodological limitations were addressed in the current study by: (1) using an ultra-short echo time (TE = 8 ms) sequence

to mitigate the confound of shorter T2 in PwP, (2) acquiring data at 7 tesla to provide higher SNR and separate quantification of overlapping metabolites (e.g., separating NAA from N-acetyl aspartylglutamate (NAAG)), and (3) including macromolecular signals in our basis set, fitting metabolites without soft constraints, and using a rigid baseline during fitting to avoid quantification errors reported in the literature. In addition to MRS, we collected blood serum samples (n=56 controls, 84 relatives, 138 PwP). Kruskal-Wallis tests analyzed group differences in non-normally distributed data.

Results: In a priori tests, NAA levels in the occipital lobe were lower in PwP and their relatives compared to controls (Kruskal-Wallis, $\chi^2=7.46$, $p=.024$). Lower NAAG concentrations in the prefrontal cortex were also evident in PwP versus controls and relatives ($\chi^2=8.10$, $p=.017$). In exploratory analyses, we observed markedly higher glucose levels in occipital ($\chi^2=7.99$, uncorrected $p=.018$, FDR-corrected $p=.18$) and prefrontal ($\chi^2=8.10$, uncorrected $p=.007$, FDR-corrected $p=.074$) cortices in PwP compared to controls and relatives. Hierarchical clustering analyses showed higher glucose levels were linked to higher psychiatric symptom levels and impairments in visual task performance. Serum glutathione levels were lower in PwP and relatives compared to controls ($\chi^2(2, N=241)=74.13$, $p < .001$). We also saw evidence of higher peripheral inflammatory marker levels (e.g., IL-6) for PwP compared to controls and relatives ($\chi^2(2, N=265)=15.40$, $p < .001$).

Discussion: We show when methodological issues are addressed, 7 T MRS reveals a pattern of neurometabolic dysfunction in PwP. Our findings point to a disruption in neural metabolism across multiple brain areas in PwP that is associated with impaired cognitive and perceptual functioning. Relatives showed intermediate occipital NAA levels, suggesting a role for genetic liability for psychosis in this metabolite, whereas relatives' occipital glucose and prefrontal NAAG and glucose levels were similar to controls and thus these metabolites may be more closely linked to disease processes in PwP. Our evidence of higher peripheral inflammation and lower antioxidant defense is consistent with the notion that altered neuronal integrity is associated with inflammation. Together results suggest widespread metabolic and immune dysfunction in PwP that is partly associated with unexpressed genetic liability for psychosis.

75. IN VIVO SYNAPTIC DENSITY LOSS IN SCHIZOPHRENIA IS SHAPED BY ANATOMICAL CONNECTIVITY AND SPREADS FROM REGIONAL EPICENTERS

Sidhant Chopra^{*1}, Patrick D. Worhunsky¹, Mika Naganawa¹, Gustavo A. Angarita¹, Kelly Cosgrove¹, Deepak C. D'Souza¹, David Matuskey¹, Nabeel B. Nabulsi¹, Yiyun Huang¹, Richard E. Carson¹, Irina Esterlis¹, Patrick D. Skosnik¹, Avram J. Holmes², Rajiv Radhakrishnan¹

¹Yale University, ²Rutgers University

Background: Converging genetic and post-mortem evidence suggests the loss of synapses is fundamental to schizophrenia pathogenesis. The radioligand [¹¹C]UCB-J now allows in vivo examination of synaptic density via positron emission tomography (PET), revealing widespread lower density in schizophrenia. However, the mechanisms explaining the spatial pattern of these alterations remain unknown. Here, we investigate whether the brain's axonal fibres act as conduits for synaptic density loss in schizophrenia, as observed in other neurological syndromes.

Methods: Using PET parametric images of [¹¹C]UCB-J binding potential from 117 individuals (92 healthy controls and 25 individuals with schizophrenia), we generated brain-wide voxel-level group difference maps. We derived representative functional and structural

connectivity patterns from an independent control group (N=100). We used coordinated deformation models to predict the extent of synaptic alteration in each parcellated area by the changes observed in areas to which the index region is structurally, or functionally, connected. To locate focal sources, or epicentres, from which synaptic density loss may spread, we used a network diffusion model, sequentially using each brain region as a starting seed.

Results: Our results demonstrated that regional synaptic density differences were strongly correlated with estimates predicted using a model constrained by structural, rather than functional, connectivity ($r=.58$; p LESS THAN .01). Finally, we identified the left temporal pole (p LESS THAN .05) as putative an epicentre from which the pathological spread of synaptic loss may initiate.

Discussion: Our findings highlight a robust and central role for the topology of the brain's white matter fibres in the spread of synaptic pathology in schizophrenia, mirroring findings reported in animal models and other neurological syndromes.

76. COMBINING NEUROMELANIN-MRI AND [18F]-DOPA PET TO EXPLORE MESOSTRIATAL DOPAMINERGIC CIRCUIT DYSFUNCTION IN SCHIZOPHRENIA

Luke Vano*¹, Robert McCutcheon², Grazia Rutigliano³, Stephen Kaar³, Valeria Finelli³, Giovanna Nordio³, Rong Ye⁴, Mattia Veronese³, Ian Everall³, Oliver Howes³

¹*Institute of Psychiatry, King's College*, ²*Oxford University*, ³*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁴*University of Cambridge, Cambridge, UK*

Background: Whilst mesostriatal dopaminergic circuit dysfunction is one of the most established findings in schizophrenia, precisely where dysfunction is most prominent and the relationship between different components of dopaminergic metabolism here has not been fully elucidated. To examine this, we first aimed to determine where dopamine overactivity was most marked in the substantia nigra (SN) and ventral tegmental area (VTA). We then aimed to explore the relationship between dopamine synthesis capacity and neuromelanin levels, produced as a product of dopamine metabolism, across the SN-VTA and striatum.

Methods: 154 subjects (74 people with schizophrenia and 80 healthy controls) underwent clinical assessments and neuromelanin-sensitive MRI (NM-MRI). 38 patients in the schizophrenia group also received [18F]-DOPA PET to measure dopamine synthesis capacity (Kicer) in the SN-VTA and striatum. First, we examined case-control differences in SN-VTA NM-MRI contrast-to-noise ratio (NM-CNR) using region of interest and voxelwise analysis. Second, we explored the relationship between SN-VTA NM-CNR, SN-VTA Kicer, and striatal Kicer in individuals with schizophrenia.

Results: We found that the schizophrenia group had significantly higher SN-VTA NM-CNR compared to controls (effect size= 0.46, $p=0.005$). This was most significant in the medial SN and lateral VTA on voxelwise analysis. In patients who underwent NM-MRI and [18F]-DOPA PET, region of interest analysis demonstrated that SN-VTA Kicer positively correlated with both SN-VTA NM-CNR ($r=0.49$, $p=0.002$) and striatal Kicer ($r=0.71$, p LESS THAN 0.001). Striatal Kicer also positively associated with SN-VTA NM-CNR ($r=0.48$, $p=0.002$). Voxelwise analysis showed that SN-VTA NM-CNR was positively correlated with striatal Kicer ($r=0.54$, $p=0.007$) and highlighted that this relationship was strongest between the ventral SN and associative striatum.

Discussion: Neuromelanin contrast in the dopaminergic midbrain is higher in individuals with schizophrenia compared to controls, with this being most significant in areas of the VTA and

nigra that project to the associative striatum, and is directly associated with dopamine synthesis capacity in both the dopaminergic midbrain and striatum. We identify specific mesostriatal dopaminergic circuits most altered in schizophrenia, with implications for novel treatment development.

77. CORTICAL FOLDING ASYMMETRY AND STRUCTURAL COVARIANCE IN AUDITORY HALLUCINATIONS: IMPLICATIONS FOR THE PSYCHOSIS CONTINUUM

Shun-Chin Jim Wu^{*1}, Héloïse de Vareilles¹, Samantha C. Mitchell¹, Atheer Al-Manea², Jane Garrison¹, Michail Mamalakis¹, Jon Simons¹, Lynn Mørch-Johnsen³, Ingrid Agartz⁴, John Suckling¹, Graham K. Murray¹

¹University of Cambridge, ²University of Birmingham, ³University of Oslo, ⁴NORMENT, Division of Mental Health and Addiction, University of Oslo, and Diakonhjemmet Hospital

Background: Cortical folding, a prenatal developmental process with a persistent pattern after the age of two, serves as a robust biomarker for early neurodevelopment. Previous studies examining the association between impaired sulcal patterns in the paracingulate sulcus (PCS) or superior temporal sulcus (STS) and hallucinations in schizophrenia patients have faced limitations such as modest sample sizes, inconsistent unilateral hemispheric findings, and categorical subject inclusion. This study addresses these issues by investigating the link between lifetime auditory hallucinations and sulcal patterns bilaterally, utilising two distinct quantitative measures, and further assessing asymmetry and structural covariance in individuals with psychotic spectrum disorders and healthy controls.

Methods: The Thematically Organized Psychosis (TOP-OSLO) study's T1-weighted MRI data were utilized, including separate examinations for schizophrenia spectrum disorders (SSD, N=194) and Bipolar spectrum disorders (BSD, N=157), as well as a combined analysis for psychotic spectrum disorders. Healthy controls (N=278) were also included. We utilized manually and automatically labelled metrics from BrainVisa, along with the automatically generated gyrification index from Freesurfer. Asymmetry of labelled metrics and structural covariances of the gyrification index were calculated to investigate interhemispheric developmental coordination within and between PCS, STS and associated networks including salience and auditory network to compare the patients with a lifetime history of auditory hallucinations (N=194), comprising of 145 with SSD and 49 with BSD, and those without such history (N=157), consisting of 49 with SSD and 108 with BSD, alongside the control group.

Results: Patients with psychotic spectrum disorders experiencing lifetime auditory hallucinations exhibited reduced leftward asymmetry in PCS length, as compared to healthy controls (nonparametric Kruskal-Wallis rank sum test statistic (χ^2) = 8.76, post hoc Dunn's test adjusted p-value = 0.03). Consistent findings were observed in SSD and BSD subgroups. Despite variabilities in the structural covariance of the psychotic spectrum disorders, both patient subgroups with hallucinations manifested augmented structural covariance in gyrification within and between sulci, and also extended networks as compared to healthy controls (χ^2 = 9.61-1416.09, post hoc adjusted p = 0.008-0.001).

Discussion: This study replicates earlier schizophrenia findings of decreased leftward asymmetry in PCS length and heightened gyrification covariance in patients with lifetime auditory hallucinations with a larger and independent dataset. The results underscore the importance of interhemispheric communication in sulcal patterns related to auditory hallucinations as enduring traits in psychosis. Differences in covariance among SSD and BSD subgroups suggest nuanced structural coordination variations across these spectra.

78. DEMONSTRATING REDOX IMBALANCE IN EARLY-STAGE SCHIZOPHRENIA USING 7-TESLA FUNCTIONAL MRS

Peter Jeon^{*1}, Michael MacKinley², Kara Dempster³, Sabrina Ford⁴, Lena Palaniyappan⁵, Jean Theberge⁶

¹Western University, ²University of Western Ontario, Lawson Health Research Institute, ³Dalhousie University, ⁴University of Western Ontario, ⁵Douglas Mental Health University Institute, ⁶St. Joseph's Health Care London

Background: Redox imbalance has been implicated in contributing to observable schizophrenia symptoms. As the brain's main antioxidant, glutathione (GSH) is expected to mount a response to redox imbalances and oxidative stress. However, traditional MRS techniques do not capture the potential dynamic or regulatory behavior of neurometabolites, which may provide a more accurate understanding of the molecular mechanisms behind schizophrenia symptoms. To this end, we propose the use of functional MRS (fMRS) to investigate potential antioxidant response abnormalities in response to short-term cognitive stress in the early stages of schizophrenia.

Methods: We recruited 33 first-episode schizophrenia (FES) and 23 patient-matched healthy control (HC) volunteers to undergo proton fMRS (1H-fMRS) using a Siemens MAGENTOM head-only 7-Tesla MRI scanner (8-Tx/32-Rx RF coil). Using a long echo-time semi-LASER pulse sequence (TR = 7500ms, TE = 100ms, 128 averages), GSH, glutamate, and glutamine concentrations were measured with a 2 x 2 x 2 cm³ voxel placed in the dorsolateral anterior cingulate cortex (ACC). The fMRS paradigm consisted of four blocks (baseline, task, recovery 1, recovery 2) with the color-word Stroop task used as the cognitive task in the second block. All transient spectra collected per block were phase- and frequency-corrected prior to averaging into a single spectrum to be used for further post-processing, spectral fitting, and quantification.

Results: A strong trend towards higher baseline GSH was observed in FES compared to HC ($t(54) = -1.829$, $p = 0.07$). No significant difference was detected between baseline glutamate and glutamine in both groups. Repeated measures ANOVA revealed an effect of time ($F(1,3) = 4.169$, $p = 0.01$), metabolite ($F(1,2) = 35.163$, $p < 0.001$), and diagnosis $\times$ metabolite $\times$ time ($F(1,52) = 5.384$, $p = 0.02$). A significant GSH level increase was observed during task activation in HC ($t(22) = -2.570$, $p = 0.03$), but not in FES ($t(32) = 0.357$, $p = 0.71$). Glutathione levels remained elevated for an additional block in HC ($t(22) = -2.570$, $p = 0.02$), even after the removal of task stimuli, before decreasing its levels in the final block. No accompanying changes were observed in glutamate or glutamine during the task period. Glutamate concentrations were significantly decreased, below baseline levels, in the final block of the fMRS paradigm for both HC ($t(22) = 3.454$, $p = 0.002$) and FES ($t(32) = 3.482$, $p = 0.001$). Additionally, a significant increase in glutamine level was detected in HC from the first to second recovery block ($t(22) = -2.194$, $p = 0.04$). Lastly, FES normalized glutamate levels in the first recovery block relative to baseline showed significant correlation to both positive ($r = 0.351$, $p = 0.045$) and general ($r = 0.404$, $p = 0.02$) PANSS-8 sub-scores.

Discussion: We note three major observations in this work. First, is the relative elevation of GSH levels in FES compared to HC, which may indicate pre-existing oxidative stress in our patient sample. Secondly, we note the difference in ability between HC and FES to significantly regulate their ACC GSH levels in response to short-term cognitive activity. Lastly, a significant reduction in glutamate levels post-task in both groups may reveal a more complex interplay among the glutamatergic metabolites in the brain. This work demonstrates the need to move

beyond using traditional MRS techniques into more dynamic tools such as fMRS when studying complex molecular mechanisms behind schizophrenia symptoms. Inability to effectively regulate antioxidants in response to stress not only supports the presence of redox imbalance in schizophrenia, but also suggests the inability to move towards redox balance in the early stages of illness.

Oral Session: Subclinical Populations, High Clinical Risk and Early Onset Psychosis

79. COMPARATIVE ANALYSIS OF CHR-P AND UHR PROFILES DERIVED FROM PSYCHS INTERVIEW: INSIGHTS FROM SIPS AND CAARMS ASSESSMENTS IN EARLY PSYCHOSIS INTERVENTION

Catalina Mourgues-Codern^{*1}, Jean Addington², Martha E. Shenton³, Barnaby Nelson⁴, Alison Yung⁵, Scott Woods¹

¹Yale University, ²Calgary University, ³Brigham and Women's Hospital, Departments of Psychiatry and Radiology, Harvard Medical School, ⁴Melbourne University, ⁵Deakin University

Background: In early psychosis intervention, the Clinical High-Risk syndrome for psychosis (CHR-P) and the Ultra-High Risk (UHR) mental state are assessed through the SIPS and CAARMS interviews. Although they are fundamentally similar in evaluating attenuated positive symptoms, various differences especially in CHR-P/UHR lead to potentially different CHR-P/UHR profiles. Few studies have conducted SIPS and CAARMS interviews in the same patients, rendering the extent of the potential differences unclear. The Positive SYMptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS) offers a unified approach to CHR-P assessment and severity scoring compatible with both CAARMS and SIPS frameworks.

Methods: The first data release from the ongoing AMP SCZ study contains screening PSYCHS data from a cohort of 339 CHR-P/UHR individuals. This cohort was drawn from the PRESCIENT (n=88) and ProNET (n=259) consortia. Participants were stratified into three groups: Group 1 (G1, n=132) consisted of individuals meeting both CAARMS UHR criteria and evidencing SIPS CHR-P progression; Group 2 (G2, n=192) included those meeting UHR criteria and SIPS CHR-P persistent, partial, or full remission; and Group 3 (G3, n=3) comprised individuals who fulfilled SIPS CHR progression criteria without meeting for UHR. A battery of clinical assessments was administered, including the PSYCHS, Brief Psychiatric Rating Scale (BPRS), Premorbid Adjustment Scale (PAS), Negative Symptom Inventory-Prodromal Risk (NSI-PR), Calgary Depression Scale for Schizophrenia (CDSS), Overall Anxiety Severity and Impairment Scale (OASIS), Social and Occupational Functioning Assessment Scale (SOFAS), Global Functioning Scale (GFS), and Global Functioning: Role (GFR).

Results: In this sample, only 3 participants were classified into G3, leading our analysis to focus on G1 (n=132) and G2 (n=192). Both groups were comparable in terms of age and sex. However, G1 exhibited substantially elevated levels of depression on the CDSS ($t(261)=2.442$, $p=.005$, $d=.306$) and anxiety on the OASIS ($\chi^2(1)=5.704$, $p=.017$). G1 was characterized by a higher incidence of BPRS total ($t(269)=2.248$, $p=.025$, $d=.274$) and specific symptoms of guilt ($t(286)=2.31$, $d=.277$) and suspiciousness ($t(285)=2.433$, $d=.291$, ps LESS THAN .05). Moreover, G1 showed higher scores than G2 in various negative symptoms, such as reduced motivation, avolition, and anhedonia, as measured by the NSI-PR ($t(269)=2.533$, $d=.306$; $t(274)=2.078$, $d=.253$; $t(190.343)=2.596$, $d=.328$; ps LESS THAN .05). G1 had higher positive symptoms on the SIPS derived from the PSYCHS ($t(321)=2.444$, $d=.277$, $p=.015$). CAARMS scores were

numerically higher for G1 than G2 ($t(321)=1.646$, $d=.192$, $p=.101$). Regarding functional outcomes, G1 displayed lower social functioning than G2 ($t(289)=2.751$, $t(311)=2.022$, $d=.327$, p s LESS THAN .05), but no significant differences were observed in role functioning between the two groups.

Discussion: In this preliminary sample, fewer than half of participants (40.7%) meeting CAARMS UHR criteria also met SIPS CHR Progression criteria. Participants meeting both criteria (G1) exhibited significantly elevated levels of depression, anxiety, and various negative symptoms and reduced social and occupational functioning compared to those meeting only CAARMS UHR criteria, but effect sizes were small. Requiring SIPS progression for ascertainment appears to produce a slightly more severely ill sample but would require exclusion of more than half of potential enrollees, relative to requiring CAARMS UHR. These trade-offs should be considered when designing and implementing CHR intervention studies.

80. THE EXPERIENCE AND ROLE OF DISSOCIATION IN SUBCLINICAL PSYCHOSIS FOLLOWING DEVELOPMENTAL TRAUMA: A MIXED-METHODS STUDY

Eirini Melegkovits^{*1}, Paul Gu-Yun Jung², Ava Mason², Tereza Bountiokou², Rui Tang², Katie Ashcroft³, Michael Bloomfield²

¹*Division of Psychiatry, UCL*, ²*University College London*, ³*Royal Holloway, University of London*

Background: Developmental trauma (DT), defined here as abuse and neglect prior to the age of 18, increases vulnerability to psychosis in adulthood. Dissociative experiences are common phenomenological characteristics and proposed candidate vulnerability mechanisms among survivors of DT with clinical psychosis. However, there is a lack of research on the phenomenology or the mediating role of dissociation among survivors of DT with subclinical psychosis. We employed a mixed-methods design to delineate the role of dissociation and phenomenological experiences in survivors of DT with subclinical psychotic experiences.

Methods: In study 1, we recruited participants based in the UK ($n=1245$) who were not receiving psychiatric medication to participate in an online survey exploring the role of DT on adult mental health. Participants were invited to complete the study if 1) they had a history of DT, 2) were hearing voices or feeling threatened, or 3) reported no difficulties with their mental health. Participants completed the Childhood Trauma Questionnaire, Dissociative Experiences Scale, the Community Assessment of Psychic Experiences, the Paranoia Scale and the International Trauma Questionnaire. In study 2, 23 participants who met threshold for subclinical psychosis (UHR) based on the CAPE-15 were invited to participate in follow-up qualitative interviews. The interviews comprised of an abridged version of the Comprehensive Assessment of At Risk Mental States (CAARMS) and an adapted version of the Intrusions Interview, focusing on the experience and impact of recent intrusive memories, images, thoughts or voices related to trauma. In study 3, 64 individuals with and without histories of DT were invited to a follow-up experimental study using the Mirror Gazing Task (MGT). We measured depersonalisation before and after the experiment using the Cambridge Depersonalisation Scale-State Version, and explored their experience using qualitative responses.

Results: In Study 1, we found that exposure to DT contributed to increased levels of total and subtypes of dissociation among participants, both with and without subclinical psychosis. Dissociative experiences mediated the relationship between DT and: 1) Frequency of positive psychotic symptoms, 2) Paranoia. The mediating role of dissociation was not moderated by the

presence of PTSD or complex PTSD based on the ITQ. In Study 2, participants meeting the threshold for UHR described various forms of dissociation, particularly experiences of detachment. Dissociation was explained in the context of DT but also as a coping mechanism for distressing emotions, interpersonal relationships, and the experience of the self relevant to both DT and psychosis. Some participants identified that dissociation served as both a cause of psychotic experiences (such as paranoia and hallucinations) and as a response to psychotic experiences. In Study 3, we observed a higher change in depersonalization among participants with DT compared to those without DT. Qualitative responses indicated that participants with DT found the MGT more distressing, more uncontrollable and inexplicable, giving rise to confusion and erroneous explanations.

Discussion: This mixed-methods study aimed to elucidate the relationship between DT, dissociation, and subclinical psychosis, as well as the role dissociation may play in giving rise to psychotic symptoms in adult survivors of DT. Primarily, trait and state dissociation appear to be common among survivors of DT and are also associated with psychotic experiences. Qualitative analyses provided rich phenomenological descriptions and supported the mediating role of dissociation in the experience of psychotic symptoms following DT, as identified in study 1. However, reverse causality needs to be taken into account, as dissociation was also described by participants meeting the UHR threshold as an automatic response to the distress of psychotic symptoms. Findings on the complex relationship between DT and psychosis are discussed, including the role of dissociation as a response peri-traumatically, but also as a way of coping with both psychotic experiences and with memories and experiences of the self following DT. Limitations of the study include the cross-sectional design, that limits causal inferences, and use of self-report questionnaires. Considering the strong association between DT, dissociation, and subclinical psychotic experiences, it is important to screen for traumatic and dissociative experiences among individuals with early presentations of psychosis and to consider them as part of formulation and treatment if necessary. Future research is needed to understand the phenomenology and mechanisms underlying the relationship between dissociation and psychosis, and to determine if dissociation is associated with a worse prognosis and treatment response in individuals with psychosis and DT.

81. IDENTIFYING MODIFIABLE BEHAVIORS THAT PREDICT TRAJECTORIES OF PSYCHOTIC-LIKE EXPERIENCES IN YOUNG ADOLESCENTS

Rebecca Cooper*¹, Maria Jalbrzikowski²

¹*Boston Children's Hospital*, ²*Children's Hospital/Harvard Medical School*

Background: While transient psychotic-like experiences (PLEs) in adolescence are common, persistent and increasing PLEs predict poorer mental health outcomes. PLEs in childhood are associated with increased risk of later developing psychosis, as well as depression and anxiety disorders, substance use disorders, functional impairment, and suicide. Emerging evidence suggests that modifiable lifestyle factors (such as quality sleep and regular exercise) can improve mental health outcomes. However, it is unclear how modifiable lifestyle factors are linked to trajectories of PLEs. Here, we sought to characterize trajectories of PLEs across early adolescence, and assess relationships between PLE trajectories and a range of modifiable behavioral and/or psychosocial predictors.

Methods: We assessed data from 10,007 children (age 9-10 years at the initial visit) from the Adolescent Brain Cognitive Development Study (data release 5.0). Yearly longitudinal data was available for four time points (2018-2021). We used data from the self-report Prodromal Questionnaire-Brief Child Version (PQ-BC) to measure PLEs. Our outcome measure was the summed total of endorsed PLEs. We used latent growth mixture models to characterize PLE

trajectories. Latent growth mixture models can identify distinct sub-groups of individuals that share similar characteristics and follow similar trajectories over time. We examined modifiable predictors available in the ABCD dataset (N=4, e.g., physical activity). For each predictor, we conducted a univariate logistic regression to predict PLE subgroups, covarying for sex at birth, ABCD site and parental education. To evaluate the goodness of fit of the regression model, we calculated Nagelkerke's R squared.

Results: Over half of young adolescents (55%, N=5493) reported persistently low levels of PLES, while the remainder (45%, N=4583) followed a persistently high PLE trajectory over time. The PLE levels in the persistently high PLE trajectory group decreased over the four year follow-up period, but still remained significantly higher than persistently low PLE group at the fourth year time point. Individuals in the elevated trajectory were more likely to be from lower socio-economic status (Nagelkerke $R^2 = 0.01$). These individuals experienced a greater amount of sleep problems (Nagelkerke $R^2 = 0.02$), participated in less regular physical activity (Nagelkerke $R^2 = 0.01$), and drank more caffeinated drinks (Nagelkerke $R^2 = 0.01$) than individuals in the low-level trajectory.

Discussion: Several modifiable behavioral variables were associated with an elevated PLE trajectory in a large sample of youth. Identification of these modifiable factors associated with PLEs provides valuable targets for future risk assessment and preventative treatments in youth. In the future, we plan to incorporate a measure of distress about the PLEs into our calculations of these developmental trajectories, as this measure may improve our ability to capture unobserved heterogeneity and better characterize youth at greatest risk for adverse mental health outcomes. We also plan to assess the predictive effect of biological variables (e.g., neuroimaging measures, polygenic risk scores) on PLE trajectories in youth, as well as moderating effects of the biological measures on the relationships between the modifiable factors and PLE trajectories. Understanding the intersection between an individual's neurobiology and their behavior may provide a comprehensive understanding of how PLEs lead to adverse mental health outcomes.

82. THE PREVALENCE OF EARLY-ONSET PSYCHOSIS AMONG CHINESE SCHOOL-ATTENDING STUDENTS AGED 6-16: A NATIONAL SURVEY

Ying Li^{*1}, Yonghua Cui², Raymond Chan³

¹*Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology,* ²*Beijing Children's Hospital, Capital Medical University,* ³*Institute of Psychology, Chinese Academy of Sciences*

Background: The occurrence of early-onset psychosis in Chinese children and adolescents is not yet fully understood. Drawing from a nationwide epidemiological survey focused on psychiatric disorders within this age group, this study delves into the prevalence of early-onset psychosis and associated symptoms among students aged 6-16 attending school.

Methods: We utilized the database from China's first epidemiological survey on psychiatric disorders in children and adolescents. Using the DSM-Oriented Psychotic Symptoms Scales (DOPSS, where a total score GREATER THAN 1.97 suggests the presence of Psychotic Symptoms), we screened for psychotic indicators. Furthermore, we assessed the prevalence of early-onset psychosis based on the Psychotic Disorders diagnosis as outlined in the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) from this survey. We determined the prevalence of psychotic symptoms or early-onset psychosis and analyzed the influence of age and gender on these rates.

Results: In our study, we analyzed a cohort of 71,929 students aged 6 to 16 years, comprising 36,304 boys and 35,625 girls. Using the DOPSS criteria, 5,140 individuals displayed psychotic symptoms, translating to a prevalence rate of 7.15% (95% Confidence Interval: 6.96-7.34). Notably, boys exhibited a higher prevalence at 7.46%, in contrast to 6.83% in girls (p LESS THAN 0.05). As for age impact, we observed a consistent yearly rise in the prevalence of psychotic symptoms from ages 6 to 16 (p LESS THAN 0.05), peaking at 12.6% for 15-year-olds. Of the cohort, only 31 were diagnosed with early-onset psychosis, leading to a prevalence rate of 0.04% (95% Confidence Interval: 0.03-0.06).

Discussion: This study represents the inaugural epidemiological exploration into the prevalence of early-onset psychosis in China, which stands at 0.04%. Additionally, our research revealed that 7.15% of Chinese children and adolescents exhibit psychotic symptoms. Notably, these symptoms are more prevalent in boys compared to girls, with a peak incidence observed at 15 years of age. Such insights are pivotal for the refinement of early screening and intervention strategies for early-onset psychosis.

83. PROFILING THE CONTRIBUTION OF COGNITION AND PERSONALITY TO PSYCHOSIS PRONENESS COURSE IN YOUNG ADULTS VIA INDIVIDUAL ENVIRONMENTAL LOADINGS

Alessandra Raio^{*1}, Linda Antonella Antonucci¹, Julian Wenzel², Alessandro Bertolino¹, Lana Kambeitz-Illankovic², Joseph Kambeitz², Giulio Pergola³

¹University of Bari Aldo Moro, ²University of Cologne, ³John Hopkins University

Background: Lifetime estimates of transient psychotic-like experiences (PLEs) involve about 15% of the healthy population. While clinically significant psychosis onset peaks in young adulthood, PLEs decrease from childhood onwards. Their persistency after childhood is associated with a fourfold increased risk of psychosis onset within the age stage from early adolescence to young adulthood. Neurodevelopmental changes in this time window may shape behavioral development, resulting in dysfunctional personality traits and low cognitive functioning. Here, we investigated how specific cognitive and/or personality patterns are intertwined over time with the cumulative exposure to environmental factors contributing to psychosis risk. We derived cognitive and personality functioning profiles in a longitudinal study. We assessed the influence of the individual cumulative load of environmental-related psychosis risk on adult PLEs measured in a naturalistic cohort.

Methods: Based on data availability, a sample of 666 participants recruited by the IMAGEN consortium was selected and included 313 males and 353 females assessed across 4 time points (Baseline-BL: 13-15 years; Follow-Up 1-FU1: 16,17 years; FU2: 18-20 years; FU3: 21-24 years). K-means clustering algorithms were separately applied to cognitive and personality data collected at BL and FU2 to identify time-specific profiles of behavioral functioning. The selected features included 22 performance scores evaluating decision-making (DM) subdomains for cognition, and 14 scores evaluating personality and temperament traits. Longitudinal cluster stability was evaluated via permuted Jaccard Index (JI) computation. We modeled the cumulative environmental risk load on PLEs levels, assessed at FU3, via Random Forest Regression (RFR), including 41 sum predictors, each evaluating substance use and stressful life events occurrence across FU1, FU2, and FU3. ANOVA and correlation analyses served to test the association of cluster assignments and cluster prototypicality, respectively, with RFR individual predictions and with the feature most contributing to RFR performance.

Results: At both BL and FU2, two cognitive clusters grouped individuals for good or poor DM scores. Three personality clusters separated “easy-going” (prone to sociability), “impulsive explorers” (novelty-seekers), and “self-focused” individuals. Although individuals changed

cluster assignments over time (all real JIs: 0.29-0.52), the overall clusters' membership reproducibility was above the chance level for all subgroups (p LESS THAN 0.001). The RFR model based on the longitudinal predictors of environmental risk predicted FU3 PLEs severity with an accuracy of 81% (Mean Percentage Absolute Error=0.19). Cumulative distress was the feature most contributing to predictive performance. At BL and FU2, only a main effect of personality cluster assignment on both PLEs environmental risk load and cumulative distress (all p LESS THAN 0.01) was significant. Environmental risk load on adult PLEs was also negatively associated with individual prototypicality for the easy-going cluster at BL ($\rho=-0.154$; $p=0.02$) and positively for the self-focused cluster at FU2 ($\rho=0.31$; p LESS THAN 0.001).

Discussion: Our data-driven behavioral subtyping of adolescent behavioral functioning at different age stages revealed a differential role of specific personality patterns in contributing to the longitudinal life stressors- and substance use-related burden on adult PLEs. No significant effect of DM styles was found. Personality functioning may therefore be a potential target of early intervention aimed at softening the environmental contribution to subthreshold symptoms' severity.

84. REGIONAL SPECIFICITY OF MORPHOMETRIC SIMILARITY NETWORK ALTERATIONS IN SUBGROUPS OF YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

Gil Hoftman^{*1}, Jakob Seidlitz², Jennifer K. Forsyth³, Charles Schleifer¹, Dylan Hughes¹, Jean Addington⁴, Kristin S. Cadenhead⁵, Barbara A. Cornblatt⁶, Daniel H. Mathalon⁷, Diana O. Perkins⁸, Ming T. Tsung⁵, Scott W. Woods⁹, Elaine F. Walker¹⁰, Tyrone D. Cannon⁹, Carrie E. Bearden¹

¹*Semel Institute for Neuroscience and Human Behavior at UCLA*, ²*Children's Hospital of Philadelphia; University of Pennsylvania*, ³*University of Washington*, ⁴*University of Calgary*, ⁵*University of California, San Diego*, ⁶*The Zucker Hillside Hospital*, ⁷*University of California San Francisco, California*, ⁸*University of North Carolina*, ⁹*Yale University*, ¹⁰*Emory University*

Background: Given increasing recognition that psychosis onset is a late stage of a neurodevelopmental illness, and the importance of early intervention, efforts are focused on understanding the pathophysiology of early stages of psychosis. Here we characterize morphometric similarity networks (MSNs), which measure within-subject structural similarity between cortical areas, using baseline structural brain imaging measures in subjects at clinical high-risk (CHR) who converted (CHRC; "converters") or did not convert (CHRCnc; "non-converters") to psychosis, relative to unaffected comparison subjects. We further investigate those subjects who did not convert but remained symptomatic (CHRCncs; "sustainers") and those whose symptoms remitted (CHRCncr; "remitters"). We incorporate postmortem transcriptomic data from the Allen Human Brain Atlas (AHBA) to relate transcriptomic and MSN cortical spatial patterns.

Methods: MRI data were available for 757 subjects from the NAPLS2 cohort at baseline, including 71 CHRC, 467 CHRCnc, and 219 unaffected comparison subjects (Age [Mean, SD]: 19.2 +/- 4.4 years old; Sex: M=58%, F=42%). For CHRCnc subgroup analysis, data were available for 220 CHRCncs and 87 CHRCncr subjects. In one analysis to increase the sample size of symptomatic CHR subjects, the 71 CHRC and 220 CHRCncs were combined to form the CHRCs group (converters and sustainers). MSNs, which represent the sum of inter-regional associations, were constructed from 7 structural MRI measures including volume, cortical thickness, surface area, and 4 curvature indices. MSNs were adjusted for site effects using

neuroCombat. MSN group differences were determined using ANOVA with FDR correction for multiple comparisons and accounting for covariates of age, sex, and site. Microarray data from the AHBA were related to MSNs using partial least squares (PLS) regression and gene ontology (GO) pathway analysis was used to annotate correlated gene groups. We used a modified granular version of the Desikan-Killiany cortical surface parcellation, consisting of 308 regions of interest.

Results: Baseline difference maps between CHR vs. unaffected comparison subjects showed significant increases in MSN degree in 17 posterior visual areas and decreases in 14 anterior frontal and temporal areas in CHR youth (all FDR $p < 0.05$). CHRcs showed significant increases in 3 posterior visual areas and decreases in 4 anterior frontotemporal areas, relative to unaffected comparison subjects (all FDR $p < 0.05$). No significant differences were observed between CHRnc vs. CHRc or between CHRcs vs. CHRncr. For the PLS regression analysis, we modeled effect sizes across cortical regions to examine regional differences in MSNs between CHR vs. unaffected comparison subjects and related them to regional gene expression from the AHBA. PLS component 1 (PLS1) for the MSN model explained 13.5% of the covariance between regional CHR vs. unaffected comparison subject MSN effect sizes and gene expression. Key markers of synaptic neurotransmission, including parvalbumin, GABAA receptor subunit delta, and sodium and potassium channel subunits were in the top 2% of PLS1 loadings. Functional annotation of all genes in the top 5% of loadings on PLS1 were associated with synaptic signaling, including glutamate, GABA and endocannabinoid signaling.

Discussion: These findings suggest that baseline differences in MSN topology between individuals at CHR for psychosis and unaffected comparison subjects cluster in specific cortical areas, are identifiable at the baseline MRI scan, and associate with markers of GABA neurotransmission and synaptic transmission-related biological pathways.

85. COURSE OF CLINICAL HIGH-RISK SYMPTOMS FOR PSYCHOSIS IN THE COMMUNITY: A LATENT CLASS ANALYSIS WITH A FOCUS ON MOVEMENT BETWEEN SUBGROUPS OVER TIME

Miriam Stübke¹, Naweed Osman², Giulia Rinaldi³, Benno G. Schimmelmann⁴, Jochen Kindler³, Frauke Schultze-Lutter⁵, Chantal Michel³

¹University of Bern, ²Medical Faculty, Heinrich-Heine-University Düsseldorf, ³University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, ⁴University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, University Hospital of Child and Adolescent Psychiatry, University Hospital Hamburg-Eppendorf, ⁵University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Medical Faculty, Heinrich-Heine-University Düsseldorf, Airlangga University, Surabaya

Background: Typically, studies of the longitudinal course of clinical high-risk (CHR) for psychosis symptoms have focussed on transition rates to manifest psychosis (mostly in help-seeking samples). However, more recent research considers clinical presentation over time, regardless of transition. Moreover, given the heterogeneity in clinical presentation of CHR symptoms, it is important to identify homogenous clinical profiles. The aim of this study was to ascertain clinical profiles of individuals in the community presenting with CHR symptoms and to examine them longitudinally.

Methods: Participants (N=829) comprised individuals from a Swiss community sample. Latent Class Analysis was applied to baseline and follow-up (FU) CHR symptom data, and class profiles were characterised across demographic and clinical variables.

Results: The best fit was the 3-class solution for both time points. Baseline: Class 1 (n=19; most impaired, persecutory ideas, cognitive basic symptoms, derealisation); Class 2 (n=25; intermediate impaired; unusual thought content, disorganized communication); and Class 3 (n=785; least impaired; low CHR probability). Follow-up: FU Class 1 (n=27; most impaired; unusual thought content, attenuated hallucinations, derealisation); FU Class 2 (n=52; intermediate impaired; perceptual abnormalities and cognitive basic symptoms); and FU Class 3 (n=750; least impaired, low CHR probability). Overall, there was some movement between all groups over time.

Discussion: Findings provide a more nuanced view of CHR symptoms in the community and their associated clinical presentation and course over time. Findings can also be used to inform psychoeducation regarding the course of CHR and associated symptoms.

Oral Session: New Pharmacological Treatments and Assessments

86. LINGUISTIC RISK SCORE FOR SCHIZOPHRENIA: APPLYING A POLYGENIC RISK APPROACH TO SYNTHESIZE MULTIVARIATE FEATURES FROM COMPUTATIONAL SPEECH AND LANGUAGE ANALYSIS

Sunny Tang*¹, Amir Nikzad¹, Michael Spilka², Yan Cong¹, Leily Behbehani¹, Sarah Berretta¹, John Kane¹, Anil K. Malhotra¹

¹Zucker Hillside Hospital, ²Winterlight Labs

Background: Computational speech analysis offers powerful methods to objectively quantify linguistic signals which can reflect the mental state of the speaker. A wide range of features can be generated to describe linguistic content: e.g., parts of speech, phrase structure, semantic coherence, graph metrics, tempo, and lexical properties, among others. These features can be analyzed in different ways, e.g., with moving windows of varying sizes, verbatim vs. filtered content, etc., and using language collected from different tasks, e.g., picture description, open-ended narratives, fluency tasks, etc. Taken together, studies employing computational speech and language analysis can easily accumulate thousands of features. Understanding and accounting for this large feature space is a prominent challenge in this field. Here, we take an analogous approach to the calculation of polygenic risk scores to first identify candidate features associated with schizophrenia diagnosis, and then calculate a single weighted sum to represent the individual's "Linguistic Risk Score" (LRS). We hypothesized that the LRS would demonstrate intermediate effects in non-psychotic psychiatric disorders, and that within individuals with schizophrenia spectrum disorders (SSD), the LRS would demonstrate both state and trait-like characteristics.

Methods: Three samples were included. Sample 1 was the training sample and included 52 healthy control (HC) and 85 SSD participants, with no significant differences in age, gender, race, or ethnicity between groups. Sample 2 was an independent cross-diagnostic test sample, including 21 randomly set-aside SSD participants, 81 participants with unipolar depression, 40 with bipolar disorder, and 22 with mood disorders with psychotic features. Sample 3 included an overlapping sample of 62 participants with SSD with up to 4 timepoints of longitudinal follow-up. Psychosis symptoms were assessed dimensionally with the Brief Psychiatric Rating Scale (BPRS).

To calculate the LRS from 1227 computational speech and language features, we first selected features which were significantly different between groups in Sample 1 and calculated a weighting factor based on the effect size. Because many features were non-parametric, the group comparison was conducted using the Mann-Whitney U test, and the effect size was calculated using Cliff's Delta. Next, for each feature in each subject, a normalized rank score ranging from -1 to 1 was computed relative to the HC training sample, such that the test subject received a -1 if they scored lower than all HC subjects, 0 if they scored at the median, +0.50 if they scored at the 75%, and +1 if they scored higher than all HC subjects, etc. The normalized rank score was multiplied by the weighting factor for each feature, then summed across all features for each participant.

Group comparisons were made using ANOVA with pairwise effects calculated with t-tests (p values corrected using FDR). Between-subject dimensional relationships to psychosis symptom dimensions were calculated with linear regressions. To assess within-individual relationships between psychosis symptoms and LRS, we examined linear mixed models with random slopes and random intercepts by participant.

Results: LRS was calculated for p-value thresholds of 0.01, 0.05 and 0.10. In each case, we first verified that the HC LRS was centered at 0 and the SSD training sample produced a significantly elevated LRS. Comparing the HC sample to the independent cross-diagnostic test samples, we found elevated LRS for all of the psychiatric groups at all of the p-value thresholds, with marginally larger effect sizes for p LESS THAN 0.01. Here, LRS in all groups was significantly elevated relative to HC with p LESS THAN 0.001 (Cohen's d: Unipolar = 1.45, Bipolar = 1.75, Mood with psychosis = 2.18, SSD = 2.33). LRS in the psychosis groups were significantly elevated relative to unipolar depression (Mood with psychosis: p=0.02, d=0.61; SSD: p=0.03, d=0.61). There was no difference in LRS between the SSD and mood with psychosis groups, and trend level differences between these and the bipolar disorder group. Cross-sectionally, higher BPRS total score was associated with higher LRS between subjects (Std. Beta = 0.28, p=0.03). Longitudinally, accounting for random effects in slope did not improve the prediction of LRS based on BPRS total score over the random intercept model. Here, we found significant values for the overall intercept (i.e., LRS when there are no active psychosis symptoms; Beta=4.06, p LESS THAN 0.001), the fixed effect of BPRS score (i.e., average relationship between LRS and BPRS; Beta=0.08, p LESS THAN 0.001), and the random effects for subject (95% CI of standard deviation: 0.96-2.29).

Discussion: We successfully calculated a LRS to summarize SSD-related effects across 1227 computational speech and language features at p-value thresholds of 0.01, 0.05 and 0.10. The LRS demonstrated expected cross-diagnostic group differences, with the highest scores in SSD and mood disorders with psychotic features, and intermediate scores in unipolar depression. For individuals with SSD, LRS appears to demonstrate both state- and trait-like effects: LRS is elevated at baseline (i.e., even when psychosis-free), and further increases with greater psychosis severity.

87. DETECTING SCHIZOPHRENIA, BIPOLAR DISORDER, PSYCHOSIS VULNERABILITY AND MAJOR DEPRESSION FROM 5 MINUTES OF ONLINE COLLECTED SPEECH

Julianna Olah^{*1}, Win Lee Edwin Wong², Atta-ul Raheem Rana Chaudhry³, Sunny X Tang⁴

¹King's College London, ²King's College London, Psyrin Ltd., ³Psyrin Ltd., ⁴Institute of Behavioral Science, Feinstein Institutes for Medical Research; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Background: Psychosis, characterised by a disconnection from reality, hallucinations, and delusions, poses substantial social and healthcare burdens. The analysis of speech is a promising approach for the diagnosis and monitoring of psychosis, capturing symptoms like thought disorder and flattened affect. Recent advancements in Natural Language Processing methodologies enables the automated extraction of informative speech features, which has been leveraged for early psychosis detection and assessment of symptomology. However, critical gaps persist, including the absence of standardized sample collection protocols, small sample sizes, and a lack of multi-illness classification, limiting clinical applicability.

Methods: We adopted online data collection methods to collect 20 minutes of speech and demographic information from individuals. Participants were given labels of “healthy”, schizophrenia, bipolar, depression, and prodromal psychosis based on self-reported clinical diagnosis and responses to the PHQ-8 and PQ-16 screening questionnaires. Text-based and paralinguistic features were extracted and ensemble learning algorithms were used to train models. A mix of cross-validation approaches and a 70%-30% test-train split were used.

Results: The final analysis sample comprised 1140 individuals and 22,650 minutes of speech. Using 5-minutes of speech, our model could discriminate between healthy individuals and psychosis individuals with 90% accuracy (AUC = 0.94, Recall = 0.83, Precision = 0.96). Furthermore, our model could discern between healthy, prodromal, bipolar and schizophrenia groups with 86% accuracy (F1 macro = 0.855, Recall Macro = 0.86, Precision Macro = 0.86). Finally in a 5-class discrimination task including individuals with depression, our model had 76% accuracy (F1 macro = 0.757, Recall Macro = 0.758, Precision Macro = 0.766).

Discussion: In summary, our ML pipeline demonstrated disorder-specific learning, achieving excellent accuracy across several classification tasks. We demonstrated that the screening of mental disorders is possible via a fully automated, remote speech assessment pipeline. First in literature, we tested our model on the highest number of classes of conditions (5 classes) and in a stratified sample of healthy control, psychosis vulnerability and two types of psychotic disorders (4 classes). We tested our model on the largest sample in the literature (N = 1150) and demonstrated best-in-class accuracy with remotely collected speech data in the psychosis spectrum.

88. THE IMPACT OF KARXT ON COGNITIVE IMPAIRMENT IN ACUTE SCHIZOPHRENIA: REPLICATION IN POOLED DATA FROM PHASE 3 TRIALS

William Horan^{*1}, Colin Sauder¹, Philip D. Harvey², Ian S. Ramsay¹, Steven M. Paul¹, Stephen K. Brannan¹

¹Karuna Therapeutics, Inc., ²University of Miami Miller School of Medicine

Background: KarXT is an M1 /M4 preferring central muscarinic receptor agonist based on xanomeline, which has been shown to improve cognition in psychiatric populations. The phase II EMERGENT-1 (NCT03697252) trial demonstrated that KarXT monotherapy improved cognition in a subgroup of acute schizophrenia inpatients with clinically significant cognitive impairment, but not in the entire sample. We sought to replicate this finding using pooled data from two similarly designed phase III trials.

Methods: The EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) studies were randomised, double-blind, placebo-controlled, 5-week inpatient trials of KarXT monotherapy in schizophrenia participants experiencing acute psychosis. Cognition was

assessed at baseline, week-3, and week-5 using the CANTAB computerised battery. Pre-specified analyses compared change from baseline on cognitive composite scores between KarXT and placebo in the full sample and, based on phase II findings, in a subsample of participants performing at least 1 standard deviation below healthy comparison norms on the CANTAB at baseline. Linear regression assessed the relation between change in cognition and Positive and Negative Syndrome Scale (PANSS) scores.

Results: There was no significant treatment effect for KarXT (N=150) vs. Placebo (N=157) in the full sample. However, in the impaired subgroup, participants taking KarXT (N=71) again showed significantly greater improvement in cognition compared to Placebo (N = 66; LSM Difference $\pm$ SE=0.31 $\pm$ 0.10; p = .004; d = 0.54). A significantly larger proportion of those who received KarXT (45.2%) compared to placebo (17.2%) achieved a 0.50 SD improvement (X^2 [1, N = 120] = 10.80, p LESS THAN .001). Change in cognition did not significantly relate to improvement in PANSS total, positive, or negative symptom scores (p s GREATER THAN 0.15).

Discussion: These clinical studies with KarXT constitute the first time that a cognitive benefit found in a phase II trial has been replicated in phase III. The KarXT benefit in a subgroup of acute schizophrenia participants with clinically significant cognitive impairment was not attributable to changes in clinical symptoms, despite substantial evidence of efficacy for psychosis. The replicable findings across phase II and III trials warrant further prospective investigation in clinically stable patients, enriched for cognitive impairment, to fully characterize the effects of KarXT on cognitive impairment associated with schizophrenia (CIAS).

89. LONG-TERM SAFETY AND EFFICACY OF OLANZAPINE/SAMIDORPHAN: RESULTS OF A 4-YEAR OPEN-LABEL STUDY

Jacob Ballon¹, Rene Kahn², Christina Arevalo³, Martin Dunbar³, David McDonnell⁴, Christoph Correll⁵, René Kahn*²

¹Stanford University, ²Icahn School of Medicine at Mount Sinai, ³Alkermes, Inc., ⁴Alkermes, ⁵Zucker Hillside Hospital; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead; Charité Universitätsmedizin

Background: This study evaluated the long-term safety, tolerability, and durability of effect of olanzapine/samidorphan (OLZ/SAM).

Methods: This phase 3, multicenter, open-label extension study assessed the long-term safety and efficacy of up to 4 years of OLZ/SAM in patients who completed the following OLZ/SAM trials: 52-week open-label studies NCT02873208 and NCT02669758, which were rollover extensions of phase 3 pivotal randomized controlled trials in adults with schizophrenia (SZ), and NCT03187769 in young adults with recent-onset SZ, schizophreniform disorder, or bipolar I disorder (BD-I). Depending on geography and enrollment date, patients in the current long-term study had the opportunity to receive up to 2 to 4 years of treatment. Safety assessments included the incidence of adverse events (AEs) and changes from baseline in body weight and waist circumference. Changes in lipid (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and total cholesterol and triglycerides) and glycemic (glucose and glycosylated hemoglobin [HbA1c]) parameters were also evaluated. Antipsychotic efficacy was assessed with the Clinical Global Impressions–Severity (CGI-S) scale.

Results: Of 524 patients enrolled in the study, 523 received ≥ 1 dose of OLZ/SAM. 188 (35.9%) patients completed between 2 to 4 years of treatment. The mean (SD) duration of exposure was 652.4 (454.8) days. Among 451 patients who were eligible to receive at least 2

years of treatment, 242 (53.7%) received ≥ 2 years of treatment. Among 335 patients who were eligible to receive 4 years of treatment, 109 (32.5%) received 4 years of treatment. In the treated population, patients were mostly male (61.6%) and White (72.7%), with a mean (SD) age of 35.1 (12.2) years. Overall, 60.0% of patients reported at least one AE; the most common were weight increased (9.8%), headache (7.1%), anxiety (6.1%), insomnia (5.9%), somnolence (5.9%), nausea (5.7%), and weight decreased (5.7%). For patients who contributed data to the 2-year assessment (n=238), mean (SD) change from baseline in body weight was 0.84 (6.84) kg and waist circumference was -0.56 (6.24) cm. For patients who contributed data to the 4-year assessment (n=108), the mean (SD) change from baseline in body weight was 2.65 (8.12) kg and waist circumference was 1.37 (8.65) cm. Lipid and glycemic parameters were generally stable over the treatment period. Patients' symptoms remained stable—for patients contributing data at 2 years, mean (SD) change from baseline in CGI-S was -0.18 (0.67) and for those at 4 years was -0.24 (0.65).

Discussion: In this 4-year open-label extension study, treatment with OLZ/SAM resulted in a safety profile consistent with previous short-term studies and was associated with small changes in body weight and minimal changes in waist circumference and lipid and glycemic parameters. Similarly, OLZ/SAM maintained symptom control during long-term treatment. Based on these results, OLZ/SAM maintained long-term antipsychotic efficacy while mitigating the weight gain and metabolic dysfunction associated with olanzapine.

This study was funded by Alkermes, Inc. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

90. EFFICACY AND SAFETY OF BREXPIPIRAZOLE IN ADOLESCENTS (AGED 13–17 YEARS) WITH SCHIZOPHRENIA: A PHASE 3, 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED AND ACTIVE-REFERENCED TRIAL

Caroline Ward^{*1}, Milica Pejović Milovančević², Eva Kohegyi¹, Marianne Dragheim³, Catherine Aurang¹, Dalei Chen¹, Klaus Groes Larsen³, Mary Hobart¹, Christoph Correll⁴

¹Otsuka Pharmaceutical Development and Commercialization Inc., ²Faculty of Medicine, University of Belgrade; Institute of Mental Health, Belgrade, ³H. Lundbeck A/S, ⁴The Zucker Hillside Hospital; The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health

Background: Schizophrenia onset in childhood/early adolescence can be associated with more chronic and severe symptoms, and poorer prognosis, compared with adult onset. Brexpiprazole is approved for the treatment of schizophrenia in adults and in adolescents aged ≥ 13 years (US and other countries). Existing approvals of brexpiprazole in adolescents were based on data extrapolation from adult studies, pharmacokinetic data, and interim data from a long-term, open-label adolescent study (includes patients from the present trial). This 6-week trial evaluated the efficacy and safety of brexpiprazole in adolescents with schizophrenia.

Methods: This was a Phase 3, 6-week, randomized, double-blind, placebo-controlled, active-referenced trial of brexpiprazole in adolescents with schizophrenia (NCT03198078), conducted June 2017 – April 2023 at 62 sites in 10 countries. Eligible patients were aged 13–17 years, with a diagnosis of schizophrenia (DSM-5 criteria; for ≥ 6 months prior to screening; confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version), and a Positive and Negative Syndrome Scale (PANSS) Total score ≥ 80 at screening and baseline. Patients were randomized 1:1:1 to brexpiprazole 2–4 mg/day, placebo, or

aripiprazole 10–20 mg/day (active reference to validate study methodology and patient population). The primary efficacy endpoint was change from baseline to Week 6 in PANSS Total score. Safety assessments included treatment-emergent adverse events (TEAEs), discontinuations due to AEs, and body weight. The safety sample comprised all randomized patients who received ≥ 1 dose of assigned treatment. The efficacy sample comprised all safety sample patients who had a baseline and ≥ 1 post-baseline PANSS Total evaluation.

Results: 316 patients were randomized to brexpiprazole (n=110), placebo (n=104), or aripiprazole (n=102); completion rates were 97.3%, 88.5%, and 95.1%, respectively. The safety sample comprised all 316 randomized patients. The efficacy sample comprised 314 patients (brexpiprazole, n=110; placebo, n=103; aripiprazole, n=101). Baseline characteristics were similar between groups (mean [SD] PANSS Total scores: brexpiprazole, 101.1 [14.9]; placebo, 102.1 [16.3]). The least squares (LS) mean (standard error) change from baseline to Week 6 in PANSS Total score (primary endpoint) was -22.75 (1.49) with brexpiprazole and -17.42 (1.58) with placebo (LS mean difference: -5.33 [95% confidence interval: -9.55, -1.10]; $p=0.0136$). The aripiprazole group also separated from placebo on the primary endpoint at Week 6, thus validating the study methodology and patient population. Over 6 weeks, the incidence of TEAEs was 40.0% (brexpiprazole), 40.4% (placebo), and 52.0% (aripiprazole). The most common TEAEs with brexpiprazole (incidence $\geq 5\%$) were headache (6.4%; placebo, 4.8%; aripiprazole, 4.9%) and nausea (6.4%; placebo, 3.8%; aripiprazole, 3.9%). With aripiprazole, the most common TEAEs were somnolence (10.8%; brexpiprazole, 4.5%; placebo, 4.8%), fatigue (7.8%; brexpiprazole, 1.8%; placebo, 0.0%), and akathisia (6.9%; brexpiprazole, 3.6%; placebo, 2.9%). There were no discontinuations due to AEs with brexpiprazole (placebo, n=2; aripiprazole, n=1). The mean (SD) change from baseline to last visit in body weight (kg) was 0.8 (2.6), 0.0 (2.2), and 0.5 (2.7) with brexpiprazole, placebo, and aripiprazole, respectively.

Discussion: In this 6-week, Phase 3 study of adolescents aged 13–17 years with schizophrenia, treatment with brexpiprazole 2–4 mg/day was associated with greater reduction in symptom severity versus placebo. The safety profile of brexpiprazole was consistent with that observed in adults with schizophrenia.

91. A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PIMAVANSERIN AS ADJUNCTIVE TREATMENT FOR THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA (ADVANCE-2)

Dragana Bugarski-Kirola*¹, I-Yuan (Cathy) Liu², Celso Arango³, Stephen R. Marder⁴

¹ACADIA Pharmaceuticals, Inc., ²ACADIA Pharmaceuticals Inc., ³Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, IiSGM, CIBERSAM. Madrid, Spain, ⁴University of California, Los Angeles, Semel Institute for Neuroscience

Background: Negative symptoms of schizophrenia (NSS) are associated with substantial burden and adverse clinical outcomes, yet few treatments are available. Evidence suggests 5-hydroxytryptamine (5-HT) 2A receptor inverse agonism may be an effective mechanism to treat NSS. Pimavanserin is a selective 5-HT_{2A} receptor inverse agonist/antagonist with low affinity for 5HT_{2C} and no affinity for dopaminergic, adrenergic, muscarinic, or histaminergic receptors. The phase 3 ADVANCE-2 study evaluated the efficacy and safety of pimavanserin as an adjunctive treatment for NSS.

Methods: ADVANCE-2 (NCT04531982) is a 26-week, phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational, outpatient study in patients with schizophrenia and predominant NSS (i.e., negative symptoms of greater severity than positive symptoms). Operationally, negative symptoms were defined at Screening and Baseline based on the Positive and Negative Syndrome Scale (PANSS) Marder negative factor items as a score ≥ 20 on the sum; a score ≥ 4 on at least 3, or ≥ 5 on at least 2 of the items; and a Clinical Global Impression of Schizophrenia Scale–Severity (CGI-SCH-S) negative symptom score ≥ 4 (moderately ill or worse). Minimal positive symptoms were defined at both Screening and Baseline based on the PANSS Marder positive factor items as a score ≤ 22 on the sum and a score where ≤ 2 of the following items have a score of 4 and none had a score ≥ 5 : P1 (delusions), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), and P7 (hostility).

Eligible patients were adults with a diagnosis of schizophrenia (≥ 1 year prior to Screening) according to the DSM-5 criteria and confirmed using the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Patients were required to have a caregiver to ensure study compliance and to have been receiving an adequate dose of an antipsychotic from a select list (not including clozapine) for ≥ 8 weeks prior to Screening. Patients with a concurrent psychiatric diagnosis other than schizophrenia were excluded. After screening (≤ 6 weeks), patients were randomized (1:1), stratified by geographic region, to receive pimavanserin (34 mg/day) or placebo. The study's primary objective was to evaluate the efficacy of adjunctive pimavanserin versus placebo for the change from Baseline to Week 26 in the Negative Symptom Assessment–16 (NSA-16) total score.

The key secondary endpoint was the change from Baseline to Week 26 for the CGI-SCH-S negative symptom score. Other secondary endpoints included the Clinical Global Impression of Schizophrenia Scale–Improvement (CGI-SCH-I) negative symptom score at Week 26 and the change from Baseline to Week 26 for the Personal and Social Performance (PSP) scale score, PANSS total score, PANSS negative subscores, and PANSS Marder factor (negative symptoms) score. Week 26 responder analyses included the proportion of negative symptom responders defined using CGI-SCH-I (i.e., negative symptoms score of 1 or 2) and NSA-16 (i.e., $\geq 20\%$ and $\geq 30\%$ reduction in total score). Safety and tolerability were also assessed.

Results: As of August 15, 2023, a total of 671 patients have been screened and 454 have been randomized to treatment. A total of 217 (32.3%) patients failed screening. Results for the primary and secondary study endpoints will be available in March 2024 and will be presented for the first time at the Schizophrenia International Research Society (SIRS) 2024 meeting.

Discussion: ADVANCE-2 has recruited and randomized a sufficient number of patients (i.e., per power analyses) to detect a true treatment difference in the primary efficacy variable. Results will be presented at the upcoming 2024 SIRS congress.

92. INITIATION REGIMENS FOR LONG-ACTING INJECTABLE ANTIPSYCHOTICS REQUIRING ORAL SUPPLEMENTATION: IMPACT ON SUBSEQUENT MAINTENANCE TREATMENT ADHERENCE AND PERSISTENCE

Stephen Thompson¹, Handing Xie¹, Robert DiEgidio¹, Sangtaeck Lim¹, Kelli R. Franzenburg², Stephen Thompson*³

¹Teva Branded Pharmaceutical Products R and D, Inc., Global Medical Affairs, ²Teva Branded Pharmaceutical Products R and D, Inc., ³Teva Pharmaceutical Industries, Ltd.

Background: Medication adherence and persistence are major challenges in the management of schizophrenia. Nonadherence is a modifiable risk factor for relapse and contributes to poor health outcomes. Long-acting injectable antipsychotics (LAIs) with complex initiation regimens may result in reduced treatment adherence and persistence (Semahegn A, et al. Syst Rev. 2020;9:17). This analysis characterized maintenance treatment adherence and persistence for patients who followed the initiation regimen (requiring oral supplementation) versus patients who did not, based on FDA-approved prescribing information for an intramuscular (im) LAI formulation of risperidone microspheres administered once every 2 weeks (q2w).

Methods: Patients diagnosed with schizophrenia in the United States (US) were identified using the MarketScan® Commercial and Medicare Supplemental claims databases during the study period between January 1, 2013, and June 30, 2021. Patients were included if they were aged ≥ 18 years with ≥ 1 im risperidone microspheres q2w claim during the study period (date of the first claim was defined as the index date). Patients were excluded if they had any LAI claims during the 12-month pre-index period. Prescribing information for im risperidone microspheres q2w requires supplementation with 21 days of an oral antipsychotic during initiation. Patients were regarded as not following the initiation regimen if they were not treated according to the prescribing information. Propensity score matching (1:1) was used to match patients who followed the initiation regimen and those who did not. Patients were matched on gender, age, major depression diagnosis, number of antidepressant claims, US region, and payer type. Adherence with LAI treatment was measured using medication possession ratio (MPR) and proportion of days covered (PDC). Patients were considered adherent if MPR or PDC was ≥ 0.80 . One-year persistence was defined as the duration of index LAI treatment during the 12 months post index, allowing gaps of ≤ 15 days.

Results: Among 1958 patients with ≥ 1 im risperidone microspheres q2w claim, 278 met inclusion criteria. Of those patients who met criteria, 137 (49.3%) followed the initiation regimen based on the prescribing information. Propensity score matching identified 117 matched pairs of patients. Baseline characteristics were well balanced between those who followed the prescribing information and those who did not after matching: 68.4% versus 63.3% were male, respectively, and mean ages were 36.4 versus 38.8 years. Treatment adherence of index LAI (MPR; PDC) was higher among patients who followed the initiation regimen (mean [SD], 0.42 [0.36]; 0.39 [0.34]) versus those who did not (0.38 [0.34]; 0.35 [0.32]). In addition, MPR and PDC adherence rates were greater for patients who followed the prescribing information (26.5% and 22.2%, respectively) versus those who did not (21.4%, 16.2%). Mean (SD) persistence duration with maintenance treatment through the first year was also longer for those who followed the prescribing information (122.7 [126.3] days) versus those who did not (98.4 [115.8]).

Discussion: Following an LAI initiation regimen is found to be potentially associated with better maintenance treatment adherence and persistence. LAIs with less complex initiation regimens may increase adherence and persistence, and subsequently improve health outcomes (ie, prevent relapse and extend life expectancy) and help manage patients' schizophrenia symptoms more effectively.

93. LONG-TERM METABOLIC OUTCOMES ASSOCIATED WITH KARXT (XANOMELINE AND TROSPIUM): INTERIM RESULTS FROM POOLED, LONG-TERM SAFETY STUDIES EMERGENT-4 AND EMERGENT-5

Amy Claxton^{*1}, George Konis², Inder Kaul¹, Andrew C. Miller¹, Steven M. Paul¹, Stephen K. Brannan¹, Ronald Marcus¹

¹Karuna Therapeutics, ²Woodland International Research Group

Background: A high unmet medical need exists for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action. Currently approved treatments for schizophrenia are associated with a variety of metabolic disturbances, including weight gain, hyperlipidemia, and increased risk of diabetes. All currently approved treatments for schizophrenia have D2 dopamine receptor blocking activity. KarXT, an investigational medication, combines the dual M1/M4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted muscarinic receptor antagonist trospium chloride without blocking the D2 dopamine receptor. The efficacy and safety of KarXT in schizophrenia was demonstrated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. In these trials, KarXT was not associated with weight gain or adverse metabolic side effects compared to placebo. Long-term safety and tolerability of KarXT is currently being assessed in the Phase 3, multicenter, 52-week, outpatient, open-label extension EMERGENT-4 (NCT04659174) study and open-label EMERGENT-5 (NCT04820309) study in de novo participants without prior exposure to KarXT.

Methods: EMERGENT-4 and EMERGENT-5 trials enrolled participants with a diagnosis of schizophrenia. Participants had either rolled over from the short-term, pivotal trials (EMERGENT-4) or had stable symptoms of schizophrenia appropriate for outpatient care (EMERGENT-5). Eligible participants were dosed with KarXT (xanomeline/trospium) starting at 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID. Data from EMERGENT-4 and EMERGENT-5 trials were pooled and analyses were conducted in the safety population, defined as all participants who received ≥ 1 dose of KarXT. Participants had to discontinue previous antipsychotics prior to receiving KarXT. At the time of the data cut, 275 (41%) subjects remained ongoing in the study.

Results: At baseline, participants had a mean BMI of 29.7 and Hemoglobin A1c (HbA1c) of 5.8%, indicating that some baseline metabolic dysfunction was present. Participants had a mean reduction in weight after 24 weeks of treatment with KarXT, and a further mean reduction after 52 weeks of treatment. More participants experienced potentially clinically significant (PCS) decreases in weight ($\geq 7\%$ decrease) versus PCS increases in weight ($\geq 7\%$ increase) over the course of long-term treatment. Cholesterol remained stable, and fewer participants had PCS high cholesterol at their last assessment compared with baseline. Mean triglycerides decreased over the course of long-term treatment, with fewer subjects experiencing PCS high triglycerides at their last assessment compared with baseline. HbA1c remained stable over the course of treatment, with fewer participants reporting high HbA1c at their last assessment compared with baseline. Data are continuing to be recorded in these ongoing studies, and updated analyses will be available at the time of the meeting.

Discussion: The findings from pooled, long-term, open label studies of KarXT provide evidence that the promise of the short-term studies appears to hold up and treatment with KarXT is not associated with long-term metabolic disturbances in participants with schizophrenia. KarXT exhibits a long-term favorable metabolic profile, as participants experienced improvements or stability in all metabolic parameters over 52-weeks of treatment, including weight, cholesterol, and HbA1c.

Lunch and Poster Session I

T1. ASSOCIATIONS OF ANXIOUS, AVOIDANT, AND DISORGANIZED ATTACHMENT WITH MULTIDIMENSIONAL SCHIZOTYPY: FINDINGS FROM A MEXICAN SAMPLE

Tamara Sheinbaum*¹, Tecelli Domínguez¹, Ana Fresán¹, Lourdes Nieto¹, Rebeca Robles¹, Neus Barrantes-Vidal²

¹*Instituto Nacional de Psiquiatría “Ramón de la Fuente Muñiz”,* ²*Universitat Autònoma de Barcelona*

Background: A growing research literature has supported the relevance of attachment theory for understanding the risk for schizophrenia-spectrum psychopathology. In this context, the study of schizotypy is valuable since it encompasses a broad continuum of clinical and subclinical manifestations and shares a common multidimensional structure with schizophrenia. Although several studies have investigated links between attachment styles and schizotypy dimensions, few studies have included the assessment of disorganized attachment and disorganized schizotypy. Furthermore, the literature would be enhanced by a greater diversity of study populations since most work has been conducted with samples from high-income countries. Guided by these considerations, the present study examined the unique associations of anxious, avoidant, and disorganized attachment with multidimensional schizotypy in a Mexican sample.

Methods: Participants were 1,550 individuals (79.2% female; age range=15-45 years; mean age=29.5 years) from the Mexican general population who voluntarily agreed to participate in an online survey administered via Qualtrics software. Measures included the Revised Psychosis Attachment Measure, which measures anxious, avoidant, and disorganized attachment, and the Multidimensional Schizotypy Scale—Brief, which measures positive, negative, and disorganized schizotypy.

Results: Linear regressions were computed for each schizotypy dimension, with anxious, avoidant, and disorganized attachment subscales entered simultaneously as predictors to examine their unique contribution. These analyses indicated that anxious attachment was positively associated with positive and disorganized schizotypy and inversely associated with negative schizotypy; avoidant attachment was positively associated with negative and disorganized schizotypy; and disorganized attachment was positively associated with the three schizotypy dimensions.

Discussion: The results revealed differential links between attachment and schizotypy that are consistent with theory and prior evidence from the attachment and psychosis fields. Furthermore, although the study's cross-sectional nature limits inferences concerning developmental course, the findings align with theoretical models highlighting disorganized attachment as a prominent vulnerability factor for the development of schizophrenia-spectrum phenomenology. Overall, the results support the utility of the multidimensional model of schizotypy and the notion that attachment may provide a promising psychological mechanism for understanding the development and expression of the schizotypy dimensions across different cultural contexts.

T2. GREY MATTER MICROSTRUCTURE AT THE EARLY STAGES OF PSYCHOSIS

Mauricio Serpa*¹, Luciano Sanchez², Leonardo Queiroz³, Tania Maria Alves³, Leonardo de Jesus³, Natalia Haddad³, Julio de Andrade³, Andrea Jafet³, Arlete Modelli³, Naomi Antunes², Fabio Duran², Mario Louza⁴, Martinus van der Bilt³, Alexandre Loch³, Wagner Gattaz³, Geraldo Busatto²

¹*Institute of Psychiatry, University of Sao Paulo*, ²*Laboratory of Psychiatric Neuroimaging (LIM21), Department and Institute of Psychiatry, Faculdade de Medicina FMUSP, Universidade de Sao Paulo*, ³*Laboratory of Neuroscience (LIM27), Department and Institute of Psychiatry, Faculdade de Medicina FMUSP, Universidade de Sao Paulo*, ⁴*Schizophrenia Research Program (Projesq), Department and Institute of Psychiatry, Faculdade de Medicina FMUSP, Universidade de Sao Paulo*

Background: Abnormalities of grey matter (GM) morphology have been consistently reported across all phases of psychotic disorders and seem to intensify with their progression. However, less is known about GM tissue architecture in such medical conditions. We sought to study differences in GM microstructure in a cohort of clinical high-risk for psychosis (CHR) subjects and first-episode psychosis (FEP) patients using a new modelling tool applied to diffusion-weighted images (DWI) known as Neurite Orientation Dispersion and Density Imaging (NODDI).

Methods: In this preliminary analysis, we studied a total of 55 subjects, comprising 40 CHR subjects and 15 patients with first-episode psychosis (FEP). DWI data was acquired using a 3T MRI scanner and a multi-shell sequence. Following the preprocessing steps, which included distortions correction and semi-automated quality control of DWI, we extracted the average NODDI indexes from the whole GM compartment for each subject. Using GLM with FDR correction for multiple comparisons, we then run between-group comparisons of such metrics: Neurite Density Index (NDI), Orientation Dispersion Index (ODI) and Isotropic Volume Fraction (IVF). We also assessed the influence of symptom severity, global functioning, IQ, and potential confounding covariates (biological sex, age, and handedness) on GM microstructure.

Results: The groups differed in the Global Assessment of Functioning (GAF) scores (mean: CHR 64.6; FEP 46.2; $p < 0.001$). Between-group comparisons of NODDI metrics showed a reduction of ODI in the FEP relative to the CHR group. Results did not change when including the covariates in the analyses. ODI was directly associated with GAF scores in the whole-sample analysis ($R^2=0.112$, $pFDR < 0.05$), and such correlation was stronger when assessing the FEP group alone ($R^2=0.532$, $pFDR < 0.05$). Total PANSS scores were inversely correlated to ODI ($R^2=0.219$, $pFDR < 0.05$) in the FEP group.

Discussion: Our findings suggest that the GM microstructure might differ between the at-risk state and the first episode of psychosis. The extent to which this finding can be applied as a marker of transition in subject-level classification algorithms should be further investigated.

T3. BURDEN OF PHYSICAL ILLNESS IN SCHIZOPHRENIA: EXPLORING THE IMPACT OF SOCIODEMOGRAPHIC FACTORS ON RISK OF MULTIMORBIDITY

Brittany Gouse*¹, Tithi Baul², Sarah Syed³, Elijah Boliver⁴, Jennifer Lancet⁵, Hannah Brown²

¹*Boston University School of Medicine*, ²*Boston University School of Medicine*, ³*Tufts University*, ⁴*Boston University*, ⁵*Boston Medical Center*

Background: While the mortality rate due to suicide has decreased over the past 30 years among individuals with schizophrenia, mortality due to cardiovascular disease and cancer has moderately increased in this population during this time period. Factors such as antipsychotic-related cardiometabolic disease, higher rates of nicotine use, and reduced preventative healthcare use due to internalization of healthcare-associated stigma contribute to the high burden of chronic physical illness in schizophrenia spectrum disorders (SSD). Individuals with multiple serious chronic physical health conditions face a high risk of mortality. To close the premature mortality gap in schizophrenia, the identification of the populations at greatest risk of severe physical comorbidity is needed to inform the design of targeted interventions.

Methods: We retrospectively analyzed a cohort of patients with a SSD (defined as International Classification of Disease Code 10th edition codes of F20, F25, F28, F29) who had an outpatient, inpatient, or emergency department visit at an urban safety-net hospital in the Northeast United States between 2016-2022. The primary outcome of multi-morbidity was defined as a Charlson Comorbidity Index score of 2 or greater. Chi-squared analyses were used to assess differences in rates of multimorbidity between demographic groups. A series of bivariate correlation analyses was used to assess for multicollinearity between demographic factors. We used multivariable logistic analyses to further explore the associations between demographic factors and multimorbidity.

Results: A total of 7,960 patients (median age of 48, 37.9% female, 50% non-Hispanic/Latino Black, 16.9% Hispanic/Latino) met the inclusion criteria. In bivariate analyses, a higher proportion of female (24.3% vs. 19.5% male, $p < .001$), unhoused (22.4% vs. 19.4% housed, $p < .001$), and had multimorbidity. A higher proportion of non-Hispanic/Latino Black and Hispanic/Latino patients had multimorbidity compared to non-Hispanic/Latino white patients (23.1% vs. 22.3% vs. 20.3%, respectively, $p < .001$). There was no association between neighborhood deprivation and multimorbidity. In fully adjusted multivariable logistic regression models, only the association between non-Hispanic/Latino Black (OR 1.65 95% CI 1.32-2.07) and Hispanic/Latino race/ethnicity (OR 1.75 95% CI 1.30-2.35) with multimorbidity remained.

Discussion: Non-Hispanic/Latino Black and Hispanic/Latino individuals living with an SSD were at higher risk of multimorbidity compared to other racial/ethnic groups. Further work is urgently needed to explore the precipitating and perpetuating factors driving this health disparity. Interventions focused on promoting the physical health of individuals with a SSD are needed to advance health equity.

T4. UNDERSTANDING THE MEDIATING INFLUENCE OF CONTROL BETWEEN THOUGHT SUPPRESSION AND SYMPTOM SEVERITY

Phillip Angelos*¹, Boris Epie¹, Catalina Mourgues-Codern¹, Albert Powers¹

¹*Yale University*

Background: Auditory verbal hallucinations (AVH), the experience of hearing voices that others cannot, are most often associated with psychosis but experienced by individuals across the general population. While many individuals seek help due to the distress they experience from their voice-hearing experiences and its consequences, some do not. Past work has demonstrated that one important predictor of help-seeking is the ability to exert voluntary

control over these voices. We sought to examine the relationship between thought suppression, degree of voluntary control over AVH, and symptom severity. We hypothesized that an individual's propensity to engage in thought suppression would be positively associated with the severity of their symptoms and that this relationship may be mediated by the individual's ability to exert control over their voices, which would attenuate the severity of their symptoms, further suggesting that individuals with higher degrees of control may experience less severe symptoms.

Methods: Data were extracted from the Control Over Perceptual Experiences (COPE) study. Our final sub-sample consisted of 650 (79% F) participants who reported hearing voices at least monthly in the past six months (17% Psychic Mediums, 21% diagnosed voice hearer's). Using the following measures: White Bear Suppression Inventory (WBSI), Launay Slade Hallucination Scale (LSHS), Auditory Hallucinations Rating Scale (AHRS) and the Yale Control over Perceptual Experiences Scale (COPE) score, bivariate correlations were conducted and two mediation models were performed in which WBSI was the independent variable, COPE was the mediator, and for Model 1 the dependent variable was LSHS and for Model 2 AHRS. The effects were assessed by the confidence intervals of 5000 bootstrapped samples, in which an interval crossing zero is considered not significant.

Results: Correlations indicated a significant relationship between these variables. All correlation coefficients were significant at $p < .001$. Positive correlations were found between the WBSI and LSHS $r(n) = .455$ and WBSI and AHRS was $r(n) = .395$. COPE scores were negatively correlated with $r(n) = -.437$ (WBSI), $r(n) = -.185$ (LSHS), and $r(n) = -.389$ (AHRS). In the first model, we found that WBSI had a direct effect on LSHS of $\beta = .4572$, [CI95: .9034, 1.2846] and had an indirect effect on LSHS through COPE of $\beta = -.0059$, [CI95: -.3790, .5150]. Greater model variance was explained by the inclusion of individuals' COPE scores ($R^2 = .1888$, $R^2 = .2038$). In the second model, we found that WBSI had a direct effect on AHRS of $\beta = .2730$, [CI95: .4607, .7859] and had an indirect effect on AHRS through COPE of $\beta = -.2651$, [CI95: -1.7612, -.9719]. Again, greater variance was explained by the introduction of COPE ($R^2 = .1909$, $R^2 = .2081$).

Discussion: Thought suppression independently predicts the propensity to hallucinate and AVH severity. Voluntary control over voice hearing mediated the effect of thought suppression on AVH severity in AHRS, but not in LSHS. We propose that the primary explanation for these results is the high percentage of the high-control group being mediums who desire voice hearing experiences, leading to greater propensity to hallucinate but with less resultant distress. Future research could benefit from further exploring bidirectional relationship between these variables. To increase understanding of what role an individual's degree of control plays in mediating the relationship between symptom severity and suppression, we plan to explore other exploratory pathways such as thought suppression as the mediator between control and distress.

T5. SUBJECTIVE AND OBJECTIVE STRESS DIFFERENTIALLY MEDIATE EFFECTS OF CHILDHOOD MALTREATMENT ON SUBCLINICAL PSYCHOSIS SPECTRUM FEATURES

Jacqueline Nonweiler^{*1}, Tamara Sheinbaum², Thomas R. Kwapil³, Neus Barrantes-Vidal⁴

¹Universitat Autònoma de Barcelona, ²Universitat Autònoma de Barcelona, ³University of Illinois at Urbana-Champaign, ⁴Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona,

Background: Stress is an important psychosocial risk factor which can be perceived differently depending on subjective and objective perception of the experience. Objective stress is characterized through the experiencing of external events (stressors) which require adaptation due to the increase in demands on an individual. Subjective stress, alternatively, takes an individual's perception of stress into account. These two differential understandings of stress may have contrasting effects on a range of mental health outcomes; nonetheless, understanding of subjective and objective stress' roles in psychosis spectrum features remains limited. This study aimed to analyze whether i) objective and subjective stress are associated with subclinical psychosis, ii) the impact of childhood adversity on subclinical psychosis is mediated by objective and subjective stress, and iii) whether this impact is moderated by attachment style.

Methods: This study is part of the Barcelona Longitudinal Investigation of Schizotypy (BLISS). The sample consisted of $n = 168$ university students who completed a childhood maltreatment measure at baseline and were re-assessed 7.8 years later for life events, attachment, and subclinical outcome (positive and negative schizotypy, suspiciousness, ideas of reference) measures.

Results: Results show that subjective stress is associated with all subclinical psychotic phenomena, while objective stress was only associated with positive schizotypy and ideas of reference. Subjective stress mediated the association of childhood maltreatment with all subclinical psychotic phenomena, while objective stress mediated the association with positive schizotypy and ideas of reference. Effect sizes of mediation coefficients for subjective stress were between two and three-times larger than those for objective stress effects. Moderated mediation by attachment style was not supported; however, several conditional indirect effects of childhood maltreatment on subclinical psychotic phenomena via subjective stress were significant at different levels of the five attachment styles.

Discussion: The current findings bolster understanding of psychosocial models of psychosis and provide support to the notion that childhood maltreatment may be related to psychosis through both objective and subjective stress appraisals.

T6. PSYCHOSIS CONTINUUM IN A SAMPLE OF BRAZIL NORTHEAST

Amannda Lima^{*1}, Dayse Cunha¹, Selma Jeronimo¹, Walter Soares²

¹Federal University of Rio Grande do Norte, ²Federal Hospital Onofre Lopes - UFRN

Background: Unlike most diseases, psychosis exists as a continuum of severity rather than an all-or-nothing phenomenon. The mere expression of symptoms is not sufficient for a diagnosis of a psychotic disorder. There is a relationship between psychotic symptoms and variables as age, level of education, and psychiatric diagnosis. Many individuals experience hallucinations in their lives, but do not seek medical evaluation because they do not consider a cause of functional impairment.

Methods: Individuals evaluated were part of a study aiming to identify mental disorders at a community level at the time of the COVID19 pandemic, in the Northeast Brazil. This sample was selected randomly, with 111 subjects from a poor region of the capital (recruited in 2021) and 383 from a rural city in the same state (recruited in 2023). The sample was assessed using general questionnaire and the Mini International Neuropsychiatric Interview (MINI), which contains questions about psychotic symptoms. Individuals were considered to have screened positive for psychotic symptoms when they answered could be (0.5 points) in at least one of the 3 questions: 1) Have you ever heard voices or sounds that no one else could hear? 2) Have you ever seen things other people couldn't see? 3) Have you ever

thought that people might be following or spying on you? Possible answers are: yes, definitely (1 point); can be (0.5 point); and No, never (0 points). Using a chi-square test, we compared city samples for the occurrence of psychotic symptoms.

Results: The prevalence in the entire sample of at least one psychotic symptom was 27.3%. 24.7% reported seeing things that no one else could see; 7.6% said they heard sounds and voices that no one else could hear, and 6.5% said they might be being stalked or spied on. The subsample of individuals from urban areas had a higher percentage of general and specific psychotic symptoms than those from rural areas, but the difference was only significant when screening for visual hallucinations (17% x 7.6%) and delusional ideas (18.2% x 5.2%) (p LESS THAN 001).

Discussion: To our knowledge, this study is the first to evaluate the presence of psychotic symptoms in a community sample from northeast Brazil, exploring the psychotic continuum idea at the time of COVID19 pandemic. The presence of psychotic symptoms in our sample was similar to that presented in the general population 9-11, considering that paranoid thinking and hallucinatory experiences are common in the general population (20-30%)¹², but without sufficient clinical relevance to conclude the diagnosis according to the DSM-5 criteria. Despite the socio-economic vulnerability faced by this population, as social inequality, low income, and violence, the prevalence of psychotic symptoms reported remained similar to those found in the literature.

T7. VIA FAMILY 2.0 – A RANDOMIZED CLINICAL TRIAL EVALUATING A MULTIDISCIPLINARY TEAM INTERVENTION FOR FAMILIES WITH PARENTAL MENTAL ILLNESS

Anne Amalie Elgaard Thorup^{*1}, Anne Ranning², Jan Sandberg³, Sidsel Ingversen⁴, Signe Heuckendorff⁵, Marlene Lauritsen⁶, Lene Falgaard Eplov⁷, Merete Nordentoft²

¹*Child and Adolescent Mental Health Center, Capital Region of Denmark*, ²*Mental Health Centre Copenhagen*, ³*Center for Relatives*, ⁴*Child and Adolescent Mental Health Center, Capital Region of Denmark*, ⁵*Mental Health Services, North Region Denmark*, ⁶*Child and Adolescent Mental Health Center, North Region of Denmark*, ⁷*Copenhagen Research Center for Mental Health - CORE*

Background: Children born to parents with mental illness have consistently been shown to have increased risks for a range of negative life outcomes including increased frequencies of mental disorders, somatic disorders, poorer cognitive functioning, social, emotional and behavioral problems and lower quality of life. Further they are often overlooked by both society and mental health services, although they represent a potential for prevention and early intervention.

A collaboration between researchers and clinicians from two regions, the Capital Region and the North Region Denmark has been established as the Research Center for Family Based Interventions. The research center will be an umbrella for a series of activities, all focusing on children in families with parental mental illness.

Methods: Method: We will conduct a large randomized, controlled trial for families with parental mental illness in order to evaluate the effect of a two-year multidisciplinary, holistic team intervention (VIA Family 2.0) against treatment as usual. Inclusion criteria will be biological children 0-17 of parents with any mental disorder treated in the secondary sector within the previous three years. A total of 870 children or approx. 600 families will be included from two sites. Primary outcomes will be Strength and Difficulties Questionnaire¹,

Family Assessment Devise², Parental Stress Scale³ and quality of the home environment, measured by interview and observation from the HOME Inventory⁴.

Results: The RCT will start including families from Jan 1, 2024, to Dec 31, 2025, and data collection will last for four years since all families will be assessed at baseline and again at end of treatment, i.e. after 24 months. Baseline data will inform the intervention team about each family's needs, problems, and motivation. A pilot study indicated good acceptability but no significant findings due to small sample size.

Discussion: Recruitment of families can be challenging but we have decades of experience. Since both the target group, their potential problems and the intervention is complex, primary outcome is hard to determine.

T8. FUNCTIONAL CONNECTIVITY AND GRAPH-THEORY MEASURES CHARACTERISE THE IMPACT OF SCHIZOTYPY AND PSYCHOTIC-LIKE EXPERIENCES ON DIFFERENTIAL MODULATION OF RESTING-STATE NETWORK IN NON-CLINICAL SUBJECTS

Igor Nenadic^{*1}, Clara Lundberg², Jonas Hoffmann², Tina Meller²

¹*Philipps-Universität Marburg / UKGM*, ²*Philipps-Universität Marburg*

Background: Conceptualising psychotic disorders as a spectrum that includes schizophrenia (and other disorders with psychotic features) as well as non-clinical or subclinical manifestations of risk traits or symptoms has impacted on our neurobiological understanding. The notion of a continuum ranging from healthy / non-clinical subjects with different degrees of psychosis proneness or minute symptoms to those with at-risk stage and manifest psychosis is paralleled by recent studies implying gradual changes of brain function and structure, e.g. in the hippocampus or medial temporal lobe. While schizotypy and psychotic-like experiences are well-established paradigms, there is still limited data on how variation of these phenotypes across individuals is related to underlying neurobiology, esp. the functional connectome of the brain. In this study, we analysed a community samples, phenotyped for trait-level and state-level risk factors for psychosis to identify associations with functional connectivity in main resting-state networks (RSN).

Methods: We analysed n=330 healthy subjects (age 18-40; 214 female, 116 male) from the local community. Phenotype characterisation included the schizotypal personality questionnaire – brief version (SPQ-B) and the prodromal questionnaire (PQ-16), capturing psychotic-like experiences. The SPQ-B provides three main factors (cognitive perceptual, interpersonal, disorganised), capturing trait-level loading for positive, negative, and disorganised schizotypy, resp., while the PQ-16 provides both frequency as well as distress ratings for psychotic-like experiences (PLE), which are typically used in early detection screening / research. Using 3T MRI, we obtained resting-state time series, which were pre-processed and analysed using the CONN toolbox. We applied independent component analysis (ICA) within CONN to extract, by means of data-driven separation, multiple RSNs. For subsequent analysis, we focussed on the default mode network (DMN), salience network (SN), fronto-parietal network (FPN), and executive control network (ECN). ICA results for RSNs were segmented into regions (as implemented in CONN toolbox), which were then used for analysis of intra-network connectivity, as well as inter-network connectivity. Correlations using general linear models were corrected for age and gender. We used FDR cluster-level correction implemented in CONN for correction of multiple comparisons. In a second analysis, we applied graph theory measures to characterise network properties.

Results: Our analysis demonstrated a significant correlation of schizotypy (SPQ-B) facets as well as PQ-16 distress levels with intra-network connectivity: positive schizotypy with intra-ECN connectivity (p-FDR=0.045), negative schizotypy with intra-DMN connectivity (p-FDR=0.004), disorganised schizotypy with intra-FPN (p-FDR=0.043); most of these intra-network correlations were positive (except for negative schizotypy). PQ-16 distress correlated with intra-DMN connectivity (p-FDR=0.04). Graph-theory analyses showed that for positive schizotypy a small cluster in the insular cortex within the SN showed significant correlation (p-FDR=0.041) with the clustering coefficient, while a left temporoparietal cluster in the FPN showed significant (p-FDR=0.044) correlation of with global efficiency. Contrastingly, for disorganised schizotypy, a mid-cingulate cluster was correlated with global efficiency (p-FDR=0.00076), and a cerebellar cluster with local efficiency (p-FDR=0.001).

Discussion: Our results demonstrate differential impact of schizotypy, a trait-level marker for psychosis proneness, vs. psychotic-like experiences (state-level, captured as prodromal symptoms). These findings suggest, that at least in the sub-clinical spectrum of schizophrenia risk markers, different facets (positive, negative, disorganised) are associated with different regional RSN connectivity – both for functional connectivity as well as network-level graph-theory measures. This provides a framework for understanding the risk antecedents manifesting as functional dysconnectivity in schizophrenia. Although our sample is larger than previous studies, we relied on an unfiltered community sample without enrichment for subjects with higher scores of schizotypy. Future analyses might also consider the interaction of schizotypy facets, as non-linear effects might result in disproportionately higher (or lower) effects when high loading on particular schizotypy facets occurs. Additional analyses will include moderation through polygenic risk (and resilience) to schizophrenia. Our findings underline that even in the absence of clinical psychotic symptoms, sub-clinical variation in the psychosis spectrum might manifest in changes of particular brain network functional connectivity parameters.

T9. USE OF ALL CAUSE MORTALITY AS AN OUTCOME TO CHARACTERIZE TREATMENT PATTERNS FOR SCHIZOPHRENIA

Sayera Dhaubhadel¹, Silviu-Alin Bacanu², Khushbu Agarwal³, Colby Ham³, Sutany Choudhury³, Ayman Fanous⁴, Benjamin McMahon*¹

¹Los Alamos National Laboratory, ²Virginia Commonwealth University, ³Pacific Northwest National Laboratory, ⁴VA Phoenix Medical Center

Background: We have used US Veterans Administration (VA) longitudinal electronic medical records (EMR) to predict 15-year all cause mortality from demographic information, the 1000 most prevalent ICD9 codes (Dx), generic medication names (Rx), and CPT procedure codes (CPT). We find roughly half of the population attributable mortality is due to cardiovascular disease and half to behavioral health related codes. Since only one of the top ten causes of death in the United States (suicide), is behavioral-health related, these risk factors should be thought of as contributors to other causes of death. Furthermore, we observe a cluster of fifty related Dx, Rx, and CPT codes, including schizophrenia (295.x), that are intertwined in their co-occurrence across typical 20-year long patient trajectories.

Methods: We performed retrospective analysis of 20 years of VA EMR data including outpatient diagnosis, pharmacy, and procedure codes on a population of two million veterans for whom up to five years of data were available prior to 2005 and an outcome of death or follow-up care was noted in the medical records. Several predictive modeling methods were applied to these data, including logistic regression on interval outcome, time-to-event (Cox)

modeling, random forest, and a simple neural network. Relationships among coded conditions and treatments were characterized with k-means and PCA on the matrix describing co-occurrence of medical codes. An ensemble of models predicting all cause mortality was constructed from the four techniques and fine tuned with the fifty codes clustering with schizophrenia to predict a variety of outcomes, including adverse outcomes, usage of psychotropic medications, and metabolic changes, from which balancing of cohorts for comparative analysis can occur.

Results: In this work, we use the artificial intelligence (AI) strategy of ensemble transfer learning to fine tune an all cause mortality prediction model to isolate the contributions attributable to schizophrenia and psychotropic medication usage. We are able to attribute risk of 15-year mortality to individual conditions without detailed feature engineering.

Discussion: Schizophrenia and other indicators of behavioral health conditions contribute forty percent of 15-year all cause mortality risk when computed from thousands of prevalent outpatient Dx, Rx, and CPT codes. These codes are, however, co-occur with complex temporal dependencies, complicating attempts to attribute outcomes and metabolic side effects to specific conditions. Since quantification of severity of behavioral health conditions is difficult, we present a process to attribute the substantial all cause mortality risk to individual conditions and treatments.

T10. OPEN BOARD

T11. ASSESSING SOCIAL BEHAVIOR AND SOCIAL COGNITION IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: IS A STANDARDIZED PERFORMANCE TASK SENSITIVE ENOUGH?

Erica Karp^{*1}, Jill Laquidara¹, Taylor Johnson², Madeline Ward¹, Lindsay Banks¹, Sarah Hope Lincoln¹

¹Case Western Reserve University, ²Sam Houston State University

Background: Social cognition and social behavior are both important for an individual's social functioning, well-being, and quality of life. However, both are impaired in individuals with schizophrenia. Additionally, evidence suggests that these deficits are also present in individuals at clinical high risk for psychosis (CHR-P). Yet there is limited understanding of how these abilities connect and how best to assess social behaviors in CHR-P individuals. High-Risk Social Challenge (HiSoc) is one task that was developed specifically to look at social behaviors in individuals at genetic high risk for psychosis. While it has been validated for use with CHR-P individuals, limited studies have explored whether it is targeting deficits specific to the high-risk groups or more general difficulties with social behaviors.

Methods: The current study clarifies whether the HiSoc task is sensitive enough to identify relationships between social behavior and social cognition across CHR-P and controls (HC). CHR-P individuals (N=23) and HC (N=28) were combined and their performance on social and emotional processing tasks and questionnaires was assessed. HiSoc task, a 45 second mock-audition for a reality show, and Multicultural Emotion Identification Task (RMET), an adaptation of the Reading the Mind in the Eyes Test, Social Comparison Scale (SCS), Davos Assessment of Cognitive Bias Scale (DACOBS) social cognition subscale, and Interpersonal Reactivity Index (IRI) were completed. Structured Interview for Prodromal Symptoms (SIPS) positive symptoms, Structured Clinical Interview for DSM-5 (SCID), and Weschler Abbreviated Scale of Intelligence II (WASI) were also administered. Finally, Global Functioning Scale: Social (GF-S) assessed current social functioning. The summary score for the HiSoc was adjusted to include three domains: social-interpersonal, affect, and odd

language and behavior. Correlation analyses were conducted to assess relationships between social behavior and social cognition. We hypothesized that social behavior would be significantly positively correlated with self-reported social cognition and social cognitive abilities. Partial-correlation tests were also used to control for IQ, verbal IQ, and SIPS positive symptoms total. Finally, a Bonferroni correction was used to adjust for multiple comparisons.

Results: Group differences were assessed prior to combining and contrary to our hypothesis, no statistically significant differences were found between CHR-P and HC for measures of social cognition or behavior (p GREATER THAN .10). Across the sample, participants performance on HiSoc task had no significant relationship with the SCS, IRI, or DACOBS social cognition subscale (p GREATER THAN .20). HiSoc summary score was significantly correlated with RMET total score ($r = .57$, p LESS THAN .01) with higher performance across domains on the social task associated with higher overall performance on the emotion recognition task. This finding held even when controlling for IQ ($r = .53$, p LESS THAN .01), verbal IQ ($r = .57$, p LESS THAN .01), and positive symptoms ($r = .55$, p LESS THAN .01). A similar pattern was shown across the three HiSoc domains with higher social-interpersonal skills ($r = .50$, p LESS THAN .01), better affect ($r = .49$, p LESS THAN .01), and more normative behavior and language ($r = .55$, p LESS THAN .01) significantly correlated with higher RMET total scores.

Discussion: Few studies have assessed the utility of a standardized, social behavior task designed specifically for individuals at risk for psychosis; thus, the current study begins to fill the gaps. While the domains targeted by HiSoc are established areas of social impairment in CHR individuals, results indicate that the task identifies social performance abilities across groups of people regardless of clinical profile. There was not a clear difference between CHR-P and HC on overall social performance ability. This finding may be due to the relatively low sample size in each group or the use of the task virtually, due to COVID-19, rather than in-person as previously implemented, which warrants consideration for future studies that include HiSoc. Combining the two groups, could have resulted in clusters significantly around two distinct poles, with the CHR-P clustering around lower scores and healthy controls around higher, yet this was not the case. There was no significant relationship between HiSoc and any of the self-report social cognitive measures. Although there were significant correlations between the RMET and HiSoc, enough participants from both groups scored high and low that it points more so to the relationship between social cognition and social behavior regardless of clinical profile. Previous work suggests that social cognitive abilities underscore social behavior, our work supports this theory. Of note, positive symptoms had no impact on the relationship between HiSoc performance, both overall and on subdomains, and RMET performance. Potentially negative symptoms would be more likely to drive variability in social cognitive and social behavior abilities than positive symptoms, future work should examine this hypothesis. The current study points to the potential to use HiSoc as a measure of social behavior, while demonstrating a need for further research with larger sample sizes and more complete symptoms profiles.

T12. CONNECTING THE DOTS: ABERRANT SALIENCE, DEPRESSIVE SYMPTOMS AND THE COMPLEX DYNAMICS OF PSYCHOSIS PRODROME

Federico Fiori Nastro^{*1}, Martina Pelle¹, Alice Clemente¹, Giuseppe Albanesi¹, Diego Cichetti¹, Giulia Ambrosi¹, Stefano Garofalo¹, Chiara Maimone¹, Emanuele Rizzo¹, Francesco Scrima¹, Alberto Siracusano¹, Cinzia Niolu¹, Giorgio Di Lorenzo¹

Background: The inclination to ascribe greater significance to irrelevant stimuli is referred to as 'aberrant salience' (AS). Based on empirical evidence, AS tends to occur as early as the prodromal stages of schizophrenia, and nowadays it has been increasingly recognized as a pertinent psychopathological characteristic in the early detection of At-risk mental states. Despite the primary role of positive symptoms in the definition of Clinical High-risk (CHR) states, depressive and anxiety symptoms are common in the early prodromal phase and they have been described as the primary reason for help-seeking in CHR individuals. Recent literature suggests that depressive symptoms (DS) may predict poorer global functioning and increase the risk of transitioning to psychosis. This study aims to explore the presence of AS in a cohort of young university students utilizing our counseling psychological service, examining its correlation with both DS and psychotic-like experiences.

Methods: A cross-sectional analytical study was conducted. 366 young adult help-seekers (70.2% female, median age= 23) were administered a self-report questionnaires battery, including the Aberrant Salience Inventory (ASI), the Beck Depression Inventory-II (BDI-II) and the Prodromal Questionnaire-16 (PQ-16). The relationships between the measured variables have been analyzed using a correlation matrix. Then, a multivariable regression linear model, adjusted for age and gender, was performed to establish the effect of AS and DS on psychotic-like experiences (PLE).

Results: The median self-report scores were BDI-II= 15 (IQR=12), PQ-16= 4 (IQR=5), ASI=13 (IQR=10). About 130 subjects (37.7%) screened positive for a prodromal condition, as shown by a PQ-16 T/F score ≥ 6 . Correlational analysis revealed a significant relationship between ASI total scores and ASI subscales with both PQ-16 total scores and BDI-II ($p < .001$). Multiple linear regression analysis showed that higher BDI and ASI scores act as significant predictors of higher rates of PLEs. In particular, three ASI subscales ("sharpening of senses", "heightened emotionality" and "heightened cognition") showed significant predictive value. Age and gender were not statistically significant. This model explained about 52.4% of the variance of the explored outcome.

Discussion: In accordance with our previous findings, this study confirms that the interconnection between AS and DS may provide useful insights into the psychosis continuum. In our study, higher rates of DS predicted more severe PLEs. This finding substantially confirms the significance of affective symptoms in young CHR patients. Recent literature highlights that depressive symptomatology may play a crucial role in psychosis, determining an increased state of vulnerability and potentially leading to poorer clinical outcomes. The statistically significant predictive efficacy of the ASI domains of "heightened emotionality" and "heightened cognition" may be construed as suggestive evidence that these dimensions bear a more proximate psychopathological association with the emergence of psychotic experiences. As the original 'at-risk mental state' approach evolves to encompass a broader array of pluripotent transdiagnostic outcomes, additional longitudinal investigations are necessary to deepen our comprehension of the association between AS and DS and to evaluate different psychopathological trajectories that the subjects will follow.

T13. THE STRUCTURE OF SELF- AND OTHER-SCHEMAS IN INDIVIDUALS WITH PSYCHOSIS

Robert Aidelbaum^{*1}, Lynn Rutledge¹, Sylvia Romanowska¹, Talia Leibovitz¹, Shreya Jagtap², Jessica D'Arcey³, Michael Best¹

¹University of Toronto Scarborough, ²Centre for Addiction and Mental Health, University of Toronto, ³University of Toronto Scarborough, Centre for Addiction and Mental Health

Background: Schemas have been linked to psychotic symptoms, with elevated negative schema charge predictive of profile. Research to date exploring the potential role of schemas as maintenance factors for psychotic symptoms has predominately focused on the self-reported charge of the endorsed schema. No research to date has analyzed the structure of such schemas and whether this characteristic predicts schema charge and symptoms. This study sought to explore the utility of the measurement of schema structure in a sample of individuals managing psychosis. This study is the first to measure schema structure in a psychotic population and to apply this methodology to measuring the structure of other-schemas in addition to self-schemas. The potential predictive capacity of schema structure for psychotic symptom severity was investigated to clarify the possible role schemas may play in the maintenance of psychosis.

Methods: The computerized Psychological Distance Scale Task (PDST) was used to measure schema structure. Eighty adjectives were rated by participants. Self/other descriptiveness was rated along an x-axis using a scale from not at all like me/others to very much like me/others. Valence was rated along a y-axis, ranging from positive to negative. The PDST produced eight scores reflecting the average interstimulus distance (ISD) between the adjectives for each of four conditions (interpersonal positive, interpersonal negative, achievement positive, and achievement negative). Schema charge was assessed via the Brief Core Schema Scale (BCSS) and psychotic symptoms via the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). Associations between the PDST subscales and the BCSS were examined. Multiple regression analyses were conducted predicting PANSS pentagonal factors as a function of the PDST subscales.

Results: Correlations amongst the PDST subscales demonstrated a valence-dependent effect. Consolidated positive/negative schemas predicted more consolidated similarly-valenced schemas. Self-referent negative achievement ISD significantly correlated with the BCSS negative self-schema ($r_s = -.50$), self-referent positive achievement ISD significantly correlated with the BCSS positive self-schema ($r_s = -.44$), and self-referent positive interpersonal ISD significantly correlated with the BCSS positive self-schema ($r_s = -.49$). Significant interaction effects between self-referent positive and negative achievement ISDs in the prediction of positive ($F(3, 56) = 2.26, p = .01, R^2 = .108, t = 2.36, p = .022$) and emotional symptoms ($F(3, 56) = 2.26, p = .002, R^2 = .230, t = 2.84, p = .006$) were observed. Similarly, self-referent positive and negative-interpersonal schema ISDs significantly interacted in the prediction of negative symptoms ($F(3, 58) = 3.52, p = .021, R^2 = .110, t = 2.44, p = .018$).

Discussion: These novel findings highlight the potential utility of schema structure as a means of assessing schemas and their covariance within the psychosis population. Evidence suggests PDST-derived structural indices of self-referent schemas measure a similar construct to that being measured by the BCSS Self-Schema subscales. Furthermore, results highlight the importance of the interaction between the structure of positive and negative schemas in the prediction of positive, negative, and emotional symptoms. In contrast, more work is needed to validate the measurement of other-referent schema structures, as these subscales returned non-significant correlations. These results highlight a novel method of assessing the role of schemas in the manifestation of psychosis and provide evidence highlighting negative and positive schemas as distinct constructs whose interactions relate to symptom profiles.

T14. STUDY OF THE PSYCHOMETRIC PROPERTIES OF THE SPANISH MULTIDIMENSIONAL SCHIZOTYPY SCALE-BRIEF (MSS-B) IN TWO NONCLINICAL SAMPLES

Karen Fagián Núñez^{*1}, Jacqueline Nonweiler², Pilar Torrecilla³, Valeria Lavín⁴, Thomas R. Kwapil⁵, Neus Barrantes-Vidal⁶

¹*Autonomous University of Barcelona*, ²*Universitat Autònoma de Barcelona*, ³*Departament de Psicologia Clínica i de la Salut, Universitat Autònoma de Barcelona*, ⁴*Department of Health and Clinical Psychology, Autonomous University of Barcelona*, ⁵*University of North Carolina at Greensboro*, ⁶*Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona*

Background: Schizotypy is a multidimensional construct that represents the phenotypic expression of vulnerability to psychotic disorders. Strong evidence supports the existence of positive, negative and disorganized dimensions of schizotypy. While various measures to evaluate schizotypy exist, the Multidimensional Schizotypy Scale-Brief (MSS-B) stands apart for its brevity, content coverage and psychometric properties. In this study, we aimed to evaluate the underlying factor structure of this self-report measure in European Spanish, and to obtain evidence of its validity in a nonclinical population.

Methods: This cross-sectional study is formed of two large independent samples. Confirmatory factor analysis using maximum likelihood estimates was performed to examine the factor structure in Sample 1 ($n = 1,049$; Mean age = 23.40, SD = 5.99). Several fit indices including Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Residual (SRMR) were estimated. Convergent validity was assessed using Sample 2 ($n = 352$; Mean age = 25.41, SD = 5.89). To analyze convergent validity, participants completed two additional questionnaire measures of schizotypy: the Schizotypal Personality Questionnaire-Brief (SPQ-B) and the Wisconsin Schizotypy Scales-Short Forms (WSS-SF). A series of zero order correlations and linear regressions were performed between the different dimensions/factors comprising the different measures.

Results: Results of the confirmatory factor analysis showed that the three-factor model presented best goodness-of-fit (CFI = .91; TLI = .91; RMSEA = .04; SRMR = .09), corresponding to the positive, negative and disorganized subscales. Associations between MSS-B subscales and their corresponding dimensions/factors on measures of convergent validity were in the expected direction, presenting moderate to strong correlation values and medium to large effect sizes.

Discussion: To our knowledge, the present study was the first to assess the psychometric properties of the Spanish version of the MSS-B. Findings provide supporting evidence of a three-factor structures of the MSS-B with strong validity and robust psychometric properties. Thus, the MSS-B is a promising brief measure that allows for the screening of positive, negative, and disorganized schizotypy dimensions in large, nonclinical samples. The reliable identification and measurement of these dimensions is essential for parsing out the heterogeneity of schizotypy and psychosis spectrum disorders. Expanding the scope of investigation using the MSS-B in the future to include clinical populations will provide a more comprehensive understanding of the applicability and utility of the measure in a broader range of individuals and enhance its clinical relevance.

T15. ASSOCIATION BETWEEN INTELLIGENCE QUOTIENT AND CORTICAL STRUCTURE IN CHILDREN AND ADOLESCENTS AT FAMILIAL HIGH-RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Patricia Camprodon-Boadas*¹, María Ortuño², Inmaculada Baeza³, Elena De la Serna⁴, Josefina Castro-Fornieles⁴, Gisela Sugranyes⁵

¹*Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)*, ²*Fundació Clínic Recerca Biomèdica - Institut d'Investigacions Biomèdiques August Pi i Sunyer, Clinical and Experimental Neuroscience*, ³*Child and Adolescent Psychiatry and Psychology Department, Hospital Clinic de Barcelona*, ⁴*Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic of Barcelona, 2014SGR489, CIBERSAM.*, ⁵*Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic of Barcelona, 2014SGR489, CIBERSAM, CERCA-IDIBAPS*

Background: Previous studies have consistently showed a positive significant correlation between Intelligence Quotient (IQ) and cortical neuroimaging measures, both in adult and pediatric healthy populations. This study aims to analyze the relationship between IQ and cortical brain structural imaging measures, specifically gray matter volume and surface area, in a sample of children and adolescent's offspring of patients with bipolar disorder (BpO), schizophrenia (SzO) or community controls (CcO).

Methods: The study involved a total of 403 data acquisitions, which included longitudinal assessments from 51 SzO, 84 BpO, and 86 CcO at different time points. Participants were matched for age and sex. All participants completed an IQ assessment using the Wechsler Intelligence Scale for Children or Adults depending on age and underwent a structural magnetic resonance imaging scan on a 3Tesla scanner. Cortical surface reconstruction was applied to measure gray matter volume and surface area for each cortical lobe. Multilevel mixed-effects linear regression models were conducted, with cortical structural measures as dependent variable, including group, IQ, IQxgroup interaction, age, sex, and total intracranial volume as fixed factors. Additionally, random effects were incorporated for family relatedness (considering subjects who were siblings) and the subject code (accounting for different number of assessments).

Results: No significant differences were observed in age or sex between groups. SzO group exhibited a significantly lower IQ ($F = 22.636$; $p < 0.001$) compared to both the BpO ($p < 0.001$) and the CcO ($p < 0.001$) groups. No differences were observed in IQ between BpO and CcO groups. Overall, IQ had an effect on the left frontal lobe cortical gray matter volume ($F = 5.781$; $p = 0.017$) and surface area ($F = 11.650$; $p = 0.001$), right frontal lobe surface area ($F = 9.508$; $p = 0.002$), left ($F = 4.818$; $p = 0.029$) and right ($F = 5.024$; $p = 0.026$) insula gray matter volume, and right temporal lobe gray matter volume ($F = 4.847$; $p = 0.028$) and surface area ($F = 6.896$; $p = 0.009$). There was also a significant IQxgroup interaction in the right cingulate lobe gray matter volume ($F = 3.929$; $p = 0.021$) and surface area ($F = 3.354$; $p = 0.036$) and in the right parietal lobe gray matter volume ($F = 3.238$; $p = 0.04$) and surface area ($F = 3.462$; $p = 0.033$). However, subsequent pairwise comparisons did not reveal significant differences between groups in these interactions.

Discussion: Our findings suggest that IQ may have a significant effect in some cortical structures of children and adolescents at familiar high-risk for schizophrenia or bipolar disorder. Moreover, it appears that IQ may exert distinct effects depending on group, particularly on the right cingulate lobe and in the right parietal lobe. However, the absence of

statistical significance in pairwise comparisons was likely constrained by the small sample size. Our results have the potential for tailored interventions targeting structural brain changes characterizing youth at genetic high-risk of psychosis. Recognizing IQ as a measure of cognitive reserve, our results imply its significant role in aiding individuals to cope with neuroimaging abnormalities associated with these populations. Further research is warranted to elucidate the underlying mechanisms and implications for early intervention strategies.

T16. UNEXPECTED FEMALE PREPONDERANCE IN A RECENT SAMPLE OF INDIVIDUALS AT A CLINICAL HIGH RISK FOR PSYCHOSIS (CHR-P)

Emily Farina^{*1}, Catalina Mourgues-Codern², Karlos Mate², Gabriel Hosein², Adrianisse Vega-Reyes², Joshua Kenney², Jean Addington³, Carrie E. Bearden⁴, Kristin S. Cadenhead⁵, Tyrone D. Cannon⁶, Barbara Cornblatt⁷, Lauren Ellman⁸, James Gold⁹, Matcheri Keshavan¹⁰, Daniel H. Mathalon¹¹, Vijay A. Mittal¹², Diana O. Perkins¹³, Jason Schiffman¹⁴, Steven Silverstein¹⁵, Gregory P. Strauss¹⁶, William S. Stone¹⁷, Elaine F. Walker¹⁸, James Waltz¹⁹, Philip Corlett², Albert Powers², Scott W. Woods²

¹Yale University, ²Department of Psychiatry, Yale University, ³University of Calgary, Department of Psychiatry, ⁴Departments of Psychiatry and Biobehavioral Sciences and Psychology, University of California, Los Angeles, ⁵Department of Psychiatry, University of California San Diego,, ⁶Department of Psychology, Yale University, ⁷Department of Psychiatry, The Zucker Hillside Hospital Zucker Hillside Hospital, Long Island Jewish, ⁸Temple University, Department of Psychology, ⁹Maryland Psychiatric Research Center, ¹⁰Beth Israel Deaconess Med. Ctr. and Harvard Medical School and Harvard Medical School, ¹¹Department of Psychiatry, University of California, San Francisco, United States and Psychiatry Service, ¹²Northwestern University, ¹³Department of Psychiatry, University of North Carolina, ¹⁴University of California, Department of Psychological Science, ¹⁵University of Rochester Medical Center, , ¹⁶University of Georgia, ¹⁷Harvard Medical School Department of Psychiatry, Beth Israel Deaconess Medical Center, ¹⁸Departments of Psychology and Program in Neuroscience, Emory University, ¹⁹Maryland Psychiatric Research Center, University of Maryland,

Background: Historically, many large CHR-P samples have been male predominant, which is consistent with incidence rates of psychotic-spectrum diagnoses, while few had a female preponderance. However, in the recent Computerized Assessment for Psychosis Risk (CAPR) sample we have noted increased rates of female enrollment. We aimed to systematically examine the observed female preponderance in the CAPR sample and to describe sex differences in the clinical profiles of CHR-P between CAPR and two waves of the North American Prodrome Longitudinal Study (NAPLS). All three projects ascertained CHR-P using the SIPS.

Methods: Sex differences were examined in the baseline data between CAPR (2020-2023, n = 651, 272 CHR), NAPLS 2 (2009-2012, n = 1043, 764 CHR), and NAPLS 3 (2015-2018, n = 806, 710 CHR). Chi-square and two-way ANOVA were used to investigate differences between sex and sample in age, and clinical characteristics [CHR symptom severity (SOPS domain scores), social and role functioning (GF:S and GF:R), and prevalence of non-psychotic comorbidities (SCID-IV and V diagnostic criteria).

Results: The sex predominance in the three CHR samples (NAPLS 2, 43% female $\chi^2(1) = 15.267$, p LESS THAN 0.001; NAPLS 3 46% female, $\chi^2(1) = 5.07$, p = 0.02; CAPR 68%

female, $\chi^2(1) = 33.88$, $p < 0.001$) differed significantly ($\chi^2(2) = 51.34$, $p < 0.001$). The female preponderance pattern in CAPR was not significantly different across the six data collection sites (53% to 82% female) and was not present in control groups.

CHR females across all three studies were consistently older, had less negative symptoms, more general symptoms, higher social functioning, and higher role functioning [age: $F(1, 1745) = 6.00$, neg: $F(1, 1681) = 4.33$, gen: $F(1, 1680) = 31.13$, GF:S: $F(1, 1701) = 4.36$, GF:R: $F(1, 1694) = 19.83$, $p < 0.05$].

Discussion: These prominent sex differences across samples may affect estimates of clinical characteristics. An important difference between the studies is that CAPR does not require in-person participation but can be completed completely on-line, whereas both NAPLS studies required in-person participation. Future directions will examine effects of recruitment strategies and treatment histories across studies, will consider possible time-limited (i.e. pandemic) effects, and will expand comparisons to other recent samples and longitudinal outcomes (including conversion rates, distress, functioning, and other indicators of a need for early identification and care).

T17. GRAY MATTER ALTERATION AND ITS ASSOCIATION WITH POSITIVE AND NEGATIVE SYMPTOM IN THOSE AT CLINICAL HIGH RISK OF PSYCHOSIS

Shuqing Si^{*1}, Emily P. Hedges¹, Stefania Tognin², Gemma Modinos¹, Mark van der Gaag³, Lieuwe de Haan⁴, Patrick D. McGorry⁵, Barnaby Nelson⁵, Anita Riecher-Rössler⁶, Rodrigo Bressan⁷, Neus Barrantes Vidal⁸, Marie-Odile Krebs⁹, Merete Nordentoft¹⁰, Stephan Ruhrmann¹¹, Gabriele Sachs¹², Bart P Rutten¹³, Jim Van Os¹³, Anthony James¹⁴, Gareth J. Barker¹, EU-GEI High Risk Study¹⁵, Steven Williams¹, Lucia R. Valmaggia¹, Philip McGuire², Matthew J. Kempton¹

¹King's College London, ²King's College London, ³VU University Amsterdam, ⁴Academic Medical Center, University of Amsterdam, ⁵University of Melbourne, ⁶University of Basel, ⁷Universidade Federal de Sao Paulo - UNIFESP, ⁸Universitat Autònoma de Barcelona, Spain, ⁹University Paris Cité - INSERM -, ¹⁰Mental Health Centre Copenhagen, ¹¹University Hospital - University of Cologne, ¹²Medical University of Vienna, ¹³Maastricht University Medical Centre, ¹⁴Highfield Unit, Warneford Hospital, Oxford, UK, ¹⁵EU-GEI High Risk Study

Background: The clinical high-risk (CHR) phase is a critical period for early intervention in psychosis, a period where brain volume abnormalities are already present. However, the extent to which brain volume is altered and its association with symptoms and later transition to psychosis is unclear. Attenuated positive symptoms and negative psychotic symptoms have also showed greater association with the transition to psychosis. In this study, we investigated differences in brain structure between individuals at CHR and healthy controls (HC) and determined whether gray matter (GM) volume at baseline is associated with later transition to psychosis. Additionally, we examined the relationship between positive and negative symptoms and brain volume at baseline.

Methods: As a part of the EU-GEI high-risk study, CHR participants with MRI scans were recruited from 9 sites (London, Amsterdam, The Hague, Basel, Cologne, Melbourne, Vienna, Copenhagen, Paris) and HC were recruited from 4 of these sites (London, Amsterdam, The

Hague, and Melbourne). Participants were scanned and assessed at baseline and followed up to 24 months. Structural 3T MRI scans were acquired using the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) protocol and regional brain volumes were determined using the FreeSurfer v6.0.0 pipeline. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS), and positive symptom severity was determined from the Comprehensive Assessment of At-Risk Mental States (CAARMS). Five key brain regions associated with psychosis and/or CHR from previous meta-analytical studies were selected a priori: anterior cingulate cortex (ACC), fusiform gyrus, insula, hippocampus, and total gray matter (GM). Regional brain volumes were statistically adjusted for age, site, total intracranial volume, and sex. When comparing CHR to HC, we limited the analysis to the 4 sites that recruited both groups, and associations with clinical variables used the entire sample. Linear regression was used to examine the differences between CHR and HC and to assess the relationship between brain volume and symptom severity. Logistic regression was applied to investigate the association of brain volume and symptoms at baseline with later transition to psychosis.

Results: Our study comprised 65 HC and 226 CHR individuals, 48 of whom later transitioned to psychosis. There were no differences in age and gender between CHR and HC, as well as between subjects who transitioned to psychosis (CHR-T) and those who did not transition (CHR-NT). Compared with HCs, CHR subjects had significantly smaller volumes of the anterior cingulate cortex (ACC), fusiform gyrus, insula and total gray matter (GM). No differences were observed in hippocampal volume between CHR and HC. None of the brain regions at baseline were associated with later transition to psychosis. At baseline, individuals who later transitioned to psychosis had a significantly higher SANS score than those who did not transition. However, no association was found between baseline brain volume and baseline negative symptoms or positive symptoms.

Discussion: Our study revealed that CHR individuals had decreased regional brain volumes compared to HC at baseline, however no volumetric differences at baseline were associated with later transition to psychosis. CHR-T individuals presented more negative symptoms, but symptom severity was not associated with brain volume. Future longitudinal MRI studies may be a more effective way to reveal the different trajectories between transition and non-transition individuals and examine the association of symptoms and brain volume.

T18. EXAMINING MODEL STABILITY ACROSS STATIC AND DYNAMIC MODELLING APPROACHES TO PREDICTING OUTCOMES FOR INDIVIDUALS AT-RISK OF PSYCHOSIS

Yanakan Logeswaran^{*1}, Dominic Oliver¹, Matthew Kempton¹, Mark van der Gaag², Lieuwe De Haan³, Barnaby Nelson⁴, Anita Riecher-Rössler⁵, Rodrigo Bressan⁶, Neus Barrantes Vidal⁷, Marie-Odile Krebs⁸, Merete Nordentoft⁹, Stephan Ruhrmann¹⁰, Gabriele Sachs¹¹, Bart Rutten¹², Jim van Os¹², Lucia Valmaggia⁴, Philip McGuire¹³, Paolo Fusar-Poli¹, Daniel Stahl¹, EU-GEI High Risk Study¹⁴

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*VU University Amsterdam*, ³*AMC Amsterdam*, ⁴*Orygen, The National Centre of Excellence in Youth Mental Health*, ⁵*University of Basel*, ⁶*UNIFESP*, ⁷*Universitat Autònoma de Barcelona*, ⁸*University Paris Descartes*, ⁹*University of Copenhagen*, ¹⁰*University of Cologne*, ¹¹*Medical University of Vienna*, ¹²*University of Maastricht*, ¹³*University of Oxford*, ¹⁴*International*

Background: Primary indicated prevention in individuals at Clinical High Risk for psychosis (CHR-P) may improve the trajectory of psychotic disorders, and potentially prevent a full-blown illness. However, psychosis risk in individuals at CHR-P is highly heterogeneous, with a 5% to 20% probability of transition to psychosis. Clinical prediction models may improve our ability to prognosticate outcomes. More recently, studies have used dynamic modelling approaches, which incorporate symptom dynamics over time, and have observed improved overall prognostic accuracy relative to static modelling approaches. However, there are concerns that the individual model predictions of psychosis risk may be unstable, given the use of small development datasets with relatively small numbers of outcome events and greater model complexity in such dynamic modelling. Thus, this study aims to compare model performance and instability across static and dynamic clinical prediction models for predicting transition to psychosis in CHR-P individuals.

Methods: CHR-P individuals were recruited as part of the EU-GEI study, a prospective 11-site observational study. Participants were followed up for two years, and the outcome (transition to psychosis) was determined by the CAARMS. Data will be checked for missingness and imputed using k-nearest neighbours where necessary. We will develop each model utilising cumulative blocks of candidate predictors: (i) age, gender, age*gender, ethnicity, CHR-P subgroup; (ii) total positive symptoms, total negative symptoms, global functioning, symbol coding, verbal learning; and (iii) childhood trauma, stressful life events, living status, employment status, and migrant status. Various static (i.e. Cox proportional hazards regression, random survival forests [RSF]) and dynamic models (i.e. joint modelling, Cox landmarking, and RSF landmarking) will be developed using a 10-fold cross-validation framework to predict transition to psychosis. We will assess the models' performance using internal validation, indexed by discrimination (area under the curve, sensitivity, specificity, balanced accuracy, and Brier score) and calibration (calibration slope and Brier score). Using bootstrapping, we will examine model instability of individual predictions through (i) prediction instability plots, (ii) classification instability plots, (iii) calibration instability plots, and (iv) the mean absolute prediction error (MAPE) between original and bootstrap model predictions.

Results: 343 CHR-P individuals (mean [SD] age at study entry = 22.4 [4.9] years; 184 [53.6%] male; 246 [71.7%] non-white ethnicity) were included in the study. Of these, 57 (17%) transitioned to psychosis within two years (median [IQR] days from baseline to transition = 195 [105-359] days). Regarding CHR-P intake groups, 25 (8%) met criteria for Brief Limited Intermittent Psychotic Symptoms, 256 (84%) met Attenuated Psychotic Symptoms criteria, and 24 (8%) met criteria for genetic risk vulnerability. Regarding comorbid psychopathology at baseline, 109/331 (33%) had a current major depressive episode, 169/326 (52%) had any anxiety disorder, and 45/303 (15%) had a personality disorder. Further, 89/282 (32%) had been prescribed antidepressants, 31/282 (11%) anxiolytics, and 31/277 (11%) antipsychotics, and 90/334 (27%) were current cannabis users.

Discussion: This study may emphasise the importance of reporting model stability in this field and perhaps emphasise the importance of harmonisation of measures across consortia to provide larger datasets for more stable, better performing clinical prediction models that can improve care for CHR-P individuals.

T19. PERCEIVED SOCIAL REJECTION IN REAL LIFE (ESM) AS A PREDICTOR OF INCREASED PARANOID THOUGHTS IN EXPERIMENTAL VR SETTINGS IN A NON-CLINICAL PARANOIA SAMPLE

Background: Paranoid thoughts are suggested to be built on increased vulnerability. Individuals with heightened rejection sensitivity have been shown to be more prone to actively seek out and selectively respond to threatening stimuli while anticipating harm or rejection from others. Despite extensive research on paranoid thoughts in the context of social rejection, experimental studies attempting to establish a potential causality are inconsistent. The purpose of this study is to apply gold-standard, ecologically valid methods to investigate whether inducing feelings of social rejection in a fully immersive virtual reality (VR) environment contributes to increased paranoid thoughts in non-clinical subjects, and whether real-time feelings of social rejection (collected through Experience Sampling Method) predict paranoid thoughts both in real-time (ESM) and under experimental conditions (VR).

Methods: A total of 103 participants (aged 18-40 years) were allocated to one of two groups: LP - low paranoia (n = 79) and HP - high paranoia (n = 24). Those scoring ≤ 1 on The Revised Green et al. Paranoid Thoughts Scale (R-GPTS) were placed in the LP group, and those scoring ≥ 35 were assigned to the HP group. First, participants were asked to complete 8 short surveys per day for 7 days, comprising of questions about emotions experienced at the time, perceived social rejection, and current paranoid thoughts. The ESM stage was followed by the Cyberball game in a VR setting. Participants were randomly assigned to one of two conditions - social inclusion or social rejection. Levels of paranoid thoughts were measured before and after Cyberball. Multilevel regression analyses were performed on the ESM data. The data were also aggregated at the subject and group levels to integrate with data obtained from the baseline measurements and VR experimental procedures.

Results: A three-way repeated measures ANOVA revealed a significant interaction of time x group x Cyberball condition ($F(1,99) = 22.935$, $p < 0.001$). HP group showed a significant increase in paranoid thoughts after social rejection and a significant decrease following social inclusion. LP subjects showed a slight, but insignificant, increase in paranoid thoughts following social rejection and no change after social inclusion. Rejection sensitivity significantly correlated with baseline paranoid thoughts ($r = 0.590$, $p < 0.001$), as well as momentary (ESM) paranoid thoughts ($r = 0.369$, $p < 0.001$) and feelings of social rejection ($r = 0.262$, $p < 0.001$). The results revealed that HP group spent significantly more time alone than with others compared to LP ($p < 0.05$), which was further associated with an increased sense of rejection ($p < 0.01$). Feeling accepted while with others predicted lower paranoid thoughts ($b = -0.09$, $p < 0.001$) and feeling threatened predicted higher paranoia ($b = 0.25$, $p < 0.001$). Momentary feelings of social rejection significantly predicted paranoid thoughts ($b = 0.2$, $p < 0.001$), and paranoia predicted feelings of rejection over time ($b = 0.52$, $p < 0.001$). Momentary negative emotions predicted increased paranoid thoughts after Cyberball manipulation ($p = 0.05$), but this effect was not significant for feelings of social rejection alone or momentary paranoia.

Discussion: Experiencing social rejection in immersive VR and momentary feelings of rejection may play an important role in fostering paranoid thoughts. Negative emotions in daily life, including but not limited to rejection, predict experimental responses, highlighting the role of ongoing daily stress in paranoia. Increased rejection sensitivity and prolonged periods of solitude contribute to increased feelings of rejection and thus paranoid thoughts, suggesting potential targets for therapeutic interventions. However, these are only preliminary analyses based on currently collected data, and the results should be interpreted with caution.

T20. THE 'STRESS-SENSITIVE SELF' IN PSYCHOSIS: PRELIMINARY RESULTS OF A CHALLENGE (STRESS) TEST OF SENSE OF AGENCY IN PSYCHOSIS PRONENESS

Yonatan Stern^{*1}, Roy Salomon¹, Dan Koren¹

¹*Haifa University*

Background: Psychosis often involves 'basic self-disturbances', impairing one's fundamental identification with their actions, body, and thoughts. This includes disrupted Sense of Agency (SoA), affecting control and recognition of one's actions, common in full-blown psychosis. Neurocognitive tests associated with self-disturbances have been shown to moderately improve early identification of psychosis and its differentiation from other psychopathologies. However, the associations between neurocognitive tests and basic self-disturbances have been mild at best in most studies. We hypothesize that bridging the gap between neutral testing settings and stressful real-world conditions can enhance early psychosis identification. Similar to stress tests in general medicine, , such as examining cardiac activity under physical exertion, we developed the 'Stress-sensitive Self' neurocognitive test, assessing SoA under psychosocial stress.

Specifically, we examined two pre-registered hypotheses (<https://osf.io/ubjeq>):(1) Increased psychosis-proneness and self-disturbances will be associated with impaired SoA and its metacognition. (2) Psychosocial stress will impair SoA more prominently in individuals with increased risk for psychosis.

Methods: To ecologically examine SoA we developed the 'Virtual Hand' (VH) task in immersive virtual reality to examine SoA. Participants' movements were mirrored by VH, either synchronously or with a temporal delay. Participants then judge whether the VH's movement is identical to their actual movement (i.e. agency question) and rate their confidence (i.e. metacognition question). The task was performed under two conditions; a neutral block, and following a psychosocial stress induction in a 'stress' block. To assess for psychosis proneness and self-disturbances the Structured Interview for Psychosis-Risk Syndromes and Examination of Anomalous Self Experiences were respectively administered. Three groups of participants were included: clinical high risk (CHR) for psychosis (N = 13), participants with non-psychotic psychopathology (N= 29) and healthy controls (N = 47).

Results: Contrary to our first hypothesis and previous work, no significant correlation was found between SoA and psychosis proneness ($r = .10$, $p = .35$) or self-disturbances ($r = .05$, $p = .9$). Likewise, metacognition was not significantly correlated to psychosis proneness ($r = .08$, $p = .50$) and self-disturbances ($r = .08$, $p = .52$). Furthermore, there was no significant difference between groups in their SoA ($F_{2,82} < 1$, $p = .78$) and metacognition ($F_{2,82} = 1.3$, $p = .28$). Regarding the effect of stress on SoA, stress caused a significant change in participant's criteria resulting in decreased self-attribution of actions ($t_{82} = 3.2$, $p = .002$, Cohen's $d = 0.35$). However, this criteria shift was not different between groups ($F_{2,82} = 1.4$, $p = .25$).

Discussion: Our findings, using clinical assessments and neurocognitive tests, unexpectedly contradict previous links between psychosis and self-cognition impairments across the psychosis spectrum. A possible explanation is the low number of CHR individuals in the current sample. Likewise, measurement of SoA may provide additional insight regarding conversion to full-blown psychosis, a measure currently being collected. Despite these caveats, the current results point to a more complex relation between clinically measured psychosis-proneness and self-related neurocognitive measures, that may have been previously under-reported in the literature.

T21. GENDER DIFFERENCES IN THE ASSOCIATIONS BETWEEN EXPOSOME AND PSYCHOSIS EXPRESSION IN A GENERAL POPULATION TWIN SAMPLE

Melike Karaçam Doğan*¹, Thanavadee Prachason², Claudia Menne-Lothmann³, Jeroen Decoster⁴, Ruud van Winkel⁵, Dina Collip³, Philippe Delespaul³, Marc De Hert⁶, Catherine Derom⁷, Evert Thiery⁸, Nele Jacobs⁹, Bart Rutten³, Jim van Os¹⁰, Laura Fusar-Poli¹¹, Sinan Guloksuz¹²

¹Karadeniz Ereğli State Hospital, ²Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand; School for Mental Health and Neuroscience, Maastricht University Medical Center, ³School for Mental Health and Neuroscience, Maastricht University Medical Center, ⁴Psychiatric Care Sint-Kamillus, Bierbeek, ⁵School for Mental Health and Neuroscience, Maastricht University Medical Center, ; University Psychiatric Centre KU Leuven, ⁶University Psychiatric Centre Katholieke Universiteit Leuven, Kortenberg, Belgium; Centre for Clinical Psychiatry, Katholieke Universiteit Leuven, Belgium; Leuven Brain Institute, Katholieke Universiteit Leuven, Antwerp Health Law and Ethics Chair, University of Antwerp, ⁷Centre of Human Genetics, University Hospitals Leuven, KU Leuven, Leuven, Belgium; Ghent University Hospitals, Ghent University, ⁸Ghent University Hospital, Ghent University, ⁹Maastricht University Medical Centre; Faculty of Psychology and Educational Sciences, Open University of the Netherlands, ¹⁰School for Mental Health and Neuroscience, Maastricht University Medical Center, ; Brain Centre Rudolf Magnus, University Medical Centre Utrecht, ; Institute of Psychiatry, King's Health Partners, King's College London, ¹¹University of Pavia, ¹²School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, the Netherlands; Yale School of Medicine

Background: Several environmental factors and coping styles are associated with psychosis expression (PE). However, available literature regarding gender differences in these connections remains inconsistent and limited. Therefore, we aimed to investigate the aforementioned gender differences in the general population.

Methods: Individuals comprising our sample were recruited from the TwinssCan study, a longitudinal examination of twins and siblings within the general population cohort. There were 791 participants aged between 18 and 35 years old. Linear regression models, considering PE as the dependent variable, were used in separate analyses for women and men. The regression coefficients of the analysis between men and women were compared using the Chow's test. PE was assessed with the Community Assessment of Psychic Experiences (CAPE). Winter birth, childhood trauma (CT), being bullied, and coping styles were independent variables. The following scales were used to assess the independent variables: The Childhood Trauma Questionnaire-Short Form for CT, Retrospective Bullying Questionnaire for bullying, the Life Events Questionnaire for negative life events, and the Utrecht Coping List for coping styles.

Results: Physical abuse, emotional abuse, and bullying, but not winter birth, were significantly associated with CAPE total and subscale scores in both genders. Emotional neglect was significantly associated with CAPE total, negative, and depressive scores in both genders, but with CAPE positive scores only in women. Physical abuse and sexual abuse were significantly associated with CAPE total, positive, and depressive scores in both genders, but with CAPE negative scores only in women. However, gender differences were not statistically significant in direct comparisons, Negative life events were associated with

CAPE total, negative, and depressive scores in both genders, but with CAPE positive scores only in women. Direct comparisons revealed significantly stronger associations of negative life events with CAPE positive and CAPE total scores in women ($\chi^2=6.54$, $P=0.010$; and $\chi^2=5.25$, $P=0.021$, respectively). Different types of coping styles were associated with CAPE scores in women and men. Particularly, the positive associations between expression of emotions and CAPE total and negative scores were stronger in women ($\chi^2=4.60$, $P=0.032$; and $\chi^2=5.64$, $P=0.018$, respectively) and negative associations between seeking social support and CAPE total, positive and depressive scores were also stronger in women ($\chi^2=9.82$, $P=0.002$; $\chi^2=11.45$, $P < 0.001$; and $\chi^2=6.25$, $P=0.012$, respectively).

Discussion: Our study investigated gender differences in the association of psychosis expression with environmental risk factors and coping strategies. Negative life events and specific coping styles, particularly expressing emotions and seeking social support, were associated with psychosis expression in women more strongly than men. Our findings emphasize the role of gender-specific associations of exposures with psychosis expression. Further exploration is needed to develop gender-informed public health measures to decrease modifiable exposures linked with psychosis.

T22. FETAL AND NEONATAL HEAD GROWTH IN OFFSPRING OF MOTHERS WITH PSYCHOTIC DISORDERS AND POPULATION-BASED CONTROLS

Lisanne van Houtum^{*1}, Dogukan Koc², Sterna Grundeman², Hans Duvekot², Hanan El Marroun², Neeltje Van Haren², Hilmar Bijma²

¹*Erasmus MC, University Medical Centre Rotterdam – Sophia, Rotterdam, the Netherlands,*

²*Erasmus Medical Center Rotterdam*

Background: Offspring of parents with severe mental illness (SMI), such as psychotic disorders, have a more than 50% increased risk for developing mental illness themselves, and over 30% develop SMI by early adulthood. There is evidence for an association between poor prenatal maternal mental health and decreased fetal head growth, suggestive of a link between high familial risk for mental illness and altered early neurodevelopment. This study aims to investigate differences in brain development, reflected in head circumference (HC) at birth and fetal HC growth trajectories, between offspring of mothers with a psychotic disorder and population-based controls. First, we investigate if offspring of mothers with a psychotic disorder have a smaller HC at birth compared to offspring of population-based control mothers. Second, we explore differences in fetal HC growth trajectories among both groups. Elucidating factors that accurately detect risk as early in life as possible is urgently needed to inform interventions to prevent mental illness in offspring at familial high risk.

Methods: In this retrospective observational study, we collected data from medical records of $N = 170$ pregnant women, who had a diagnosis of a psychotic disorder. As a control population, all pregnant women and their offspring participating in the Generation R study, having a singleton pregnancy with at least one HC measurement of their child will be included ($N = 8184$). Women who self-reported having a psychiatric disorder will be excluded from analyses. For our clinical cohort, fetal ultrasonography assessments were performed at approximately 20, 30, and 36 weeks of gestational age (GA). For controls, assessments were done around 13, 20, and 30 weeks GA. HC was additionally measured at birth with measuring tape. Multilevel modelling will be used to examine differences in neonatal HC between groups, while taking sibling data into account. To analyze how fetal HC growth varied as a function of group, we will use Generalized Additive Mixed Models. In both analyses, GA at assessment, child's sex, maternal national origin, maternal age, pre-

pregnancy BMI, parity, smoking, and psychotropic medication use will be included as potential confounders.

Results: We performed preliminary analyses on our clinical cohort data, comparing offspring of mothers diagnosed with schizophrenia or schizoaffective disorder (schizophrenia spectrum disorder (SSD) offspring; n=76) with offspring of mothers diagnosed with brief psychotic disorder or psychotic disorder not otherwise specified (PNOS offspring; n=65). Compared to PNOS offspring, SSD offspring exhibited significantly smaller fetal HC in the third trimester, i.e., both at 30 weeks GA ($F(1,136) = 8.591, p = .004$) and 36 weeks GA ($F(1,136) = 6.568, p = .011$), while controlling for GA, infant's sex, and maternal age. However, no significant differences in fetal HC at 20 weeks GA ($F(1,136) = .412, p = .522$) or HC at birth ($F(1,135) = .064, p = .801$) were found between the groups.

A next step will be to compare our clinical cohort with population-based controls. Findings will be presented as differences in HC at birth, as well as the trajectories of fetal HC change with GA.

Discussion: Preliminary findings may imply altered fetal neurodevelopment during the third trimester in offspring of mothers with SSD compared to PNOS. Comparison to population-based controls is necessary to confirm these findings and will be done in the next few months. Potential differences between groups will increase our knowledge about aberrant perinatal brain development in children at risk for SMI, and give us directions for possible underlying neural mechanisms related to the intergenerational transmission of mental illness.

T23. PROTOCOL: CHARACTERISTICS OF STUDY SAMPLES USED FOR THE DEVELOPMENT AND EVALUATION OF WEB-BASED WEIGHT LOSS PROGRAMS: A MENTAL HEALTH PERSPECTIVE

Naiiri Ghazari¹, Irina Papazova², Alkomiet Hasan²

¹*Psychiatry and Psychotherapy Faculty of Medicine University of Augsburg*, ²*Psychiatry and Psychotherapy Faculty of Medicine University of Augsburg*

Background: Weight gain is one of the main undesirable side effects of antipsychotic treatment leading to health complications, higher mortality and lower treatment compliance in people with schizophrenia. Web-based weight loss programs are a feasible way to address this issue. However, little is known about the strategies for the development and evaluation of these programs, specifically about their inclusion and exclusion criteria and applicability for patients with mental illness. This may lead to an inadequate prescribing for the excluded patient samples and therefore be stigmatizing for vulnerable groups who are specifically in need of such programs. This review attempts to access the characteristics of study samples used for the development and evaluation of web-based weight loss programs viewed from a mental health perspective with a focus on people with schizophrenia. Moreover, we will analyze the pros and cons of different web-based models regarding weight loss programs for people with severe mental illnesses.

Methods: We will conduct a search of peer-reviewed articles including the terms “web-based program”

“app*” AND “body mass index”, “weight reduc*” with focus on the exclusion and inclusion criteria in development and evaluation. We will search electronically for studies in English via the following databases: PubMed, PsycINFO, Embase and Cochrane Library database. Studies on other weight loss programs or combined interventions (web-based and in person) will be excluded.

Results: Ongoing systematic review, results will be provided by the time of the conference.

Discussion: Analysis of exclusion and inclusion criteria for a study population to test an intervention is essential. Excluding patients with schizophrenia in the development and the following evaluation of such programs could potentially neglect them. Therefore, an examination whether such supply gap exists is of importance as it may harm and reduce access to such programs for this vulnerable population.

T24. GENDER MODERATES THE ASSOCIATION BETWEEN BIRTH WEIGHT AND COGNITIVE BIASES IN A COMMUNITY SAMPLE OF ADOLESCENTS

Elena Estefania Gago Quintela^{*1}, Meritxell Tost Bonet², Montse Pamias³, Sara Perez⁴, Berta Blasco³, Itziar Montalvo Aguirrezabala⁵, Javier Labad⁶

¹Hospital del Mar, ²Parc Taulí Hospital Universitari, I3PT, Universitat Autònoma de Barcelona. CIBERSAM. Sabadell, Barcelona, ³Department of Mental Health, Parc Taulí Hospital Universitari, Sabadell, Spain., ⁴Translational Neuroscience Research Unit I3PT-Inc-UAB, Institut d'Innovació i Investigació Parc Taulí (I3PT), Institut de Neurociències, Universitat Autònoma de Barcelona, Spain., ⁵Hospital Universitari Parc Taulí, I3PT, Universitat Autònoma de Barcelona. CIBERSAM. Sabadell, SPAIN, ⁶Consorti Sanitari del Maresme, Mataró, Spain

Background: Genetic and environmental factors are involved in the pathogenesis of psychosis (Lemvigh, 2021;). Obstetric complications such as low birth weight (LBW) are one of the most widely studied environmental risk factors (Costas-Carrera, 2020; Sormunen, 2019). LBW is a well-documented risk factor for schizophrenia (Stilo, 2019). Psychotic experiences (PE) are more prevalent in young than in adults, most are non-pathological, typically transient, not associated with functional impairment and do not develop in psychotic disorder. However, the presence of PEs in childhood non-help-seeking community samples is associated with a 4-fold risk of a psychotic disorder (Tyson, 2019).

The present study aimed to examine the occurrence of PE in adolescents ages 14-15 and investigated whether environmental factors of early stress such as LBW would increase the presence of psychotic experiences and cognitive biases. We also explored if the relationship is moderated by gender.

Methods: Our sample was composed of 240 adolescents (147 girls; 93 boys, 1 transgender) born in 2004 (aged between 14 and 15 years) who were studying in high schools from Sabadell (Spain). A psychoeducation session on psychosis and risk for psychosis was conducted for each recruited high school followed by the anonymous self-applied online questionnaires on google forms to obtain sociodemographic and clinical information on psychotic experiences and cognitive biases of participants. The following questionnaires were administered: The 15-item Community Assessment of Psychic Experiences – Positive Scale [CAPE-P15]) (Capra, 2013); The Cognitive Biases Questionnaire for Psychosis [CBQp], with some items adapted for adolescents) (Peters, 2014); birthweight was obtained from childhood booklet. Multiple linear regression analyses were used for exploring the association between birthweight and psychometric scales while adjusting for gender, previous mental health history. The interaction between gender and birthweight was tested in all analyses, and only significant interactions were kept in the final model. We conducted a multiple linear regression analysis for each psychometric scale, which was considered the dependent variable. Therefore 6 regressions were tested for cognitive biases (CBQ total score plus 5 CBQ subscores) and 4 regressions were tested for positive psychotic-like experiences

(CAPE total score and 3 CAPE subscores). Significance was set as $p < 0.05$ (two-sided).

Results: There were significant differences between boys and girls in birth weight, as girls had a lower birth weight. The proportion of LBW was 4.3% in boys and 15.4% in girls ($p = 0.022$). Regarding the association between birth weight and psychometric scales, no associations were found for CAPE scores. However, for cognitive biases, the multiple linear regression analyses indicated significant gender by birth weight interactions in two CBQ domains: dichotomous thinking and jumping to conclusions. In girls, lower birth weight was associated with more cognitive biases in these two CBQ domains, whereas in boys an inverse association was found.

Discussion: PE and cognitive biases in adolescent general population are important predictors of transition to psychosis. Our study suggests that birth weight can be a risk factor for cognitive biases with sex differences. If our Results: are replicated in other adolescent populations, the assessment of birth weight might be useful for identifying adolescents at risk of presenting cognitive biases, a known risk factor of developing psychotic experiences and symptoms.

T25. HIPPOCAMPAL FUNCTIONAL CONNECTIVITY-BASED NEUROCOGNITIVE PREDICTION IN PATIENTS WITH CLINICAL HIGH RISK FOR PSYCHOSIS

Guanfu Wu^{*1}, Xiaochen Tang¹, LiHua Xu¹, HuiRu Cui¹, Zhenying Qian¹, Yanyan Wei¹, TianHong Zhang¹, Jijun Wang¹, Yingying Tang¹

¹*Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai Key Laboratory of Psychotic Disorders, Shanghai*

Background: Neurocognitive impairments have occurred in patients with clinical high risk for psychosis (CHR) and are candidates to predict the risk of transition to schizophrenia. The hippocampus is highly related to the pathophysiology of schizophrenia and its functional connectivity (FC) with other brain regions might underpin distinct neurocognitive domains. Therefore, it is important to identify the hippocampal FC-neurocognition associative patterns and whether/how these patterns are different between CHR and healthy control (HC) populations.

Methods: We recruited 226 CHR patients and 215 HC at the Shanghai Mental Health Center (part of the second phase of the Shanghai At-Risk for Psychosis Program). All CHR patients completed neurocognitive assessments using the MATRICS Consensus Cognitive Battery. Structural and resting-state functional MRI (fMRI) scans were acquired using a 3T Siemens Verio MRI scanner. The individual resting-state fMRI images were parcellated into 300 cortical parcels and 84 subcortical parcels using the AICHA atlas. The hippocampus was segmented into anterior and posterior subfields in each hemisphere and the FC map was obtained from each hippocampal subfield with the whole brain regions (383 FC for each subfield). We used support vector regression and performed 10 repeats of 10-fold cross-validation to build the FC-based neurocognitive prediction model. The model performance was measured by the Pearson's correlation coefficient between the predicted score and the actual score in each task. To find out the most predictive model for each task, we iteratively included an increasing number of FC from 1 to 383. The order of the included FC was based on each FC's absolute Pearson's correlation coefficient with the actual task score. Permutation test was performed by repeating 10-fold cross-validation 500 times while

shuffling the real task score. The predictive model with the best performance and passed the permutation test ($p < 0.05$) was identified for the specific neurocognitive task.

Results: We found that the anterior hippocampal subfields FC played an important role in predicting the Brief Assessment of Cognition in Schizophrenia Symbol Coding Test (BACS) and Brief Visuospatial Memory Test-Revised (BVRT) performances.

For the BACS task, FC between the bilateral anterior hippocampus (antHippo) and the left superior prefrontal gyrus, left precentral sulcus, bilateral temporal pole, left caudate, and left thalamus could well predict the BACS scores in HC (left antHippo: $r = 0.363$, $p = 0.048$; right antHippo: $r = 0.361$, $p = 0.046$). However, the predictive model for BACS scores in CHR showed a right-hemisphere effect, consisting of FC between the right antHippo and the right precentral sulcus, bilateral paracentral lobule, left occipital lobe, and right temporal pole ($r = 0.372$, $p = 0.046$). The predictive model in CHR included hippocampal FC with more widespread regions (sensorimotor areas) compared with HC (executive control network).

Regarding the BVRT task, there was no stable predictive model for HC. In CHR, FC between the left antHippo and the left prefrontal gyrus, left precentral sulcus, bilateral anterior cingulate, bilateral temporal lobe, and bilateral lingual cortex could predict their BVRT scores ($r = 0.357$, $p = 0.046$).

Discussion: We identified hippocampal FC-based predictive models for BACS and BVRT tasks, which were changed in CHR compared to HC. More importantly, the anterior hippocampal FC patterns may provide new insights into the underlying mechanism for impaired visuospatial learning and processing speed functions in CHR.

T26. THE ASSOCIATION BETWEEN ANTIPSYCHOTIC MEDICATION AND MORTALITY RISK IN PATIENTS WITH SCHIZOPHRENIA: EVIDENCE FROM THE 20-YEAR FOLLOW-UP

Chao Li^{*1}, Huiquan ZHOU¹, Kit Wa Sherry Chan¹

¹*The University of Hong Kong*

Background: Schizophrenia is associated with a higher mortality risk than other psychiatric disorders. Previous studies reported many risk factors related to greater and earlier mortality among individuals with schizophrenia. Among these related factors, the effects of antipsychotic medication on premature mortality have not reached a unanimous conclusion yet, especially in long-term mortality risk. We aimed to explore the association of antipsychotic medication with all-cause, natural cause, and unnatural cause mortality risk from the 20-year follow-up.

Methods: This cohort study included 1400 participants with a diagnosis of schizophrenia-spectrum disorders between July 1, 2001, to June 30, 2003. All participants were followed up until death or the end of the study (September 30, 2021). Information about time, cause of death, and clinical symptoms was obtained from the Clinical Management System (CMS) in Hong Kong. Antipsychotic medication information was collected from the Hong Kong Clinical Data Analysis and Reporting System (CDARS).

Results: A total of 1149 participants were included in the final analysis, and 108 participants died during 20 years of follow-up. In the whole follow-up period, longer duration of having antipsychotics was reported to be a protective factor of all-cause (HR, 0.9994; 95%CI, 0.9993-0.9995) and unnatural cause mortality (HR, 0.9993; 95%CI, 0.9992-0.9994) among patients with schizophrenia, and larger number of antipsychotic drugs was a risk factor of all-

cause (HR, 1.2143; 95%CI, 1.0949-1.3467) and unnatural cause mortality (HR, 1.214; 95%CI, 1.071-1.377). In the last year before death, longer duration of having antipsychotics (all-cause: HR, 1.0160; 95%CI, 1.0124-1.020; unnatural cause: HR, 1.0110; 95%CI, 1.0090-1.0140; natural cause: HR, 1.0330; 95%CI, 1.0240-1.0430) or the more significant number of discontinuous doses (all-cause: HR, 1.489; 95%CI, 1.208-1.834; unnatural cause: HR, 1.578; 95%CI, 1.405-1.771; natural cause: HR, 2.186; 95%CI, 1.428-3.346) were all reported to be the risk factors of all-cause, natural cause, and unnatural cause mortality among patients with schizophrenia.

Discussion: These findings suggested that longer antipsychotic medication duration could have long-term protective effects on mortality. In contrast, larger number of antipsychotic drug counts for a long period could increase long-term mortality risk among participants with schizophrenia. The antipsychotic medication over a long period has a different effect than that of the year before death, highlighting the importance of future research on antipsychotic medication in psychiatric patients both over a long period and over different periods.

T27. CLIMATE CHANGE, A MAJOR DETERMINANT OF MENTAL HEALTH AND A TARGET FOR EARLY INTERVENTION

Philippe Conus^{*1}, Yaëlle Fouvy¹, Philippe Golay¹, Céline Bourquin¹

¹*Lausanne University Hospital*

Background: Many elements in the scientific literature suggest that climate change has a negative influence on mental health. Considering this impact, we wanted to explore this link which may support the idea that acting against climate change may become a valid early intervention strategy in mental health.

Methods: We conducted an extensive literature review on the subject and conducted a large survey among 15'000 students at Lausanne university in order to explore various potential impact of climate change issues on the mental health of the young people aged 18 to 25.

Results: Many elements of the literature suggest there is a link between climate change and mental health which can be defined as direct (during major natural disasters), progressive (due to drought or rise in sea levels) and indirect (through mechanisms such as solastalgia and ecoanxiety). Amongst university students, 86% are worried to extremely worried about climate change, 55% exclude having children due to this problem and 26% consider themselves as suffering from ecoanxiety.

Discussion: Climate change has an important impact on mental health and may drive our societies to an important increase in the prevalence of many disorders such as PTSD, anxiety and depressive disorders and suicide. In addition, students are at high risk of mental health issues due to this phenomenon. Considering these elements, acting on climate change is a valid strategy for early intervention in mental health.

T28. EFFORT-BASED DECISION MAKING IN SUBCLINICAL PSYCHOTIC SYMPTOMS AND ITS RELATIONSHIP WITH AMOTIVATION

Sai Ting Chu^{*1}, CoCo Ho Yi Tong¹, Corine Sau Man Wong², Wesley Chor Yin Tang¹, Charlotte Cheuk Lok Chan¹, Christy Lai Ming Hui¹, Kit Wa Sherry Chan¹, Edwin Ho Ming Lee¹, Simon Sai Yu Lui¹, Yi Nam Suen¹, Eric YH Chen¹, Wing Chung Chang¹

¹The University of Hong Kong, ²School of Public Health, LKS Faculty of Medicine, The University of Hong Kong

Background: Research suggests that people with subclinical psychotic symptoms (PS) exhibit similar abnormalities in various cognitive functions with, albeit in a milder degree than, schizophrenia patients. Suboptimal effort-based decision-making with reduced willingness to exert effort for high-probability/high-value reward is observed in schizophrenia patients and is related to diminished motivation, but is understudied in PS. This study aimed to examine effort-allocation in PS individuals and its association with amotivation.

Methods: We recruited 100 individuals with PS and 100 demographically-matched healthy controls based on Psychosis Module of Composite International Diagnostic Interview (CIDI), from Hong Kong Youth Epidemiology Study of Mental Health (HK-YES), a population-based mental health study examining over 3500 youths in Hong Kong. Participants with lifetime diagnosis or family history of psychotic or bipolar disorder, or history of antipsychotic treatment were excluded. A well-validated computerized Effort-Expenditure for Reward Task (EEfRT) was administered to quantify physical effort allocation (hard vs easy task based on button pressing) for monetary reward (small, medium, high and highest) of varying magnitude and probability levels (12%, 50% and 88%). In addition, negative/amotivation symptoms were assessed by the Brief Negative Symptom Scale (BNSS). Individuals with PS were categorized into high-amotivation and low-amotivation groups based on a median-split of BNSS amotivation domain score.

Results: Our results showed marginally significant group by probability interaction effect (in two-group comparison) ($p=0.064$) on effort task performance. Selected EEfRT performance indices revealed that people with PS displayed marginally smaller increase in effortful options from low- to high-probability (probability-difference score) than controls ($p=0.063$). When median-splitting BNSS amotivation score, we observed a significant group by probability interaction ($F_{3,79,373.06}=2.80$, $p=0.028$). Post-hoc contrast tests on probability by group interaction were all non-significant (all p GREATER THAN 0.05). Three-group comparison analyses on selected EEfRT performance indices revealed that high-amotivation individuals with PS displayed significantly less increase in effortful options from low- to high- probability (probability-difference score) than controls ($p=0.022$), and a significant and marginally significant between-group effects from low-probability/low-value to high-probability/high-value reward (probability/reward-difference score) than low-amotivation individuals ($p=0.049$) and controls ($p=0.095$) respectively.

Discussion: Our findings indicated subtle effort-allocation abnormalities in PS individuals with high levels of diminished motivation. Our results in general aligned with subtle findings in studies in schizotypy and PS.

T29. PROGNOSTIC MODELS PREDICTING TRANSITION TO PSYCHOTIC DISORDER USING BLOOD-BASED BIOMARKERS: A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL

Jonah Byrne^{*1}, David Mongan², Jennifer Murphy³, Colm Healy³, Melanie Föcking³, Mary Cannon³, David Cotter³

¹Royal College of Surgeons in Ireland, ²Queen's University Belfast, ³RCSI University of Medicine and Health Sciences

Background: Accumulating evidence suggests individuals with psychotic disorder show abnormalities in metabolic and inflammatory processes. Recently, several studies have employed blood-based predictors in models predicting transition to psychotic disorder in risk-enriched populations. A systematic review of the performance and methodology of prognostic models using blood-based biomarkers in the prediction of psychotic disorder from risk-enriched populations is warranted.

Methods: Databases (PubMed, EMBASE and PsycINFO) were searched for eligible texts from 1998 to 15/05/2023 which detailed model development or validation studies. The checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) was used to guide data extraction from eligible texts and the Prediction Model Risk of Bias Assessment Tool (PROBAST) was used to assess risk of bias and applicability of the studies. A narrative synthesis of included studies was performed.

Results: 17 eligible studies were identified: 16 eligible model development studies and one eligible model validation study. Several biomarkers were assessed including nucleic acids, proteins, metabolites and lipids. The range of C-index (area under the curve) estimates reported for the models was 0.67-1.00. No studies assessed model calibration. According to PROBAST criteria, all studies were at high risk of bias in the analysis domain.

Discussion: While a range of potentially predictive biomarkers were identified in the included studies, most studies did not account for overfitting in model performance estimates and all models were at high risk of bias according to PROBAST criteria. External validation of the models is needed to provide more accurate estimates of their performance. Future studies which follow the latest available methodological and reporting guidelines and adopt strategies to accommodate required sample sizes for model development or validation will clarify the value of including blood-based biomarkers in models predicting psychosis.

T30. COURSE OF NEUROCOGNITIVE DEVELOPMENT IN CHILDREN AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER: A PROSPECTIVE COHORT STUDY FROM 7 TO 15 YEARS OF AGE. THE DANISH HIGH RISK AND RESILIENCE STUDY – VIA 15

Andreas Færgemand Laursen^{*1}, Anette Faurskov Bundgaard², Nanna Lawaetz Steffensen², Merete Birk³, Sinnika Rohd⁴, Martin Wilms⁵, Marta Schiavon⁶, Doris-Helena Feodora Bjarnadóttir Olsen⁶, Jens Richardt Møllegaard Jepsen⁷, Torill Ueland⁸, Merete Nordentoft⁹, Ole Mors¹⁰, Anne A.E. Thorup¹¹, Aja Neergaard Greve², Nicoline Hemager¹²

¹Aarhus University Hospital Psychiatry, Psychosis Research Unit., ²Aarhus University Hospital, ³The Psychosis Research Unit, Aarhus University Hospital Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ⁴Copenhagen Research Center for Mental Health – CORE, Mental Health Center Copenhagen, Mental Health Services; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ⁵CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, ⁶Copenhagen University Hospital, ⁷Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Mental Health Services - Capital Region of Denmark, Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, ⁸Oslo University Hospital HF and University of Oslo, NORMENT, K.G. Jebsen, Psychosis Research Unit/TOP; University of Oslo, Norway,

⁹*Copenhagen University Hospital, Mental Health Center Copenhagen, Copenhagen Research Center for Mental Health - CORE,* ¹⁰*The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Psychosis Research Unit, Aarhus University Hospital,* ¹¹*Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research,* ¹²*Research Unit at Mental Health Center, Capital Region of Denmark and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH)*

Background: Schizophrenia (SZ) and bipolar disorder (BP) are severe mental disorders with shared and distinct clinical, cognitive, and genetic risk factors. These risk markers are also present in the offspring, who have an increased risk of developing severe mental disorders. SZ is a neurodevelopmental disorder and neurocognitive impairments are presenting years before the manifestation of overt clinical symptoms. Findings regarding premorbid neurocognitive impairments in BP are less conclusive. Investigating the course of neurocognitive development before illness offers insights into both shared and disorder-specific vulnerability markers.

The neurocognitive results from previous assessments of the presented cohort showed stable neurocognitive deficits in children at familial high risk (FHR) of SZ and stable neurocognitive functioning in children at FHR-BP that were comparable to population-based controls (PBC).

The aim of the current study is to characterize the neurocognitive development in children at FHR-SZ and FHR-BP compared with PBC from age 7 to 15 and to identify potential subgroups of children across high-risk groups, with distinct neurocognitive profiles and developmental patterns.

We hypothesize that children at FHR-SZ will display either stable deficits or neurocognitive lags compared with PBC at age 15, and that children at FHR-BP will display stable comparable neurocognitive development or incipient lags at age 15 compared with PBC.

Methods: The Danish High Risk and Resilience Study is a population-based cohort of 522 children (202 FHR-SZ, 120 FHR-BP, and 200 PBC). They were assessed at baseline at age 7 (the VIA 7 study) and at first follow-up at age 11 (the VIA 11 study) with a retention rate of 89%. The VIA 15 study is the third wave of assessments at 15 years of age and started May 2021. Neurocognitive functioning is assessed with a comprehensive neurocognitive test battery of validated tasks covering a wide range of neurocognitive functions. The tests were selected to target neurocognitive functions known to be impaired in SZ and BP, including intelligence, processing speed, attention, verbal and visuospatial memory, verbal fluency, working memory, and executive functions.

Results: Data collection is ongoing and will be finalized in the spring of 2024.

Discussion: Examining the development of neurocognitive deficits in children at FHR-SZ and FHR-BP will elucidate shared and distinct endophenotypes and help differentiate the pathophysiology of these severe mental disorders. The long-term perspective is the ability to use the knowledge about the developmental trajectories to guide intervention studies and inform preventive interventions to improve functioning, quality of life, and potentially even prevent transition to mental disorders.

T31. THE LONGITUDINAL RELATIONSHIP BETWEEN PSYCHOTIC EXPERIENCES AND DISORDERED EATING IN HIGH SCHOOL ADOLESCENTS: BODY IMAGE AS A MEDIATOR

Feten Fekih-Romdhane*¹, Lilia Houissa¹, Souheil Hallit², Alexandre Andrade Loch³, Majda Cheour¹

¹Tunis El Manar University, Faculty of Medicine of Tunis, ²Holy Spirit university of Kasik, Lebanon, ³Universidade de Sao Paulo

Background: Despite all the evidence on the highly prevalent co-occurrence of psychosis and disordered eating (DE), the relationship between these psychopathological entities remains a challenging area of research to which little interest has been paid. As the vast majority of previous studies were hindered by a cross-sectional design and an inability to establish temporal associations or their corresponding underlying mechanisms, it is still unclear whether DE precedes or follows the onset of psychosis. In addition, previous evidence was mainly based on clinical samples at advanced stages of the diseases, which precludes investigation of the relationship psychosis-DE along the continuum, particularly in early stages where confounders such as chronicity of the disease and treatment effects are excluded. Using longitudinal data, we aimed to explore the hypothesis that the pathways from psychotic experiences (PEs) to DE and body-mass index (BMI) are mediated by body-image disturbances.

Methods: A prospective longitudinal study was performed. High-school students (N=510, 61.2% females, mean age of 16.05±1.01 years) were asked to complete three scheduled assessments (Baseline, 6 months, and 12 months).

Results: Two body image components, i.e. Overweight Preoccupation and Body Area Satisfaction, mediated the prospective association between baseline PEs and DE 12 months later. Direct effects were significant. After accounting for indirect effects through more severe body image concerns at 6 months, higher baseline PEs were significantly associated with greater DE at 12 months. Baseline PEs and 6-month body image explained a significant proportion of variance in 12-month DE. However, we did not find evidence of a direct prospective association between PEs and BMI.

Discussion: To the best of our knowledge, the present study provides, for the first time in literature, empirical evidence of direct and indirect longitudinal associations between PEs and DE through body image in non-clinical adolescents from an Arab North-African country. The first key finding that emerged from this study is that two body image components, i.e. Overweight Preoccupation and Body Area Satisfaction, mediated the prospective association between baseline PEs and DE 12 months later. Second, direct effects were significant. After accounting for indirect effects through more severe body image concerns at 6 months, higher baseline PEs were significantly associated with greater DE at 12 months. Together, baseline PEs and 6-month body image explained a significant proportion of variance in 12-month DE. However, we did not find evidence of a direct prospective association between PEs and BMI. These findings suggest that the identification of PEs as valid and reliable early markers of DE can further enhance our ability to detect its emergence in adolescents from the general population before it progresses to more severe stages. In addition, body image disturbances may be the key to reducing the impact of PEs on the emergence of later DE and are thus recommended to be the focus of prevention and individualized early intervention strategies.

T32. RISK OF HOMELESSNESS AFTER PRISON RELEASE AND RECIDIVISM IN DENMARK: A NATIONWIDE, REGISTER-BASED COHORT STUDY

Sandra Nilsson^{*1}, Merete Nordentoft², Seena Fazel³, Thomas Munk Laursen⁴

¹*Copenhagen Research Center for Mental Health - CORE*, ²*Mental Health Centre Copenhagen*, ³*University of Oxford*, ⁴*Aarhus University*

Background: Transitional periods between and across services have been linked to homelessness. We aimed to study the prior homelessness and psychiatric disorders according to the risk of post-release homelessness and the post-release homelessness and the risk of recidivism.

Methods: We did a register-based nationwide cohort study of 37,382 people aged at least 15 years released for the first time from prison in Denmark from 1 Jan, 2001, until 31 Dec, 2021, born 1980-2007. Information on release date, homeless shelter contact, psychiatric disorders (severe mental illness defined as any schizophrenia spectrum disorder or any bipolar disorder), and new convictions were obtained from the linked population-based registers. We estimated incidence rate (IR) and incidence rate ratio (IRR) using Poisson regression analysis adjusting for confounders and calculated cumulative incidences of post-release homelessness and recidivism.

Results: The study cohort included 37,382 individuals (34,792 males (93.1%) and 2590 females (6.9%)) aged 15-41 years of age who were released from prison during 2001-2021, accounting for 202,197 person-years (mean follow-up: 5.4 person-years) at risk. Overall, 1843 (4.9%) individuals became homeless. One year after release from prison, 2.1% had at least one homeless shelter contact, and it was 20.7% in those with homelessness prior to the index-imprisonment. The IR of post-release homelessness was 102.5 per 1000 person-years for individuals with prior homelessness and 6.7/1000 person-years in individuals without (IRR 16.4, 95% CI 14.8-18.2 adjusted for sex, age, and calendar year). Individuals who additionally had a severe mental illness had a similar IRR (16.2, 95% CI 12.8-20.7) compared with those without either, but higher for those with prior homelessness and drug use disorder (IRR 25.0, 21.6-28.9). Within two years post-release, the cumulative probability of recidivism was 73.2% (95% CI 72.8-73.7). People experiencing post-release homelessness had an IRR for recidivism of 1.5 (95% CI 1.3-1.7) compared with no homelessness. Individuals who experienced homelessness after prison release who also had a severe mental illness had 1.9-times increased rate of recidivism (95% CI 1.3-2.9) compared with no homeless shelter contact after release and no severe mental illness. Higher risk was found for homelessness in combination with drug use disorder or substance misuse comorbidity.

Discussion: Particularly attention to mental health and pre-prison homelessness and unstable housing is warranted for individuals incarcerated, to reduce the risk of further homelessness and other negative outcomes post-release.

T33. ABNORMAL GESTATIONAL AGE PREDICTS PSYCHOSIS RISK SYNDROME IN CHILDREN AND ADOLESCENTS: RESULTS FROM THE CAPRIS STUDY

Inmaculada Baeza^{*1}, Elena De la Serna², Olga Puig-Navarro³, Daniel Ilzarbe⁴, Gisela Sugranyes⁵, Adriana Fortea⁶, Andrea Juez-Gali⁷, Jordina Tor⁸, Daniel Muñoz-Samons⁸, Marta Rodriguez-Pascual⁸, Xavier Álvarez-Subiela⁸, Montse Dolz Abadia⁹

¹*Hospital Clinic de Barcelona*, ²*Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM*, ³*Child and Adolescent Psychiatry and Clinical Psychology Dept. H Clínic Barcelona*, ⁴*Institute of Neuroscience, Hospital Clinic de Barcelona*, ⁵*Instituto de*

Investigaciones Biomedicas de Barcelona, CSIC-IDIBAPS-CIBERSAM, ⁶Department of Child and Adolescent Psychiatry, Hospital Clinic / Fundació Clinic per la la Recerca Biomèdica (FCRB) / Universitat de Barcelona, ⁷Hospital Clínic de Barcelona, Spain; Universidad Internacional de la Rioja, ⁸Hospital Sant Joan de Déu, Barcelona, ⁹Hospital Sant Joan de Deu Barcelona

Background: Obstetric complications (OCS) are risk factors for a first episode of psychosis (Davies et al, 2020), but in clinical high risk states or psychosis risk syndrome (PRS) the results are controversial (Mittal et al, 2009; Yun et al, 2005). However, in children and adolescents with PRS no studies have addressed this issue.

The objective was to study the differences in OCS in children and adolescents with PRS for psychosis and healthy controls (HC).

Methods: An 18-month prospective longitudinal study (CAPRIS) in which help-seeking minors meeting PRS criteria were recruited from two hospitals in Barcelona, Spain. A sample of HCs were also included. At baseline, the Semistructured Interview for Prodromal Syndromes and Scale (SIPS/SOPS) were administered, as well as a clinical scale battery. To measure OCS, the Obstetric Complications Scale (Lewis and Murray, 1988) was used. Either definite or equivocal ratings were considered an indication of OCS.

Results: 198 PRS subjects and 153 HC were included. No differences were found in age between the samples (15.1 ± 1.7 v 15 ± 2) but 69.5% of PRS subjects were girls, significantly different than the 57.5% in HC ($\chi^2 = 5.425$, $p = 0.024$).

Subjects with PRS presented more OCS than HC (56.6 vs. 42.5%, $\chi^2 = 6.847$, $p = 0.010$). Moreover, 12.4% of PRS subjects had their birth at a definite abnormal gestational age vs. 3.6% of HC ($\chi^2 = 7.769$, $p = 0.005$). No other significant differences were found in the other OCS nor birth weight.

Logistic regression showed an association of abnormal gestational age with PRS (OR=1.68 95%CI:1.00-2.82, $p = 0.048$).

Discussion: OCS were more frequent in CHR subjects, specifically, abnormal gestational age, in line with previous studies of risk factors of psychosis (Fusar-Poli et al, 2017; Davies et al, 2020). The role in transition to psychosis and other psychopathological outcomes in this at risk young population deserves further study.

This study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects PI21/00391 and PI21/0009, and co-funded by the European Union.

T34. AN EXAMINATION OF THE EARLY AND LATE STARTER TYPOLOGY OF CRIMINOGENIC BEHAVIOUR AND ITS RELATION TO IMPULSIVITY, PSYCHOTIC SYMPTOMS, AND AGGRESSION IN A SAMPLE OF INDIVIDUALS EXPERIENCING A FIRST EPISODE OF PSYCHOSIS

Shreya Jagtap^{*1}, Marco Kilada², Cory Gerritsen¹

¹Centre for Addiction and Mental Health, University of Toronto, ²Centre for Addiction and Mental Health

Background: Individuals with psychosis are at an increased risk, relative to the general population, of committing an aggression-related criminal offence, with up to one third of individuals experiencing their first episode of psychosis (FEP) engaging violence. Thus, early intervention of factors predicting aggression in this population is crucial. Past research has

identified two groups of offenders with major mental illnesses: early starters and late starters. These groups can be differentiated based on a range of factors which co-occur with criminogenic activity. One of these factors includes impulsivity, with greater impulsivity and lower behavioural control being characteristic of early starters (those who have committed criminal acts prior to the age of 18). Both psychotic symptoms and cognitive and behavioural impulsivity are shown to be predictive of aggression, however, little research has examined the relationship between these variables and aggressive behaviour in a FEP sample. The primary aim of this study was to determine whether individuals experiencing a FEP who are differentiated based on the early and late starter typology exhibit significant differences in levels of psychotic symptoms and cognitive and behavioural impulsivity.

Methods: This study recruited a sample of 24 individuals with a diagnosis of FEP syndrome who entered the mental healthcare system through both forensic (incarceration) and non-forensic (hospitalization) pathways. Cognitive impulsivity was assessed using contrast scaled scores of the interference trial of the Delis Kaplan Colour-Word Interference Test, and behavioural impulsivity was assessed using the Barrett Impulsiveness Scale. Current psychotic symptoms were assessed using factor dimensions from the Brief Psychiatric Rating Scale (BPRS). Aggressive incidents over childhood, adolescence, and adulthood were assessed using the Brown-Goodwin Aggression Scale. Three multiple linear regression models were conducted to examine if psychotic symptoms and cognitive and behavioural impulsivity predicted aggression in adolescence/childhood as well as during adulthood.

Results: Results of the first linear regression model indicated that model was statistically significant, $F(7,16) = 2.74$, $p = .045$, and the BPRS factors of negative ($\beta = -.48$, $p = .046$) and positive symptoms ($\beta = .65$, $p = .010$) significant predicted childhood and adolescent aggression, when controlling for adult aggression. Results from the second linear regression indicated that the model was statistically significant, $F(6,17) = 3.26$, $p = .026$, with the BPRS factor of anxiety/depression ($\beta = .55$, $p = .021$), as well as positive ($\beta = .62$, $p = .009$) and negative symptoms ($\beta = -.53$, $p = .017$) found to significantly predict childhood and adolescent aggression. Our third model was not found to be significant, $F(6,17) = 1.40$, $p = .270$, however, the BPRS factor of anxiety/depression was found to significantly predict adult aggression ($\beta = .60$, $p = .033$).

Discussion: Our findings highlight that current psychotic symptoms were demonstrated to be significantly linked to aggression in childhood and adolescence. These findings converge with existing literature supporting the existence of a predisposing factor related to aggression that is present prior to adulthood (e.g., conduct disorder), representing a possible distinct subtype of psychosis, which the current research suggests may be related to symptom severity during FEP. Of note, neither behavioural nor cognitive impulsivity predicted aggression in either childhood/adolescence or adulthood, suggesting that current symptoms are more related to past aggression than impulsivity in FEP, even when controlling for current aggression.

T35. THE ASSOCIATION OF AUTISTIC TRAITS AND PSYCHOSIS PRONENESS WITH ALLOCENTRIC AND EGOCENTRIC INTERPERSONAL DISTANCE

Ahmad Abu-Akel*¹, Mais Kanaan¹

¹University of Haifa

Background: People with autism and psychosis spectrum disorders (ASD and PSD, respectively) present more social isolation than any other diagnostic group and have smaller social networks than people from the general population. Interpersonal distance is a key

component of social behavior, which when violated may cause significant discomfort or distress and might help explain social isolation and functioning in both ASD and PSD. However, despite these similarities, the relationship between ASD and PSD and their extended phenotypic continua in the general population on how they might impact interpersonal distance within the same individual is yet to be examined. To address this gap, this study examines how variations in co-occurring autistic traits and psychosis proneness, and their specific phenotypes are similarly or differently associated with preference for interpersonal distance.

Methods: Data were obtained from 87 neurotypical adults from the general population (M/F = 27/61; Mean Age = 27.7; SD = 10.44) in whom both autistic traits and psychosis proneness were assessed in tandem. Autistic traits were assessed using the Abridged Version of the Autism-Spectrum Quotient (AQ-28) and psychosis proneness was assessed with the positive subscale of the Community Assessment of Psychic experiences. Analyzing subclinical expressions of ASD and PSD confers several advantages such as eliminating the confounding effects of medication, active symptomatology or illness chronicity. Participants were asked to indicate their preferred interpersonal distance from another person in a social setting under two conditions: when approaching a person (the egocentric condition) and when being approached (the allocentric condition). For each of the experimental conditions, regression analyses estimated the association of autistic traits, psychosis proneness and their interaction with preferred interpersonal distance. In a separate analysis, we also estimated for both conditions the association of autistic (social skills ,routine ,focus of attention, imagination ,and numbers and patterns) and psychosis proneness subscales (bizarre experiences, perceptual abnormalities, persecutory ideation, and magical thinking) with preferred interpersonal distance.

Results: The regression analyses showed that increased overall autistic traits were significantly associated with preference for greater interpersonal distance in both the egocentric and allocentric conditions. Overall psychosis proneness or its interaction with overall autistic traits were nonsignificant predictors. The regression analyses estimating the association of autistic and psychosis proneness phenotypes with preferred interpersonal distance revealed a more nuanced picture. In the egocentric condition, higher levels of autistic focus of attention traits were associated with greater distance, whilst higher levels of bizarre experiences were associated with shorter distance. In the allocentric conditions, higher levels of autistic focus of attention traits and higher levels of persecutory ideation were associated with greater distance, whilst higher levels of bizarre experiences were associated with shorter distance.

Discussion: Co-occurring psychosis proneness and autistic traits are associated with preferred interpersonal distance through both overlapping and diametric pathways. Increased focused of attention and bizarre experiences may respectively contrast in terms of rigid versus flexible self-boundaries. Persecutory ideation in the allocentric condition may relate to perceived threat and thus may be associated with a different mechanism pertaining to social isolation and self-protection. This study highlights the benefit of adopting a transdiagnostic, multidimensional approach in examining the impact of psychiatric and mental health conditions on the individual's social functioning and practices.

T36. TIME EXPECTATION AND SENSE OF SELF: THE ROLE OF MOTOR PREPARATION

Anne Giersch^{*1}, François Foerster², Brice Martin³, Ellen Joos¹, Jennifer Coull⁴

¹INSERM (French Medical Research Institute), ²INSERM U1114, ³Centre Hospitalier Drôme Vivarais, Montéleger-Valence, ⁴UMR 7291, Aix-Marseille Université, and Service Universitaire de Psychiatrie. Hôpital Ste Marguerite. Marseille

Background: It has long been proposed that individuals with schizophrenia (SZ) experience a breakdown of the experience of time continuity, and that this relates to disorders of the minimal self. This proposal relies on the patients' self-reports and the phenomenological analysis of their verbal descriptions. Recent experimental evidence supported this proposal by exploring time expectation in parallel with phenomenological evaluations (the EASE, Martin et al. 2017, Sci Rep), and by showing a link between disorders of the minimal self and of time expectation. Time expectation is indexed by the ability to benefit from the passage of time. This is observed when individuals react to a visual target appearing at various delays after a cue: expectation increases with time, leading to shorter reaction times when the target occurs after a long than after a short delay. Such expectation is implicit, as it does not require to explicitly think about time. It is close to conditions in everyday life. However, our former study required the target to be processed before giving a response (the subjects had to press to the side of the target), meaning that participants could not prepare their motor response in advance. This is a limitation because time accumulation is associated with SMA activation (Coull and Giersch, Nat Rev Psychol 2022) and involves motor aspects. Here we explored the benefit of the passage of time associated with motor preparation. To make sure the preparation was not altered by a 'surprise' effect (e.g. a target appearing earlier than on the previous trial), we considered only consecutive trials with identical delays.

Methods: Twenty four outpatients with SZ and 22 neurotypicals were recruited in a first study, and eighteen outpatients with SZ and 18 neurotypicals in a second study (in a different centre). In the first study, the target was shown 400 or 1000 ms after a neutral cue. Targets were shown on the left or on the right but participants could choose the side of their response. The second task took place in virtual reality, the target was always displayed in the centre, and delays were 900 and 1500 ms. There was no interaction with the task, and for the sake of simplicity here we display the results over the two tasks put together. We extracted a common factor reflecting the benefit of the passage of time by calculating the difference in RT between the short and long delays. We normalized the data by dividing this difference by the sum of RTs for short and long delays. The minimal self was evaluated with the EASE scale in the first study.

Results: The benefit of the passage of time was observed only in neurotypicals; it was not present in patients with SZ. Moreover, in study 1, we observed a correlation between the calculated benefit and the subscale 'presence'. Sub-group analyses confirmed that patients who feel as not being immersed in the world (EASE) do not benefit from the passage of time, consistent with previous results.

Discussion: The results confirm a fragility in time expectation in individuals with SZ, and generalize the results to motor preparation. They also confirm a link between this vulnerability and minimal self disorders, consistent with the idea that individuals with minimal self disorders (altered immersion in the world) display a breakdown of time continuity. The generalization of the effect to motor preparation means a disruption close to bodily self disorders, and is consistent with prior work suggesting altered motor planning.

T37. COGNITIVE CONTROL OVER SOCIAL THREAT: A TRUST VARIANT OF THE AX TASK PREDICTS PERSECUTORY IDEATION IN PSYCHOSIS PATIENTS AND HEALTHY ADULTS

Angus MacDonald*¹, Rebecca Kazinka²

¹University of Minnesota, ²University of Minnesota Medical School

Background: Failures of dorsolateral prefrontal cortex (DLPFC) on non-social cognitive control tasks have been replicably associated with the disorganization symptoms of psychosis patients (Chun, et al., 2018). In contrast, positive symptoms such as persecutory ideation have been modeled as the result of predictive coding errors which are largely unrelated to DLPFC (Sheffield, et al., 2022). However, recent imaging work suggests dysconnectivity between DLPFC and emotional and salience networks predicts suspicious decision making on a modified trust game (Wisner, et al., 2021; Kazinka, et al., in press). The current study used a social variant of a DLPFC-related task, the expectancy AX task, to scrutinize how cognitive control related to the expression of persecutory ideation.

Methods: In two studies (Study 1 n=117 undergraduate students; Study 2 = 46 psychosis patients and n=44 persecution-matched controls) participants responded as to whether or not to accept a “deal” from an individual identified by their face to obtain a favorite snack that they had picked. On most trials, participants were presented with a partner’s face (hereafter A) that was commonly followed by the preferred snack the partner would never actually give (hereafter X). Other faces (B’s) presenting that preferred snack would give it. Similarly, partner A would also be willing to give lesser snacks (Y’s) The task had 144 trials, with 72% AX, 11% AY, 11% BX, 6% BY trials. Participants were rewarded with a snack based on a random deal at the end of the experiment. Participants were psychometrically assessed for persecutory ideation, and patients were additionally interviewed.

Results: In both Studies 1 and 2, participants made relatively few errors when rejecting the untrustworthy A partner when offered the X snack, and made the most errors when attempting to trust that partner for other Y snacks. However, participants with the highest levels of persecution also failed to trust the B partners when they were offered their preferred X snack. Furthermore, patients showed more impairment on these trials than healthy adults.

Discussion: This social cognitive control task suggests an important role for the breakdown of the representation and maintenance of a trustworthy partner. This failure seems to occur in individuals expressing persecutory ideation and even more moderate levels of suspiciousness. This has important implications for understanding how common network and connectivity failures may manifest in different symptom factors and adds cautions to our interpretation of persecution as being simply a function of early reward-learning based predictions.

T38. INTRAUTERINE POSITION EFFECTS SHAPE RISK AND RESILIENCE IN A MOUSE MODEL OF MATERNAL IMMUNE ACTIVATION

Ron Schär*¹, Flavia Müller², Ulrike Weber-Stadlbauer³, Urs Meyer⁴

¹University of Zürich, ²Institute of Pharmacology and Toxicology, University of Zurich - Vetsuisse, Zurich, ³Institute for Veterinary Pharmacology and Toxicology, University of Zurich – Vetsuisse, ⁴Institute of Pharmacology and Toxicology, University of Zurich-Vetsuisse, Zurich

Background: Rodent models of maternal immune activation (MIA) are widely used as experimental tools to study the neuronal and behavioral dysfunctions in relation to immune-mediated mental illnesses, including psychotic disorders. Using a viral-like MIA model that is based on prenatal poly(I:C) exposure in mice, we have recently identified the existence of subgroups of MIA-exposed offspring that show dissociable behavioral, transcriptional, brain network and inflammatory profiles even under conditions of genetic homogeneity and

identical MIA. Interestingly, this variability in the effects of MIA was found to be largely driven by within-litter rather than between-litter variation. Here, we tested the hypothesis that intrauterine position, which are known to shape individual variability in litter-bearing mammals through variations in fetal hormone exposure, contribute to the variable outcomes of MIA in mouse models.

Methods: MIA was induced by maternal administration of poly(I:C) (5 mg/kg, i.v.) on gestation day 12 in C57BL/6N mice. In a first cohort, MIA-exposed and control offspring were delivered by Cesarean section (C-section) in order to determine possible intrauterine position effects on behavioral outcomes in adulthood. Offspring delivered by C-section were raised by foster mothers with identical treatment histories, whereby each foster mother kept 2 of its own (vaginally born) pups and received 6 C-sectioned pups. In a second cohort of offspring, MIA-treated and control dams were killed to collect fetal brains 3 hrs or 5 days after poly(I:C) or vehicle treatment. Fetal brain specimens were then used to measure pro- and anti-inflammatory cytokines (IL-1 α , IL-6, IL-10, and TNF- α) and testosterone.

Results: Adult offspring of MIA-exposed mothers displayed deficits in social approach behavior and prepulse inhibition (PPI) of the acoustic startle reflex, but only under conditions when fetuses were not neighbored by males in utero (0M-MIA offspring). In contrast, MIA-exposed offspring developing between 1 or 2 males in utero (1/2M-MIA offspring) did not show significant deficits in social approach behavior or PPI at adult age. These intrauterine position effects similarly emerged in male and female offspring. At 3 hrs after poly(I:C) administration, MIA elevated fetal brain levels of pro- and anti-inflammatory cytokines independent of the precise intrauterine position and sex of adjacent fetuses. At the later sampling interval (i.e., 5 days after treatment), however, fetal brain levels of TNF- α remained elevated specifically in 0M-MIA offspring, whereas all cytokine levels normalized in 1/2M-MIA offspring to levels measured in control fetuses. As expected, 1/2M offspring generally showed higher testosterone levels in the fetal brain as compared to 0M offspring, confirming the transfer of testosterone from male fetuses to adjacent male or female fetuses.

Discussion: The present study provides the first direct evidence suggesting that intrauterine position effects contribute to variable outcomes in schizophrenia-related behaviors and inflammatory responses in a widely used mouse model of MIA. In broader context, our findings highlight that individual differences in fetal testosterone exposure may be a perinatal factor that shapes risk and resilience to MIA.

T39. TEMPORAL ORDER AND CAUSALITY JUDGMENTS IN SCHIZOPHRENIA

Cristina Rusu¹, Brice Martin², Anne Giersch¹, Cristina Rusu*³

¹INSERM (French Medical Research Institute), ²Centre Hospitalier Drôme Vivarais, Montéleger-Valence, ³INSERM

Background: Ordering events in time is involved in the understanding of causal relationships between successive events. Faulty causal interpretations can lead to false beliefs, which might eventually result in an altered perception of reality. We repeatedly showed that individuals with schizophrenia (SZ) have difficulties to judge the temporal order of two events (Capa et al., 2014, Schiz Res; Arrouet et al., 2022, Timing and Time Perception). Here we explored how temporal difficulties affect causality. We adapted a paradigm typically used to explore causality (the Michotte paradigm) in order to evaluate causality and order judgements on the same material, i.e. to explore the relation between those two judgements in individuals with SZ vs. neurotypicals.

Methods: Twenty eight outpatients with SZ and 21 neurotypicals were recruited for this study. The two groups were matched on age, sex and education level. All participants ran three successive tasks entailing exactly the same trials. However, each task required different judgements. On each trial a square moved at 2°/second on a horizontal axis, starting from 1.7° in the periphery (left or right) and moving in the direction of the center of the screen. It stopped when it reached the position of a second square, which was displayed on the opposite side of the screen (1.7° left or right from the screen center). This second square remained static, and was displayed at various time delays (17, 32, 64, 128, 256 or 512 ms) before or after the stop of the moving square. In one task the participant evaluated to which amount the static square stopped the moving square, and answered by giving a number between 0 and 100. On the other causality task, the participant evaluated to which amount the moving square caused the appearance of the static square, and again answered with a number between 0 and 100. The order of the two causality tasks was randomized. In the third task participants had to emit a temporal order judgement, by pressing to the side of the first event, i.e. the stop of the moving square (event M) or the onset of the static square (event S).

Results: In controls causality judgement dropped when the delay between events M and S was more than 200 ms. Judgements of causality in individuals with SZ were similar to neurotypicals for short delays between events M and S (LESS THAN 200 ms), but remained high, and significantly higher than controls for large delays between events M and S (GREATER THAN 200 ms). In the temporal order judgement task, patients gave less correct responses than neurotypicals for delays larger than 200 ms, despite the fact that these are the easiest conditions. In addition at short delays, neurotypicals, but not individuals with SZ, were biased to answer that event S was the first one.

Discussion: This study brings further evidence for a difficulty in temporal order processing in SZ. Importantly it shows that difficulty at correctly detecting temporal order is accompanied by increased perceived causality when two successive events are temporally separate. Such a difficulty may contribute to aberrant causality. The bias at short delay appears to be due to an attentional bias following causality judgements. Motion is believed to play an important role in causality judgements. Conversely having to judge whether the static square stopped the moving one may have biased the participants' attention towards the S event. The lack of bias in individuals with SZ shows that causality judgements do not impact their temporal order perception. Their judgement of causality may be of a different nature if they have difficulty to determine order, and may be more noisy. In turn if their causality judgements are noisy, they may not influence temporal judgements as strongly as in controls.

T40. COGNITIVE REMEDIATION THERAPY FOR EXECUTIVE FUNCTION AND AGGRESSIVE BEHAVIOURS IN FORENSIC PSYCHOSIS

Cecelia Shvetz*¹, Patrizia Pezzoli², Jasmin Yee¹, Yuvika Dandiwal³, Katie Bush¹, Nicole Rodrigues⁴, Sanjiv Gulati⁴, Michael Seto³, Synthia Guimond³

¹Carleton University, ²University College London, ³University of Ottawa Institute of Mental Health Research, ⁴Brockville Mental Health Centre

Background: Executive function deficits are a core feature of psychosis, encompassing difficulties in planning, strategic thinking, problem-solving, and appropriate behavioural responses^{1,2}. In forensic patients with psychosis, executive function deficits can interfere with rehabilitation outcomes and may relate to displays of verbal and physical aggression³. Cognitive remediation therapy (CRT) can be used to improve executive function⁴ and relevant outcomes, including aggressive behaviours^{5,6} in schizophrenia. Despite chronic and

persistent executive function deficits in forensic patients with psychosis, CRT is not a standard component in forensic rehabilitation programs⁷. Therefore, further testing of CRT with forensic patients is required.

Methods: Thus far, 16 forensic psychiatry patients with psychosis (target N = 30) participated in a randomized, double-blinded randomized controlled trial using CRT. Groups are referred to as A and B for blinding purposes. Training visits occurred twice per week for 5 weeks. Executive function was assessed using a subset of tests from the Cambridge Neuropsychological Test Automated Battery⁸, psychiatric symptoms were assessed using the Clinical Outcomes in Routine Evaluation-Outcome Measure⁹, incidents of aggressive behaviours were assessed through the Aggression Questionnaire¹⁰, and functional capacity was assessed using the Generalized Self-Efficacy Scale¹¹. All variables were assessed at three timepoints one-week pre-training (T1), one-week post-training (T2), and 3-months post-training (T3). Paired-sample t-tests were used for the preliminary analyses, and Cohen's d was used to measure effect sizes.

Results: All participants had a primary diagnosis of schizophrenia, schizoaffective disorder, or bipolar I disorder with psychotic features, except one participant with a diagnosis of major depressive disorder. Executive function: Group A showed a significant decline from T1 to T2 ($t(4) = 2.90$, $p = 0.04$), and T1 to T3 ($t(3) = 3.61$, $p = 0.04$), but not T2 to T3 ($p > 0.05$). Group B showed no significant changes across timepoints (all $p > 0.05$), but moderate improvements were found from T1 to T2 (Cohen's $d = 0.69$) and T1 to T3 (Cohen's $d = 0.77$), and small improvements from T2 to T3 (Cohen's $d = 0.69$). Mental health symptoms: No significant differences were found across timepoints in either Group A or B (all $p > 0.05$), but small improvements were found from T2 to T3 (Cohen's $d = 0.32$) and T1 to T3 (Cohen's $d = 0.45$) in Group A and from T1 to T2 (Cohen's $d = 0.24$), and large improvements from T2 to T3 (Cohen's $d = 0.95$) and T1 to T3 (Cohen's $d = 1.27$) in Group B. Aggressive behaviours: Group A showed significant improvements from T2 to T3 ($t(3) = 4.38$, $p = 0.02$), and small, but statistically insignificant improvements (all $p > 0.05$) from T1 to T2 (Cohen's $d = 0.24$) and T1 to T3 (Cohen's $d = 0.47$). Group B showed significant improvements in self-reported aggressive behaviours between T1 and T2 ($t(2) = 5.47$, $p = 0.03$), and statistically insignificant but a small improvement was seen from T2 to T3 (Cohen's $d = 0.23$).

Discussion: Group A showed significant reductions in executive function from T1 to T2 and T2 to T3 and significant improvements in aggressive behaviours from T2 to T3. No other comparisons were significant. Group B showed no significant change; however, we observed moderate improvements in executive function from T1 to T2 and T1 to T3, and large improvements in mental health symptoms from T2 to T3 and T1 to T3. While our results are still blinded, we cannot draw direct conclusions on the efficacy of CRT in forensic patients. After achieving our target sample size of 30 participants, we intend to use mixed-effect models to compare outcomes in the two groups, thus more conclusively evaluating the efficacy of CRT in improving cognitive, behavioral, and clinical outcomes in forensic psychiatry patients.

References:

1. Orellana, G., and Slachevsky, A. (2013). *Frontiers in psychiatry*, 4, 35.
2. Yuan, P., and Raz, N. (2014). *Neuroscience and Biobehavioral Reviews*, 42, 180–192.
3. Broderick, C., et al., (2015). *CNS Spectrums*, 20(3), 319–330.
4. Best, M. W., et al., (2019). *American Journal of Psychiatry*, 176(4), 297–306.
5. Quinn, J., and Kolla, N. J. (2016). *The Canadian Journal of Psychiatry*, 62(2), 94–101.

6. Pezzoli, P., et al., (under review) Reducing antisocial behavior through cognitive training: A systematic review and meta-analysis.
7. Ross, E. H., and Hoaken, P. N. S. (2010). *Criminal Justice and Behavior*, 37(6), 656–677.
8. Sandberg M.A. (2011) *Encyclopedia of Clinical Neuropsychology*. Springer, New York, NY.
9. Evans, C., et al., (2000). *Journal of Mental Health*, 9(3), 247–255.
10. Buss, A. H., and Perry, M. (1992). *Journal of Personality and Social Psychology*, 63, 452–459. DOI: 10.1037/0022-3514.63.3.452
11. Schwarzer, R., and Jerusalem, M. (1995). Generalized Self-Efficacy scale. In: Weinman, J., Wright, S., and Johnston, M. (eds), *Measures in Health Psychology: A User's Portfolio. Casual and Control Beliefs* (pp 35-37). Nfer-Nelson, Windsor, UK.

T41. DEFICITS IN VISUAL AND AUDITORY EMOTION RECOGNITION AND AMYGDALAR VOLUME ABNORMALITIES IN AT-RISK MENTAL STATES AND SCHIZOPHRENIA

Francesca Serio^{*1}, Matthew Cotter², Alessia McGowan², Cheryl Corcoran², Shalaila Haas³

¹*Icahn School of Medicine at Mount Sinai; University of Milan*, ²*Icahn School of Medicine at Mount Sinai*, ³*Icahn School of Medicine at Mount Sinai Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS)*

Background: Schizophrenia is characterized by profound deficits in visual and auditory emotion recognition. These deficits are related to poor disease outcome, with lack of efficacy of pharmacological treatments. Different studies demonstrated links between reduced amygdalar volumes and ability to recognize emotions, specifically of threats, in schizophrenia (SZ). Evidence suggests that these alterations might be present years before the onset of the disease, still, little is known about individuals at clinical high risk (CHR) for psychosis. In this study, we investigated visual and auditory emotion recognition in CHR and SZ individuals and its association with amygdala volumes in structural MRI.

Methods: The Penn Emotion Recognition and Discrimination Task for face emotion recognition (FER) and the Brief Swedish Task for auditory emotion recognition (AER), were administered to 38 healthy controls (HC; age[SD]=25.88 [4.44]; 17 [49%] females), 72 CHR subjects (age=23.03 [4.99]; 33 [51%] females), and 21 schizophrenia patients (SZ; age=26.92 [5.27], 6 [38%] females). Additionally, all participants included in the study underwent T1w brain structural neuroimaging, and Freesurfer v7.1.0 was used to extract left and right amygdala volumes. ANOVA and Bonferroni post-hoc t-tests were used to evaluate group differences, and Spearman's correlations were performed to identify associations between AER and FER, and their links with bilateral amygdala across the three cohorts.

Results: There was no significant difference in sex between the groups ($\chi^2=0.48$, $P = 0.79$), however there was a significant difference in age ($F = 7.70$, $P = 6.97E-4$) with CHR younger than both the HC and SZ groups. One-way ANOVA revealed significant differences in FER ($F = 3.88$, $P = 0.02$), with post-hoc t-tests revealing significant pairwise group differences between HC-CHR ($P = 0.05$) and HC-SZ ($P = 0.04$). Across all subjects, there were significant positive correlations between FER and AER total scores ($\rho = 0.35$, $P = 9.26E-5$), and between threats emotions of anger ($\rho = 0.27$, $P = 3.51E-3$) and fear ($\rho = 0.26$, $P = 4.03E-3$). Within CHRs, there were significant correlations between anger FER and left ($\rho = 0.36$, $P = 0.03$) and right ($\rho = 0.33$, $p 0.05$) amygdala volumes. In SZ, there were significant

correlations between anger AER and left ($\rho = 0.68$, $P = 0.03$) and right ($\rho = 0.68$, $P = 0.03$) amygdala was found. No other associations were significant.

Discussion: In this study, we identified group differences in emotion recognition across the psychosis spectrum, and links between auditory and visual emotion recognition. Although we did not identify associations between overall auditory and emotion recognition with amygdala volume in CHR and SZ, differential modalities were linked with amygdala volume for anger across the psychosis spectrum, with bilateral amygdalar volumes associated with the recognition of anger in visual and auditory expressions within CHR and SZ, respectively. This study supports findings indicating amygdala dysfunction may contribute to alterations in emotion recognition in at various stages of schizophrenia.

T42. SOCIAL WITHDRAWAL IN PSYCHOSIS PHENOTYPE IN THE GENERAL POPULATION: NOVEL INSIGHTS FROM THE NETWORK ANALYSIS PERSPECTIVE

Michal Hajdúk^{*1}, Hana Kutlikova¹, Alexandra Straková¹, Vladimír Ivančík¹, Jakub Januška¹, Adam Kurilla¹, Natália Čavojská¹, Anton Heretik¹

¹*Comenius University in Bratislava*

Background: Psychosis symptoms are also observable in the non-clinical population and have been shown to be linked to the same risk factors as those found in individuals with psychotic disorders. More specifically, the severity of positive and negative symptoms is linked to the indicators of social withdrawal, such as loneliness, a smaller number of social contacts, or perceived rejection. These associations are present even in the general population. The aim of this study is to examine unique associations of symptoms with indicators of social withdrawal in the general population using a network analysis approach.

Methods: The sample was representative of the general adult Slovak population. The final sample consisted of 1200 participants, of whom 51,5% were female. Data were collected via a professional survey agency. The psychotic phenotype was measured by the Community Assessment of Psychic Experiences - CAPE-42. The UCLA loneliness scale, Social Functioning Scale, NIMH Perceived Rejection, and WHO-DAS-2 were utilized to assess social withdrawal. In addition, we administered self-report measures of social motivation and mentalizing. A Gaussian Graphical Model with EBIC Lasso regularization was used for network estimation. The centrality of nodes in the network was evaluated using Strength centrality. The stability of the network was evaluated with the Bootstrap approach.

Results: Bizarre experiences were strongly connected to other positive psychotic-like experiences. Paranoia was a link between positive psychotic-like symptoms and negative symptoms. Social approach motivation was connected to other social functioning domains, as well as to social withdrawal measured by CAPE-42. Out of all negative symptoms, paranoia was primarily connected to perceived rejection. The most central nodes in the estimated network were delusion-like experiences, social withdrawal (from CAPE-42), approach social motivation, avolition, and paranoia. The nodes with the lowest importance, showing few or weak connections within the networks, were perceived rejection, participation activities, social engagement measured by SFS, mentalizing, and grandiosity. Based on the Bootstrap analysis, the estimated network was very stable. The CS coefficient was very high ($CS=0.75$).

Discussion: The results reveal that positive and negative symptoms in the general population have specific links to particular domains of social withdrawal. More specifically, paranoia is linked to negative perception of others, while negative symptoms are linked to the aspects related to the approach motivation and social engagement. Supported by VEGA: 1/0493/23

T43. BREAKING DOWN PROCESSING SPEED: MOTOR AND COGNITIVE INSIGHTS IN FIRST-EPISODE PSYCHOSIS AND UNAFFECTED FIRST-DEGREE RELATIVES

Ángel Yorca-Ruiz*¹, Rebeca Magdaleno Herrero², Nancy Murillo-García³, García de la Foz Víctor⁴, Rosa Ayesa-Arriola⁵

¹Valdecilla Research Institute, ²Marqués de Valdecilla University Hospital, IDIVAL, ³Valdecilla Biomedical Research Institute. Research Group on Mental Illnesses., ⁴Marqués de Valdecilla University Hospital. IDIVAL, Instituto de Investigación Valdecilla. Santander, Spain. CIBERSAM, ⁵Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria

Background: Processing Speed (PS) deficits represent a fundamental aspect of cognitive impairment, evident not only in schizophrenia but also in individuals undergoing their first episode of psychosis (FEP) and their unaffected first-degree relatives. This observation suggests a potential hereditary component within this cognitive domain. While the Digit-Symbol Coding Test (DSCT) is considered the gold standard for assessing PS in schizophrenia, the involvement of motor and cognitive subcomponents in task performance may not precisely indicate a specific measure of PS. In light of this, our study aims to comprehensively explore several tests related to PS, revealing the implications of motor and cognitive subcomponents across various PS tests in FEP patients, their parents and siblings, and a control group.

Methods: The study involved 579 participants, including 133 individuals with FEP, 146 parents, 98 siblings, and 202 healthy controls. Neuropsychological assessments covered verbal and visual memory, executive functions, working memory, PS, motor dexterity, attention, and premorbid IQ. Tasks were selected wherein execution time served as an indicator of PS and included the Trail Making Test part A and B, DSCT, Grooved Pegboard Test, and Stroop Word and Color subtests. From the selected PS tests, ANCOVA analysis of covariance was administered to observe differences between groups. Pearson correlation was applied to scrutinize the relationships between the tests across groups. Subsequently, a model was derived by applying Exploratory Factor Analysis (EFA) within the control group. Finally, Confirmatory Factor Analysis (CFA) was implemented across the FEP, sibling, and parent groups to determine whether individuals with FEP and their first-degree relatives shared a cognitive structure in PS.

Results: FEP obtained the lowest scores in all tests compared to the sibling, parent, and control groups. Post-hoc tests showed that first-degree relatives obtained intermediate scores between the controls and FEP, except for the Stroop color test, where the siblings group scored lower than the other groups. The data were suitable for factor analysis (KMO: 0.732). EFA reveals a two-factor structure; resolution accounted for 62.9% of the total variance, with Factor 1 explaining 45.09% of the variance and Factor 2 explaining 17.85%. CFA confirms the two-factor model across groups, with varying correlations between factors.

Discussion: The two-factor model, common to all the groups, shows a Factor 1 reflects the motor subcomponent, and Factor 2 is associated with the cognitive subcomponent. Patients exhibit higher motor factor loadings, while relatives show intermediary patterns showing heritability. Cognitive dedifferentiation, as indicated by correlations between Factor 1 and Factor 2, suggesting a loss of functional specialization, is observed in individuals experiencing their FEP and their relatives. The distinct patterns of involvement in various PS

subcomponents suggest the adoption of compensatory strategies to succeed in PS tasks. Motor subcomponent performance in PS is preserved in first-degree relatives, whereas deficits in response selection are shared with FEP, implying the involvement of hereditary factors. A profound understanding of the nuances of processing speed has the potential to guide precise diagnostic assessments and targeted interventions in schizophrenia spectrum disorders.

T44. SYNERGISTIC, LONG-TERM EFFECTS OF GLUTAMATE DEHYDROGENASE 1 DEFICIENCY AND MILD STRESS ON COGNITIVE FUNCTION AND MPFC GENE AND MIRNA EXPRESSION

Kfir Asraf*¹, Hiba Zaidan¹, Inna Gaisler-Salomon¹

¹*University of Haifa*

Background: To investigate gene x environment interactions in a mouse model of cognitive deficits, we examined the impact of mild stress in mice genetically modified to express deficient levels of glutamate dehydrogenase 1 (GDH). GDH (gene name: Glud1) plays a central role in glutamate metabolism and is downregulated in the hippocampus of patients with schizophrenia. Mice with a full deletion of Glud1 in CNS (C-Glud1^{-/-} mice) previously showed abnormally high glutamate levels and a wide range of behavioral deficits.

Methods: Here, we exposed heterozygous C-Glud1^{+/-} mice and their C-Cre⁺ controls to mild stress in early adulthood. Stress-naïve mice of both genotypes were used as controls. Seven days later, mice were tested in a battery of behavioral tests assessing locomotor activity, social behavior and cognitive function. Fourteen days following behavior, medial prefrontal cortex samples were removed and analyzed for expression changes in transcriptome and select microRNA molecules using RNA-seq and RT-PCR, respectively. In a second cohort, brains were extracted immediately after the stress.

Results: Stress-exposed C-Glud1^{+/-} mice showed novelty-induced hypo-locomotion and impaired spatial acquisition and reversal. Transcriptomic analyses revealed vast changes in glutamatergic, GABAergic and stress-related genes, which were unique to stress-exposed Glud1-deficient mice. These behavioral and molecular deficits were absent in stress-naïve CNS-Glud1^{+/-} mice and in stress-exposed CNS-Cre⁺ controls. MiR203-5p emerged as a potential mechanism for the effect of stress exposure.

Discussion: Our findings indicate that CNS-Glud1^{+/-} mice exposed to stress in early adulthood display cognitive deficits, as well as molecular abnormalities, which are also relevant to stress exposure and psychopathology.

T45. A REVIEW OF SPEECH MARKERS IN BIPOLAR DISORDER MENTAL STATES

Farida Zaher*¹, Jessica Ahrens², Alban Voppel³, Lena Palaniyappan⁴

¹*McGill University*, ²*Douglas Research Centre*, ³*McGill University, Department of Psychiatry*, ⁴*Douglas Mental Health University Institute*

Background: Bipolar disorder (BD) is a chronic, recurrent, and life-long disorder that is characterized by mild to severe fluctuations in mood and energy, lasting anywhere from days to months. Early intervention for BD is especially important because it is more responsive to

treatment in the early phases of the illness. The occurrence of psychotic symptoms in bipolar disorder further impacts illness severity, increasing the likelihood of comorbid disorders, rates, and duration of hospitalization. BD is commonly misdiagnosed, especially in the initial presentation, however, there is increasing evidence that an at-risk bipolar state could potentially be targeted through speech because it can capture various bipolar mental states, such as psychosis, mania, depression, and other mood fluctuations; manic and depressive episodes have been characterized by speech abnormalities, such as pressured speech and poverty of speech. Therefore, this review aims to summarize the current research on speech markers in bipolar mental states.

Methods: We searched MEDLINE, PubMed, and Google Scholar databases in July 2023. All published human studies written in English relating to speech markers during any bipolar mood state were included.

Results: We initially screened 636 studies and selected 40 studies investigating speech in patients with BD. Results demonstrated observable linguistic patterns across bipolar mood states. Manic states were associated with pressured speech, derailment, increased grammatical errors, word repetition, verb, and pronoun use, as well as decreased adjective and preposition use. Associations were found between depressive states and increased use of personal pronouns, modifying adverbs, and poorer verbal fluency. Pressured speech was found to be able to differentiate between bipolar-depressed and unipolar-depressed youth. Hypomania and depression were differentiated using speech-based classifiers. Voice quality parameters and features were also found to correlate with emotional states, with an increased accuracy in the classification of manic and mixed states compared to depressive states.

Discussion: Due to the nature of the mood swings that occur in BD, the risk of suicide is significantly higher than the rest of the population. Identifying speech markers that characterize a manic, psychotic, or depressive state may facilitate the development of prediction and prevention frameworks for early intervention and treatment. The ability to use speech to identify mental state fluctuations in BD could lessen the consequences associated with this mental illness, by providing patients and clinicians with a more reliable and objective method to predict an oncoming mood episode, for accurate diagnosis, early intervention, and treatment. Also, if we can use speech to distinguish between bipolar mental states, then we can also use these same speech markers to further our study of psychosis, schizophrenia, and depression.

T46. UNLOCKING COGNITIVE POTENTIAL: THE EFFICACY OF CO.DI.S INTERVENTION AND QUALITATIVE AND QUANTITATIVE ANALYSIS OF AUDIO-RECORDED SPEECH IN PSYCHOTIC SPECTRUM DISORDER

Valerio De Lorenzo^{*1}, Federico Fiori Nastro², Fabiola Ferrentino³, Francesca Russo³, Syria Dimonte², Valeria Gosti², Maria Chiara Scaramella², Alberto Siracusano², Cinzia Niolu², Giorgio Di Lorenzo²

¹*University of Rome Tor Vergata*, ²*University of Rome Tor Vergata, Rome, Lazio*, ³*Institute of Neuroscienze NEOMESIA, KOS Group*

Background: Psychosis spectrum disorders are complex and lifelong conditions marked by atypical cognitive, linguistic, and social functioning. Recently, cognitive dysfunctions have been identified as a predictor of unfavorable functional outcomes in the psychosis prodrome.

Language domain has been demonstrated to be impaired in various aspects, including syntax, semantics, and pragmatics. Studies have consistently shown disruptions in the coherence and organization of speech and challenges in expressing thoughts cohesively.

Psychosocial interventions consistently demonstrate advantages in restoring cognitive abilities.

This study aims to validate the effectiveness of specific cognitive exercises for semantic differentiation (*esercizi Cognitivi di Differenziazione Semantica, Co.Di.S*) as reinforcement of standard cognitive remediation rehabilitation treatment. Additionally, it seeks to conduct a qualitative and quantitative analysis of audio-recorded voice samples from a group of patients suffering from psychotic spectrum disorder.

Methods: Preliminary data were collected from a longitudinal research investigation. A cohort of 19 participants (79% males; age mean: 29.4 years) was recruited from the psychiatric outpatient program of Policlinico Tor Vergata in Rome. Inclusion criteria encompassed individuals with psychotic spectrum disorder, clinically stabilized for a minimum of 3 months, without a history of head trauma, comorbid neurological diseases, or IQ deficiency.

Global cognitive and functional assessments were administered, including the MATRICS Consensus Cognitive Battery (MCCB), Rey Auditory Verbal Learning test (RAVLT), Babcock, Verbal Fluency-Semantic Category, and the Life Skills Profile (LSP). Furthermore, the Faux Pas assessment and the screening of the video Monsterbox were employed for all subjects to delve into social cognition skills, with vocal audiological samples recorded during these evaluations.

All participants engaged in a conventional cognitive remediation treatment (Cogpack®) enhanced by the Co.Di.S.

Results: A paired-sample t-test was employed to assess the efficacy of the treatment across various cognitive domains. Notably, statistically significant improvements were identified in verbal learning (HVL) ($p < .001$) and working memory (LNS) ($p = .003$). Additionally, RAVLT and Verbal Fluency-Semantic Category, which investigated verbal learning, also exhibited statistically significant enhancements ($p = .003$ and $p = .010$, respectively). Finally, the LSP demonstrated a statistically significant improvement ($p = .003$).

The audiological speech analysis indicates improvement in social cognition and perception. Additionally, evidence of extended pauses and increased specificity and quality of words and sentences suggest reduced response impulsivity. Finally, the increased density of expressions with affective content implies a broader range of emotional features in patients' speech.

Discussion: The study is a preliminary validation of the efficacy of Co.Di.S intervention in improving cognitive and social functioning among individuals with psychotic spectrum disorders. Considering the restricted effectiveness observed in pharmacological treatments for cognitive and language impairments in psychosis, the integration of psychosocial and rehabilitation interventions becomes imperative. Subsequent investigations will be conducted to assess the impact of semantic fluency improvement on both positive and negative symptomatology. Future research endeavors should expand the study's sample size and compare treatment effectiveness with a control group.

T47. PRELIMINARY STUDIES ON THE GRAMMATICAL PROSODY OF SCHIZOPHRENIA PATIENTS

Leonardo Lopes¹, Daniela Coelho², Marcelo Sousa³, Igor Oliveira³, Lucas Mantovani², João Salgado⁴, Tommaso Raso³, Bruno Rocha³, Joao Salgado*⁵

¹other, ²Instituto Raul Soares/ FHEMIG, ³Universidade Federal de Minas Gerais (UFMG), ⁴Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais (UFMG), Instituto Raul Soares/ FHEMIG, ⁵Federal University of Minas Gerais

Background: Schizophrenia is a disorder that encompasses, with high interindividual variability, anomalies in different language domains, such as prosody. Successful interpersonal communication requires individuals capable of expressing and receiving varied information through verbal and non-verbal stimuli. Moreover, they must possess the necessary skills for language comprehension, with prosody being one of the most important pragmatic tools. According to evidence in the medical literature, affective prosody seems compromised in its production and recognition in schizophrenia patients, while studies involving the subdomain of grammatical prosody in these patients still appear scarce. Through acoustic recordings obtained from the C ORAL-ESQ corpus, we obtained preliminary linguistic data (words per speech turn, per terminal prosodic sequences, and per tonal units) that facilitated attempts to verify correlations with clinical parameters.

Methods: The C-ORAL-ESQ, a corpus of schizophrenic patients speaking Brazilian Portuguese, records audio from psychiatric consultations with schizophrenic patients. After recordings, alignments, transcriptions, and segmentations are performed based on criteria proposed by the Language in Action Theory (L-Act), a theory focused on understanding the informational structure of speech. The technical treatment of acoustic recordings provides prosodic data that can be compared with data obtained from C ORAL-BRASIL, a reference corpus composed of healthy controls. The corpus includes stable schizophrenia patients aged 18 to 65, assessed for the PANSS positive domain, among other parameters. Exclusions are based on nosological criteria, clinical instability, or neurological comorbidities. Once selected, patients undergo various tests to evaluate clinical parameters.

Results: Two groups of speakers were compared (not balanced in gender, age, and schooling): 38 from C-ORAL-BRASIL (27,932 words) and 29 from C-ORAL-ESQ (42,222 words). We extracted measurements and observed a higher standard deviation in C-ORAL-ESQ for the following metrics: number of words per turn (mean 14.1 vs. 11.7; median 11.1 vs. 9.8; s.d. 9.8 vs. 5.8); words per utterance (mean 8.5 vs. 6.8; median 8.4 vs. 6.2; s.d. 4.2 vs. 2.6), words per prosodic units (mean 3.8 vs. 2.9; median 3.0 vs. 2.8; s.d. 2.0 vs. 0.4). This is notable, given that C-ORAL-BRASIL speakers engage in different yet similar communicative situations, while patients are not affected by this variable.

For us, this finding points to an important factor of interindividual variability in the group of schizophrenia patients, which may be related to various specificities such as the pattern of negative symptoms in these patients or their prescription profiles. After appropriate and reviewed statistical tests, however, we did not find correlations between the severity of negative symptoms and the dose of antipsychotics in chlorpromazine equivalents with the number of words per turn, per tonal unit, and per terminal prosodic ending.

Discussion: It is possible that the parameters studied, albeit preliminary, may indicate a significant sensitivity of prosodic aspects to the specificities of schizophrenia, such as symptom profiles and pharmacological prescription. Although our initial analyses were not successful, a more in-depth evaluation of the prosodic informational structure of speech may provide valuable insights that point to potential correlations with clinical parameters.

T48. THE C-ORAL-ESQ AND THE STUDY OF GRAMMATICAL PROSODY IN PATIENTS WITH SCHIZOPHRENIA

Leonardo Lopes¹, João Salgado², Lucas Mantovani³, Daniela Coelho³, Marcelo Sousa⁴, Igor Oliveira⁴, Lucas Attoni³, Bruno Rocha⁴, Tommaso Raso⁴, Joao Salgado*⁵

¹other, ²Universidade Federal de Minas Gerais, Instituto Raul Soares/ FHEMIG, ³Instituto Raul Soares/ FHEMIG, ⁴Universidade Federal de Minas Gerais, ⁵Federal University of Minas Gerais

Background: Schizophrenia is a disorder that encompasses highly variable language anomalies among individuals, such as prosody - a fundamental pragmatic tool for interpersonal communication. According to evidence in the medical literature, this tool appears compromised in production and recognition in schizophrenia patients, making it a significant subject of study. The C-ORAL-ESQ is a corpus aiming to document the speech of schizophrenia patients, enabling linguistic and medical studies. This corpus will be available for free consultation after analysis of prosodic and pragmatic parameters, facilitating the development of new medical and linguistic research.

Methods: C-ORAL-ESQ records audio from everyday psychiatric consultations with schizophrenia patients. After recordings, alignments, transcriptions, and segmentations are performed based on criteria proposed by the Language Into-Act Theory (L-ActT), a theory focused on understanding the informational structure of speech. Technical treatment of acoustic recordings provides quantitative and qualitative prosodic-grammatical data, such as words per turn, per prosodic terminal unit, and per tonal unit, along with the ratio of dialogical and non-dialogical informational units. Linguistic findings can be compared with C-ORAL-BRASIL, a corpus of healthy Brazilian Portuguese speakers. The corpus includes stable schizophrenia patients aged 18 to 65, assessed for positive PANSS domain, among other parameters. Exclusions are based on nosological criteria, clinical instability, or neurological comorbidities.

Results: Currently, C-ORAL-ESQ has 40 audio recordings, totaling about 48,000 words spoken by patients and 659 minutes of conversations between doctors, patients, and their companions. Recordings are in various stages of processing, so parameters of interest are not fully accessible. We extracted measurements and observed a higher standard deviation in C-ORAL-ESQ in comparison with C-ORAL-BRASIL for the following metrics: number of words per turn (mean 14.1 vs. 11.7; median 11.1 vs. 9.8; s.d. 9.8 vs. 5.8); words per utterance (mean 8.5 vs. 6.8; median 8.4 vs. 6.2; s.d. 4.2 vs. 2.6), words per prosodic units (mean 3.8 vs. 2.9; median 3.0 vs. 2.8; s.d. 2.0 vs. 0.4). This is notable, given that C-ORAL-BRASIL speakers engage in different yet similar communicative situations, while patients are not affected by this variable.

Discussion: Prosody plays a crucial role in interpersonal discourse, emotional rapport, and understanding intentions and feelings of interlocutors. Its compromise may be linked to observed social performance issues in schizophrenia patients. Access to various prosodic parameters through C-ORAL-ESQ allows for studying the topic and establishing potential correlations with clinical variables, such as negative symptoms and pharmacological prescription profiles. Schizophrenia is a disorder that involves highly variable anomalies in various language domains among individuals, such as prosody - a fundamental pragmatic tool for establishing interpersonal communication. Evidence from medical literature suggests that this tool appears compromised in production and recognition among schizophrenia patients, making it a significant subject of study. The C-ORAL-ESQ is a corpus aiming to

document the speech of schizophrenia patients, enabling linguistic and medical studies. This corpus will be available for free consultations after analyzing prosodic and pragmatic parameters, facilitating the development of new medical and linguistic research.

T49. SLEEP ON IT: DOES SLEEP QUALITY AFFECT COGNITION AND METABOLIC SYNDROME IN SCHIZOPHRENIA?

Marta Bosia^{*1}, Michele Francesco D'Incalci², Jacopo Sapienza³, Carolina Passani³, Andrea Fortunato³, Salvatore Novello⁴, Giulia Agostoni⁵, Margherita Bechi³, Mariachiara Buonocore², Francesca Martini³, Marco Spangaro⁵, Guglielmino Carmelo³, Cocchi Federica³, Roberto Cavallaro⁶, Stefano Comai⁷

¹*Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy,* ²*IRCCS San Raffaele Scientific Institute, Milan, Italy,* ³*IRCCS San Raffaele University Scientific Institute,* ⁴*Vita-Salute San Raffaele University,* ⁵*IRCCS San Raffaele University Scientific Institute,* ⁶*Vita Salute San Raffaele University,* ⁷*University of Padua*

Background: Cognitive impairment still represents one the the main cause of poor outcome in patients with schizophrenia and current pharmacological treatment does not satisfactorily address it. Additionally, individuals suffering from schizophrenia are intrinsically at higher risk to develop metabolic syndrome (MetS), also because of the side effects of antipsychotic medications. MetS aggravates the prognosis of patients with schizophrenia, as it leads to higher mortality and cardiovascular diseases.

Up to 80% of patients with schizophrenia suffer from sleep disturbances, which have been associated with worsening of both cognition and metabolic profile.

Despite converging evidence, to date few studies have investigated the relationship between poor sleep and either metabolic alterations or cognition in schizophrenia, and their interplay has not yet been explored.

Based on these premises, this study aims to better characterize the impact of sleep disturbances on cognition, MetS and psychopathology in schizophrenia, as well as to elucidate the possible interplay between sleep and metabolic syndrome on cognitive functions.

Methods: Seventy-seven patients with a diagnosis of psychotic disorder were enrolled and assessed for: sleep quality and habits with the Pittsburgh Sleep Quality Index (PSQI) questionnaire and the Mornigness Eveningness Questionnaire (MEQ); cognition with the Brief Assessment of Cognition in Schizophrenia (BACS); psychopathology with the Positive And Negative Syndrome Scale (PANSS).

Pearson's correlation analysis was used to explore the relationship between sleep quality and habits and psychopathology, cognition and MetS. The effects of sleep quality on cognitive abilities and MetS parameters were then analyzed by means of forward stepwise regressions, taking into account confounding factors. Finally, to disentangle the interplay between sleep quality and MetS on cognitive abilities, we performed separate slope models.

Results: The analysis showed significant correlations between general and overall psychopathology as evaluated by PANSS and short sleep duration. Concerning cognition, significant correlation emerged between working memory, verbal memory, processing speed and planning and sleep efficiency, sleep disturbances and sleep habits. Regarding MetS, positive correlations were found between sleep disturbances, higher triglycerides and lower

HDL, and between MetS severity and both daytime dysfunction because of sleepiness and global sleep quality.

The regressions highlighted a main role of sleep disturbances on core cognitive domains of verbal memory, processing speed and planning, as well as specific effects of sleep parameters on fasting glucose, triglycerides and overall MetS severity. Finally, the separate slope model showed a significant interaction between sleep disturbances and MetS on planning ability, with a stronger negative impact of sleep disturbances in patients with MetS.

Discussion: Our data confirm the impact of sleep quality and habits on clinical and cognitive outcome, as well as on physical health in patients with schizophrenia. In particular, results suggest that cognitive abilities are mainly affected by sleep disturbances, while metabolic parameters are differentially influenced by sleep latency and use of hypnotic drugs. Innovatively with respect to previous literature, our study also shows an interactive effect between sleep and MetS on cognition, contributing to better clarify the relation between sleep alterations, cognitive deficits and MetS.

Our findings further highlight the importance of monitoring and managing sleep in patients with schizophrenia to possibly ameliorate cognitive deficits and metabolic syndrome, which, due to the limitations of antipsychotic treatments, are among the biggest challenges that patients with schizophrenia have to face.

T50. ROLE OF ASTROCYTES IN THE DEVELOPMENT OF ADULT BRAIN PATHOLOGY AFTER TRANSIENT PREFRONTAL MICROGLIA DEFICIENCY IN ADOLESCENCE

Sina-Maria Schalbetter^{*1}, Ron Rabin¹, Anja Krütli¹, Anina Sara von Arx¹, Olga Krzyzaniak¹, Han-Yu Lin¹, Johanna Furrer¹, Tina Notter¹, Urs Meyer¹

¹*University of Zurich*

Background: Microglia, the innate immune cells of the central nervous system, play a crucial role in synaptic pruning during adolescence. Using a mouse model of cell-specific, transient and local depletion of microglia, we recently showed that deficiency of prefrontal microglia during adolescence is sufficient to induce an adult emergence of impairments in cognitive functions, dendritic complexity, and synaptic structures and functions. Based on previous findings suggesting that astrocytes may functionally compensate microglia deficiencies, we explored the role of astrocytes in development of adult brain pathology after transient prefrontal microglia deficiency in adolescence. A special emphasis was placed on inositol trisphosphate (IP3)-dependent Ca²⁺ signaling in astrocytes, given that this pathway is upregulated in reactive astrogliosis.

Methods: Brain region-specific and transient depletion of prefrontal microglia during adolescence was induced by a single, bilateral stereotaxic injection of clodronate disodium salt (CDS) into the medial portion of the PFC in 6-week-old C57BL/6 mice. Control mice received a bilateral stereotaxic injection of phosphate-buffered saline (PBS). Immunohistochemistry and confocal microscopy were used to ascertain the density of microglia and astrocytes at 1, 5, 10, and 40 days post-injection (dpi), whereas the expression of genes involved in astrocyte-mediated synaptic pruning (Mefl0, Mertk) and the astrocytic activity marker glial fibrillary acidic protein (Gfap) was assessed via quantitative real-time PCR (qRT-PCR) at the same dpi intervals. Astrocytic IP3 signaling was blocked using recombinant adeno-associated virus (rAAV) expressing an inhibitory peptide from β -

adrenergic receptor kinase 1 (i β ARK) under the GFAP promoter. To ensure brain region specificity, stereotaxic bilateral injections, of rAAVs expressing i β ARK or a corresponding control rAAV, in the medial PFC were conducted 10 days before microglia depletion. A battery of PFC-dependent cognitive tests, including social recognition memory and temporal order memory, was used to explore the functional role of astrocytes in mediating the adult emergence of cognitive dysfunctions after prefrontal microglia deficiency in adolescence.

Results: A single intra-PFC injection of CDS led to a robust (~ 80% depletion) but temporary (~ 1 week) depletion of microglia in the adolescent PFC. Even though the density of S100 β -immunoreactive astrocytes was not altered, the CDS-induced prefrontal microglia depletion led to a marked (2-3 fold) upregulation of Gfap expression in the PFC at 1 and 5 dpi. These changes were, however, not associated with alterations in the expression of genes involved in astrocyte-mediated synaptic pruning (Megf10, Mertk). Furthermore, blocking astrocytic IP3 signaling through GFAP-driven i β ARK expression did not prevent the adult emergence of social recognition memory and temporal order memory deficits after prefrontal microglia depletion in adolescence

Discussion: The present study provides novel insights into the intricate interactions between microglia and astrocytes. Our findings suggest that prefrontal astrocytes become transiently reactive during temporary microglia depletion, but astrocytic IP3 signaling does not seem to play a major role in mediating the adult emergence of cognitive dysfunctions after transient prefrontal microglia deficiency in adolescence. Hence, the astrocytic contribution to brain pathology after prefrontal microglia deficiency likely involves mechanisms beyond astrocytic IP3 signaling.

T51. OLFACTORY BIOMARKER FOR SOCIAL ANHEDONIA IDENTIFIES ANTERIOR CINGULATE ABNORMALITIES IN PATIENTS WITH SCHIZOPHRENIA

Julie Walsh-Messinger*¹, Eugene Ruby², Oded Gonen³, Dolores Malaspina⁴

¹University of Dayton, ²University of California, Los Angeles, ³NYU Langone School of Medicine, NY USA, ⁴Icahn School of Medicine at Mount Sinai

Background: Anhedonia, or the diminished capacity to experience pleasure, is a common feature of depression and schizophrenia and is widely considered to reflect reward circuitry dysfunction. However, the processing of information on “self” vs “other” for social motivation and pleasure is associated with activity in the anterior cingulate cortex (ACC). Olfaction, which is associated with emotion function along with social and emotional impairments in schizophrenia, shares close neural connections to the ACC. The present study investigated associations between biomarkers for cellular processes in the anterior cingulate, psychiatric symptoms, social anhedonia, and olfaction in schizophrenia patients.

Methods: Nineteen individuals diagnosed with a DSM-IV schizophrenia spectrum disorder (11 male, 8 female) underwent three-dimensional 3-T voxel proton magnetic resonance spectroscopy (MRSI) to measure biomarkers for cellular processes, including neuronal integrity (N-acetylaspartate- NAA), energetics (creatine-Cr), myelin (choline -Cho) and glia (myo-inositol -mI) concentrations in the ACC. Spearman correlations were computed to examine associations between these metabolites, PANSS five factor scores, chapman physical and social anhedonia scales, along with olfaction based on Sniffin’ Sticks odor threshold, identification and discrimination.

Results: The combination of reduced cellular energy usage (Cr) and hypomyelination (Cho) in the ACC, respectively, predicted more severe positive ($r=-.555$, $p=.014$; $r=-.522$, $p=.022$),

negative ($r=-.499$, $p=.030$; $r=-.564$, $p=.012$), autistic preoccupation ($r=-.607$, $p=.006$; $r=-.677$, $p=.001$) and social anhedonia ($r=-.503$, $p=.034$; $r=-.524$, $p=.026$) symptoms. Reduced glia predicted autistic symptoms ($r=-.481$, $p=.037$) and social anhedonia ($r=-.540$, $p=.021$). By contrast, impaired odor identification and discrimination, was robustly associated with blunted affect ($r=-.523$, $p=.021$; $r=-.523$, $p=.021$), physical anhedonia ($r=-.628$, $p=.005$), and the myelin reduction ($r=.582$, $p=.001$; $r=.504$, $p=.028$) that likewise predicted social anhedonia.

Discussion: The association between olfactory dysfunction and social anhedonia is sensitive to hypomyelination in the ACC. Despite apparently preserved neuronal integrity, schizophrenia symptoms were associated with reduced myelin and glia and associated reductions in cellular energetics. The strong associations of olfactory function with negative symptoms and anhedonia were specifically indicative of reduced ACC myelin.

T52. REVISITING THE OBVIOUS: A META-ANALYTIC UPDATE ON THE PROCESSING SPEED IMPAIRMENT IN SCHIZOPHRENIA

Danielle Pratt^{*1}, Vijay Mittal¹

¹*Northwestern University*

Background: A global cognitive impairment is well established for people with schizophrenia. Dickinson et al. (2007) meta-analyzed cognitive studies and found that the digit symbol coding test, a measure of processing speed, was the most impaired test across studies and asserted that this task taps into an information processing inefficiency that is a central feature of the cognitive impairment in schizophrenia. As an answer to this meta-analysis, Knowles et al. (2010) reexamined these results (with the addition of 11 new studies up through January 2009) and found that the processing speed impairment is substantially affected by several moderating factors, including publication year, IQ difference from controls, and chlorpromazine dose equivalents. As nearly 15 years have passed since this last analysis of the processing speed impairment, in which time measurement of cognition has changed substantially, this study aims to revisit the evidence for a specific processing speed impairment and the potential moderating factors.

Methods: Articles were identified through a series of searches of the PubMed and PsycINFO electronic databases with combinations of the key words *schizophreni**, *cogniti**, *neuropsychologi**, *digit symbol*, *symbol coding*, *processing speed*, *perceptual speed*, and *psychomotor speed* from February 1, 2009 to November 2, 2023. Inclusion criteria require studies to report results for a symbol coding task and two other cognitive domains, contrast people with schizophrenia to healthy controls, and include sufficient detail to calculate effect sizes. New articles will be assessed alongside and with the previously identified articles. Effect sizes for each cognitive variable from each study will be calculated as the mean difference between schizophrenia and healthy control performance divided by the pooled standard deviation and adjusted for small sample bias (Hedges g). We will also calculate 95% confidence intervals, chi-square statistics, Q (homogeneity of effect sizes), and Orwin's fail-safe N (publication bias).

Results: 4530 articles were identified through the initial search and 2876 of those were removed due to being duplicates. The final number of articles for inclusion is still being finalized and results for this study are impending.

Discussion: There has been extensive focus on cognition in people with schizophrenia in the last 15 years and methods have evolved over time. This study provides the opportunity to

directly test whether the previous findings of a specific processing speed impairment, as well as the impact of moderating factors, are still present.

T53. PSYCHOMETRIC PROPERTIES OF THE FRENCH VERSIONS OF THE COMBINED STORIES TEST (COST) AND THE SOCIAL KNOWLEDGE TEST (SKT) IN PEOPLE WITH SCHIZOPHRENIA

Audrey Cayouette*¹, Élisabeth Thibaut², Frédéric Haesebaert³, Caroline Cellard⁴, Amélie M Achim⁵

¹Université Laval, ²McGill University, Douglas Mental Health University Institute, ³CH le Vinatier, Lyon, France, ⁴Centre De Recherche Université Laval Robert-Giffar, ⁵Département de psychiatrie et de neurosciences Université Laval; VITAM - Centre de recherche en santé durable; Centre de recherche CERVO

Background: Individuals with schizophrenia often present with social cognition deficits, including theory of mind (ToM) and social knowledge deficits. Among the measures available to assess these abilities, the Combined stories test (COST) and the Social knowledge test (SKT), that respectively target ToM and social knowledge, have shown promising psychometric properties in prior studies. However, test-retest reliability was only examined in healthy participants, and participant's subjective appreciation of these tasks has never been examined. The objective of this study was thus to further document the psychometric properties of the COST and the SKT and to document the participant's appreciation for both tests, in people with schizophrenia (SZ) and in healthy controls (HC).

Methods: Thirty-four (34) participants (33 men) with SZ (mean age = 39.8 (11.9); duration of illness = 13.5 (10.3) years) and 46 HC (mean age = 35.7 (14.0)) were assessed twice with the French versions of the COST and SKT, about 4 weeks apart (T1 and T2), and were also asked to rate their appreciation of the tests on a 10-point scale. The COST is a story-based ToM test in which participants must answer 26 second-order ToM questions (COST-QToM) and includes a control condition with 6 non-social reasoning questions (COST-QR). The SKT includes 14 situations for which participants are asked to report the emotions that most people would typically experience in that situation. For all three scores (COST-QToM, COST-QR and SKT), the following properties were examined: inter-rater reliability, test-retest reliability, practice effects, and ceiling effects.

Results: The inter-rater reliability was excellent in the SZ group, for the COST-QToM ($\alpha = .883$), the COST-QR ($\alpha = .858$) and the SKT ($\alpha = .941$) and in the HC group for the COST-QToM ($\alpha = .892$), the COST-QR ($\alpha = .898$) and the SKT ($\alpha = .976$).

For the test-retest reliability, the correlations between T1 and T2 for the SZ group were good ($r = .814$) for the COST-QToM, and for the SKT ($r = .673$), though the COST-QR (control condition) showed poorer test-retest reliability ($r = .296$). In the HC group, the correlations between T1 and T2 were acceptable ($r = .59$) for the COST-QToM, for the COST-QR ($r = .468$) and for the SKT ($r = .596$).

Some practice effects were observed. In the SZ group, the analyses revealed a significant practice effect only for the COST-QToM ($t(33) = -2.29$, $p = .029$, Effect size d (ESd) = 0.39), whereas no significant practice effect was observed for the COST-QR ($t(33) = 1.10$, $p = .281$) or for the SKT ($t(36) = -1.18$, $p = .246$). In the HC group, significant practice effects emerged for both the COST-QToM ($t(45) = -4.72$, $p < .001$ ESd = 0.70) and the

SKT ($t(45) = -2.46$, $p = .018$, $ESd = 0.36$), whereas no significant practice effect emerged for the COST-QR ($t(45) = -0.11$, $p = .914$).

The only evidence for a ceiling effect emerged for the COST-QR for both SZ and HC groups. Finally, the average appreciation scores for the COST and the SKT were of 6.8/10 and 8.3/10 in the SZ group and of 7.7/10 and 8.2/10 for the HC group.

Discussion: These results add to the previously reported psychometric properties and that show globally adequate psychometric properties for these tests. While the observed practice effects were surprising given the previous results in healthy participants, practice effects are common for social cognition measures. The ceiling effects observed for the COST-QR, particularly in the HC group, may be explain by the number of participants that obtained a perfect score at T1. The appreciation ratings by participants from both groups were generally positive. Therefore, these two measures prove to be valuable options for clinicians to use in their practice, especially given the few options in French.

T54. COMPUTERIZED ADAPTIVE TESTING IMPROVES PRECISION AND EFFECT SIZE IN EXPERIMENTAL PSYCHOPATHOLOGY RESEARCH

Michael Thomas^{*1}, Anastasia Sares¹, Emily Sturm¹, John Duffy¹, Maiele Mignard¹, Tessa Mitchell², Max Henneke¹, Haley Pyscher², Jazmin Diaz¹, Donald Rojas¹, Jason Tregellas¹, Jared Young³

¹Colorado State University, ²University of Colorado Anschutz Medical Campus, ³UC San Diego School of Medicine

Background: Cognitive testing plays a pivotal role in studies of psychosis and other forms of serious mental illness. Unfortunately, many of these tests lack psychometric refinement, leading to weakened effect size and poor statistical power. At the same time, psychometric refinement is a slow, iterative process that requires large amounts of data, and is therefore not feasible in many settings. However, newer statistical approaches based on item response theory make it possible to improve measurement precision with novel tasks, even with limited data, using methods like computerized adaptive testing. This study demonstrates this technology by administering an adaptive version of a cross-species cognitive control task: the multi-choice continuous performance test (MC-CPT). We hypothesized that adaptive testing would produce more precise estimates of ability and larger effect size than non-adaptive testing.

Methods: Participants included 37 healthy controls (HCs) and 35 individuals diagnosed with schizophrenia or schizoaffective disorder (SZs) who were administered the MC-CPT using the free and open-source stimulus presentation package PsychoPy. During the task, participants pressed a key corresponding to a circle that appeared briefly on a screen in one of four positions or withheld their response if circles appeared in all four positions. Task difficulty was manipulated using a backward visual mask, in this case, a set of squares that covered the possible circle locations after the circle was presented. For the fixed version of the task, the backward mask onset times were predetermined. For the adaptive version of the task, an algorithm chose the backward mask onset time in a manner that optimized precision (minimized standard error) for each participant on a block-trial basis. Fixed and adaptive versions of the task were administered on separate days in a counterbalanced order.

Results: As hypothesized, the adaptive MC-CPT produced more precise estimates of ability than the non-adaptive version, and the effect size comparing ability estimates between HCs

and SZs was larger for the adaptive versus fixed version of the test. Participants' tolerability ratings of each test version did not significantly differ.

Discussion: Our findings underscore the potential of adaptive testing and advanced psychometric tools to enhance novel and previously unrefined measures of cognition in experimental psychopathology research. Adaptive technology not only enhances precision but also improves effect size and statistical power, which will benefit numerous studies, especially those evaluating neurocognitive theories of psychosis. Our group has developed CogIRT, a free and user-friendly R package that facilitates the development and implementation of adaptive neurocognitive tests, including the MC-CPT.

T55. RELATIONSHIP BETWEEN COGNITIVE PERFORMANCE AND PLASMA RATIO OF CLOZAPINE TO N-DESMETHYLCLOZAPINE IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

Bomin Kim^{*1}, Hyejin Sim¹, Seoyoung Kim², Euitae Kim²

¹Seoul National University, ²Seoul National University Bundang Hospital

Background: Cognitive deficits and poor prognosis are commonly observed in patients with treatment-resistant schizophrenia (TRS) due to their inadequate therapeutic responses to first-line antipsychotic treatments. However, the effect of clozapine (CLZ), the most efficacious antipsychotic for TRS, on cognition remains inconclusive. According to previous studies, clozapine and its main metabolite, N-desmethylclozapine (NDMC), have opposing pharmacological profiles at the muscarinic receptor, known for its association with cognition. While clozapine acts as an antagonist at M1 receptors, leading to anticholinergic burden, NDMC operates as a partial agonist, enhancing cognitive functions. Considering these opposing mechanisms, this study focused not only on the two individual concentration levels but also on the CLZ/NDMC ratio to investigate their associations with cognitive performance.

Methods: Forty-four patients with TRS completed baseline and follow-up assessments before and 18 weeks after initiating clozapine treatment, respectively. The assessments included Positive and Negative Syndrome Scale (PANSS), MATRICS Consensus Cognitive Battery (MCCB), and blood trough levels of CLZ and NDMC.

Results: Multiple regression found significant negative associations between CLZ/NDMC ratio and MCCB scores after controlling for age, gender, duration of illness, antipsychotics equivalent dose, baseline MCCB score, and PANSS score. In path analysis, higher clozapine dose and clozapine concentration were associated with lower MCCB scores, whereas the effect of NDMC concentration did not reach statistical significance.

Discussion: With the association between CLZ/NDMC ratio and MCCB scores, our finding implies that careful observation of the CLZ/NDMC ratio is important to monitor cognitive treatment outcomes. Furthermore, elevated clozapine plasma levels seem to hinder the improvement of cognitive functions in patients with TRS. However, the expected pro-cognitive effect of NDMC remains unclear. This suggests that further investigation is required to fully understand the relationship between cognition and clozapine-related pharmacological factors.

T56. PRIMALS AND PSYCHOSIS: A NOVEL APPROACH TO UNDERSTANDING THE ROLE OF WORLD BELIEFS IN DELUSIONS AND HALLUCINATIONS

Emma Palmer-Cooper*¹, Jeremy Clifton²

¹*University of Southampton*, ²*University of Pennsylvania*

Background: Primal world beliefs ('primals') are simple observations about the world's overarching qualities, and can be conceptualised as schemas. Whilst beliefs about the world, and their role in psychopathology, are not a new concept, novel methods of assessment have supported empirical study of these beliefs. Primals also allow mapping of beliefs to different dimensions, fitting to a hierarchical structure. The belief that the world is Good (vs. bad) is considered the Primary primal, and secondary primals include beliefs the world is Safe (vs. dangerous), Enticing (vs. dull) and Alive (vs. mechanistic). Primals can be assessed with self-report questionnaire measures, with options to measure different dimensions of interest. Primals appear stable over time, similar to Big Five personality traits, and demonstrate considerable variation across individuals. Interestingly, primals appear to poorly describe the objective conditions people are experiencing, and notable changes in global circumstances. For example, belief the world is dangerous did not appear to be more prevalent during the Covid-19 pandemic. Recent work has demonstrated that primals are associated with different aspects of psychopathology, including depression, anxiety, suicide history, life satisfaction, and positive affect.

There is currently no research investigating primals in psychosis-spectrum disorders. We aimed to investigate possible differences in primary (Good) and secondary primals (Safe, Enticing and Alive) between people experiencing psychosis-spectrum disorders and controls with no experience of psychosis. We also aimed to understand associations between primals and psychosis-related experiences of hallucinations, delusions, and interpretations of these experiences.

Methods: This online, cross-sectional, self-report study included 99 participants. Participants were individuals with a psychosis-spectrum disorder (n=47; mean age = 34.89, SD = 12.23), and control participants with no experience of psychosis (n=52; mean age = 38.87; SD = 13.12). In the psychosis-spectrum group, 48.9% had a primary diagnosis of psychotic disorder, with the remaining participants having another serious mental health problem with psychotic features.

All participants were screened for psychosis using the Prodromal Questionnaire-16 (PQ-16) and were assessed for hallucination-proneness with the Multi-Modality Unusual Sensory Experiences Questionnaire (MUSEQ) and delusion-proneness using the Peters' Delusion Inventory-21 (PDI). Primals were measured using the Primals Inventory (PI-18). The PI-18 measures primal beliefs the world is Good (vs bad), as well as Safe (vs. dangerous), Enticing (vs. dull) and Alive (vs. mechanistic). Participants are asked to indicate how much they agree with 18 statements, such as 'On the whole, the world is a dangerous place'.

Results: Individuals with a psychosis-spectrum disorder reported more negative primals than controls, relating to fewer beliefs that the world is Good, Safe and Enticing. Beliefs the world is less Safe were associated with more psychotic symptoms, subjective distress about symptoms, and preoccupation with delusions. Positive delusions of inflated self-worth were associated with belief that the world is Good, and delusions of magical thinking were positively associated with beliefs that the world is more Enticing and Alive.

Discussion: Our findings indicate that experience of psychosis leads to more negative views about the world as being a Bad, Dangerous and Dull place. Relatedly, the world is considered more dangerous as severity and distressing experiences increase. As people experiencing psychosis have often experienced adversity, we suggest there is a cumulative impact of

biopsychosocial factors that result in development of negative schemas about the world and aberrant processing of stimuli as threatening and pervasive.

The number of positive symptoms was not related to primals. However, breaking down delusional ideation into different factors revealed that positive delusions of inflated self-worth and magical thinking were related to a more positive world view. We suggest that it is therefore more likely the case that biased cognitive schemas that influence a person's interpretations of their experiences and views about the world, rather than the number or frequency of symptoms themselves.

Primals may be a useful construct to address in psychotherapies to shift world views, and thus life experiences, to be less distressing. Future work should consider if changes in primals over time are related to changes in individual interpretations and content of symptoms, in order to better understand clinical implications and applications.

T57. REINFORCEMENT LEARNING IN PEOPLE WITH SCHIZOPHRENIA: A META-ANALYSIS OF 16 EXPERIMENTS CONDUCTED AT THE MARYLAND PSYCHIATRIC RESEARCH CENTER

Adam Culbreth*¹, James Gold², James Waltz³, Shuo Chen³

¹*Maryland Psychiatric Research Center, University of Maryland School of Medicine,*

²*MPRC,* ³*Maryland Psychiatric Research Center*

Background: Alterations in aspects of reinforcement learning have been widely reported in people with schizophrenia. In many studies, these deficits are also associated with core clinical characteristics of schizophrenia, including severity of negative symptoms and cognitive impairment. In the current analysis, we aimed to quantify the consistency of group differences in reinforcement learning between people with schizophrenia and healthy controls, as well as associations with negative symptoms and global measures of cognition.

Methods: We aggregated 15 separate datasets (total sample size: HC = 530, SZ = 709) collected by our group at the Maryland Psychiatric Research Center, which included a reinforcement-learning task, negative symptom interview (the Scale for the Assessment of Negative Symptoms (SANS)), and neuropsychological measure of premorbid intellectual function (Wechsler Test of Adult Reading (WTAR)). We hypothesized that across these studies individuals with schizophrenia would show lower reinforcement learning task performance (overall task accuracy) compared to healthy controls, and that negative symptom severity and premorbid intellectual function would be significantly associated with reinforcement-learning task performance.

Results: Consistent with our hypothesis, across our 15 experiments, people with schizophrenia showed reduced reinforcement learning (percent correct) compared to healthy controls (Cohen's $d = -0.48$, 95%-CI [-0.60 to -0.37], z -value = -8.03, p -value LESS THAN 0.001). Further, reinforcement learning was significantly associated with measures of premorbid intellectual function (r -value = 0.28, 95%-CI [0.21 to 0.35], z -value = 7.10, p -value LESS THAN 0.001) such that participants with schizophrenia with lower premorbid IQ showed lower performance on reinforcement learning tasks. When examined continuously, associations between negative symptom severity and reinforcement learning were in the hypothesized direction but were not statistically significant (r -value = -0.06, 95%-CI [-0.15 to 0.03], z -value = -1.36, p -value = 0.17). When examined categorically, patients with severe avolition showed significantly weaker reinforcement learning compared to

patients without severe avolition (Cohen's $d = -0.17$, 95%-CI [0.0063; 0.3484], z -value = -2.03, p -value = 0.042)

Discussion: Taken together, these results demonstrate robustness of RL impairment in people with schizophrenia, as well as associations to particular aspects of the disorder. In analyses presented at the SIRS meeting we will further contextualize these findings through supplemental analyses examining interactions of the above effects with reinforcement-learning task features including valence and probability contingencies, as well as more nuanced measures of symptoms (e.g., separating expressive vs. experiential negative symptoms).

T58. PREPAREDNESS FOR CLIMATE-DRIVEN HURRICANES IN SEVERE MENTAL ILLNESS

Mary Gorora^{*1}, Gabrielle Wong-Parodi², Zelde Espinel³, James Shultz⁴, Philip D. Harvey⁵

¹University of Miami Miller School of Medicine, ²Stanford University, Department of Earth System Science, ³University of Miami Miller School of Medicine, Department of Psychiatry and Behavioral Sciences, ⁴University of Miami Miller School of Medicine, Department of Public Health Sciences, ⁵University of Miami Miller School of Medicine, Department of Psychiatry and Behavioral Sciences / Miami VA Healthcare System

Background: Individuals with severe mental illness (SMI), such as schizophrenia and bipolar disorder, face distinct challenges in preparing for climate-related disasters, particularly hurricanes. This study aims to explore how cognitive impairments, specifically in prospective memory (PM) and introspective accuracy (IA; the ability to self-assess various cognitive and functional abilities), affect their preparedness. Understanding these impairments is crucial for developing more effective hurricane preparedness guidelines tailored to the unique needs of the SMI population.

Methods: We conducted a comprehensive survey with 40 SMI patients (20 with schizophrenia, 20 with bipolar disorder) and their respective informants. The survey assessed participants' PM, hurricane risk perception, and adaptation appraisal using a modified disaster behavioral health model. A shortened Prospective Memory Concerns Questionnaire was employed to evaluate PM, and introspective accuracy was gauged by comparing patient self-reports with informant observations.

Results: In the schizophrenia group, self-reported PM scores exhibited a significant negative correlation with IA scores (-0.686 , $p=0.005$), while informant reports on the patients' PM displayed a positive correlation (0.577 , $p=0.024$). This pattern of impaired IA was similarly observed in the bipolar group, with patient self-reports and informant assessments showing correlations of -0.710 ($p < 0.001$) and 0.869 ($p < 0.001$), respectively. Both groups reported a higher need for assistance in executing the most helpful preparedness tasks (SCZ: 0.702 , $p < 0.001$; BP: 0.526 , $p=0.017$). Moreover, there was a notable discrepancy between the patients' perceived self-efficacy and the informants' assessment of the patient's abilities, with negative correlations observed in self-efficacy scores and IA for both schizophrenia (-0.668 , $p=0.002$) and bipolar groups (-0.589 , $p=0.008$), and positive correlations in informant reports (SCZ: 0.818 , $p < 0.001$; BP: 0.712 , $p < 0.001$).

Discussion: Our findings highlight significant deficits in introspective accuracy among SMI patients, impacting not only their prospective memory but also their adaptation appraisal abilities. These IA deficits are likely a key factor in being underprepared for hurricanes. The

pronounced contrast between self-assessment and informant evaluation suggests a notable gap in self-awareness about their own preparedness capabilities. Tailoring hurricane preparedness guidelines to accommodate these cognitive challenges is critical. Developing specialized support and strategies, considering these cognitive impairments, could significantly enhance the safety and preparedness of this vulnerable group in the face of impending disasters.

T59. TRANSDIAGNOSTIC COGNITIVE BIASES IN PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Katie Lavigne^{*1}, Jiaxuan Deng², Delphine Raucher-Chéné¹, Adèle Hotte-Meunier², Chloe Voyer², Lisa Sarraf³, Martin Lepage¹, Genevieve Sauve⁴

¹McGill University, Douglas Mental Health University Institute, ²Douglas Mental Health University Institute, ³Douglas Mental Health University Institute, Carleton University, ⁴Douglas Mental Health University Institute, Université du Québec à Montréal

Background: Psychiatric disorders, including schizophrenia, bipolar disorder, and depression, are characterized by cognitive deficits, which have been proposed as a transdiagnostic feature of psychopathology (“C” factor). Similarly, cognitive biases (e.g., in attention, memory, and interpretation) represent common tendencies in information processing that are often associated with psychiatric symptoms, such as delusions and hallucinations in schizophrenia-spectrum disorders, and emotion regulation in mood disorders. However, the question remains whether cognitive biases are also transdiagnostic or are specific to certain psychiatric disorders or symptoms. We sought to address whether the proposed “C” factor of transdiagnostic cognitive dysfunction in psychopathology can be extended to cognitive biases and transdiagnostic symptom dimensions of psychopathology.

Methods: We performed a systematic review of the literature on cognitive biases in psychiatric disorders reporting group differences or associations with symptoms and including two or more diagnostic categories from the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD). Title and abstract screening was performed by at least 2 reviewers, who showed good agreement (83%, AC1 = 0.671, SE = 0.013, CI = [0.645, 0.698], $p < 0.001$). Biases were categorized as either attention, memory, or interpretation biases and were reverse coded when necessary (e.g., reaction times, difference scores) to ensure that higher values equated to greater bias severity. Symptoms were categorized into transdiagnostic super-spectra based on the Hierarchical Taxonomy of Psychopathology (HiTOP): general psychopathology (p factor) emotional dysfunction, psychosis, and externalizing. Traditional random-effects meta-analyses were conducted by bias category to examine (1) group differences between patients and non-clinical controls (Hedge’s g) and (2) associations between biases and transdiagnostic symptom categories (Fisher’s r -to- z). Network meta-analyses were then conducted by bias category to compare direct and indirect effects between diagnoses with non-clinical controls as a reference group.

Results: Overall, 31 studies comprising 4401 participants (2536 patients, 1865 non-clinical controls) across 21 diagnostic categories met inclusion criteria, assessing 19 cognitive biases with most studies focusing on interpretation ($k = 22$) and attention ($k = 11$) biases, with only 2 assessing memory biases. Traditional meta-analyses found a moderate effect size ($g = 0.32$) for more severe cognitive biases in all patients relative to non-clinical controls, as well as small but significant associations between interpretation biases and transdiagnostic symptom categories (general psychopathology: $r = .20$, emotion dysfunction: $r = 0.17$, psychotic

symptoms: $r = 0.25$). Network meta-analyses revealed significant patient versus control differences on attention and interpretation biases across diagnoses, as well as significant differences between diagnoses, with highest severity for attention biases in panic and other anxiety disorders and for interpretation biases in obsessive-compulsive and other anxiety disorders as well as schizophrenia-spectrum disorders.

Discussion: The current findings support a big “C” interpretation of transdiagnostic cognitive dysfunction in psychiatric disorders, extending the concept to cognitive biases and transdiagnostic symptom dimensions, particularly emotion dysfunction and psychosis symptoms. They also suggest that while the presence of cognitive biases is transdiagnostic, bias severity differs across diagnoses, as is the case for traditional neurocognitive deficits.

T60. PUTTING A LABEL ON SOMEONE: IMPACT OF SCHIZOPHRENIA STIGMA ON EMOTIONAL MIMICRY, LIKING, AND INTERPERSONAL CLOSENESS

Mathilde Parisi*¹, Stéphane Raffard², Pierre Slangen³, Till Kastendieck⁴, Ursula Hess⁴, Heidi Mauersberger⁴, Tifenn Fauviaux³, Ludovic Marin³

¹*EuroMov Digital Health in Motion*, ²*Epsilon Laboratory Dynamic of Human Abilities and Health Behaviors, University of Montpellier 3, Montpellier, France.*, ³*EuroMov Digital Health in Motion, Univ Montpellier, IMT Mines Ales, Montpellier, France.*, ⁴*Department of Psychology, Social and Organizational Psychology, Humboldt-Universität zu Berlin, Berlin, Germany*

Background: Affiliation has been shown to be both an antecedent and a consequence of emotional mimicry (i.e., the imitation of a counterpart’s emotional expression). For instance, interacting with an unlikeable partner can decrease emotional mimicry, leading to diminished liking. This perpetuating circle has not been investigated in the context of mental health stigma yet. Schizophrenia is a mental disorder associated with social interaction deficits and heavy public stigma. Consequently, this study aimed to test the influence of the label “schizophrenia” on emotional mimicry, liking, and interpersonal closeness.

Methods: We conducted an online experiment ($n=200$). Participants recruited from the general population were shown several videos of actors displaying emotional expressions. Actors were described with one of four labels (“schizophrenia”, “healthy”, “diabetes”, and a negative adjective) to discern whether stigma, a specific diagnosis, or a negative label influenced participants' response to the schizophrenia label. While watching the videos, participants were filmed with their computer’s webcams. We assessed emotional mimicry using OpenFace 2.2, which is an automated coding software for facial expressions. Liking and interpersonal closeness were measured using questionnaires.

Results: Results demonstrated decreased liking and interpersonal closeness of the actors with the schizophrenia label compared to all other labels. However, no effect on emotional mimicry was found. We also found that decreased liking of the schizophrenia actors was explained by lack of knowledge of schizophrenia. In addition, decreased liking, and interpersonal closeness of the actors with the schizophrenia labels were associated with increased willingness to socially distance from individuals with schizophrenia.

Discussion: Our study contributes to the literature on schizophrenia stigma by demonstrating implicit stigmatized reactions through decreased liking and interpersonal closeness. However, in contrast to other studies that demonstrated that liking and interpersonal closeness predict emotional mimicry, we could not find any influence of the schizophrenia label on emotional

mimicry. These results could be explained by the fact that despite being a validated tool, OpenFace 2.2 was shown to be less sensitive than other emotional mimicry measurement tools (e.g., electromyography). Consequently, small effects might not have been detected. Our work encourages future studies to reconduct this experiment using other methodologies. Implications and recommendations for future studies are discussed.

T61. SOCIAL MOTIVATION TENDENCIES IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: RELATIONSHIP WITH SYMPTOMS AND ROLE FUNCTIONING

Suzanne So¹, Anson Kai Chun Chau¹, Xiaoqi Sun², Sandra Sau-man Chan¹, Wing Chung Chang³, Lyn Ellett⁴, Mike Rinck⁵, Anson Kai Chun Chau*⁶

¹The Chinese University of Hong Kong, ²Hunan Normal University, ³The University of Hong Kong, ⁴University of Southampton, ⁵Radboud University, ⁶The University of New South Wales

Background: Social disconnection is common in schizophrenia spectrum disorders (SSD). Based on research on anxiety disorders, it has been postulated that, compared to healthy individuals, patients with SSD may show biases in social motivation characterised by a stronger tendency to avoid aversive social stimuli and a milder tendency to approach pleasant social stimuli. However, empirical evidence has been inconsistent possibly due to how social motivation is assessed.

Methods: This study examined social motivation tendencies in SSD using an enhanced version of the Approach Avoidance Task (AAT; Heuer et al, 2007). In this task, participants were asked to respond to pictures of faces by pushing or pulling the joystick according to the colour of the pictures (push upon grey pictures and pull upon sepia pictures). This is an implicit measurement of social motivation because the reaction time (RT) difference of pushing and pulling for each emotion embedded in the faces was of interest.

Three methodological improvements were built into this task. Firstly, on top of happy and angry faces (i.e. pleasant and aversive social stimuli respectively), neutral faces were included as control. This allowed for calculations of both the 'difference score' (RT difference (push-pull) within each target emotion, with a positive score indicating approach and a negative score indicating avoidance) and the 'double-difference D-score' (the discrepancy between the difference score for emotionally-valenced faces and the difference score for emotionally-neutral faces divided by the standard deviation of the participant's RTs). Secondly, faces carrying both straight and averted gazes were included, allowing for more nuanced differences in social motivation to emerge. Thirdly, to increase sense of familiarity and salience, faces of Chinese models were pilot-tested and used in our Chinese sample. Patients were assessed on social motivation (192 trials of AAT presented in 4 blocks), clinical symptoms (Positive And Negative Syndrome Scale and Calgary Depression Scale for Schizophrenia), and role functioning (Role Functioning Scale).

Results: The sample consisted of 95 patients with SSD (mean age = 34.34; 54.7% female), among whom 93 participants completed the AAT and had an error rate LESS THAN 20%. Trials with extreme RTs (LESS THAN 300ms, GREATER THAN 2000ms, and GREATER THAN 3 SDs from the participant's mean) were excluded. In both straight- and averted-gaze conditions, there was an approach tendency towards angry faces (ps LESS THAN .050), which was stronger than neutral faces (ps LESS THAN .050). There was no

significant approach/avoidance tendency towards happy faces (p GREATER THAN .050). The double-difference D-score was greater for angry faces than happy faces on the averted-gaze condition (p LESS THAN .001), indicating a stronger tendency to approach angry faces than happy faces.

Level of approach towards angry faces was negatively correlated with severity of PANSS positive and general psychopathology scores and depressive symptoms (p s = -0.21 to -0.24; p s LESS THAN .050). Level of approach towards happy faces was negatively correlated (p = -0.26) with depressive symptoms and positively correlated (p = 0.22) with role functioning (p s LESS THAN .050).

Discussion: The modified AAT provided a sensitive assessment for social motivation tendencies for patients with SSD, revealing meaningful relationships with symptoms and role functioning. Contrary to the hypothesis, patients tended to approach rather than avoid angry faces. Unlike in anxiety disorders, an approach tendency towards angry faces correlated with less severe symptomatology in our sample. Our results add to the accumulating evidence of social motivation tendencies across psychiatric disorders.

T62. NEURAL CORRELATES OF SOCIAL-PERCEPTUAL COMPONENT OF THEORY OF MIND IN SCHIZOPHRENIA

Cemal Demirlek^{*1}, Nabi Zorlu², Merve Karakılıç², Ecenaz Sarıkaya², Adem Bayrakçı², Burcu Verim³, Funda Gülyüksel², Berna Yalınçetin³, Elif Oral², Fazıl Gelal⁴, Emre Bora³

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Department of Psychiatry, Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey,* ³*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey,* ⁴*Department of Radiodiagnostics, Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey*

Background: Theory of mind skills are disrupted in schizophrenia. This multimodal neuroimaging study aimed to identify the neural correlates of social-perceptual (mental state decoding) component of theory of mind in schizophrenia and healthy controls (HCs) using structural (T1-weighted) and diffusion-weighted (DTI) magnetic resonance imaging (MRI).

Methods: Sixty-two patients with schizophrenia and 34 HCs were included. The Reading the Mind in the Eyes (RMET) test were used to evaluate social-perceptual component of theory of mind. Correlations between theory of mind and cortical parameters (thickness, volume, surface area), or DTI scalars (fractional anisotropy, axial diffusivity, radial diffusivity) were cluster-based corrected for multiple comparisons.

Results: RMET scores showed positive correlations in 3 clusters, including left insula thickness, right superior-temporal thickness, left superior-temporal-sulcus volume in schizophrenia. DTI analysis revealed that fractional anisotropy showed positive correlations in 3 clusters, including right inferior-fronto-occipital fasciculus, left forceps-major, left inferior-fronto-occipital fasciculus in schizophrenia.

Discussion: In conclusion, this study provided evidence for the involvement of particular cortical regions and white matter tracts in social-perceptual (mental state decoding) component of theory of mind in schizophrenia. These findings have implications for targeted interventions development and treatments aimed at improving social functionality in patients with schizophrenia.

T63. RETINAL MICROVASCULATURE AND COGNITIVE FUNCTIONS IN FIRST-EPISODE PSYCHOSIS

Cemal Demirlek*¹, Merve S. Gurbuz², Ferdane Atas³, Berna Yalincetin², Burcu Verim², Ezgi Cesim², Muhammed Demir², Simge Uzman-Ozbek⁴, Ekin Sut⁵, Burak Baykara⁵, Berna B. Akdede⁴, Mahmut Kaya⁶, Emre Bora⁴

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey,* ³*Department of Ophthalmology, Cerkezkoy State Hospital, Tekirdag, Turkey,* ⁴*Department of Psychiatry, Dokuz Eylul University Medical School, Izmir, Turkey,* ⁵*Department of Child and Adolescent Psychiatry, Dokuz Eylul University Medical School, Izmir, Turkey,* ⁶*Private Practice, Izmir, Turkey*

Background: Both schizophrenia and its associated neurocognitive impairments, along with retinal abnormalities, constitute significant aspects of the condition. Impairments in neurocognitive functions are evident in both chronic and first-episode psychosis, with notable deficits observed in processing speed, memory, and executive functions. During embryogenesis, the eye originates from the diencephalon, making it part of the central nervous system (CNS) and often regarded as a window into the brain. Its vascular development is closely tied to neural development through neurovascular coupling. Studies employing fundus photography have revealed abnormalities in retinal microvasculature in psychotic disorders, encompassing variations in vascular caliber, fractal dimension, branching, and tortuosity. Additionally, despite some conflicting results in OCT-angiography (OCT-A) studies, individuals with schizophrenia exhibit reduced vessel densities and perfusion. Notably, retinal microvasculature abnormalities have been linked to the cognitive functions in patients with chronic schizophrenia. In this present study, our objective is to explore the connection between cognitive functions and retinal microvasculature in first-episode patients, utilizing OCT-A as a diagnostic tool.

Methods: Before OCT-A imaging, each participant underwent assessment of premorbid ability using the Wechsler Intelligence Scale for Children-R (WISC-R) or the Wechsler Adult Intelligence Scale-R (WAIS-R) information subtests. Processing speed was evaluated through the Digit Symbol Substitution Test (DSST), while visual memory (both immediate and delayed recall) was measured using the Visual Reproduction Test. Executive functions were assessed using the Wisconsin Card Sorting Test (WCST) and the Stroop Color and Word Test. Outcome variables included the number of categories completed and perseverative errors from the WCST, as well as the Stroop interference score and Stroop error score. Swept-source OCT-A images of the macular region (3 x 3 mm) for both the right and left eyes were acquired using the DRI Topcon Triton to visualize the retinal superficial capillary plexus. While OCT-A images were obtained for both eyes of all participants, only the right eye was utilized to ensure accurate and unbiased results. Vessel area density, fractal dimension, and mean tortuosity in the superficial capillary plexus were quantified using MATLAB and ImageJ software.

Results: Thirty patients with first-episode psychosis included in this study. Stroop interference score was positively correlated with retinal vessel area density ($p = 0.008$, $r = 0.477$) and fractal dimension ($p = 0.009$, $r = 0.468$), but not with mean tortuosity ($p = 0.199$) in patients with first-episode psychosis. Additionally, the other cognitive domains were not significantly associated with any retinal microvasculature measures in first-episode patients ($p > 0.05$).

Discussion: The findings of this study offer intriguing insights into the relationship between retinal microvasculature and cognitive functions in first-episode psychosis patients. Notably, a positive correlation was observed between the Stroop interference score and both retinal vessel area density and fractal dimension. This association implies that changes in retinal microvascular structure may reflect alterations in cognitive processing, particularly in the domain of attention and executive functioning as measured by the Stroop test. Considering the embryological link between the eye and the central nervous system, these findings support the hypothesis that retinal abnormalities could serve as a non-invasive biomarker for neurocognitive impairments in psychotic disorders. This is particularly relevant given the challenges associated with direct assessments of CNS abnormalities in these patients. However, the study's limitation to the small sample size should be noted, as these factors might limit the generalizability of the results. Future research could expand upon these findings by including a larger and more diverse sample, examining longitudinal changes in retinal microvasculature and their correlation with cognitive trajectories in psychosis, and exploring potential mechanisms underlying these associations.

T64. OCULOMICS AND CONNECTOMICS IN EARLY PSYCHOSIS

Cemal Demirek*¹, Burcu Verim², Muhammed Demir², Ferdane Atas³, Berna Yalincetin², Berna B. Akdede⁴, Mahmut Kaya⁵, Nabi Zorlu⁶, Emre Bora⁷

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey,* ³*Department of Ophthalmology, Cerkezoy State Hospital, Tekirdag, Turkey,* ⁴*Department of Psychiatry, Dokuz Eylul University Medical School, Izmir, Turkey,* ⁵*Private Practice, Balçova, Izmir, Turkey,* ⁶*Department of Psychiatry, Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey,* ⁷*Dokuz Eylul University, School of Medicine, Department of Psychiatry, Balçova, Izmir*

Background: Recent studies reported parallel changes in anatomy and function in the eye and the brain in neuropsychiatric diseases. In addition to the eye's role as an easily and non-invasively accessible research target to develop biomarkers and to investigate the pathophysiology of neuropsychiatric diseases, the eye also may have significant pathophysiological relationships with the brain. Therefore, this study aimed to investigate; i) ocular differences between first-episode psychosis (FEP) and healthy controls (HC), ii) structural occipital cortex differences between FEP and HCs, iii) relationship between the ocular measures and cortical structure and global functional brain networks in FEP.

Methods: Nine-teen patients with FEP and 13 HCs included in this study. All participants underwent psychiatric evaluation, ocular imaging with optical coherence tomography, brain imaging with 3 Tesla T1-weighted magnetic resonance imaging (MRI), and resting-state functional MRI (fMRI). FEP patients were from the Early Intervention Unit, while HCs had no personal/family history of mood/psychotic disorders. Imaging the eyes was performed using a spectral-domain OCT. Ocular imaging measured retinal layers, and T1-weighted MRI analyzed cortical regions in the occipital cortex. The retinal layers include: the nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL). fMRI analysis involved preprocessing steps, and graph theory analyses were conducted on resting-state fMRI data. Freesurfer was used for analysis of T1-weighted structural MRI. fMRIPrep software was used for the resting state fMRI analysis. Graph-based network analysis were performed using

Brain Connectivity Toolbox as implemented in MATLAB. Statistical analyses were performed using SPSS to compare FEP and HC differences and relationships between ocular and graph-theory based connectome parameters.

Results: There were no significant differences in gender and age between the FEP and HC groups ($p > 0.05$). All participants with FEP were clinically stable. Regarding demographic and clinical parameters, the age of patients with FEP was 21.6 ± 3.93 , and the age of patients with HCs was 24.3 ± 3.54 . The Scales for the Assessment of Positive Symptoms score was 18.18 ± 11.8 , and the Brief Negative Symptom Scale score was 30.7 ± 15.44 in patients with FEP. For structural MRI analysis, occipital cortex regions were not significantly different between FEP and HCs. Furthermore, functional brain networks also were not significantly different between FEP and HCs. For the right eye, retina total thickness ($p = 0.01$), GCL volume ($p = 0.01$), IPL volume ($p = 0.029$), INL volume ($p = 0.005$) were increased in patients with FEP compared to HCs. For the left eye, GCL volume ($p = 0.005$), IPL volume ($p = 0.026$), INL volume ($p = 0.003$) were increased in patients with FEP compared to HCs. The thicknesses of retinal layers of both the right and left eyes were not significantly different between groups. In patients with FEP, characteristic path length was significantly associated with NFL volume ($p = 0.41$, $r = 0.687$), GCL volume ($p = 0.007$, $r = 0.685$), OPL volume ($p = 0.034$, $r = 0.567$). Cluster coefficient was significantly associated with the total retina central thickness ($p = 0.003$, $r = 0.686$), GCL thickness ($p = 0.018$, $r = 0.622$), IPL thickness ($p = 0.019$, $r = 0.576$), OPL thickness ($p = 0.003$, $r = 0.686$). The small-worldness was associated with the total retina central thickness ($p = 0.022$, $r = 0.567$), IPL thickness ($p = 0.009$, $r = 0.626$), OPL thickness ($p = 0.023$, $r = 0.564$). Modularity was significantly associated with the total retina central thickness ($p = 0.02$, $r = 0.574$), GCL thickness ($p = 0.015$, $r = 0.636$), OPL volume ($p = 0.027$, $r = 0.587$) and thickness ($p = 0.04$, $r = 0.517$). Global efficiency was associated with NFL thickness ($p = 0.045$, $r = 0.676$), GCL thickness ($p = 0.42$, $r = 0.550$), OPL thickness ($p = 0.022$, $r = 0.567$). In patients with FEP, the total retina thickness was significantly associated with lateral occipital cortex thickness ($p = 0.006$, $r = 0.605$), and showed non-significant trend with lingual thickness ($p = 0.059$, $r = 0.441$). The total retina volume was not significantly associated with any occipital cortex region volumes.

Discussion: To the best of our knowledge, this is the first study identifying the relationship between ocular parameters and brain structure and function in patients with FEP. These findings contribute to the growing body of research in oculomics and connectomics aspects of early psychosis. Intriguingly, while there were no significant differences in occipital cortex structures and functional brain networks between FEP and HCs, ocular imaging with OCT revealed notable differences. Patients with FEP exhibited increased volumes in certain retinal layers, particularly GCL, IPL, and INL. These correlations could reflect underlying systemic changes affecting both the eye and the brain, possibly mediated by common neurobiological pathways such as aberrant neurodevelopment. In summary, our study contributes to the growing body of evidence suggesting that oculomics could be a valuable tool in understanding and potentially detecting early psychosis.

T65. PSYCHOSIS AND TRAUMA – MEASUREMENTS OF BLOOD-BASED EXOSOMAL BIOMARKERS FROM BRAIN ORIGINS

Charles Desmeules^{*1}, Olivier Corbeil², Laurent Béchard³, Maxime Huot-Lavoie¹, Colombe Claveau⁴, Chantale Thériault⁵, Coraline Canivet⁶, Anne-Marie Essiambre⁵, Élisabeth Anderson⁷, Marie-France Demers⁸, Marc-André Roy¹, Jessica Deslauriers⁸

¹Universite Laval Faculty of Medicine, ²Faculty of Pharmacy, Universite Laval, ³Faculty of Pharmacy, Laval University, ⁴CERVO Brain Research Center, ⁵CERVO Brain Research Centre, ⁶CHU de Québec Research Center, ⁷School of Psychology, Laval University, ⁸Pharmacy Faculty, Laval University

Background: Due to its reliance on heterogeneous symptomatology, accurate diagnosis of first-episode psychosis (FEP) remains challenging for clinicians. As early intervention has substantial benefits for long-term outcomes, early diagnosis of FEP is imperative to improve recovery for affected individuals. However, the lack of specific biomarkers poses a significant limitation for early diagnosis of FEP. It is therefore urgent to identify specific diagnosis biomarkers of FEP.

History of past psychotrauma is an important risk factor for developing psychosis. As chronic inflammation is observed in both FEP and trauma history pathogeneses, this suggests a sub-category of psychosis characterized by the history of a psychotrauma with an inflammatory component. To date, the mechanisms underlying the development of psychosis after a traumatic experience and the contribution of inflammation to this association are still unknown.

Another limitation in biomarker discovery studies is that circulating biomarkers are not reflecting neurological changes. Brain-derived exosomes have aroused increasing interest in recent years as they are produced by brain cells and cross the blood-brain barrier to release inflammatory cargo once they reach the bloodstream. Brain-derived exosomes are therefore a powerful and non-invasive tool to examine inflammatory marker specific to their brain origin. The present study aims to: (1) examine inflammatory content of several brain-derived exosomes in the FEP vs healthy populations; and (2) determine the effect of past psychotrauma on the brain-derived exosomal content in FEP individuals vs those without history of past trauma.

Methods: 50 healthy controls, 25 FEP individuals without psychotrauma and 25 FEP with psychotrauma were recruited. Psychopathological measures were collected with the Positive and Negative Syndrome Scale, as well as Childhood Trauma Questionnaire and Life Events Checklist scales for trauma history. Exosomes from astrocytes, microglia and neurons were isolated and enriched from collected plasma samples by immunocapture with anti-GLAST, anti-TMEM119 and anti-CD171 antibodies, respectively. Characterization of inflammatory content of brain-derived exosomes was conducted using high-sensitivity multiplex essays. Kruskal-Wallis analyses were performed to compare the biological parameters in healthy, FEP without trauma, and FEP with trauma groups.

Results: Preliminary results from a subgroup of participants (n=4-6/group) have been generated for several immune markers (IL-10, IL-12p70, IL-17, IL-1 β , IL-2, IL-4, IL-6, TNF- α and IFN- γ) from astrocyte-, neuron-, and microglia-derived exosomes. Individuals with history of trauma tends to exhibit higher levels of neuron-derived IL-12p70 (p LESS THAN 0.10 vs healthy group) and elevated levels of microglia-derived IFN- γ (p LESS THAN 0.09 and p LESS THAN 0.11 vs healthy and FEP without trauma groups, respectively). Complete analyses, namely analysis of covariables with sex as covariable, and including all participants will be presented at the meeting.

Discussion: As the history of past trauma in the FEP population tends to be associated with specific immune content from neuron- and microglia-derived exosomes, our findings highlight that: (1) that trauma history modulates psychotic risk via specific neuroimmune signaling pathways; and (2) that past trauma induces a distinct FEP biosignature. Importantly, our study: (1) strengthens the potential of brain-derived exosomes as accessible and non-invasive biomarkers that reflect neurological changes in humans; and (2) is a crucial step in

our understanding of the role of neuroinflammation in FEP and the association with traumatic history in a brain cell-specific manner.

T66. A MULTIMODAL ARCHITECTURE FOR DISTINGUISHING SCHIZOPHRENIA SPECTRUM DISORDER FROM BIPOLAR DISORDER USING LEXICAL FEATURES FROM TRANSCRIBED SPEECH

Omar Alqahtani¹, Julianna Olah^{*2}

¹UCL, ²King's College London

Background: Speech abnormalities, represented in the form of quantifiable deviations from normal language use, are characteristic of psychotic disorders and present even in the prodromal stage. Different methodologies have been proposed to automatically measure such differences. These methods root in an exponentially growing field, Natural Language Processing (NLP). However, the application of one of the most disruptive and successful technological developments of NLP, Large Language Models (LLM's) have not been explored in psychosis research.

Methods: In this project, we explored the potential of Large Language Models (LLMs) for classifying psychiatric disorders, with a focus on distinguishing between Bipolar Disorder (BD) (N = 189) and Schizophrenia Spectrum Disorder (SSD) (N = 83). We also considered representations of the general population, categorised as Healthy Control (N = 318) and Prodromal Psychosis (PP) (N = 332). To this end, we employed DistilRoBERTa as the core of a Multimodal model, integrating both lexical and non-lexical features.

Results: This unified approach achieved moderate performance to predict BD, SSD, PP demonstrating the potential of fine-tuned LLMs as reliable diagnostic tools in clinical settings. Moreover, the model's design and training addressed challenges commonly associated with mental health data, such as limited sample sizes and class imbalances.

Discussion: We discuss general considerations and challenges related to the technical applications and suggestions for target LLMs for deployment. We present technical solutions to overcome difficulties in health care applications (e.g. data scarcity, limited computational power, feeding in non-lexical information, multimodal assessment) and use our experiment data to present a know-how of fine-tuning LLM's for psychosis-related applications.

T67. THE ROLE OF ENDOCANNABINOID IN LIPID METABOLISM IN PATIENTS AT HIGH RISK OF PSYCHOSIS

Alex Dickens^{*1}, Edward Chesney², Partho Sen³, Matthew Kempton⁴, Amedeo Minichino⁵, Neus Barrantes-Vidal⁶, Conrad Iyegbe⁷, Merete Nordentoft⁸, Thomas Pollak⁹, Anita Riecher-Rössler¹⁰, Stephan Ruhrmann¹¹, Gabriele Sachs¹², Rodrigo Bressan¹³, Marie-Odile Krebs¹⁴, G. Paul Amminger¹⁵, de Haan Lieuwe¹⁶, Mark Van der Gaag¹⁷, Lucia Valmaggia¹⁸, Tuulia Hyötyläinen¹⁹, Matej Oresic¹⁹, Philip McGuire²⁰

¹University of Turku/Turku Centre for Biotechnology, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London, ³Turku Bioscience Center, University of Turku and Åbo Akademi University, Turku, Finland, ⁴Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK, ⁵University of Oxford, ⁶Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona,

Spain, ⁷Department of Psychological Medicine, ⁸Mental Health Centre Copenhagen, ⁹Institute of Psychiatry, King's College London, ¹⁰University of Basel Psychiatric Clinics, ¹¹Dept. of Psychiatry and Psychotherapy, University of Cologne, ¹²Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria, ¹³Universidade Federal de Sao Paulo - UNIFESP, ¹⁴University Paris Cité - INSERM -, ¹⁵Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Australia, ¹⁶Academic Medical Center, Amsterdam, the Netherlands, ¹⁷VU University Amsterdam Clinical Psychology, ¹⁸Institute of Psychiatry, Psychology and Neuroscience, King's College London, ¹⁹Örebro University, ²⁰King's College London

Background: Recently we identified a set of lipid biomarkers which associated which could stratify patients at clinically high risk of psychosis and could their clinical progression. This was developed in the EU-GEI cohort. However, the reasons for these lipid changes remain unclear. Therefore, we sought to identify potential lipid mediators that could start to identify why the lipids change in these individuals. Our recent study demonstrated that upon first episode psychosis there is a clear breakdown in the association between the CB1 receptor availability in the CNS compared to the circulating endocannabinoids. The ECS comprises of a complex interaction between endogenous cannabinoids (endocannabinoids), the enzymes involved in the up and down stream metabolism of endocannabinoids and the cannabinoid receptors (CB1 and CB2). Current knowledge regarding the endogenous endocannabinoids (ECs) is mostly limited to the two major ECs, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These two ECs are known to act at both CB1 and CB2 receptors. In addition to these two molecules there is a chemically diverse set of related compounds more broadly known as long chain N-acylethanolamines (NAE)s and 2-monoacylglycerols. To understand the role of the ECS in early psychosis we quantified endocannabinoids and related structures with mass spectrometry in the serum taken from the EU-GEI cohort. We then combined this data with the previously published lipidomic data to understand how the changes in circulating endocannabinoids impacted the lipid metabolism. Given the previous sex effects observed in CB1 receptor availability we also stratified the patients based on sex to observe if there were any differences between the interaction of the lipid metabolism and the endocannabinoid system.

Methods: The samples were obtained from the EU-GEI (European Network of National Schizophrenia Networks Studying Gene-Environment Interactions) High Risk study which is a multicenter longitudinal observational study of CHR individuals. 344 CHR individuals from 11 sites. Previous exposure to antipsychotic medication was not an exclusion criterion for CHR subjects, but it was for HC subjects. The lipidomic analysis was carried out using an untargeted high resolution mass spectrometry (MS) analysis. The circulating endocannabinoids were quantified with a targeted QqQ MS based assay.

Results: When comparing the HC to the CHR the PCR analysis showed a high degree of association between the circulating EC system and the lipids in the healthy controls. However, these associations were lost in the CHR group. This trend was especially observed in the n-linked ECs such as AEA, PEA, and OEA. The only exception to this was SEA which was close to the limit of detection of the mass spectrometer thus making quantification less reliable. The downstream metabolite AA also showed a similar pattern, however, AG which is an o-linked EC did not show such a dramatic reduction in R². Interestingly, the associations were different between males and females. AG, AEA and PEA showed a similar trend in both males and females but the R values in the females were larger in all lipids in the females. 2-AG were positively associated with all lipid classes except LPC. In AEA and PEA there was a similar pattern except for the TGs which were generally had a negative regression coefficient with the ECs. AA, OEA, and PEA the patterns of associations between male and

female were very different. In females these lipids showed a similar pattern to AEA and PEA. However, in males there was no clean pattern when the lipids were grouped according to class.

Discussion: This study demonstrates that there is a clear role of the ECS in early psychosis and it has an effect on the lipids that change early in disease. This could suggest that the ECS plays a key long range signalling role in brain to periphery communication. The non-classical NAEs clearly need further investigation in psychosis to fully understand their role in disease development.

T68. UNVEILING VOICES: A PREREGISTERED CLUSTER APPROACH TO IDENTIFY PROSODY PATTERNS IN SCHIZOPHRENIA

Carlos Martínez-Asensi¹, Victor Ortiz-García de la Foz², Rosa Ayesa-Arriola*³

¹UNED; Valdecilla Biomedical Research Institute IDIVAL, ²University Hospital Marques de Valdecilla -IDIVAL; University of Cantabria; CIBERSAM, ³Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria

Background: The intrinsic relationship between language and cognition has led to the exploration of language and speech analysis as a gateway to a better understanding of the underlying mental processes. Thus, language also emerges as a means of assessing the processes underlying dysfunctions, such as SSD.

Automatic speech analysis has been used to identify acoustic features to provide greater reliability for the diagnosis of SSD. However, the absence of pre-registration in some studies, heterogeneity in data acquisition protocols among teams, and utilization of supervised learning models could lead to a lack of generalization of their results.

One facet of language, prosody, is responsible for conveying paralinguistic information that could play a pivotal role in the identification of the speaker's mental processes.

In this context, this study focuses on addressing some of the methodological challenges and current limitations of automatic language analysis. The working hypothesis is that language prosody exhibits characteristics that enable the differentiation of individuals with SSD diagnoses.

Methods: This is a preregistered (<https://osf.io/fq4u3>), cross-sectional, observational, retrospective and confirmatory study.

Prosody data will be computationally extracted from masked discourse audio recordings. Interviews with a non-probabilistic convenience sample, comprising 51 patients with SSD and 48 healthy controls (HC), were carried out following the DISCORSE consortium protocols.

The study comprises two steps: 1) a simulation study based on data from other works in the field and 2) clustering modelling with our sample masked data. The simulation study is used to estimate the effect size and power and to test which analysis choices and clustering model could yield better performance in terms of precision and generalization. We then perform clustering modelling with data from our sample, following the findings of the simulation. The grouping variable (SSD or HC) will serve as a criterion for cross-validating the quality of the model, once unmasked.

Results: From the simulation study, we aim to identify the analytical choices that could lead to better performance in the subsequent cluster analysis. These choices include the type and number of prosodic variables, reduction (or lack thereof) of dimensions, and type of clustering model. Additionally, we will estimate the effect size and power of the clustering technique. Based on previous results from our colleges, we expect sufficient effect size and power to be able to cluster SSD patients separately from other individuals.

After obtaining the simulation results and pre-registering them, we will apply these findings to analyze our sample data. Our expectation is to develop a model that achieves more than 90% sensitivity, specificity, and precision in detecting SSD patients, as measured in model cross-validation tests, in comparison to clinical assessments.

Discussion: In this study, we use a pre-registry of analytical procedures, following precise standardized protocols in the acquisition of data, and use unsupervised learning modelling as a tool to overcome the lack of generalization and precision that some previous studies had suffered when trying to detect language features to diagnose SSD.

T69. A COGNITIVELY INFORMED BIOMARKER AND ASSESSMENT TOOL OF POSITIVE THOUGHT DISORDER: THE STRATEGIC USE OF LARGE LANGUAGE MODELS

Lin Wang¹, Anthony Yacovone², Victoria Sharpe², Sabrina Ford³, Lena Palaniyappan³, Gina Kuperberg*¹

¹Tufts University and Mass. General Hospital, ²Tufts University, ³McGill University

Background: Positive thought disorder (PTD) is prominent in schizophrenia and characterized by patients' over-reliance on local associations and under-reliance on the global discourse during language processing. Traditional clinical assessments of PTD (e.g. diagnostics of loosening of associations, derailment, and tangentiality) are subjective and time-consuming. We argue that Large Language Models (LLMs) can be used as objective, automatic assessment tools for measuring PTD. In this study, we used two LLMs, BERTopic and Word2Vec, to characterize the nature of global and local representations present in naturally produced speech. We find that these measures successfully capture the linguistic consequences of PTD.

Methods: We analyzed 3 picture descriptions (~1 minute each) from 70 first-episode psychosis patients (all unmedicated and treatment-naïve) and 34 demographically matched controls. We used the Disorganization subscore from the Thought and Language Index (TLI) to measure PTD. Symptoms and domain-general cognitive function were assessed using the PANSS-8, Semantic Fluency, Digit-Symbol Substitution, and the Trail-Making Test.

Results: Model 1 (BERTopic): We used a pre-trained BERTopic model with 2376 common topics ascertained from the Wikipedia corpus to assess how "topics" shifted throughout each picture description. Specifically, for each participant, we ascertained the variability in their topic representation, and characterized that variability as entropy. We then regressed these values onto TLI (while controlling for description length, age, gender, and SES). We found that TLI significantly predicted topic entropy such that participants with greater TLI scores produced more topics in their descriptions ($b = 0.06$, $SE = 0.03$, $t = 2.17$, $p = 0.03$).

Model 2 (Word2Vec): We used a pre-trained Word2Vec model with 300-dimensional word embeddings to calculate the pairwise cosine similarity for a given content word with each of its five preceding content words. For our analyses, we averaged similarity values across all content words for each pairing. We then regressed similarity values onto TLI, word pairing,

their interaction, and the control variables above. We found that larger TLI scores resulted in greater similarities between words and their local contexts ($b = 0.01$, $SE = 0.003$, $t = 2.88$, $p = 0.005$), and this similarity begins to weaken at 4 words back.

Model 3 (Classification): We also asked if entropy and cosine similarity values can jointly discriminate between patients and controls. To do this, we divided the data into training and testing sets (80-20), and trained a model to predict patients and controls using their entropy and similarity values. The model can effectively distinguish between patients and controls: overall accuracy = 0.86, sensitivity = 1.0, precision = 0.83, and AUC = 0.91.

Discussion: This work has clinical, neurocognitive, and computational implications: LLMs can provide linguistic biomarkers for fast, automated, and objective quantification of language disorganization, as PTD predicts the entropy and local similarity in patients' speech. LLM biomarkers can be used for illness detection, symptom monitoring, and outcome predictions. These results bridge the clinical characterizations of PTD with neurocognitive evidence for selective atypicalities in patients' language processing. Our work supports hierarchical generative models of psychosis, and future work will situate these findings within the biologically plausible, Predictive Coding framework, to provide a mechanistic account for over-reliance on local associations and under-reliance on the global discourse during language processing.

T70. METALLOPROTEINASE-9 IN FIRST EPISODE PSYCHOSIS: INTERPLAY OF GENE-ENVIRONMENT INTERACTIONS

Joao Roberto Lisboa^{*1}, Camila Marcelino Loureiro², Fabiana Corsi-Zuelli², Olga da Costa², Shuhama Rosana³, Aline Esposito⁴, Menezes Paulo Rossi⁵, Paulo Louzada-Junior⁶, Riccardo Lacchini⁴, Del-Ben Cristina Marta³, Felipe Villela Gomes⁷

¹Ribeirão Preto Medical School, University of São Paulo,, ²Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil., ³Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, USP, Ribeirão Preto, Brazil., ⁴Department of Psychiatric Nursing and Human Sciences, Ribeirão Preto College of Nursing, University of São Paulo, Ribeirão Preto, Brazil., ⁵Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, São Paulo, Brazil., ⁶Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto Brazil., ⁷Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.

Background:

Metalloproteinase-9 (MMP9), a broadly expressed metalloproteinase in the central nervous system, has wide ranging effects on extracellular matrix (ECM) structure and function. Disruptions in MMP9 may be caused by psychosocial trauma during critical periods of development, such as childhood and adolescence, and are proposed to underlie abnormalities in the ECM with detrimental downstream effects implicated in schizophrenia (SCZ), including an altered excitatory/inhibitory balance. Thus, early adverse events may modulate MMP9 expression, influencing the risk of developing psychosis. Recent studies indicate elevated MMP9 in peripheral blood of SCZ patients. Here, we investigated interactions between MMP9 gene polymorphisms and MMP9 protein blood levels with childhood trauma in first episode psychosis (FEP).

Methods:

Subjects were enrolled from a case-control study, including FEP (n=143) (60.1% male, 46.9% non-white) and community controls (n=286) (48.3% male, 31.5% non-white). Sociodemographic and clinical assessments were conducted for all participants along with the Childhood Trauma Questionnaire (CTQ). Blood samples were drawn at the nearest feasible time to psychosis onset. MMP9, pro-MMP9, and TIMP-1 levels were measured by gel zymography. Genetic testing characterized four MMP9 gene polymorphisms (rs3918242, rs17576, rs17577, rs20544). We investigated the impact of childhood trauma, genetic polymorphisms of the MMP9 gene, and their interaction in FEP individuals. These variables were also analyzed regarding their relation to expressed plasma levels of MMP9, pro-MMP9 and TIMP-1. Statistical analysis included chi-square and logistic regression analysis for CTQ-FEP and Generalized linear models (GLMs) to examine relationships between CTQ, FEP, MMP9 gene polymorphisms, and MMP9 protein levels.

Results:

A positive history of childhood trauma conferred an increased risk for FEP (OR=3.443; p LESS THAN 0.001). No associations between genetic polymorphisms and FEP or MMP9 plasma levels were found. In a GLM including both FEP and community controls, a positive association emerged between childhood trauma and increased pro-MMP9/TIMP-1 ratio (B=0.602; p=0.001). Another GLM indicated that the FEP group exhibited elevated pro-MMP9 levels compared to controls (B=0.256, p=0.041). Additionally, within this model, a robust interaction emerged between a history of trauma and FEP, revealing higher levels of both pro-MMP9 (B=0.428; p LESS THAN 0.013) and pro-MMP9/TIMP1 ratio (B=0.901; p LESS THAN 0.001) in participants with a positive trauma history within the FEP group. Another GLM revealed an interaction between a positive trauma history and the dominant model of the rs20544 polymorphism, resulting in increased pro-MMP9 (B=0.517; p=0.003) and pro-MMP9/TIMP1(B=0.917; p LESS THAN 0.001) ratio in participants with a trauma history and TT or CT genotypes.

Discussion:

Our findings confirmed a robust direct association between childhood trauma and FEP and revealed that trauma is associated with increased pro-MMP9/TIMP1 ratio. FEP patients exhibited heightened pro-MMP9, particularly in those with trauma history. Furthermore, we observed a gene-environment interaction involving an MMP9 gene polymorphisms and childhood trauma, influencing pro-MMP9 protein expression. No findings were observed for the active MMP9 molecule. These findings highlight the complex interplay of gene-environment interactions in SCZ, and how specifically trauma may modulate protein expression of MMP9, which may lead to neurodevelopmental abnormalities that increase risk for FEP.

T71. ENHANCING COGNITIVE RESERVE: HDL CHOLESTEROL AS A BIOLOGICAL PROXY

Rebeca Magdaleno Herrero^{*1}, Ángel Yorca Ruiz¹, Nancy Murillo-García¹, Jorge Crespo-Álvarez², Antonio Vita³, Rafael Penadés⁴, Benedicto Crespo Facorro⁵, Rosa Ayesa-Arriola⁶

¹Marqués de Valdecilla University Hospital, IDIVAL, ²Faculty of Health Sciences, Universidad Europea del Atlántico (Uneatlántico), ³University of Brescia, ⁴Hospital Clinic Barcelona, ⁵Hospital Universitario Virgen del Rocío. CIBERSAM. Universidad de Sevilla, IBiS, Sevilla, ⁶Department of Psychiatry. Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria, Santander, Spain Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

Background: Cognitive Reserve (CR) is the brain's capacity to enhance the efficiency of existing neural networks or employ alternative neural networks when conventional cognitive strategies failed to yield desired outcomes. In the case of schizophrenia spectrum disorders (SSD), CR has been observed to play a significant role in the onset and course of the disease. However, its estimation relies on heterogeneous proxies with limitations. The inclusion of biological measures, linked to cognitive performance, as CR proxies holds promise for refining its estimation. Attending the relationship between SSD and metabolism, and highlighting the role of lipids on the central nervous system, an association could be stabilised between high-density lipoprotein cholesterol (HDL) levels and alterations in various cognitive domains observed in SSD. The aim of this study is to validate a CR estimation composed by years of education and HDL levels.

Methods: A total of 378 first-episode psychotic disorder (FEP) patients and 149 healthy controls provided sociodemographic, clinical, HDL levels and neurocognitive data. The sample was classified into CR1 (years of education, occupation, and premorbid IQ) and CR2 (years of education and HDL levels). This classification enables comparative evaluations for both indices using machine learning models.

Results: The classification of FEP patients into CR1 and CR2 was very similar. In the CR1 group, 50.8% of FEP patients had low CR1, and 49.2% had high CR1. Similarly, in the CR2 group, 54.2% of FEP patients had low CR2, and 45.8% had high CR2. Neurocognitive comparisons reveal that, regardless of CR1 or CR2 classification, all cognitive domains assessed indicated that FEP patients with both low CR groups exhibit poorer performance compared to both high CR groups, as well as diminished global cognitive functioning (GCF). The Support Vector Machine (SVM) model was the best for predicting the Area Under the ROC Curve (AUC) of CR2 in FEP patients, it achieved an AUC of 0.725 ± 0.109 (95% CI: 0.616-0.834) for FEP patients. In comparison to CR1, CR2 achieved superior performance scores in metrics: accuracy (CR1: 62%; CR2: 66%), F-1 score (CR1: 59%; CR2: 69%), sensitivity (CR1: 54%; CR2: 70%), precision (CR1: 66%; CR2: 69%), and revealed an ROC curve characterized by higher discriminative capacity.

Discussion: The results of this study emphasize the significant predictive capacity of the combination of years of education and HDL levels in estimating CR in FEP patients. These findings are supported by previous evidence in the scientific literature, which has also highlighted the predictive ability of these two variables in relation to cognitive performance in FEP patients. The inclusion of years of education as an indicator is crucial due to its early in life establishment and its influence on lived experiences and cognitive enrichment during early life stages. Additionally, education stimulates neuroplasticity prior to the onset of the disease, which can provide cognitive protection against the negative effects of psychosis. Levels of HDL, on the other hand, provides specific information about metabolic functioning and cardiovascular health, which are essential for cognitive performance and mental well-being. Previous studies demonstrated a relationship between higher levels of HDL and better overall functioning and social relationships, as well as positive association lower levels of HDL and cognitive deficits in individuals with psychosis. The inclusion of HDL levels into CR index provides a more comprehensive understanding of cognitive performance in SSDs and enhances the predictive capacity of the model.

T72. DOPAMINE RELEASE FOLLOWING D-AMPHETAMINE IS PREDICTIVE FOR OUTCOME IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA

Nicole Praschak-Rieder*¹, Ana Weidenauer¹, Ulrich Sauerzopf¹, Irena Dajic¹, Katharina Landesmann¹, Cornelia Diendorfer¹, Martin Bauer², Matthäus Willeit¹

¹Department of General Psychiatry, Medical University of Vienna, ²Social psychiatric outpatient clinic Donaustadt - SPA 22, PSD Vienna

Background: Three observations currently support the dopamine theory of schizophrenia: (i) untreated psychotic patients with schizophrenia show higher dopamine synthesis rates, (ii) they show greater behavioral and neurochemical sensitivity towards dopamine-releasing agents like amphetamines, (iii) antipsychotics relieve psychotic symptoms by blocking dopamine D2/3 receptors. However, up to one third of patients show no adequate response and poor overall clinical outcome. Aiming at its potential for predicting response, we measured D-amphetamine-induced dopamine release using the selective D2/3 dopamine receptor agonist radioligand [11C]-(+)-PHNO and positron emission tomography (PET) in untreated patients with first-episode psychosis. Thereafter, we assessed one-year clinical outcomes in these patients.

Methods: Twenty-one antipsychotic-naïve patients (6 female) underwent two [11C]-(+)-PHNO PET scans in a randomized balanced cross-over design. For estimating dopamine release, one scan was performed with, and another one without oral D-amphetamine pretreatment, as previously described by Weidenauer et al. (2020). The Positive and Negative Symptoms Scale (PANSS) was performed at baseline and at seven follow-up visits over one year. Patients received antipsychotic treatment in a naturalistic setting (Clinical Trial Registry: EUDRACT 2010-019586-29).

Results: Greater D-amphetamine-induced dopamine release in ventral striatum was associated with greater reductions in positive symptoms ($r=0.54$, $p=0.04$); greater dopamine release in globus pallidus was associated with reductions in PANSS negative ($r=0.58$, $p=0.02$), general ($r=0.53$, $p=0.04$), and total symptom scores ($r=0.063$, $p=0.01$). Greater dopamine release in substantia nigra/ventral tegmental area predicted larger reductions in general symptoms ($r=0.51$, $p=0.05$). Post-amphetamine radioligand binding in putamen correlated positively with negative symptom scores at baseline ($r=0.66$, $p=0.005$) and throughout all follow-up visits.

Discussion: Our data show a relationship between D-amphetamine-induced dopamine release and the expression, severity, and persistence of symptoms during the first year of illness in patients with first-episode schizophrenia. Higher [11C]-(+)-PHNO binding potentials in the putamen of patients with more pronounced negative symptoms indicate that the expression of negative symptoms of schizophrenia goes along with a relative deficiency in dopamine transmission. Thus, excess and deficiencies in dopamine signaling seem to coexist in subcortical brain regions of patients with schizophrenia, contributing to the expression of symptoms in their own way.

T73. THE BRIGHT SIDE OF SCHIZOTYPY: CHARACTERIZATION OF SCHIZOTYPY CLUSTERS IN NONCLINICAL YOUNG ADULTS

Valeria Lavín^{*1}, Pilar Torrecilla², David Gallardo³, Neus Barrantes-Vidal², Tom Richard Kwapił⁴

¹*Autonomous University of Barcelona*, ²*Department of Health and Clinical Psychology, Autonomous University of Barcelona*, ³*Department of Psychology, University of Barcelona*, ⁴*Department of Psychology University of Illinois at Urbana-Champaign*

Background: Schizotypy is defined as a multidimensional construct indexing liability for psychosis-spectrum psychopathology that is expressed across a broad range of traits, subclinical and clinical features. However, increasing evidence has shown that the impairment differs greatly for the distinct dimensions integrating the schizotypy construct (i.e., positive, negative and disorganized). Previous studies have reported that individuals with high positive schizotypy but with low negative and disorganized traits show preserved levels of functioning and well-being and may even present positive features such as creativity; in contrast, those who present overall high schizotypy scores usually report the poorest outcomes. The present study aimed to replicate previous findings by identifying schizotypy clusters in nonclinical young adults. We then compared the different clusters on depressive and anxiety symptoms, social functioning, and positive mental health outcomes.

Methods: A total sample of 1118 non-clinical young adults between the ages of 18 and 35 (mean=22.3; SD=3.4 ;76.2% female) completed a comprehensive battery of self-reported measures. Schizotypy dimensions were assessed using the Multidimensional Schizotypy Scale. Characterization of the clusters was performed with measures of anxiety (Beck Anxiety Inventory), depression symptoms (Beck Depression Inventory-II), social functioning (Social Functioning Questionnaire), well-being (Warwick-Edinburgh Mental Wellbeing Scale), resilience (Connor Davidson Resilience), self-reported creativity (Runco Ideational Behavior Scale), self-esteem (Rosenberg Self-Esteem Scale), and emotional clarity and attention to emotions (Trait Meta-Mood Scale). A K-means iterative cluster analysis was performed with the schizotypy dimension scores and then comparisons across variables were examined using one-way ANOVA.

Results: A forced four-cluster model yielded the following groups: 'Low schizotypy' (50%), characterized by overall low schizotypy; 'High Positive' (21.87%), presenting high positive but low negative schizotypy scores; 'High Negative' (10.44%) with the high scores in the negative dimension but low in the disorganized and positive ones; and 'High disorganized' (17.67%), presenting the highest scores in the disorganized dimension and medium scores in the negative and positive ones. The 'High Disorganized' group showed the poorest outcomes, including high anxiety and depression and low scores on functioning, well-being, resilience, self-esteem, emotional clarity, and attention to emotions. However, they surpassed the 'Low Schizotypy' group in creativity. The 'High Negative' cluster had lower scores in emotional clarity, attention to emotions, well-being, and social functioning compared to 'Low Schizotypy', whereas the 'High Positive' group showed slightly lower positive outcomes and higher anxiety and depression levels, and no notable differences in emotional clarity. Nevertheless, this group excelled in creativity and attention to emotions compared to the other clusters.

Discussion: This study replicates and expands previous work regarding the cluster structure underlying the multidimensional heterogeneity of schizotypy dimensions by using a larger sample of nonclinical adults and incorporating the disorganized dimension. The results underscore the importance of considering the specificities of these distinct yet associated dimensions when examining the relationship between schizotypy and various mental health variables. Furthermore, it adds support to previous studies reporting an association between positive schizotypy and creativity.

T74. RETINAL CYTOARCHITECTURE AS A BIOMARKER: A TRANS-DIAGNOSTIC META-ANALYSIS OF RETINAL MARKERS ACROSS PSYCHIATRIC DISORDERS

Nils Kallen*¹, Giacomo Cecere², Foivos Georgiadis³, Stephanie Homan⁴, Finn Rabe⁵, Erich Seifritz⁶, Philipp Homan⁷

¹Psychiatric University Hospital Zurich, ²Psychiatric Hospital, University of Zurich, Zurich, Switzerland, ³University Hospital of Psychiatry, University of Zurich, ⁴University Hospital of Psychiatry/University of Zurich, ⁵Department of Psychiatric Research, Psychiatric University Hospital Zurich, ⁶Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, 8032 Zurich, Switzerland, ⁷Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital of the University of Zurich, Zurich, Switzerland

Background: Psychiatric disorders involve a complex interplay of diverse genetic and environmental factors, often with shared mechanisms. In clinical settings, we often see an overlap of symptoms or syndromes between distinct diagnostic entities with different or opposite causes.

This diagnostic heterogeneity has proven problematic for both research and clinical practice. Different biomarkers have been investigated across the psychiatric spectrum, as endophenotypes could bridge the gap between observable symptoms and underlying disease mechanisms. In the last 20 years, many publications have explored the retina in different psychiatric and neuropsychiatric disorders.

In this meta-analysis, we review the current body of evidence and analyze whether and in what way retinal parameters could help to discriminate between diagnostic groups. Previous meta-analyses investigated changes in the retina in schizophrenia spectrum disorder (SSD) and, to a much lesser extent, affective disorders such as bipolar disorder (BD) and major depression (MD).

This is the first study to our knowledge with a trans-diagnostic approach across the psychiatric spectrum investigating SSD, affective disorders, obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD).

We hypothesize that differences in retinal cytoarchitecture, especially in retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL), are more pronounced in or could be specific to disorders associated with psychotic symptoms such as SSD and BD.

Methods: We conducted a comprehensive search of MEDLINE and EMBASE databases for studies investigating retinal layers in psychiatric disorders. We included case-control studies in psychiatric disorders (diagnosed by DSM-V or ICD-10) reporting measurements of the thickness and volume of the RNFL, GCL, or the macula using optical coherence tomography (OCT).

We found 259 studies, of which we included 77 studies that fulfilled our inclusion criteria. We assessed study quality using the Newcastle-Ottawa-Scale. Statistical analysis and meta-regression were done in R Version 4.2.3. We investigated heterogeneity using the I² score and publication bias using Egger's Test.

Results: We included 77 studies in the final analysis across several psychiatric disorders. We found 36 studies investigating retinal markers in SSD, 20 studies investigating bipolar disorder (BD), 5 investigating MD, 5 investigating ADHD, and 3 for OCD.

Consistent with previous research, we found RNFL to be thinner in SCZ patients (SMD -0.42, $p < 0.01$) and BD patients (SMD -0.56, $p < 0.01$). In contrast, compared to controls, the RNFL thinning was less pronounced in major depression (SMD -0.23, $p = 0.01$) and OCD (SMD -0.27, $p = 0.03$). In ADHD, we found no significant differences between patients and controls (SMD -0.21, $p = 0.27$).

Discussion: Our meta-analysis revealed a significant reduction in RNFL thickness in SSD and BD, consistent with previous data. More research is needed, especially investigating additional disorders without psychotic symptoms, to further evaluate the specificity of these findings in a clinical context. In addition, longitudinal studies would provide further insight into the dynamics across disease states.

T75. FURTHER EVIDENCE OF THE LACK OF ASSOCIATION BETWEEN SCHIZOPHRENIA POLYGENIC RISK AND SCHIZOTYPY OR PSYCHOTIC-LIKE EXPERIENCES

Araceli Rosa^{*1}, Patricia Mas-Bermejo², Sergi Papiol³, Pilar Torrecilla⁴, Valeria Lavín⁵, Jackie Nonweiler⁶, Marc Via⁷, Irene Martínez-Alonso², Thomas R. Kwapił⁸, Neus Barrantes-Vidal⁴

¹Universitat de Barcelona, ²Secció de Zoologia i Antropologia Biològica, Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Universitat de Barcelona, Barcelona, Spain. Institut de Biomedicina de la Universitat de Barcelona, Barcelona, Spain, ³IPPG / LMU, ⁴Departament de Psicologia Clínica i de la Salut, Universitat Autònoma de Barcelona, Spain, ⁵Department of Health and Clinical Psychology, Autonomous University of Barcelona, ⁶Universitat Autònoma de Barcelona, ⁷Department of Clinical Psychology and Psychobiology, Universitat de Barcelona, Barcelona, Spain. Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain. Institut de Recerca Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, ⁸University of Illinois at Urbana-Champaign, United States of America

Background: According to the dimensional view of mental disorders, schizophrenia can be conceived as the extreme expression of a continuum of traits that are present in the general population. However, although many attempts have been made to identify the shared genetic background between these traits and the disorder itself, the general lack of significant findings has led to believe that this overlap might not be as robust as initially hypothesized. In a previous work, we tested the association between polygenic risk for schizophrenia and two of these disorder-related traits (i.e., schizotypy and psychotic-like experiences) in a sample of 253 nonclinical subjects and found no significant associations (Mas-Bermejo et al. 2023. Eur Arch Psychiatry Clin Neurosci). Here, we aim to replicate this study in a newly collected and larger sample of 941 nonclinical individuals, thereby overcoming the likely lack of statistical power of our previous analyses, to draw definitive conclusions.

Methods: Schizotypy and the positive dimension of psychotic-like experiences were assessed in these 941 subjects with the Multidimensional Schizotypy Scale and the Community Assessment of Psychic Experiences, respectively. Polygenic Risk Scores for schizophrenia (SZ-PRS) were computed for each participant with the PRS-CS method based on the latest schizophrenia genome-wide association study. Linear regressions were used to test the associations between the SZ-PRS and the psychometric variables.

Results: Our analyses did not reveal any significant association of the SZ-PRS with either the positive, negative or disorganized dimensions of schizotypy. Likewise, no association was found with the positive dimension of psychotic-like experiences.

Discussion: Our results seem to replicate once more, the lack of clear evidence that a genetic overlap between these disorder-related traits and schizophrenia truly exists regarding common genetic variation. One cannot rule out, however, that variants with larger penetrance (CNV, exonic variants, ultra-rare variation...) that are not included in the calculation of current SZ-PRS might contribute to such a shared genetic risk background between schizophrenia and disorder-related traits in the general population.

T76. THE BRAIN ENDOCANNABINOID SYSTEM IS DIFFERENTIALLY REGULATED IN MALES AND FEMALES WITH FIRST-EPISODE PSYCHOSIS

Heikki Laurikainen¹, Reetta-Liina Armio¹, Lauri Tuominen², Anna Kirjavainen³, Olof Solin³, Merja Haaparanta-Solin³, Raimo K R Salokangas¹, Jarmo Hietala¹

¹University of Turku, ²University of Ottawa, ³Turku PET Centre

Background: The endocannabinoid system (ECS) is a ubiquitous signaling system capable of modulating excitatory and inhibitory neurotransmission in the human brain. A sex difference of the endocannabinoid system has been documented in both human and animal studies. Further, the endocannabinoid system is dysregulated in male patients with first-episode psychosis (FEP). A difference in the ECS could potentially explain part of the demographic and clinical sex differences seen in psychotic disorders. We postulated that the ECS is differentially regulated in male and female patients with FEP.

Methods: In this cross-sectional case-control study brain endocannabinoid receptor type 1 (CB1R) availability was measured in medicated male (n=8) and female (n=10) patients with FEP, and age matched male (n=11) and female (n=10) healthy control (HC) subjects. CB1R availability was measured as distribution volumes (VT) of the selective CB1R radiotracer [18F]FMPEP-d2 using positron emission tomography (PET) and metabolite corrected arterial input. Assignment of group status was done according to the structured clinical interview for DSM-IV diagnoses. Female subjects using oral hormonal contraception were excluded.

Results: A total of 39 male and female subjects were included in the analyses. A rmANOVA model of CB1R availability in the anterior cingulate, hippocampus, thalamus and putamen revealed main effects of group ($F(1, 35) = 6.87, p = .013$), and sex*group interaction ($F(1, 35) = 4.30, p = .045$). Within-subjects analyses showed regionally differential effects of group ($F(1, 105) = 5.96, p = .0009$), and group*sex ($F(1, 105) = 4.31, p = .007$). There were no significant differences between female FEP and HC subjects ($F(3, 54) = 0.10, p = .96$). Female and male FEP patients showed a significant main effect of sex ($F(3, 48) = 3.429, p = .024$) in post-hoc pair-wise group analyses.

Discussion: The availability of CB1R is differentially altered in males and females with first-episode psychosis with most robust effect in the anterior cingulate. Further, our data suggest that CB1R dysregulation is seen preferentially in male patients with first-episode psychosis. The ECS sex difference increases our understanding of the pathophysiological processes in psychosis, and may further open new avenues for individualized treatment strategies.

T77. RELATIONSHIP OF ERYTHROCYTE OMEGA-3 FATTY ACIDS AND PLASMA BIOMARKERS IN ULTRA-HIGH-RISK PSYCHOSIS: A REPORT OF THE NEURAPRO CLINICAL TRIAL

Subash Raj Susai*¹, David Mongan², Colm Healy³, Jonah Byrne⁴, Rachel Davis¹, NEURAPRO Investigators⁵, Patrick D McGorry⁶, Melanie Föcking¹, G. Paul Amminger⁷, David Cotter¹

¹Royal College of Surgeons in Ireland, ²Queen's University Belfast, ³University College Dublin, ⁴RCSI University of Medicine and Health Sciences, ⁵International sites, ⁶Orygen - The National Centre of Excellence in Youth Mental Health, ⁷Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Australia

Background: Increasing evidence indicates the derangement of poly-unsaturated fatty acid (PUFA) mediated membrane function in the pathophysiology of schizophrenia. Various preclinical studies and clinical trials on non-psychiatric population have identified the anti-inflammatory properties of omega-3 fatty acids (FA). Even though early intervention with omega-3 supplementation is considered in various psychiatric disorders, their biologically role in psychosis is not clearly understood. In this study, we investigated the influence of omega-3 supplementation on peripheral immune markers in an ultra-high-risk (UHR) population.

Methods: Materials and methods: We quantified inflammatory cytokines and plasma proteins using immune assays and mass-spectrometry (MS) at baseline (n=293) and at follow-up (n=171) in plasma samples of UHR subjects. The relationship of erythrocyte membrane levels of total omega-3 FA with inflammatory markers was subsequently analysed using a linear regression model. Then using mediation analysis, we investigated whether immune-markers or plasma proteins mediated the relationship between change in omega-3 FAs and clinical outcomes.

Results: In linear regression models, the baseline plasma concentrations of Interleukin (IL)-15, Intercellular adhesion molecule (ICAM)-1 and Vascular cell adhesion molecule (VCAM)-1 were negatively associated with baseline omega-3 index. In addition, 6-month change in IL-12p40 and TNF- α showed a negative association with change in omega-3 index. In longitudinal analyses, the baseline and 6 month change in omega-3 index was negatively associated with VCAM-1 and TNF- α respectively at follow-up. Mediation analyses provided little evidence for mediating effects of plasma immune markers on the relationship between omega-3 FAs and clinical outcomes. On the other hand, 24 plasma proteins measured using MS showed association with omega-3 PUFAs. Pathway analysis revealed the complement and coagulation pathway as the main biological pathway to be associated with change in omega-3 PUFAs. However, The inflammatory protein complement C5 and protein S100A9 negatively mediated the relationship between change in omega-3 PUFAs and positive symptom severity, while C5 positively mediated the relationship between change in omega-3 and functional outcome. The relationship between change in omega-3 PUFAs and cognition was positively mediated through coagulation factor V and complement protein C1QB.

Discussion: Our results indicate a predominantly anti-inflammatory relationship of omega-3 FAs on plasma immune markers in CHR individuals, but this did not appear to convey clinical benefits at 6 month and 12 month follow-up. However, for the first time our findings provide evidence for a longitudinal association of omega-3 PUFAs with complement and coagulation protein changes in the blood. Further, the results suggest that an increase in omega-3 PUFAs decreases symptom severity and improves cognition in the CHR state through modulating effects of complement and coagulation proteins.

T78. EXAMINING PROTEIN MARKERS RELATED TO AGING AND PSYCHOSIS IN THE HUMAN CONNECTOME PROJECT FOR EARLY PSYCHOSIS

Johanna Seitz-Holland^{*1}, Moritz Haaf², Ana Paula Mendes-Silva³, Cornelius Berberich¹, Lauren Breithaupt⁴, Nora Penzel⁴, Sylvain Bouix⁵, Mike J. Coleman¹, Elana Bayla Kotle¹, Nicholas Kim¹, Omar John¹, Kathryn Eve Lewandowski⁶, Daphne Holt⁴, Matcheri S. Keshavan⁷, Dost Öngür⁶, Alan Breier⁸, Martha E. Shenton¹, Breno S. Diniz⁹, Steven E. Arnold⁴, Marek Kubicki¹

¹Brigham and Women's Hospital, Harvard Medical School, ²University Medical Center Hamburg, ³Department of Molecular Brain Science at the Centre for Addiction and Mental Health (CAMH), ⁴Massachusetts General Hospital, Harvard Medical School, ⁵École de technologie supérieure, ⁶McLean Hospital, Harvard Medical School, ⁷Beth Israel Deaconess Medical Center, Harvard Medical School, ⁸Indiana University School of Medicine, ⁹UConn Center on Aging

Background: Cumulative evidence suggests that the pathophysiology of psychosis involves an increased vulnerability to premature aging. However, this knowledge has not been translated into clinical practice due to the lack of understanding of the biological underpinnings and biomarkers. The present study addresses these challenges by examining aging-associated protein markers in the Human Connectome Project for Early Psychosis (HCP-EP). Specifically, we examined over 300 peripherally circulating plasma proteins associated with inflammation and cardiometabolic health. In addition, we calculated specific indices related to cell aging based on senescence-associated secretory phenotype (SASP) proteins.

Methods: The HCP-EP study was carried out across four recruiting and three scanning sites. It recruited individuals within five years of the onset of a DSM-5 diagnosis of psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified, delusional disorder, brief psychotic disorder, major depression with psychosis, or bipolar disorder with psychosis) as well as matched healthy individuals. Individuals underwent extensive testing, including NIH Toolbox, a structural and diffusion-weighted magnetic resonance imaging (MRI) scan, and a blood draw.

Protein expression levels from 380 proteins from 126 individuals were characterized by a commercial platform (O-link) for our primary analyses. Thirty-seven individuals were healthy individuals, 64 were diagnosed with non-affective psychosis, and 37 with affective psychosis. The groups were matched based on age and sex.

1. We ran data-driven analyses using all proteins to compare individuals with psychosis and healthy individuals while correcting for the effects of age and sex. In addition, we examined the main effects of sex and sex by diagnosis interactions. Last, we also split the psychosis group into individuals with non-affective psychosis versus affective psychosis.

2. We used principal component analyses to calculate a so-called SASP protein index based on a selected set of proteins that was used in previous studies performed in individuals with Alzheimer's disease and depression.

3. We used this SASP index to explore the association with clinical and cognitive variables.

Results: The data-driven analyses demonstrated differences between individuals with psychosis and healthy individuals in several proteins related to inflammation, cell communication, blood pressure, and cardio-metabolic regulation (e.g., Renin, Tumor necrosis

factor receptor superfamily member 9, Neuropilin 1, or Leptin; p LESS THAN 0.1 after FDR correction). In addition, we saw widespread sex effects but few sex-by-diagnoses interactions. The following steps will include the analyses of genetic pathways and networks to characterize these proteins further.

When calculating SASP indices, we found trend-level group differences between healthy individuals and individuals with psychosis (p LESS THAN .1). The effects were more pronounced in individuals with non-affective psychosis. As predicted, individuals with psychosis presented with higher SASP indices. Furthermore, the SASP indices in individuals with psychosis were significantly associated with age, sex, body mass index, and alcohol consumption (all p LESS THAN 0.05), but associations with cognition were only trend-level significant.

Discussion: The present study provides a first step toward developing novel protein-based biomarkers to identify individuals vulnerable to premature aging in psychosis. Aligning with previous studies on serious mental illness, we saw an increase in proteins related to inflammation and aging. The interaction of these variables with physical health parameters highlights the importance of studying schizophrenia as a whole-body disorder and might help in the understanding of comorbidity.

T79. SEX-DIFFERENCE IN THE EFFECT OF AN ADDITIONAL OXIDATIVE STRESS IN AN ANIMAL MODEL OF REDOX DYSREGULATION, RELEVANT FOR SCHIZOPHRENIA

Daphné Daphné Vorburger^{*1}, Basilio Giangreco², Enea Parietti², Pascal Steullet², Paul Klauser³, Daniella Dwir²

¹Center for Psychiatric Neuroscience, Lausanne University Hospital and the University of Lausanne, ²Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne, Lausanne, Switzerland, ³Center for Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland

Background: Schizophrenia (SZ) is a mental disorder with multifactorial origins including both genetic and environmental risk factors. Converging evidence points to impaired immune system and redox dysregulation as being central in the pathophysiology of SZ. More specifically, alterations in the glutathione (GSH) antioxidant system, the major antioxidant of the brain, has been associated with SZ. The alterations of these pathways, especially during early brain development affect the proper maturation of parvalbumin expressing interneurons (PVI) and their perineuronal net (PNN), producing a neuronal desynchronization, observed at the early stage of SZ. In this line of research, a transgenic mouse model of glutathione (GSH) deficiency (gclm-KO mice) displays increased oxidative stress (OxS) and a morphological phenotype relevant for SZ. The gclm-KO mice treated with GBR-12909 dihydrochloride (GBR), a dopamine reuptake inhibitor mimicking the increase in extracellular dopamine in the prefrontal cortex induced by a psychosocial stress, showed decreased PV/PNN, as well as increased microglia activation. Moreover, we have previously found that the matrix metalloproteinase 9 (MMP9) is involved in the PV/PNN alterations. This phenotype had been investigated in males only, but it may be different in females as the redox system is sensitive to sexual hormones. In this study, the effect of an additional OxS insult (GBR treatment) during early brain development was investigated on gclm-KO female mice.

Methods: To induce an additional oxidative stress, females gclm-KO and WT were subcutaneously injected with GBR for 10 days from postnatal day (PND) 10 to PND 20. Control animals were injected with PBS for the same duration. Then animals were sacrificed at PND 20 (N=4-5) or PND 90 (N=5-7) by intracardiac perfusion and coronal slices were performed. Immunohistochemistry was carried out to quantify PV-immunoreactive (IR) cell number and intensity, PNN-IR cell number and intensity, microglia number and morphology (intensity, area, number of branches) and MMP9-IR cell number. Images were acquired on a spinning disk microscope and analyzed on Imaris software. Two factors ANOVA tests were used to assess the statistical difference between genotype (gclm-KO vs WT) and treatment (GBR vs PBS).

Results: Firstly, PVI and PNN were not affected in female KO as compared to female WT mice, even after GBR injection, at both PND20 and PND90. However, a significant decrease of MMP9-IR was found in the KO mice compared to WT, without any effect of the GBR injection, at both time-points. In addition and irrespective of GBR treatment, an increase in number and activation of microglia was observed in KO compared to WT.

Discussion: We found no alterations in PV/PNN, a decrease in MMP9-IR and an increase in microglia activation in females gclm-KO at both PND20 and 90. Interestingly, no effect was observed for the GBR treatment on these outcomes. Thus, our results support a gender-specific effect of the genetic vulnerability to redox dysregulation in the gclm-KO, but also of the additional OxS induced by GBR. It is therefore essential to better understand the sex-specific mechanisms in order to optimize individualized treatments. Additional studies are needed to further explore the sex difference in gclm-KO mice, regarding sex-specificity in SZ.

T80. THE LINGUISTIC PROFILES OF PATIENTS DIAGNOSED WITH SCHIZOPHRENIA BASED ON NATURAL LANGUAGE PROCESSING.

Hironobu Nakamura*¹, Yoshinobu Kano², Genichi Sugihara³, Yusei Yamaguchi³, Masaaki Shimizu³, Mari Iizuka⁴, Saaya Tashiro⁵, Momoko Kitazawa⁴, Ayako Sento⁴, Hidehiko Takahashi³, Taishiro Kishimoto⁴

¹Tokyo Medical and Dental University, ²Faculty of Informatics, Shizuoka University, Shizuoka, Japan, ³Department of Psychiatry and Behavioral Sciences, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, ⁴Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan, ⁵Tokyo Medical and Dental University School of Medicine, Tokyo, Japan,

Background: Linguistic characteristics in the speech of schizophrenia patients, in relation to formal thought disorder (FTD), have been studied extensively. Recent studies have utilized natural language processing (NLP) to examine these features, yielding effective machine learning models. However, these studies are limited by small sample sizes, a narrow range of linguistic features and methods, and a lack of task variety. Therefore, we conducted a comprehensive analysis of Japanese speech data from schizophrenia patients and healthy controls, using three NLP tasks across extensive speech datasets, to identify disease-specific linguistic features. Our study included a large dataset of 102 schizophrenia patients and 91 healthy controls.

Methods: This study is a part of the Understanding psychiatric illness through natural language processing (UNDERPIN) project. Our sample included 102 schizophrenia patients and 91 healthy controls, derived from the UNDERPIN dataset. Participants were recruited

from seven Japanese hospitals and three outpatient clinics. Inclusion criteria included inpatients and outpatients aged 20 years or older, diagnosed with schizophrenia according to DSM-5 or ICD-11 criteria. Healthy subjects were individuals with no history of psychiatric disorders who volunteered to participate in the study and were at least 20 years old at the time of consent. Participants were required to attend two to five visits over the course of the study. The Positive and Negative Syndrome Scale (PANSS) was used as the clinical rating scale. Participants underwent 30-60 minute interviews, including free conversation, picture description, and storytelling tasks. Speech data were transcribed into text. Transcribed text was used to isolate patient speech and form the corpus for NLP analysis. NLP methods analyzed the corpus, identifying approximately eighty linguistic features at morphological, syntactic, and semantic levels, including word usage probabilities and named entities. GiNZA (spaCy Japanese-language model) was used for morphological and syntactic analysis and named entity recognition. Word2Vec and sentenceBERT were employed for semantic similarity, and N-gram analysis calculated word usage probability. Features were normalized by total morpheme count where necessary. Principal component analysis (PCA) was used to identify feature relationships and for dimension reduction. Generalized estimating equations (GEEs) were used for statistical analysis of the hierarchical data.

Results: Significant statistical differences were observed between the groups in the linguistic features such as total number of morphemes and content words, ratio of personal named entity, mean and variance of word similarity, variance of sentence similarity and so on. Features like total number of morphemes and variance of sentence similarity had a negative correlation with PANSS negative syndrome scales, whereas ratio of personal named entity had a positive correlation with PANSS positive symptom scales.

Discussion: This study features the largest sample size yet for the quantitative NLP-based analysis of linguistic abnormalities in schizophrenia. Covering crucial linguistic areas like morphology, syntax, semantics, and probability, it utilizes an extensive range of Japanese linguistic features. Features like sentence similarity variance were quantitatively identified only after analyzing patients' entire utterances, distinguishing this approach from traditional methods focused on local pathological findings.

T81. SYNTACTIC NETWORK ANALYSIS IN FIRST-EPISODE PSYCHOSIS: A GENERALIZABILITY STUDY

Silvia Ciampelli¹, Janna de Boer², Alban Voppel³, Hugo Corona-Hernández², Sanne Koops², Natalia Mota⁴, Iris Sommer²

¹University of Groningen, University Medical Center Groningen, ²Department of Biomedical Sciences of Cells and Systems, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, ³Douglas Mental Health Institute, McGill university, Montreal, QC, Canada, ⁴Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Background: Natural Language Processing (NLP) provides tools for modelling and quantifying language deviations associated with psychosis. However, previous research has highlighted limitations in the generalizability of NLP measures, hindering their implementation in clinical settings. Here, we evaluated the generalizability of a previously developed NLP method to quantify syntactic relations in speech from patients with psychosis. Cross-linguistic (Dutch vs. Portuguese), domain (chronic vs. first-episode psychosis), and

methodological generalizability (semi-structured interview vs. picture description) were evaluated.

Methods: In the present Portuguese sample, speech was collected from 27 individuals who experienced a first episode of psychosis (FEP) and 37 controls using a picture description task. In our previous Dutch sample, speech from 63 patients with developed schizophrenia and 63 controls was collected using a semi-structured interview. Symptom severity was measured in patients with the Positive and Negative Syndrome Scale (PANSS).

Markers of syntactic complexity were obtained by quantifying structural properties of syntax trees with 11 network analysis measures: Leaf fraction, Node count, Diameter, Efficiency, Stress centrality, Leaf count, Degree, Betweenness centrality, LCC node count, LCC diameter, LCC degree. Syntax trees were obtained with LX Parser, a computational parser for the Portuguese language.

Two multivariate analyses of covariance (MANCOVA) were conducted to compare network measures between groups. The first included group and sex as factors, with age as a covariate; the second added education as a covariate.

Associations between network measures, PANSS, and chlorpromazine equivalent dose were examined using Bivariate Pearson Correlations. A random forest (RF) algorithm, trained with 10-fold cross-validation, classified participants into FEP or control based on syntactic measures.

Results: FEP patients and controls differed in age and education (both $p < .001$). Group and age had a significant effect on syntactic network measures ($(F(11,42) = 2.418, \text{Pillai's trace} = 0.388, p = .020)$, $(F(11,42) = 2.272, \text{Pillai's trace} = 0.373, p = 0.028)$, respectively). No effect of sex or interaction between sex and group was found (both $p > .05$). When education was added in the MANCOVA as a covariate, the effects of group and age on syntactic measures were not significant (all $p > .05$). When trained on syntactic network measures, the RF had an accuracy of 81%, with 85% sensitivity (68%–94% confidence interval) and 78% specificity (63%–89% confidence interval). The Area Under the Curve was 0.82 with confidence intervals 0.71–0.93. No association between psychotic symptoms, medication, and syntactic measures was found (all $p > .05$).

Discussion: This study shows that our previously developed NLP method to quantify the complexity of syntactic relations, is generalizable across languages (Dutch vs. Portuguese), illness stages (chronic vs. first-episode psychosis), and tasks (semi-structured interview vs. picture description). Significant differences in nearly all syntactic complexity measures were observed between FEP patients and healthy individuals. Using syntactic measures, a RF classified FEP patients vs. controls with 81% cross-validated accuracy.

When education was considered as a covariate, the effects of group and age on syntactic measures were not significant. This is likely due to differences in education between groups, making it challenging to disentangle the influence of diagnosis and education on syntax in this sample. Further research is needed to explore the relationship between formal education and syntactic development in individuals with psychosis.

T82. EXAMINING RETINAL VASCULAR FRACTIONAL DIMENSION AS AN ENDOPHENOTYPIC MARKER FOR SCHIZOPHRENIA

Veena R^{*1}, Anantha Padmanabha², Abhishek Appaji³, Suma H N³, Vijay Kumar², Naren P Rao⁴

¹National Institute of Mental Health and Neuro Sciences (NIMHANS), ²National Institute of mental health and neuro sciences (NIMHANS), ³BMS college of Engineering, ⁴Manoshanti mental health care center

Background: Recent research has emphasized on identifying endophenotypic markers as objective tools in psychiatric diagnoses. Vascular theories of schizophrenia propose microvascular brain abnormalities during development, impacting the functionality of brain. Given the shared embryological origin between the retina and brain, the retina serves as a window to observe brain abnormalities in-vivo. Retinal vascular fractal dimension indicates vascular branching complexity, helps understand developmental vascular abnormalities of the brain and is a potential endophenotypic marker for schizophrenia.

Our study aimed to examine the retinal vascular fractal dimension in individuals with schizophrenia, their unaffected first-degree relatives and in healthy controls.

Methods: We recruited 49 individuals with schizophrenia, 49 unaffected first-degree relatives and 101 healthy volunteers. Non-mydratic color fundus images of both the left and right eye were acquired using 3nethra classic Fundus Camera. Retinal vascular fractal dimension was calculated using the box-counting method (software used: MATLAB). Means of fractal dimension were compared across the three groups using ANOVA. Co-variates of age, sex and body mass index were accounted for using ANCOVA. The calculation of fractal dimension was computerized and rater bias did not confound the analysis.

Results: The groups were comparable across age ($p = 0.268$) and sex ($p = 0.830$). The individuals with schizophrenia had statistically significantly reduced retinal vascular fractal dimension (mean - 1.4732, SD - 0.0293) as compared to the healthy volunteers (mean-1.4874, SD - 0.0261) with p-value of 0.008, even after adjusting for the confounders (age, sex and BMI) with p-value of 0.009. There was no significant difference between the retinal vascular fractal dimension of individuals with schizophrenia and their first-degree relatives (mean - 1.4769, SD - 0.0261), with p-value of 0.777 (after adjusting for covariates, p-value of 0.926). There was trend towards significance noted between the retinal vascular fractal dimension values of first degree relatives of individuals with schizophrenia and healthy volunteers, with a p-value of 0.065 (after adjusting for confounders, p-value of 0.248). Individuals with schizophrenia had a negative correlation between the duration of schizophrenia and the retinal vascular fractal dimension.

Discussion: Our study suggested that the degree of complexity of retinal vascular branching patterns in unaffected first-degree relatives of individuals with schizophrenia was between the values for healthy populations and individuals with schizophrenia, with the latter having significantly reduced complexity of vascular branching pattern. This is suggestive of developmental abnormalities in the brain micro-vasculature associated with schizophrenia, providing further evidence to the ongoing research on the vascular etiology of schizophrenia. As the retina is easily accessible through fundus photography, the retinal vascular fractal dimension could serve as a proxy indicator for neuro-vascular changes associated with schizophrenia. Further studies are required to confirm the findings in a larger sample size and determine the quantitative cut-off values for using the retinal vascular fractal dimension as a biomarker for identifying individuals at risk for schizophrenia and aid in early intervention.

T83. RETINAL STRUCTURE AND ITS RELATIONSHIP WITH PREMORBID AND CLINICAL VARIABLES IN YOUNG SPANISH PATIENTS WITH EARLY-COURSE SCHIZOPHRENIA SPECTRUM DISORDERS

Jairo Gonzalez-Diaz^{*1}, Bernardo Sanchez-Dalmau², Anna Camos-Carreras³, Salut Alba⁴, Silvia Amoretti⁵, Sergi Salmerón⁶, Anaid Pérez⁷, Florencia Forte⁸, Maria Serra⁸, Miquel Bernardo⁹

¹*Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clínic of Barcelona, Neuroscience Institute, Barcelona, Spain; Department of Medicine, School of Medicine and Health Sciences, Institute of Neurosciences (UBNeuro), University of Barcelona (UB), Barcelona, Spain; UR Center for Mental Health—CERSAME, School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia; Clinica Nuestra Señora de la Paz - OHSJD, Bogota, Colombia,* ²*Department of Ophthalmology, Hospital Clínic de Barcelona, Barcelona University, Barcelona, Spain; Institut d'Investigacions Mèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.,* ³*Ophthalmology Service, Hospital Clínic Barcelona, Barcelona, Spain.,* ⁴*Department of Neurology and Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.,* ⁵*Barcelona Clinic Schizophrenia Unit (BCSU). Bipolar and Depressive Disorders Unit. Hospital Clínic of Barcelona. University of Barcelona. IDIBAPS, CIBERSAM,* ⁶*Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic de Barcelona, Barcelona, Spain. Bipolar and Depressive Disorders Unit, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain. Biomedical Research Networking Centre Consortium on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain. Department of Medicine, School of Medicine and Health Sciences, Institute of Neurosciences (UBNeuro), University of Barcelona (UB), Barcelona, Spain.,* ⁷*Barcelona Clinic Schizophrenia Unit (BCSU). Hospital Clínic of Barcelona. University of Barcelona. IDIBAPS, CIBERSAM,* ⁸*Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, 170 Villarroel st, 12-0, 08036, Barcelona, Spain,* ⁹*Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clínic of Barcelona. University of Barcelona. IDIBAPS, CIBERSAM*

Background: Several studies have suggested that the retina structure is affected in schizophrenia spectrum disorders (SSD) (González-Díaz et al., 2022). This study aims to validate the hypothesis that individuals diagnosed with Schizophrenia Spectrum Disorders (SSD) within five years exhibit distinct retinal structures compared to matched healthy controls. These structural differences are expected to correlate with various clinical and course-related variables.

Methods: Employing a cross-sectional design, individuals diagnosed with SSD were compared to age- and gender-matched healthy controls (HCs). Participants with pre-existing retinal/ocular pathology, a history of craniocerebral or ocular trauma, previous ocular surgery, diabetes, or high blood pressure were excluded. The Peripapillary Retinal Nerve Fiber Layer (pRNFL), Macular Ganglion Cell Layer and Inner Plexiform Layer Thickness (GCL+IPL), Macular Volume and Macular Thickness were assessed with Optical Coherence Tomography. Data from each eye (i.e., right eye [OD] and left eye [OS]) were analyzed independently, and both global and quadrant information were assessed. Premorbid, Clinical, Functional, and Course-related data were assessed with several scales, including CGI (Guy, 1976), PANSS (Kay, 1987), FAST (Rosa, 2007), and PAS (Canoon-Spoor, 1982).

Results: Two HCs were included for each case to increase the power of the study (n=18 vs 36), with a similar proportion of genders in each group (n male cases: 10 (55.6%) vs. n male HCs: 20 (55.6%); $p=0.61$) and comparable age (Cases Mean age in years (SD): 30.17 (1.36) vs. Cases Mean age in years (SD): 30.11 (0.96); $p=0.96$). Consistent with existing literature, the macula was thinner in all quadrants in cases. Surprisingly, a statistically significant thickening in pRNFL was observed in SSD patients compared to HCs (OD: Mean (SD): 106.89 μm (9.64) vs. 100.11 μm (8.10), $t=2.720$, $p=0.009$; OS: 04.89 μm (9.00) vs. 99.08 μm (8.21), $t=2.373$, $p=0.021$). A mirrored pattern was observed in the GCL+IPL, with a thinning in the inner nasal and thickening in the outer nasal quadrant in the right eye (Inner Nasal: 93.00 μm (5.87) vs. 99.72 μm (7.72), $t=-3.248$, $p=0.002$; Outer Nasal (71.56 μm (6.20) vs. 67.83 μm (5.16), $t=2.335$, $p=0.023$) and a thinning in the inner temporal and thickening in the outer temporal quadrant in the left eye (Inner Temporal: 86.89 μm (6.12) vs. 93.19 μm (8.25), $t=-2.867$, $p=0.006$; Outer Temporal: 73.28 μm (6.51) vs. 69.08 μm (5.57), $t=2.467$, $p=0.017$). A negative correlation was found between macular measures and premorbid adjustment (OD: Macula Total Volume: $r=-0.488$, $p=0.040$; OS: Macula Thickness Outer Temporal Quadrant: $r=-0.476$, $p=0.046$) and symptom severity (OD: Macula Total Volume: $r=-0.476$, $p=0.046$). Untreated psychosis duration did not correlate with any retinal measure.

Discussion: Previous studies in the Spanish population have yielded analogous paradoxical findings, suggesting the absence of pRNFL thinning in recent psychotic episodes and implicating potential localized retinal inflammation. Our results suggest characteristics resembling papilledema, indicating possible retinal inflammation at the first stages of the illness in young patients. Alternatively, it raises the possibility of past generalized retinal edema resolving initially in the macula yet persisting in the optic disc. A previous meta-analysis from our group suggested that the macula would be better indicators of retinal thinning in patients with SSD (Gonzalez-Diaz et al., 2022). The findings in GCL+IPL align with the retrograde transsynaptic degeneration phenomenon (RTSD), in which the potential loss of occipital cortical tissue leads to the death of cell bodies in the GCL (Adámek et al., 2022; Lai et al., 2020). Several significant correlations between clinical variables and retina structure in a homogeneous sample of early-course SSD suggest that the macula might aid in identifying the most symptomatic patients, as it has been proposed in previous studies. However, to the best of our knowledge this is the first study to explore premorbid variables and its relationship with retinal measures. These findings underscore the complexity of retinal alterations in early-stage SSD, highlighting unexpected pRNFL thickening and nuanced changes in ganglion cell layers.

T84. ESCAPE GAME FOR MENTAL HEALTH

Trang Nu Thuy TON^{*1}, Marion Feron²

¹none, ²Service CRISALID CHI Clermont de l'Oise

Background: Half of all mental difficulties and disorders begin between the ages of 15 and 25.

JENESIS, an early intervention mental health service in a predominantly rural and landlocked area (Oise department, Hauts-de-France region, France), offers a fast-track approach to adolescents and young adults aged between 17 and 25 with a variety of mental health problems that have been evolving for less than 2 years, associated with a lasting functional impact of more than 1 month and less than 2 years, or with an emerging mental health problem.

The support offered is graduated and varied in nature (case-management, cognitive remediation, study support, psycho-education, integrative therapies) and mode of delivery (face-to-face or distance learning).

But the journey can be hampered by fear of stigmatization, lack of commitment and mood-dependent behaviors.

The idea is to use the game as support, such as an escape game, as a non-stigmatizing gateway to an early mental health intervention pathway (high-risk or ultra-high-risk clinical situations).

Methods: The escape game approach combines a playful experience with a multisensory educational approach to promote the appropriation of mental health awareness, empathy and mutual aid, and appears to be well suited to the target population.

It could meet the need for motivation and commitment, the development of psycho-social skills to reinforce empowerment, the prevention and management of crisis and emergency situations, and the fight against stigmatization.

The game is seen as a learning space where knowledge and skills are experimented with freely, and as a mediator for the transfer of skills.

Results: To meet this objective, JENESIS has linked up with SimUSanté.

This is a center for active pedagogy and simulation in healthcare, developed by the CHU Amiens Picardie in partnership with the Université Picardie Jules Verne. It helps to meet the training needs of all those involved in healthcare, but also of the general public. Their work has focused on escape games: Janus' Traps (raising awareness of depression among students); Lord Hades' Secrets (cyber security); and Ludantibio (the correct use of antibiotics).

Mobilizing a multi-professional, multi-expertise team (psychiatry, clinical psychology, educational sciences, edutainment, pedagogical engineering, technical support....) to co-construct the puzzles could facilitate primary and secondary prevention actions (substance abuse, self-injurious behavior) and provide skills and reflexive abilities.

A trained multi-professional team, including a peer health mediator, will lead the activity.

At the end, a supervised psychological debriefing (neuropsychologist, psychiatrist) will be carried out to initiate metacognitive work and collect verbatims.

Discussion: The mental health escape game will be proposed to the people concerned at the beginning of 2024.

The target population of people concerned by a clinical situation at risk will be 40 participants per year.

An ongoing qualitative and quantitative evaluation procedure will be undertaken in terms of acceptability, satisfaction, textual analysis of verbatims collected and impact criteria on secondary prevention (psycho-social skills, psychological flexibility, sense of self-efficacy, self-monitoring skills and coping strategies).

In a second phase, after training, a portable version could be proposed for national distribution.

T85. AN EXPLORATION OF CANNABIS USE AND SUICIDAL THOUGHTS AND BEHAVIORS AMONG ADOLESCENTS WITH HALLUCINATIONS

Elizabeth Thompson*¹, Sarah Thomas¹, Danae Papadea², Jennifer Wolff¹

¹*Alpert Medical School, Brown University*, ²*Rhode Island Hospital*

Background: Early psychosis is characterized as a high-risk period for suicidal thoughts and behaviors, especially during initial presentation for psychiatric care. Cannabis use is markedly prevalent among youth with psychosis-spectrum symptoms and associated with both acute and long-term symptomatology. Although adolescent substance use is considered a significant risk factor for suicidal ideation and attempts, the relations between concurrent use of cannabis and suicidality in youth with psychosis-spectrum symptoms is unclear. The present study aimed to explore the associations between acute suicidality, i.e., suicidal attempt within 30 days before hospitalization and suicidal ideation, concurrent cannabis use, and hallucinations among psychiatrically hospitalized adolescents. We hypothesized that current hallucinations and cannabis use would be associated with suicidal ideation and past 30-day attempt, and the relation between current hallucinations and suicide outcomes would be moderated by past 30-day cannabis use.

Methods: Upon hospital admission, teens completed self-report measures of suicidal ideation (Suicidal Ideation Questionnaire – Junior; score range 0-90), suicidal attempts, cannabis use, depressive symptoms (PROMIS Short Form; score range 8-40), and demographics, including age and sex at birth. Teens were also asked whether they experienced hallucinations (auditory or visual) within the past 30 days (yes/no) as part of a brief diagnostic interview.

Results: The full sample includes 368 teens (Mage = 14.97; 65% female at birth); 109 teens (29.6%) endorsed current hallucinations and 99 (26.9%) endorsed past 30-day cannabis use. Correlations indicated that endorsement of current hallucinations was associated with suicidal ideation ($r = .30$, $p < .001$) and depression ($r = .25$, $p < .001$), but not past 30-day suicide attempt or past 30-day cannabis use. Depressive symptoms were also positively correlated with suicidal ideation ($r = .72$, $p < .001$) and past 30-day suicide attempt ($r = .22$, $p = .001$). Surprisingly, past 30-day cannabis use was not associated with any variables besides age ($r = .25$, $p < .001$). Linear regression explored the association between current hallucinations and suicidal ideation. Suicidal ideation was statistically predicted by the presence of current hallucinations ($R^2 = .08$; $\beta = 0.28$, $t = 4.46$, $p < .001$). This effect remained significant ($\beta = 0.10$, $t = 2.16$, $p = .032$) when controlling for the effects of depressive symptoms ($\beta = 0.65$, $t = 13.52$, $p < .001$) and sex ($\beta = 0.17$, $t = 3.71$, $p < .001$), as well as the non-significant effects of past 30-day cannabis use and age ($R^2 = .56$). The relation between hallucinations and suicidal ideation was not moderated by past 30-day cannabis use. Moderation analyses revealed trend-level evidence of an interaction between current hallucinations and past 30-day cannabis use in the statistical prediction of past-30-day suicide attempt. For adolescents who used cannabis in the past 30 days, current hallucinations were associated with past-month suicide attempt at a trend level ($B = 0.98$, $z = 1.90$, $p < .06$). For adolescents who denied past-month cannabis use, there was no significant association between current hallucinations and past 30-day suicide attempt.

Discussion: Findings suggest that recent cannabis use may be associated with increased imminent risk for suicide attempt among youth with hallucinations. Further analyses for this presentation will include exploration of other characteristics of cannabis use (age of onset, motivations, and forms of intake) and their relation to hallucinations and suicide outcomes. Implications for treatment will be discussed.

T86. THE ASSOCIATION OF HYPERPROLACTINEMIA EXPOSURE WITH HEIGHT GROWTH AND TANNER STAGE IN CHILDREN AND ADOLESCENTS RECEIVING TREATMENT WITH ANTIPSYCHOTIC MEDICATION

Morten Thorsen*¹, Marlene Briciet Lauritsen², Anne Katrine Pagsberg³, Marianne Skovsager Andersen⁴, Ulla Schierup Nielsen⁵

¹*Research Unit for Child and Adolescent Psychiatry, Aalborg University Hospital,* ²*Aalborg University Hospital, Research Unit for Child and Adolescent Psychiatry, North Denmark Region,* ³*Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark,* ⁴*Department of Endocrinology, Odense University Hospital,* ⁵*Research Unit for Child and Adolescent Psychiatry, Aalborg University Hospital,*

Background: Antipsychotic-induced hyperprolactinemia (AIH) is a common challenge during treatment of children and adolescents with antipsychotic medication. Children with hyperprolactinemia caused by prolactinoma may experience growth arrest and pubertal delay. However, the consequences of AIH on height growth and pubertal development is not known. This knowledge is essential, given that children and adolescents are treated with antipsychotics during an essential period of life for this growth and development. In this study we therefore aimed to investigate whether AIH is associated to disturbances in height growth and pubertal development.

Methods: In this retrospective cohort study, we included a population of children and adolescents aged 7-18 years, in treatment with antipsychotic medication. By using past prolactin measurements, we calculated total prolactin exposure during antipsychotic treatment was calculated as the area under the curve of prolactin level versus time. We investigated the association between total prolactin exposure and current height (adjusted for height of parents) and Tanner using regression analysis. Prolactin measurements that were assessed before estimated start of puberty were excluded from Tanner stage analysis.

Results: 90 patients were included. Sex distribution was 47/43 (male/female). Mean age at start of antipsychotic treatment was 13.9 years [Range: 7.9; 18.1]. Mean duration of antipsychotic treatment was 2.38 years [Range: 2.23; 9.82]. No association between prolactin exposure and height development was found (0.23 cm/1000 mIU prolactin, 95% CI: -0.0499; 0.5166, p=0.106). No association between prolactin exposure and pubertal development was found.

Discussion: This study did not find any association between AIH and respectively height growth and pubertal development. These are however preliminary data, where factors such as BMI, estradiol containing oral contraceptives and patients who had already reached target height at start of treatment has not been adjusted for. These data will be available at the conference.

T87. PSYCHOTIC EXPERIENCES AND RISK OF SUICIDALITY IN ADOLESCENTS: RESULTS BASED ON LONGITUDINAL DATA FROM A LARGE NATIONWIDE BIRTH COHORT

Stephen Austin*¹, Katrine Ineson², Merete Nordentoft³, Trine Madsen²

¹*Psychiatric Research Unit, Region Zealand Psychiatry,* ²*Danish Research Institute of Suicide Prevention, Copenhagen Research Center for Mental Health Mental Health Center Copenhagen,* ³*CORE - Copenhagen Research Centre for Mental Health, Copenhagen University Hospital*

Background: Psychotic experiences (PE) in childhood have been linked to suicidal ideation (SI) and suicide attempt (SA), however often in cross-sectional studies. Longitudinal research based on large samples with possibilities for confounder adjustments have been called for in a recent systematic review to better establish the association between childhood PE and suicidality. The aim of this study was to examine the association of PE with suicidality in The Danish National Birth Cohort (DNBC).

Methods: The study cohort included adolescents who participated at both the 11-year-follow-up and the 18-year-follow up of DNBC. The 11-year-follow-up included seven questions on PE and social environmental-, behavioural- as well as mental well-being factors. At the 18-year-follow-up the adolescents were asked about lifetime SI and SA. Data from DNBC were linked with individual level data from Danish Registers enabling further information on hospital contacts for SA and a range of parental socio-demographic variables to also be included. Associations were estimated using multinomial logistic regression models and adjusted for a wide range of social, behavioural, and mental well-being factors. Further, to account for sample selection, we applied inverse probability weighting, based on data from the entire national birth-cohort born in the same period as the DNBC-birth cohort participants.

Results: Out of the 27,657 participants 3,235 (11.7%) reported having had at least one psychotic experience at DNBC-11. At DNBC-18 this number was 2991 (11.2%). Those young people that had reported at least one psychotic experience at age 11 had an increased risk of suicidal ideation (OR=1.91, 95% CI 1.76-2.08) and suicide attempt (OR=3.37, 95% CI 2.81-4.04) at 18 years compared to those that had not reported a psychotic experience. The greater number of concurrent psychotic experiences reported, the greater the increased the risk of suicidality. For those youths that reported a psychotic experience at both 11 and 18 years there was markedly higher risk of both suicide ideation (OR=4.00, 95% CI 3.41-4.70) and suicide attempt OR=12.92, 95% CI 10.07-16.58) compared with those people that reported no PE's. Analysis of content of auditory hallucinations and suicidality revealed that those young people that reported voices that called their name or commented had an increased risk of suicide ideation (OR 3.80 95% CI 3.25-4.46) and (OR 12.84 95% CI 10.14-16.26) and suicide attempt (OR= 4.74, 95% CI 4.02-5.58) and (OR=20.03, 95% CI 16.02-25.04) respectively, compared to those that did not report auditory hallucinations. Young people that reported auditory hallucinations with negative comments had an increased risk of suicide ideation (OR=8.89, 95% CI 6.49-12.17) and a marked greater risk of suicide attempt (OR=66.15, 95%, CI 6.78-93.53) compared to those youths that did not report auditory hallucinations.

Discussion: This large longitudinal study found a significant increased risk of suicide ideation and suicide attempt in young people reporting psychotic experiences. The greatest risk of suicide attempt was associated with young people reporting auditory hallucinations with negative comments. Whilst acknowledging the limitations of self-report measures, the findings indicate the longitudinal association between childhood psychotic experiences and risk of suicidality during teenage life, even after extensive confounder adjustments. Implications of these results will be discussed.

T88. IT'S ALL ABOUT THE TIMING: SLEEP SPINDLE CLUSTERING IN INDIVIDUALS WITH YOUNG SCHIZOPHRENIA COMPARED TO HEALTHY CONTROLS

Maria E. Dimitriadis*¹, Alejandro Osorio-Forero², Susanne Walitza³, Reto Huber¹, Miriam Gerstenberg¹

¹*Psychiatric University Hospital Zurich, Kinderspital Zurich, University of Zurich,*

²*Netherlands Institute for Neuroscience,* ³*Psychiatric University Hospital Zurich, University of Zurich*

Background: Reductions in sleep spindles, a major electrophysiological oscillation during sleep, have been identified in patients with schizophrenia (SZ). Recently, sleep spindle clustering on a 50-second time scale has been shown to tightly regulate aspects of sleep-dependent memory consolidation and arousal driven by locus coeruleus activity in the healthy, adult population. As memory impairments, difficulties maintaining sleep, and locus coeruleus dysfunction are commonly reported in SZ, it is hypothesized that individuals with the disorder have irregular timing of sleep spindles during NREM sleep. Thus, we are assessing the presence and strength of sleep spindle clustering on a 50-second time scale in individuals with Early-Onset Schizophrenia (EOS) and healthy controls (HC).

Methods: Sleep electroencephalic data of patients with EOS (N=11, 16.38 +/- 1.43 years old; 36.4% female) and age- and sex-matched healthy controls (HC; N=11, 16.50 +/- 1.69 years old; 36.4% female) are analyzed.

Results: Preliminary results indicate that sleep spindles cluster on a 50-second time scale in both groups. The strength of the clustering comparing patients with EOS to HC is currently being investigated.

Discussion: Sleep spindle clustering on a 50-second time scale is detectable in children and adolescent populations. Early findings suggest that young patients with SZ may have differences in the timing of sleep spindle clustering. Next steps investigating the relationship between sleep spindle clustering, working memory, and arousal are underway.

T89. SEX-SPECIFIC INTERACTIONS BETWEEN STRESS AXIS AND REDOX BALANCE ARE ASSOCIATED WITH INTERNALIZING SYMPTOMS AND BRAIN WHITE MATTER MICROSTRUCTURE IN ADOLESCENTS

Zoé Schilliger*¹, Yasser Alemán-Gómez², Zeynep Celen³, Ben Meuleman³, Pascal Steullet¹, Kim Do¹, Philippe Conus⁴, Arnaud Merglen⁵, Camille Piguet³, Daniella Dwir¹, Paul Klauser¹

¹*Center for Psychiatric Neurosciences, Lausanne University Hospital,* ²*Connectomics Lab, Department of Radiology, Lausanne University Hospital and University of Lausanne,*

³*Department of Psychiatry, Faculty of Medicine, University of Geneva,* ⁴*Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital,* ⁵*Division of General Pediatrics, Geneva University Hospitals and Faculty of Medicine, University of Geneva,*

Background: While the prevalence of schizophrenia is comparable between sexes, women show differences in age of onset (3-5 years later than men) and symptoms, with more affective disturbances and depressed mood. Schizophrenia onset typically occurs during early adulthood but is frequently preceded by internalizing symptoms (depressed mood, anxiety) during adolescence. Incidentally, the adolescent period is critical for the maturation of brain networks of emotion and mood regulation and witnesses a peak incidence in internalizing disorders, especially in females. Altered Hypothalamic-Pituitary-Adrenal (HPA)-axis function and pro-oxidant/antioxidant imbalance have both been associated with internalizing disorders and schizophrenia and may represent critical factors for the development of

emotional and affective regulation during adolescence. Furthermore, glucocorticoids and impaired glutathione (GSH) antioxidant balance have been related to brain white matter alterations, which are commonly observed in both affective disorders and schizophrenia. However, sex-specific interactions between these biological factors, internalizing symptoms and brain white matter maturation remain unexplored.

Methods: Adolescents aged 13 to 15 from the general population ($n = 68$, 57% females) provided self-report of internalizing symptoms (STAI-trait and BDI), blood samples and underwent diffusion-weighted MRI. Peripheral glutathione-cycle redox homeostasis (i.e., antioxidant activity of the GSH-peroxidase (GPx) and reductase (Gred)) was measured in red blood cells and cortisol, its precursor 11-deoxycortisol and their ratio (cortisol/11-deoxycortisol ratio) were measured by LC-MS in the serum. Using linear regressions, we investigated sex-specific associations between blood markers, internalizing symptoms and indices of brain white matter microstructure (generalized fractional anisotropy (gFA)).

Results: Female adolescents displayed higher levels of trait anxiety and depressive symptoms, GPx activity and cortisol/11-deoxycortisol ratio than males. There was a strong correlation between GPx and Gred activities in females only. The cortisol/11-deoxycortisol ratio, related to HPA-axis activity, was associated with internalizing symptoms in both sexes, whereas GPx activity was associated with internalizing symptoms in females specifically. The cortisol/11-deoxycortisol ratio mediated sex-differences in internalizing symptoms and the association between anxiety and GPx activity in females specifically. In females, GPx activity was positively associated with generalized fractional anisotropy in widespread white matter brain regions.

Discussion: In summary, we found that higher levels of internalizing symptoms in female adolescents than in males relate to sex-differences in HPA-axis function. In females, our results suggest an important interplay between HPA-axis function and GSH-homeostasis, a parameter strongly associated with more advanced patterns of brain white matter maturation.

T90. CHILDHOOD ADVERSITY AND INCIDENT PSYCHOTIC EXPERIENCES IN EARLY ADULTHOOD: COGNITIVE AND PSYCHOPATHOLOGICAL MEDIATORS

Andrea Cortes Hidalgo^{*1}, Gemma Hammerton¹, Jon Heron¹, Koen Bolhuis², Paul Madley-Dowd¹, Henning Tiemeier³, Marinus van IJzendoorn⁴, Stanley Zammit¹, Hannah Jones¹

¹University of Bristol, ²Erasmus Medical Center Sophia Children's Hospital, Rotterdam, ³Harvard T.H. Chan School of Public Health, ⁴UCL

Background: Childhood adversity is often described as a potential cause of incident psychotic experiences, but the underlying mechanisms are not well understood. We aimed to examine the mediating role of cognitive and psychopathological factors in the relation between childhood adversity and incident psychotic experiences in early adulthood.

Methods: We analysed data from the Avon Longitudinal Study of Parents and Children, a large population-based cohort study. Childhood adversity was measured prospectively from birth to age 11 years, mediators (anxiety, depression, external locus of control (LoC), negative symptoms) were assessed at approximately 16 years of age, and incident psychotic experiences were assessed at ages 18 and 24 years. Mediation was examined via the counterfactual g-computation formula.

Results: In total, 7% of participants had incident suspected or definite psychotic experiences in early adulthood. Childhood adversity was related to more incident psychotic experiences

(ORadjusted = 1.34, 95% CI = 1.21; 1.49), and this association was partially mediated via all mediators examined (proportion mediated: 19.9%). In separate analyses for each mediator, anxiety, depression, external LoC, and negative symptoms were all found to mediate the link between adversity and incident psychotic experiences. Accounting for potential confounders did not modify our results.

Discussion: Our study shows that cognitive biases as well as mood symptomatology may be on the causal pathway between early-life adversity and the development of psychotic experiences. Future studies should determine which mediating factors are most easily modifiable and most likely to reduce the risk of developing psychotic experiences.

T91. A SYSTEMATIC REVIEW OF COGNITIVE REMEDIATION FOR ADOLESCENTS WITH PSYCHIATRIC DISORDERS: METHODOLOGICAL CONSIDERATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Caroline Cellard^{*1}, Audrey Cayouette¹, Matteo Cella², Kelly Allott³, Frederic Haesebaert⁴, Caroline East-Richard¹

¹Université Laval, ²Institute of Psychiatry, Psychology and Neuroscience King's College London, ³Orygen and Centre for Youth Mental Health, The University of Melbourne, ⁴PSYR2 Team, INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, Université Claude Bernard Lyon

Background: The clinical and functional effects of cognitive remediation have been widely documented in adults with psychiatric disorders. However, the specific effects in adolescents with psychiatric disorders remain poorly documented. The purpose of this review and meta-analysis is twofold: 1) to determine the effects of cognitive remediation on cognition for adolescents with psychiatric disorders and 2) to evaluate the methodological quality of studies that investigate the effects of cognitive remediation among adolescents with psychiatric disorders – such as schizophrenia spectrum disorders.

Methods: A systematic review and meta-analysis were conducted with randomized controlled trials on cognitive remediation with psychiatric adolescent population. Specifically, searches were conducted in Pubmed, PsycInfo and Embase for studies pertaining to cognitive remediation therapy (CRT) effects on cognition, social functioning, and clinical symptoms. Methodological quality was assessed using the Clinical Trials Assessment Measure (CTAM).

Results: Fifteen studies (N=15) were included in the review, with 12 independent samples (k=12, 641 participants). Participants had various psychiatric disorders (e.g., psychotic disorder, mood disorder, attention deficit hyperactivity disorder, eating disorder). A significant negligible to small effect was found for CRT on cognition (g=0.16, p LESS THAN 0.05). Nonsignificant effects were found for clinical symptoms (g=0.06, p=0.40) and social functioning (g=0.06, p=0.39). Follow-up studies revealed few sustained improvements compared to the control groups. Methodological quality of included studies was variable, ranging from poor to good quality.

Discussion: Included studies showed a negligible to small significant effect of CRT on cognition, and nonsignificant effects on clinical symptoms and social functioning in adolescent with psychiatric disorders. Some factors may explain the lack of effects, such as the motivation during treatment, the absence of an inclusion criterion regarding cognitive deficits, and the absence of a CRT therapist. Core features for CRT have been identified by

an expert working group in adults with schizophrenia population. Such core ingredients should be considered for designing future CRT studies with adolescents.

T92. TDCS-MODULATED COGNITIVE TRAINING AS A POTENTIAL INTERVENTION FOR TREATING COGNITIVE IMPAIRMENT IN SERIOUS MENTAL ILLNESS

Lingyan Yu¹, Rebecca Kazinka¹, Lei Xuan¹, Donovan Roediger¹, Bryon Mueller¹, Kelvin Lim¹, Angus MacDonald*¹

¹*University of Minnesota*

Background: Cognition-based intervention has long been used and studied for treating neuropsychiatric patients with cognitive deficits, particularly those with serious mental illness (SMI). In patients with schizophrenia, the frontoparietal control network was found to be implicated in the cognitive deficits of schizophrenia and responsive to cognitive remediation (Ramsay et al., 2015). Due to mixed evidence on the generalizability of treatment outcomes, cognition-based interventions have been paired with various neuromodulation techniques to promote neuroplasticity, which then facilitates learning transfer to patients' overall cognitive functioning. Research on the synergy of transcranial direct current stimulation (tDCS) and cognitive training just accumulated over the last decade for tDCS's ease of use and focal noninvasive stimulation (Bikson et al., 2013). In this study, we aimed to test the incremental benefit of concurrent tDCS on cognitive training and to understand the change mechanism by examining the control network utilization in response to training.

Methods: We recruited 58 healthy adults with an estimated IQ between 70 and 115 for a gamified cognitive training protocol with three 45-minute training sessions each week for 12 weeks. Each session consisted of training on working memory (N-back paradigm), context processing (Dot Expectancy paradigm), and inhibitory control (Flanker paradigm), and the first 20 minutes of each session were paired with prefrontal tDCS, where participants were randomized into left anodal tDCS (L-tDCS), right anodal tDCS (R-tDCS), and sham tDCS with triple blinding. fMRI scanning and the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) were administered at baseline, mid-point, and post-training, and the scanning was paired with an untrained N-back task. We used the Yeo-17 Networks atlas (Schaefer et al., 2018) to locate the control network to look at the 2-over-0-back brain activations.

Results: 38 participants completed all training. Completers performed better on the untrained 2-back task ($F(2, 68) = 21.57$, $p < .001$) and the MCCB ($F(2, 66) = 24.29$, $p < .001$) from baseline to midpoint and post-training, though no tDCS group effect or time-group interactions was found. Task-based brain activations in the control network decreased significantly from baseline to midpoint and post-training ($F(2, 68) = 46.55$, $p < .001$). In the left frontal control regions, there was a significant main effect for tDCS ($F(2, 68) = 25.84$, $p = 0.02$), where the left tDCS group showed the greatest task-based activations. The decrease in task-based control network activations was not associated with improvement in the untrained 2-back or the MCCB. Improvement in the MCCB was however predicted by improvement in the untrained 2-back ($F(1, 30) = 5.62$, $p = .02$), and there was a trend-level interaction between 2-back improvement and tDCS treatment group ($F(2, 30) = 2.72$, $p = .08$).

Discussion: Our results support a generalization of training outcomes, though the incremental effect of concurrent tDCS still needs further investigation. TDCS-modulated cognitive

training appears to be a feasible and well-tolerated intervention with the potential to be used to target the under-treated cognitive impairment in SMI patients.

T93. A CLINICAL QUALITY REVIEWER CALIBRATION MODEL: ENHANCING RELIABILITY IN PANSS SCORING ACROSS DIVERSE REGIONS

Kia Crittenden-Ward*¹

¹*Signant Health*

Background: Successful clinical trials depend on accurate and precise diagnostic assessments and symptom severity ratings [1]. A calibrated team of Clinical Quality Reviewers (CQRs) can be utilized to independently review site-administered interviews, offering feedback and remediation of aberrant interview techniques and scoring practices [2]. This proactive approach serves as an important early warning system, identifying and addressing data quality issues promptly [3]. The effectiveness relies on the high calibration and standardization of CQRs. However, challenges arise from variability in symptom presentation across global clinical trial regions [4, 5]. This report describes an innovative training methodology tailored to address this challenge, emphasizing training and calibration for North America, Asia Pacific, and Eastern Europe.

Methods: We present Positive and Negative Syndrome Scale (PANSS) scoring patterns of 48 CQRs in a global phase III schizophrenia trial. CQRs monitored data in local languages grouped by North America (English and Spanish), Asia Pacific (Chinese, Japanese, Korean), and Eastern Europe (Bulgarian, Croatian, Latvian, Polish, Romanian, Russian, Serbian, Ukrainian). Twenty-one CQRs reviewed only Eastern European data, 12 Asia Pacific, and 13 North America. Two CQRs reviewed data from Eastern Europe and North America.

Before participating, each CQR completed rigorous training and qualification exceeding site rater requirements. Credential vetting and curriculum covering scale and subject matter training were mandatory. Forty-eight CQRs completed the study-specific training and calibration program. Their qualified status required ongoing participation in an In-Study CQR Quality Assurance program, including calibration events every 4 months. Events aimed to harmonize CQRs in PANSS assessment, falling into two categories: 1) All CQR PANSS Calibration using the same English dataset, and 2) Language-Level PANSS Calibration with language-specific subgroups using local datasets.

Results: Over the 3-year focus of this descriptive review, four All-CQR calibration events occurred. Twenty-three CQRs participated in all, eight CQRs participated in three, five participated in two, and 12 participated in only one exercise. Twenty-seven Language-Level calibrations took place across 10 languages. The calibration details will be described with a reporting of scores and measure of inter-rater reliability for two English PANSS interviews conducted with actors trained to portray a typical trial participant and two English interviews recorded from consenting patients. Country- and language-specific interviews were scored with greater differences predicted for the Eastern Europe and Asia Pacific regions when using real data compared to scripted sessions. The ratings for PANSS items P1 Delusions, P3 Hallucinatory behavior, and P6 Suspiciousness/persecution, were highly consistent across regions. Larger differences were observed in N1 Blunted affect, with more variability in Actor ratings vs. Patient ratings.

Discussion: Cross-regional calibration of rating symptoms of psychosis requires attention to both universal standardization and appreciation of regional differences in symptom presentation and the rating of symptoms. Combined use of both universal training with region-specific calibration can ensure that ratings are consistent across the study and can address nuances that might be present within certain cultures and regions.

T94. ULOTARONT DELAYS GASTRIC EMPTYING TIME IN SCHIZOPHRENIA PATIENTS WITH METABOLIC SYNDROME (NCT05402111)

Seth Hopkins^{*1}, Snezana Milanovic², nina dedic³, Rob Lew⁴, Michael Camilleri⁵, Kenneth Koblan⁶

¹*Sumitomo Pharma America, Cambridge,* ²*Snezana.Milanovic@us.sumitomo-pharma.com,*
³*nina.dedic@us.sumitomo-pharma.com,* ⁴*robert.lew@us.sumitomo-pharma.com,*
⁵*camilleri.michael@mayo.edu,* ⁶*kenneth.koblan@us.sumitomo-pharma.com*

Background: Metabolic syndrome, which can be induced or exacerbated by the current class of antipsychotic drugs, is highly prevalent in schizophrenia patients and presents challenges to lifetime disease management. Ulotaront is a TAAR1 agonist in clinical development for schizophrenia. In line with other TAAR1 agonists, ulotaront improves glycemic control and reduces body weight in rodent models via peripheral effects on glucose homeostasis as well as central regulation of energy balance. Given that TAAR1 agonists improve oral glucose tolerance in rodents by delaying gastric emptying (a mechanism implicated in the beneficial effects of GLP-1 receptor agonist), our aim was to assess the effect of ulotaront on gastric emptying in schizophrenia patients with metabolic syndrome at high risk to develop diabetes.

Methods: Twenty seven schizophrenia patients with metabolic syndrome were randomized to receive in open-label fashion either a single dose of ulotaront (150 mg) or their prior antipsychotic in a 2-sequence crossover design. Subjects were required to maintain a stable dose and regimen for one of 4 antipsychotics as treatment for schizophrenia at the time of screening (risperidone, olanzapine, quetiapine, or aripiprazole). Subjects fulfilled at least 3 of 5 metabolic syndrome criteria, and to demonstrate glycemic-derived insulin resistance by either HbA1c values between 5.7% and 6.4% or fasting HOMA-IR values equal or above 2.22. Prior to the single dose of ulotaront, subjects underwent a washout period (of 3 to 16 days) of their prior antipsychotic drug. Following an overnight fast, subjects received a single dose of either ulotaront or the prior antipsychotic medication, underwent scintigraphic measure of solid gastric emptying, and after receiving a 99mTc-labeled meal (320kcal, 30% fat meal), successive γ camera abdominal images (anterior and posterior) were performed every 60 minutes over a 4 hour period. Primary endpoints were gastric emptying half-time, T1/2 (GE T1/2) and gastric retention (%GR) at 4h. Secondary endpoints were %GR at 1h and 2h.

Results: Following single-dose of 150 mg ulotaront, gastric emptying was delayed (T1/2 = 145 ± 17 min; median $\pm$ SE) compared to subjects receiving a single dose of their prior antipsychotic drug (125 ± 4 min, p-value 0.0028). The median percent gastric retention post-dose (1h, 2h, 4h) was significantly greater following ulotaront (83%, 66%, 17%) compared to prior antipsychotic (76%, 51%, 7%, respectively).

Discussion: Ulotaront significantly delayed gastric emptying following a single dose. In this first study of its kind, we enrolled schizophrenia patients with metabolic syndrome, and who were at high risk for diabetes. The within-subject crossover design allowed the comparison of the effect of ulotaront in each subject to the effects of their prior antipsychotic medication.

Further studies of ulotaront in this patient population (NCT05463770, NCT05542264) will be required to elucidate its potential for benefit on glycemic control and body weight.

T95. FUNCTIONAL OUTCOME OF FIRST-EPISODE PSYCHOSIS AND LONG-TERM SCHIZOPHRENIA

Olsson Anna-Karin^{*1}, Torill Ueland², Linn Sofie Sæther³, Christine Mohn³

¹*NU-Hospital Groups*, ²*NORMENT Norwegian Centre for Mental Disorders Research*, ³*NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical medicine, University of Oslo*

Background: Impaired functional outcome has been documented in both first-episode psychosis (FEP) and long-term schizophrenia spectrum disorders (SZ), but has seldom been directly compared between the two groups. Functional outcome can be described using real world measures of functioning as well as measures of functional capacity. Both types of measures have been found to be related to cognitive functioning. In the current study, we compare participants with FEP and SZ on measures of functional capacity, real world functioning and a measure of cognition.

Methods: The participant group consisted of 349 patients, 156 with FEP and 193 with SZ. The FEP group consisted of 103 men and 53 women, mean age 26.7 (SD 6.9) years, while the SZ group consisted of 128 men and 65 women, mean age 49.3 (SD 9.9) years. In the FEP group, 60% had a diagnosis of schizophrenia while the corresponding number in the SZ group was 70%. The groups were compared on socio-demographic characteristics, clinical symptoms, and functional outcome. Symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning Scale-symptom (GAF-symptom). Real world functioning was measured with the Global Assessment of Functioning Scale-function (GAF-function), functional capacity was assessed with the University of California, San Diego Performance-Based Skills Assessment-Brief (UPSA-B), and processing speed was assessed with the Trail Making Test A (TMT-A).

Results: There was no significant gender difference between the groups. The FEP group was significantly younger than the SZ group ($t = -24.05$, $p < .001$). In the FEP group, 74 individuals were employed or currently studying, and in the SZ group the number was 25 ($X^2 = 74.43$, $p < .001$). There were no differences in symptom levels between the groups as measured by the PANSS. However, the GAF-symptom score was lower in the SZ group ($t = 3.71$, $p < .001$). The FEP group had significantly higher real world function (GAF-function, $t = 2.87$, $p < .005$) and functional capacity (UPSA-B total, $t = 5.28$, $p < .001$) compared to the SZ group. Moreover, the sub scales of the UPSA-B also showed better function in the FEP group (Finances $t = 9.38$, $p < .001$ and Communication $t = 3.54$, $p < .001$). Finally, performance on a measure of processing speed, the TMT-A, was significantly lower in the FEP group ($t = -6.78$, $p < .001$), indicating better cognitive function.

Discussion: Despite similar psychosis symptom levels, the FEP group exhibited better real-world functioning, functional capacity, and cognitive functioning compared to the SZ group. This finding could suggest that the capacity to perform practical everyday activities and cognitive function of FEP patients be better preserved if interventions and support targeting these outcomes are performed early in the course of illness. Such interventions may not only hinder the deterioration of functions, but also can facilitate for these patients to complete education and gain employment.

T96. BEYOND NUMBERS: UNRAVELING THE FREQUENCY OF NEUTROPENIA AND AGRANULOCYTOSIS IN CLOZAPINE USERS

Natalia Daher*¹, Ary Gadelha¹, Raffael Massuda², Pedro Lorencetti¹, Renan Biokino¹, Mateus Diniz¹

¹Federal University of Sao Paulo, ²Universidade Federal do Parana

Background: Treatment-resistance affects approximately 37% of patients with schizophrenia and is defined by the failure of two antipsychotics used at appropriate dosage, duration, and adherence levels (DINIZ et al., 2023, HOWES et al., 2017). Only one antipsychotic medication has proven to be more effective for these patients, which is clozapine. Each antipsychotic tried before clozapine in treatment-resistant schizophrenia reduces the likelihood of a response to clozapine by about 8 to 11%. On the other hand, the chance of improvement in functionality decreases by 15% for each year of delay in starting clozapine (NIELSEN et al., 2010). Various hematologic disorders can be encountered, including leukopenia, neutropenia, agranulocytosis, thrombocytopenia, anemia, and eosinophilia. Agranulocytosis, a rare complication of clozapine, affects 0.4% of users (LI XH et al., 2020). There are few studies addressing hematologic dyscrasias in Brazil, none in the central area of the country.

Methods: This is a real-world study in which data available at a clozapine distribution reference center were analyzed. A total of 6,160 complete blood counts from patients at the CEMAC - High-Cost Medication Center Juarez Barbosa, covering the years 2011 to 2018, were examined. This center is a reference facility in the state of Goiás for dispensing clozapine and oversees approximately 900 patients in total. The patient group consists of adults and seniors, ranging from 18 to 73 years old, diagnosed with a chronic psychotic disorder and currently using clozapine. The demographic characteristics were collected by the administrative staff of CEMAC.

Results: The study sample comprised 486 patients monitored between 2011 and 2018, who underwent a total of 6,180 complete blood counts. Analyzing by the total number of blood counts, neutropenia rates were 1.10%, with mild neutropenia at 0.99%, moderate at 0.11%, and severe at 0%. No cases of agranulocytosis were identified in any blood count. On the other hand, analyzing by the total number of patients, neutropenia rates were 4.32%, with mild neutropenia at 3.7%, moderate at 0.62%, and severe at 0%. No cases of agranulocytosis were found in any patient. For male patients, the neutropenia rate was 3.96%, while for female patients, it was 4.68%. Among patients aged 20 to 29, 9% exhibited neutropenia. For those aged 30 to 39, the neutropenia rate was 6%, while for those aged 40 to 49, it was 3.5%. Among those aged 50 to 59, the neutropenia rate was 1%, and for those aged 60 or older, it was 10%. While examining recurrent neutropenia - defined by two consecutive blood exams, 21 out of the 486 patients exhibited neutropenia, with 9 showing recurrent mild neutropenia (42.85%) and 2 showing recurrent moderate neutropenia (9.5%).

Discussion: Clozapine is globally underutilized due to clinicians' reluctance to prescribe it, even for treatment-resistant patients. Studies indicate that the main reason for this reluctance is concern about adverse reactions and the difficulty in monitoring complete blood counts. The data collected reveal low rates of neutropenia overall, especially recurrent neutropenia, and no cases of agranulocytosis. This database can provide insights into monitoring complications associated with clozapine use in low- and middle-income countries (LMICs). These results contribute compelling information from the South American population and could assist in guiding clinical and public health decisions to ease blood monitoring guidelines for clozapine users.

T97. FOOD FOR BRAIN DISORDERS: DESIGN OF THE BRAIN ANTI-INFLAMMATORY NUTRITION DIET AND 'NO GUTS, NO GLORY' STUDY - AN OPEN-LABEL RCT

Sophie van Zonneveld*¹, Greetje Huisman¹, Ellen van den Oever¹, Emmy Grandjean², Ondine van de Rest², Benno Haarman¹, Iris Sommer¹

¹University Medical Center Groningen, ²Wageningen University and Research Wageningen

Background: Elevated systemic inflammation, stemming from increased intestinal permeability, significantly affects brain functioning in a subset of patients. Gut health offers a promising avenue for therapeutic intervention, with an anti-inflammatory dietary pattern potentially altering the course of brain disorders. Patients are eager to know what foods can optimize their brain health; however, comprehensive dietary guidelines are currently lacking. To address this gap and provide guidance to patients, a narrative review was conducted to offer an overview of the current evidence at the food group level. Drawing upon this evidence, the Brain Anti-Inflammatory Nutrition (BrAIN) diet was formulated. Presently, the efficacy of this anti-inflammatory diet on global functioning and (gut)health of patients with schizophrenia spectrum disorders (SSD), bipolar disorder (BD), and Parkinson's disease is researched in the 'No Guts, No Glory' clinical trial (NL9851).

Methods: A comprehensive review was conducted to assess the potential effects of various food groups on gut health, inflammation, and symptoms in schizophrenia spectrum disorders (SSD), bipolar disorder (BD), and Parkinson's disease. Based on this evidence the Brain Anti-Inflammatory Nutrition (BrAIN) diet was designed, that is researched in a randomized controlled open-label trial with a cross-over intervention lasting 12 weeks and a 24-week wash-out period. The study population comprised patients with SSD (n=25), BD (n=25), and PD (n=50). All visits occurred at the patient's home or UMC Groningen. Primary outcome is global functioning assessed with Outcome Questionnaire 45 (OQ-45).

Results: The BrAIN diet contains a minimum of 30-40 grams of dietary fiber a day from fruits, vegetables, legumes, wheat, and wholegrain products. Furthermore, fatty fish, fermented dairy (such as yoghurt, kefir, and buttermilk), nuts, olive oil, herbs, and spices are recommended. In contrast, red meat, other dairy products, and sugar should be limited. Finally, ultra-processed foods, salt, alcohol, and sweetened beverages should be avoided. The results of the clinical trial were not available during abstract submission.

Discussion: This comprehensive review focuses on anti-inflammatory properties of foods providing a foundation for future dietary guidelines in this domain. Furthermore, our clinical study explores the therapeutic potential of an anti-inflammatory dietary pattern in modifying the course of brain disorders through the gut-brain axis. Additionally, we present the Brain Anti-Inflammatory Nutrition (BrAIN) diet, developed based on evidence linking food groups to gut health, inflammation, and symptoms in psychiatric and neurodegenerative disorders.

T98. ESKETAMINE FOR NEGATIVE AND DEPRESSIVE SYMPTOMS IN SCHIZOPHRENIA – PRELIMINARY OBSERVATIONS FROM AN ONGOING RANDOMIZED CONTROLLED CLINICAL PILOT STUDY

Matthäus Willeit*¹, Ulrich Sauerzopf², Cornelia Diendorfer², Fridolin Stockreiter², Lisa Müller², Irena Dajic², Katharina Landesmann², Lucie Bartova², Martin Bauer³, Ana Weidenauer², Nicole Praschak-Rieder²

¹Medical University of Vienna, ²Department of General Psychiatry, Medical University of Vienna, ³Social psychiatric outpatient clinic Donaustadt - SPA 22, PSD Vienna

Background: Negative symptoms account for a large proportion of the socioeconomic burden associated with schizophrenia (SCZ). They are persistent, severely disrupt social relationships, and lead to poor clinical and psychosocial outcomes. Conventional treatments have only marginal effects, even when administered over many weeks. Ketamine, a non-specific NMDA receptor antagonist, has recently gained wide acceptance as a fast-acting and effective antidepressant. However, most likely due to its reported psychotogenic properties, evidence on using ketamine to treat depressive or negative symptoms in SCZ remains anecdotal (1, 2).

Here we report on the protocol and preliminary observations from an ongoing prospective, monocentric, randomized, double-blind, placebo controlled, phase III pilot study.

Methods: The trial aims at studying 20 patients with a diagnosis of schizophrenia according to DSM-5. Main inclusion criteria are a minimum score of 39 (at least moderate severity across all items) on the Brief Negative Symptom Scale (BNSS; 3) or a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS; 4), and stable pharmacological or psychosocial treatments for at least one month prior to inclusion. Main exclusion criteria are the presence of unstable arterial hypertension, cardiovascular disorders, or acute suicidal or homicidal ideations. Patients are randomized to receive either six doses of intravenous esketamine (first dose 0.25mg/kg, then 0.5mg/kg body weight) over approximately two weeks, then, after a two-week washout period, intravenous diphenhydramine (first dose 30mg, then 60mg), or vice versa. Changes in negative and depressive symptoms are measured using BNSS and MADRS. Possible changes in positive symptoms are quantified using the positive and general psychopathology items of the Positive and Negative Symptom Scale (PANSS; 5).

Results: To date, blinded clinical trial data are available for eight patients. Both interventions were well tolerated and there were no serious adverse drug reactions. Importantly, none of the patients enrolled to date have experienced psychotic exacerbation or worsening in any symptom domain.

Discussion: Statements on the efficacy of esketamine in the treatment of negative and depressive symptoms will have to await unblinding at the end of the study. However, our preliminary data suggest that esketamine is well tolerated and does not exacerbate positive symptoms in patients with SCZ.

T99. A FAMILY-CENTERED PSYCHOEDUCATIONAL PROGRAM FOR EARLY PSYCHOSIS: IMPACT FOR YOUNG PEOPLE AND THEIR FAMILIES AND FEEDBACK FROM HEALTH PROFESSIONALS

Claire Rasclé*¹, Emilie Musset², Marina Pivette³, Marie-Cécile Bralet⁴

¹University Hospital Lille, ²CSN2R HDF CHU de Lille, ³CSN2R HDF CHU de Lille, ⁴CRISALID-HDF-Pole PRERPS-Centre Hospitalier Isarien-EPSM Oise

Background: A Family-Centered Psychoeducational Program for Early Psychosis : Impact for young people and their families and feedback from caregivers.

Psychoeducational programs in early intervention should be a key tool improving outcomes, increasing understanding of psychosis. We promote an adaptable program, based on cooperative pedagogy, free choice, concerted objectives, led by a trained multidisciplinary team (including peer health mediator) as a key element of recovery. We shared the program with French early intervention health teams and Transition network.

Methods: We provided a short unifamilial program tailored for each individual need with a collaborative approach. The program targeted subjective dimensions (self esteem, empowerment, understanding, trust in future) for young people and their families with a pre-post evaluation. We present a qualitative practice analysis feedback (efficiency on commitment, wellness, hope and recovery,...) of health professionals.

Results: We showed the improvement of various subjective dimensions. Self-esteem improves for youngs and caregivers. Self-esteem profiles are changed in youngs towards higher self-esteem as well as sense of understanding of the health accident and ability to seek out more information on their own. We showed that Trust in future stay stable both in youngs and families.

We showed in health professionals the variations of a subjective feelings of the psychoeducational program.

Discussion: Psychoeducational programs based on personal needs and resources supports efficiently personal and family's recovery. They are shared freely (with training and team support). They enlighten specific tools in early intervention. It rolls with the implementation of Early Intervention care on the territory. Our aim is to sustain meaningful and hopeful cares for young people and their families in early intervention in psychosis.

T100. EVALUATION OF M4 MUSCARINIC RECEPTOR OCCUPANCY BY EMRACLIDINE USING [11C]MK-6884 PET IN HEALTHY VOLUNTEERS

Sridhar Duvvuri¹, Philip Iredale*¹, Sokhom Pin¹, Deborah Smith¹, Jianbo Zhang¹, Amy Giugliano¹, Michel Koole², Koen Van Laere², Jan de Hoon², Vasily Belov³, Nicolas Guehl³, Georges El Fakhri³, Marc Normandin³

¹Cerevel Therapeutics, ²University Hospitals Leuven, ³Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School

Background: Emraclidine, a novel highly-selective M4 muscarinic acetylcholine receptor-positive allosteric modulator, is currently in clinical development for the treatment of schizophrenia and Alzheimer's disease psychosis (Krystal et al. Lancet. 2022;400:2210-2220). Emraclidine showed favorable brain penetration and direct target engagement in preclinical rodent studies and exhibited robust in vivo antipsychotic-like activity in animal models (e.g., reversal of amphetamine-stimulated locomotion and prepulse inhibition). In recent positron emission tomography (PET) imaging studies evaluating M4 receptor occupancy (RO) as a function of emraclidine dose and plasma concentration in nonhuman primates, in vivo target engagement and overall exposure-occupancy relationship of emraclidine were confirmed using the [11C]MK-6884 radioligand (Duvvuri et al. Presented at ACNP 2021). This PET imaging trial evaluated RO of emraclidine in human volunteers.

Methods: Healthy adult volunteers were enrolled across 3 cohorts in this phase 1, open-label trial (NCT04787302) using an adaptive study design. M4 RO from each cohort informed emraclidine dose selection (single dose) in the subsequent cohort. Participants in the first cohort received the maximal dose of 30 mg, anticipated to achieve ~80-90% M4 RO based on in vitro binding affinity data. A baseline PET/magnetic resonance imaging (MRI) scan was performed up to one week before emraclidine dosing and a second PET/MRI scan was performed immediately after dosing, with intravenous administration of 10-20 mCi [¹¹C]MK-6884 and 90-minute scanning with arterial blood sampling and metabolite analysis for full tracer pharmacokinetic (PK) modeling. Blood samples were obtained 30, 60, and 90 minutes after emraclidine dosing for PK analysis during the PET scan. The primary endpoint was estimation of emraclidine RO (%) in the striatum (averaging values from caudate and putamen), with the cerebellum as a reference region. Overall M4 RO (%) was calculated as the difference from baseline in M4 nondisplaceable binding potential (BP_{nd}) after emraclidine dosing (BP_{nd} [baseline] and BP_{nd} [dose]), divided by BP_{nd} [baseline]. An exposure-response model informed by the maximum estimated RO (E_{max}), emraclidine plasma concentration (C), and the concentration at which 50% of maximum RO is achieved (EC₅₀) assessed the relationship between M4 RO and emraclidine plasma exposure (assuming a Hill coefficient [γ] of 1): $RO = (E_{max} \times C_{\gamma}) / (EC_{50}^{\gamma} + C_{\gamma})$

Results: A total of 9 participants received a single dose of emraclidine 30 mg, 15 mg, or 5 mg (n=3 for each dose). Emraclidine PK exposure parameters decreased with decreasing emraclidine dose (median [range] average plasma concentration during the scan duration: 30-mg dose, 634 [425-888] ng/mL; 15 mg dose, 347 [186-374] ng/mL; 5 mg dose, 143 [128-167] mL). Mean (SD) M4 RO in the striatum was 52.7% (1.31%), 41.8% (11.9%), and 20.1% (7.30%) after a single 30-, 15-, or 5-mg dose of emraclidine, respectively. A positive relationship was observed for M4 RO in the striatum versus emraclidine plasma concentration, with RO ranging from 14% to 54%; RO GREATER THAN 50% was observed across emraclidine plasma concentrations ranging from 350 to 900 ng/mL. The mean (SE; 95% CI) E_{max} was 80.1% (17.6%; 46.8%-113%) and the corresponding mean (SE; 95% CI) EC₅₀ was 321 (157; 23.9- 618) ng/mL.

Discussion: These data demonstrate M4 RO of ~60% across a wide range of emraclidine plasma concentrations, suggesting potential receptor saturation. Overall, these results corroborate recent emraclidine data obtained in primates using the same radiotracer and confirm the target binding of emraclidine to M4 receptors in the striatum of humans.

T101. AN OVERVIEW OF LOW ENROLLING SITES ACROSS 15 SCHIZOPHRENIA CLINICAL TRIALS

Alan Kott^{*1}, Xingmei Wang¹, Petra Reksoprodjo¹, David G Daniel¹

¹*Signant Health*

Background: Clinical trials rely on research sites to identify and recruit adequate study population and to provide valid and reliable assessments of study participants' symptom severity and its changes over the course of the trial. Low recruiting sites represent a large financial burden for the trial sponsor and may pose a risk to the trial success because of possible suboptimal study participant selection or high prevalence of data quality issues.

Methods: Data were obtained from 15 trials in early schizophrenia. Sites were categorized as low recruiting if the number of study participants randomized was five or less. Additionally, as extremely low recruiting sites we identified those site that randomized a single subject

only, and as non-contributing sites those sites that did screen at least one potential study participant but failed to randomize any. Descriptive summary statistics are provided.

Results: Data were extracted from 633 sites (342 unique sites) from 15 protocols in schizophrenia. A total of 5,963 subjects were screened and 3,888 subjects randomized with a randomization rate of 65%. Of the 633 sites in the database, 79 (12.5%) sites did not randomize any study participants, 93 (14.7%) sites randomized a single study participant. A total of 390 (61.6%) sites did randomize no more than 5 subjects. Taking the Pareto principle, 288 (45.5%) sites randomized 80% of all the study participants, the remaining 345(54.5%) sites randomized the remaining 20% of the study participants.

Discussion: Our retrospective analysis identified that there is a substantial proportion of participating sites that contribute very little if at all to the study. These sites represent a potential risk to the trial as data quality concerns and suboptimal subject selection are typically seen during the initial weeks and months of each site participation and decrease over time with feedback and remediation provided. Additionally, these sites represent considerable financial burden to the study sponsor related to site initiation and study personnel training. Additional analyses are planned to quantify the contribution of these low recruiting sites to data concerns.

T102. EMPOWERING THE NEXT GENERATION: A PHASE 2 PROGRAM TO EVALUATE EMRACLIDINE, A SELECTIVE M4 POSITIVE ALLOSTERIC MODULATOR (PAM), FOR THE TREATMENT OF SCHIZOPHRENIA

George Konis¹, Erica Koenig*², Koji Takahashi², Philip Iredale², Meera Tugnait², Javier Waksman², Ih Chang², Shauna Blackmon², Matthew Leoni², Raymond Sanchez²

¹Woodland International Research Group, ²Cerevel Therapeutics, LLC

Background: Emraclidine is a novel, highly selective positive allosteric modulator of M4 muscarinic acetylcholine receptors currently in development for the treatment of schizophrenia and Alzheimer's disease psychosis. By selectively activating M4, emraclidine may reduce excess dopamine signaling in the striatum, potentially leading to a reduction in psychotic symptoms. The phase 2 EMPOWER program will fully evaluate the efficacy, safety, tolerability, and dose range of once-daily (QD) emraclidine in patients with schizophrenia.

Methods: EMPOWER-1 and EMPOWER-2 are two adequately powered, multicenter, randomized, double-blind, placebo-controlled, parallel group, 6-week inpatient studies of emraclidine monotherapy at fixed doses (EMPOWER-1, 10 mg QD and 30 mg QD; EMPOWER-2, 15 mg QD and 30 mg QD). The trials are enrolling adult participants with schizophrenia who are experiencing an acute exacerbation of psychosis with a Positive and Negative Syndrome Scale (PANSS) Total Score between ≥ 85 and ≤ 120 and a Clinical Global Impression – Severity (CGI-S) score ≥ 4 at baseline. De novo participants and those who complete EMPOWER-1 or EMPOWER-2 are eligible to participate in EMPOWER-3, a 52-week open label extension trial evaluating the long-term safety and tolerability of emraclidine in adults with stable schizophrenia.

Results: Detailed study designs for the EMPOWER program will be presented. The primary outcome measure for EMPOWER 1 and 2 is change from baseline in PANSS total score at Week 6. Other outcome measures include change from baseline in CGI-S score at Week 6. Data from EMPOWER-3 will contribute to the overall safety and tolerability evaluation of emraclidine in adults with schizophrenia.

Discussion: The EMPOWER program aims to establish the efficacy, safety, tolerability, and appropriate dose-range of emraclidine in the treatment of schizophrenia.

T103. CLASSIC TRIAL DESIGN AND DIGITAL HEALTH IN SCHIZOPHRENIA: SOUND METHOD OR BLIND ALLEY?

Sean Kidd¹, Jessica D'Arcey^{*2}, Leah Tackaberry-Giddens³, Toni-Rose Asuncion³

¹University of Toronto, ²University of Toronto Scarborough, Centre for Addiction and Mental Health, ³Centre for Addiction and Mental Health

Background: The rationale regarding the need for validated digital health tools in schizophrenia service delivery has been made clear by patients and care providers. However, the development of effective and accessible digital health tools for schizophrenia populations has been a fraught path to date. For those seeking to use rigorous research approaches to develop and validate digital tools, there have been significant challenges in applying gold-standard trial methods derived from pharmacological and behavioral intervention science. These challenges, paired with the even more daunting commercialization and implementation hurdles, have made for slow progress, leaving patients and providers frustrated. This presentation considers digital health research for schizophrenia populations and reviews trends in a literature characterized by one-off pilots and failed trials, connecting trend-level patterns to the findings of two recent randomized controlled trials (RCTs) of digital interventions.

Methods: The presentation highlights gaps and future directions from a recent systematic review of research examining digital health intervention trials in schizophrenia and observations from RCTs of a text-based intervention in an early psychosis clinic (n=70) and a mobile health intervention for broader schizophrenia populations (n= 91). Both trials were conducted in a large urban tertiary care setting and leveraged several data sources, including interviews and self-reports, clinician-reported data, technology engagement metrics, and electronic medical records.

Results: The literature review raises questions about the fit between traditional trial designs and most digital health intervention approaches. The text-based trial found that individuals in the active group displayed improved attitudes toward medication but decreased attendance rates compared to the control group, with significant differences in secondary subscale findings (e.g., social functioning and aspects of therapeutic rapport). While affected by the pandemic, the mobile health intervention trial evidenced no difference between the treatment as usual control and the intervention arm across symptom, treatment adherence and quality of life metrics.

Discussion: Schizophrenia populations continue to face significant barriers with respect to accessing evidence-based care. Yet, the promise of digital health remains untapped despite advances in core technologies and improved access to such technologies by people with schizophrenia. The two trials presented here, and lessons learned from the existing literature, suggest the need for a different approach than the traditional research pipeline of pilot to RCT to implementation trials. Such approaches include the need for iterative and dynamic co-design embedding industry partners in the process, reflexive integrated clinical trials in open and randomized formats, an emphasis on implementation science frameworks, and centring technological and contextual feasibility based on best practices.

T104. EFFECTS OF LAMOTRIGINE, THE PDE9 INHIBITOR BI 409306, AND GLYT1 INHIBITOR BI 425809 ON ATTENUATION OF KETAMINE-INDUCED MEMORY IMPAIRMENT: AN EXPLORATORY STUDY IN HEALTHY SUBJECTS

Christian Schultheis*¹, Holger Rosenbrock², David Walling³, Larry Ereshefsky⁴, Howard Hassman⁵, Anja Hoch², Janos Zambori⁶, Yury Shatillo¹

¹Boehringer Ingelheim Pharma GmbH and Co. KG, ²Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach an der Riss, ³CenExel - CNS, ⁴Follow the Molecule: CNS Consulting and CenExel Research, ⁵CenExel - HRI, ⁶Boehringer Ingelheim International GmbH

Background: There are currently no pharmacotherapies available for the treatment of cognitive impairment associated with schizophrenia (CIAS). Lean and fast studies for early testing of clinical effects are desirable for the development of novel treatments. One promising approach is the attenuation of ketamine-induced cognitive deficits in healthy subjects, which resemble, at least partly, impairments observed in patients. To validate this clinical model, several pharmacological treatments have been evaluated for attenuation of ketamine-induced cognitive deficits.

Methods: A randomized, placebo-controlled, double-blind, double-dummy, 3-way crossover Phase I study was conducted at 2 sites in the US. Healthy males (aged 18–55) were randomized to 1 of 18 treatment sequences, comprising 3 single doses of placebo, and 2 of 3 active treatments (lamotrigine 300 mg, BI 409306 50 mg (a phosphodiesterase 9 [PDE9] inhibitor), and BI 425809 25 mg (a glycine transporter 1 [GlyT1] inhibitor). At the anticipated time of maximum exposure for each treatment, subjects received an intravenous ketamine infusion (bolus of 0.26 mg/kg over 1 min, followed by continuous infusion of 0.0073 mg/kg/min over 89 minutes [reduced by 10% every 15 min]). Cognitive testing was performed before and during ketamine infusion using the following tasks from the Cantab Battery (Cambridge Cognition, Cambridge, UK): Paired Associates Learning (PAL; total errors adjusted 28) for episodic memory, Spatial Working Memory (SWM; between errors 468) for working memory, and Rapid Visual Information Processing (RVP; RVPA') for attention. Treatment effects relative to placebo were analyzed using a linear mixed-effects model. The study was designed to detect a numerical effect size of treatments; 0.35 would be considered clinically meaningful.

Results: Of 40 randomized subjects, 35 completed the trial. Across treatment sequences, n=33 treatments for placebo, n=21 for BI 425809, n=21 for BI 409306 and n=24 for lamotrigine were used for analysis. Ketamine elicited consistent worsening of cognitive performance assessed with all 3 tasks in placebo-treated subjects: PAL (+10.3 errors, standard deviation (SD) 14.8), SWM (+5.9 errors, SD 9.2) and RVP (-0.047, SD 0.052). Treatment with either lamotrigine, BI 425809, or BI 409306 elicited limited placebo-corrected effects with standardized effect sizes (SES) LESS THAN 0.35 (except for lamotrigine and RVP): Lamotrigine: PAL (-1.9; 95% confidence interval [CI]: -11.0, 7.2; SES -0.11), SWM (-2.1; -6.5, 2.4; SES -0.23), RVP (0.031; 0.01, 0.05; SES 0.62); BI 409306: PAL (4.3; 5.2, 13.8; SES +0.26), SWM (-0.3; 5.0, 4.4; SES -0.03), RVP (0.006; -0.01, 0.02; SES 0.11); BI 425809: PAL (-0.4; -10.0, 9.1; SES -0.03), SWM (0.9; -3.7, 5.5; SES 0.10), RVP (-0.002; -0.02, 0.02; SES -0.03). All adverse events (AEs) were mild to moderate, with no serious AEs reported. One AE on placebo led to discontinuation. The most frequent AEs were nausea, somnolence, and vomiting. Most AEs occurred after ketamine infusion.

Discussion: In line with published data, ketamine led to consistent worsening of cognitive performance. Treatment with lamotrigine, BI 425809, or BI 409306 elicited limited effects on cognition and did not demonstrate a relevant attenuation of episodic or working memory

impairment. Potential reasons for the low treatment effects may relate to study design (e.g., ketamine dose, drug dose, cognition tasks used), be specific for the tested treatments (targeting NMDAR signaling) or indicate that ketamine-induced cognitive deficits are not a suitable human model for early clinical testing of investigational drugs.

Funding: Boehringer Ingelheim International GmbH (NCT04602221).

T105. THE NORTH QUEENSLAND DIETARY INTERVENTION TRIAL (NQDIT) IN PSYCHOSIS: A RANDOMISED, PLACEBO CONTROLLED CLINICAL TRIAL OF KETOGENIC DIET IN COMMUNITY PATIENTS WITH BIPOLAR DISORDER AND SCHIZOPHRENIA

Calogero Longhitano*¹, Sabine Finlay², Omer Sherif³, Shaileigh Gordon³, Jaymee-Leigh Swift⁴, Flavia Fayet-Moore⁵, Isabella Peachey², Brett McDermott⁶, Christopher Palmer⁷, Shebani Sethi⁸, Zoltan Sarnyai²

¹James Cook University, ²James Cook University, ³Townsville University Hospital, ⁴Mater Hospital and Aurora Health Care, ⁵FoodIQ, University of Newcastle, ⁶University of Tasmania, ⁷Harvard Medical School, ⁸Stanford University,

Background: Bipolar Affective Disorder and Schizophrenia are severe and enduring psychotic disorders presenting with high comorbidity of metabolic disorders, leading to a reduced life expectancy of up to 25 years. Nutritional ketosis has been successfully used to treat a range of neurological disorders to include treatment resistant epilepsy and migraines. Preclinical data has convincingly shown potential for its use in animal models of psychotic disorders and recent clinical data in uncontrolled clinical trials and case series has pointed towards a significant reduction in psychotic, affective and metabolic symptoms in both schizophrenia and bipolar affective disorder. The intervention was well tolerated and feasible in this patient population. However, no randomised controlled clinical trials exist.

Methods: We propose a 14-week controlled dietary intervention in a north Queensland outpatient chronic psychotic population with co-morbid metabolic disorders. We aim to investigate the efficacy of a Well Formulated Ketogenic Diet (WFKD) in adult non-hospitalised participants with either bipolar disorder or schizophrenia. Participants will be randomly assigned to one of two groups: the experimental (KD) and the control (Australian Guide to Healthy Eating - AGHE) diet. Face-to-face clinical assessments by psychiatrists and dietitians will be obtained at week 0, week 8, and week 14. Up to 100 participants will be recruited and randomly allocated to one of the dietary groups if they meet diagnostic and safety criteria, and consent to the dietary changes. The participants will be blind to the study hypothesis and interact with clinicians who are, in as far as possible, blind their group allocation. Participants in both groups will be treated identically in all respects except for the intervention being tested. Participants will receive baseline psychiatric, cognitive and dietary assessments and asked to adhere to their allocated diet for a period of 12 weeks following an introductory 2 week period. They will receive detailed dietary instructions and material to foster independent meal preparation. Progress will be supported using a parallel group design that includes weekly group supervision and daily individualised monitoring obtained with a mixture of face to face and telematic means. Dietary education consisting in specialised information about the dietary requirements of their allocated group and existing evidence base for nutrition in mental health will be provided. Participants will be treated identically in

all respects except for the intervention being tested. Pre-existing psychiatric and metabolic treatment will continue as per treating team's advice. Metabolic medication might be adjusted for those in the KD group in collaboration with their physician in order to minimise the risk of hypoglycaemia. Capillary blood ketones and glucose levels will be measured daily and strictly monitored.

Results: Participants will be assessed for a range of psychiatric and metabolic outcome measures, to include the Positive and Negative Syndrome Scale: PANSS, the Affect Liability Scale: ALS-18, the Young Mania Rating Scale: YMRS, the WHO Disability Assessment Schedule-2: WHODAS-2, the Cambridge Cognitive Battery: CANTAB, the Beck Depression Inventory: BDI. Additionally, metabolic measures will be taken to include liver and renal function, lipid profile, insulin resistance and cardiovascular health indicators. Biometric testing will be taken via wearable devices (OURA ring and EMBRACE wristband) in the form of skin conductance, oximetry, continuous monitoring of pulse, respiratory rate, movement tracking and sleep quality. A small hair and a stool sample will be taken at baseline and endpoint, to measure for changes in stress hormones and gut microbiota. Any adverse effects will be strictly monitored and reported. Adherence to the dietary regime and feasibility of both diets in a chronic psychotic population will be recorded and measured.

Discussion: Brain energy deficits are increasingly considered central in the pathophysiology of psychotic disorders. Putative mechanisms put forward include altered kinase, ion channels, oxidative phosphorylation processes and insulin receptor like dysfunctions in neuronal mitochondria and membranes, ultimately resulting in ineffective glycolytic pathways. Epigenetic modulation may play a role in the translation of developmental trauma and lifestyle factors in susceptible populations. The KD fundamentally bypasses cellular glycolysis to promote energy production via ketone cycles, Krebs and TCA, thus restoring neural function. Based on the encouraging results from established preclinical research and clinical data from other neurodevelopment disorders as well as from soon to be published open trials in bipolar and schizophrenia, we predict that the intervention will be well tolerated and result in significantly improved metabolic and psychiatric outcome measures as well as global measures of social and community functioning. We predict that a significant correlation will exist between the level of ketosis achieved and the metabolic, cognitive and psychiatric outcomes measured in the treatment group.

T106. EFFICACY AND SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMISED CONTROLLED TRIAL PROGRAMME

Corey Reuteman-Fowler^{*1}, Zuzana Blahova², Satoru Ikezawa³, Stephen R. Marder⁴, Peter Falkai⁵, John H. Krystal⁶

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Boehringer Ingelheim RCV GmbH and Co. KG, ³International University of Health and Welfare, Mita Hospital, ⁴Semel Institute for Neuroscience at UCLA, David Geffen School of Medicine, ⁵Ludwig Maximilians University Munich, ⁶Yale University School of Medicine

Background: Cognitive impairment associated with schizophrenia (CIAS) is a core feature of the disease and a major determinant of poor functional outcomes. Currently, there are no approved pharmacotherapies for the treatment of CIAS. Deficits in glutamatergic signalling play a key role in the neuropathology of schizophrenia, particularly in cognitive symptoms. Iclepertin (BI 425809), a novel inhibitor of glycine transporter-1, enhances N-methyl-D-

aspartate receptor signalling in the brain by increasing synaptic levels of its co-agonist glycine. A 12-week, Phase II, proof-of-clinical-concept trial (NCT02832037) that included 509 patients demonstrated that iclepertin was well tolerated and significantly improved cognition in patients with schizophrenia. The Phase III CONNEX programme aims to confirm the efficacy, safety and tolerability of iclepertin in improving CIAS and functioning using a larger cohort of patients with schizophrenia.

Methods: CONNEX consists of three replicate randomised, double-blind, placebo-controlled parallel-group trials in patients with schizophrenia (NCT04846868, NCT04846881, NCT04860830) currently stable on antipsychotic treatment. Each trial aims to recruit ~586 patients, 18–50 years old, treated with 1–2 antipsychotic medications (≥ 12 weeks on current drug; ≥ 35 days on current dose prior to treatment), who have functional impairment in day-to-day activities and interact ≥ 1 hr per week with a designated study partner. Patients with cognitive impairment due to developmental, neurological or other disorders, or receiving cognitive remediation therapy within 12 weeks prior to screening, will be excluded. Participants will be recruited from 41 countries in Asia, Australia, New Zealand, North and South America and Europe, and randomised 1:1 to receive either oral iclepertin 10 mg (n=293) or placebo (n=293) once-daily over 26 weeks. The primary efficacy endpoint is change from baseline in the MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score. Key secondary efficacy endpoints are change from baseline in Schizophrenia Cognition Rating Scale total score and change from baseline in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool. Long-term safety and tolerability data will be collected in an open-label safety extension study (CONNEX-X).

Results: The studies are currently recruiting (first participants were enrolled Aug–Sept 2021), with completion expected in Quarter 1 of 2025. Here we present an overview of the current study status, including any information relating to screening failures and the experience of collecting these data as part of a large multicountry, multicentre study.

Discussion: To date, most large, industry-sponsored studies testing various compounds to address cognitive function have failed to show proof-of-clinical concept. Demonstration of efficacy of iclepertin in improving cognition in this Phase III programme would provide important insight into the role of glutamate in cognitive symptoms, that may also have relevance for other cognitive disorders. Iclepertin may represent the first efficacious medication for cognitive impairment associated with schizophrenia.

This study is funded by Boehringer Ingelheim (NCT04846868, 1346-0011; NCT04846881, 1346-0012; NCT04860830, 1346-0013).

T107. THE EFFICACY OF LUMATEPERONE 42 MG IN THE TREATMENT OF SCHIZOPHRENIA SYMPTOMS ASSOCIATED WITH SOCIAL FUNCTIONING: POST HOC ANALYSIS OF AN ACUTE PLACEBO- AND ACTIVE-CONTROLLED TRIAL

Philip Harvey¹, Suresh Durgam², Jason Huo², Hassan Lakkis², Tobie Escher², Kimberly E Vanover², Robert E Davis², John Edwards^{*3}

¹Miller School of Medicine, University of Miami, ²Intra-Cellular Therapies, Inc, ³Intra-Cellular Therapies, Inc.

Background: Deficits in social functioning are a core feature of schizophrenia and may be due to the interaction of multiple factors including negative symptoms, mood states, and

deficits in social cognition. Social and functional impairment in schizophrenia can be difficult to treat, commonly does not correlate with improvements in psychotic symptoms, and has been associated with poor long-term patient outcomes. Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. Lumateperone is mechanistically novel, simultaneously modulating serotonin, dopamine, and glutamate neurotransmission. In a Phase 2, randomized, double-blind, placebo- and active-controlled trial (Study 005, NCT01499563), lumateperone 42 mg significantly improved schizophrenia symptoms compared with placebo and had a favorable safety profile in adults with an acute exacerbation of schizophrenia. This post hoc analysis of Study 005 evaluated the effects of lumateperone 42 mg on schizophrenia symptoms associated with social function by the Positive and Negative Syndrome Scale (PANSS)-derived Prosocial factor (PANSS items P3, P6, N2, N4, N7, G16), which has been utilized previously to evaluate the efficacy of various antipsychotics on this functional domain.

Methods: Eligible adults (18-55 years, inclusive) with an acute exacerbation of schizophrenia were randomized to 28-day inpatient treatment with lumateperone 42 mg, placebo, or risperidone 4 mg. Change from baseline in the PANSS Prosocial factor was assessed in the intent-to-treat (ITT) population and in patients with prominent negative symptoms (PNS, score ≥ 4 on ≥ 3 negative symptom items) or moderate-to-severe depression symptoms (Calgary Depression Scale for Schizophrenia [CDSS] ≥ 6) at baseline. Inferential analysis was conducted using a mixed-effects model for repeated measures.

Results: The ITT population comprised 231 patients (placebo, $n=80$; lumateperone 42 mg, $n=76$; risperidone 4 mg, $n=75$); the PNS and CDSS ≥ 6 populations comprised 110 and 54 patients, respectively. Lumateperone 42-mg treatment was associated with significantly greater improvement compared with placebo on the PANSS Prosocial factor at Day 28 (least squares mean difference vs placebo [LSMD], -2.7 ; $P < .001$). Risperidone also was superior to placebo on the PANSS Prosocial factor (LSMD, -1.8 ; $P < .05$). Similar treatment effects for lumateperone 42 mg were seen on the PANSS Prosocial factor in patients with PNS at baseline (LSMD, -2.6 ; $P < .01$). Conversely, in patients with PNS, risperidone treatment showed small and non-significant treatment effects on the PANSS Prosocial factor (LSMD, -0.4 ; $P=.707$). In patients with moderate-to-severe depression symptoms at baseline, marked and significant improvements on the PANSS Prosocial factor were seen in lumateperone-treated patients (LSMD, -4.9 ; $P < .001$) but not in risperidone-treated patients (LSMD, -1.3 ; $P=.397$).

Discussion: Lumateperone 42 mg significantly improved socially-relevant schizophrenia symptoms in patients with an acute exacerbation of schizophrenia. In contrast to risperidone, lumateperone was associated with similar or greater treatment effects on the PANSS Prosocial factor in patients with PNS or moderate-to-severe depression symptoms at baseline. These results suggest that lumateperone has benefits on schizophrenia symptoms associated with social function with multiple potential means of influence.

T108. DESIGN OF A POTENTIALLY PIVOTAL, PHASE 3, INTERNATIONAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL EVALUATING EVENAMIDE AS ADD-ON TREATMENT FOR TREATMENT-RESISTANT SCHIZOPHRENIA (TRS) PATIENTS

Ravi Anand^{*1}, Alessio Turolla², Giovanni Chinellato³, Francesca Sansi², Rodolfo Giuliani², Richard Hartman⁴

¹Anand Pharma Consulting, ²Newron Pharmaceuticals SpA, ³Newron pharmaceuticals, ⁴NeurWrite LLC

Background: Treatment resistant schizophrenia is associated with higher hospitalization rates, comorbidity, suicidality, and mortality (Solanki et al., 2009; Pompili et al., 2017). Most patients with TRS are maintained on antipsychotic (AP) polypharmacy, despite evidence that this strategy is not effective but increases side effects (Pandarakalam et al., 2019). Increasing evidence suggests that glutamatergic abnormalities, rather than excessive dopamine synthesis, are noted in these patients; such findings are confirmed by neuroimaging studies in TRS patients (Demjaha et al., 2014). This may explain the failure of 5HT₂/D₂ antipsychotics to produce a beneficial response in TRS patients and suggest that glutamate modulation may constitute a promising therapeutic alternative (Potkin et al., 2020).

Evenamide, an orally available NCE, is a voltage-gated sodium channel blocker devoid of biological activity at GREATER THAN 130 CNS targets. Pre-clinical studies demonstrated its efficacy in normalizing excessive glutamate release induced by aberrant sodium channel activity, without affecting basal glutamate levels. Evenamide was associated with benefit in animal models of psychosis, both as monotherapy and add-on to 5HT₂/D₂-blocking APs, suggesting synergies in mechanisms that could be beneficial for patients responding poorly to APs (Anand et al., 2018). Increasing and sustained benefit of evenamide in TRS patients has been demonstrated across all efficacy measures (PANSS, CGI-S, CGI-C and LOF) in a pilot, phase II, open-label, rater-blinded, 1-year study, in addition to a substantial proportion of patients meeting a clinically important level of response up to 1 year (Anand et al., 2023).

Methods: Study 016 is a prospective, potentially pivotal, phase 3, randomized, double-blind, placebo-controlled, 1-year international study that will evaluate the efficacy and tolerability of evenamide as add-on treatment in TRS patients. Eligible patients will be randomized equally to either two fixed doses of evenamide (15 and 30 mg bid) or placebo. The study will enrol GREATER THAN 500 patients diagnosed with TRS according to the TRIP criteria (Howes et al., 2017), requiring a history of failure on at least 2 APs (2 different chemical classes; at least one second-generation AP) given at therapeutic doses for an adequate period (GREATER THAN =6 weeks); moreover, the 6-week screening period will confirm treatment-resistance by determining plasma levels of the background AP to ensure compliance with treatment. Selection criteria include schizophrenia diagnosis (DSM-V-TR), CGI-S score 3-6; BPRS total score GREATER THAN 45, with a score GREATER THAN =18 on positive symptoms of psychosis, and PANSS total score GREATER THAN 70. Patients will be enrolled based on acceptability of their screening data by an Independent Eligibility Committee. Patients improving GREATER THAN =20% on the BPRS or GREATER THAN =1 category on the CGI-S during the 6 week screening period will be excluded. Plasma levels of the background APs and study medication will be determined at selected visits. Efficacy and safety will be evaluated at regular intervals, with the pivotal efficacy endpoint at Week 12 and long-term efficacy endpoints at Week 26 and Week 52.

Efficacy measures include: PANSS total, CGI-S, CGI-C, Q-LES-Q-SF and PSP scales, assessment of cognition and pharmacoeconomic outcomes. Safety measures include vital signs, ECG, laboratory tests, physical/neurological/eye examinations, ESRS-A, CDSS, and C-SSRS.

Results: The results of the study will demonstrate if evenamide, a selective modulator of excessive glutamate release, can benefit TRS patients receiving adjunctive APs, thus confirming the benefit seen in the 1-year pilot study.

Discussion: Positive results from this phase 3 study could change the current management of TRS patients, demonstrating the effectiveness of glutamate modulation as a new therapeutic strategy for this condition.

T109. EFFECT OF PSYCHOACTIVE DRUGS ON NATURAL LANGUAGE PROCESSING MARKERS OF SPEECH: A SYSTEMATIC REVIEW

Sachin Ahuja*¹, Farida Zaher², Lena Palaniyappan³

¹*Schulich School of Medicine and Dentistry*, ²*McGill University*, ³*Douglas Mental Health University Institute*

Background: Language disturbance is a core component of psychosis, and natural language processing (NLP) analysis of speech is promising for the clinical assessment of psychosis patients. Psychoactive drugs including psychedelics, cannabinoids, entactogens and psychostimulants can exert symptoms and speech effects similar to those of psychosis, thus are a potential complication to NLP-based assessment of patients with psychosis symptoms. This systematic review summarizes the effects of those psychoactive drugs on NLP markers, providing an important comparative reference for research and implementation of NLP in psychosis.

Methods: We systematically searched the Medline and Embase databases in June of 2023 and included studies that report natural language processing analyses of psychoactive drug-influenced speech collected in controlled settings. This included drugs from psychedelic, hallucinogen, entactogen, cannabis/cannabinoid, and psychostimulant classes.

Results: 15 studies were included, revealing that psychoactive drugs induce diverse speech alterations. Findings include that ketamine can increase repetitiveness and decrease verb density; LSD has complex effects suggesting simpler, more disconnected language; MDMA can increase cognitive process words and semantic proximity to concepts like friend and empathy; psychostimulants like methamphetamine and d-amphetamine can increase verbosity and decrease pause duration; and cannabis affects vowel production.

Discussion: Replication studies are required to confirm the effects of psychoactive drugs on NLP markers to complement ongoing research on NLP in psychosis management.

T110. LONGITUDINAL DYNAMICS OF THE TRANSDIAGNOSTIC PRODROME TO SEVERE MENTAL DISORDERS: A TEMPORAL NETWORK ANALYSIS INFORMED BY NATURAL LANGUAGE PROCESSING AND ELECTRONIC HEALTH RECORDS

Maite Arribas*¹, Joseph M Barnby², Rashmi Patel³, Robert McCutcheon⁴, Daisy Kornblum⁵, Hitesh Shetty⁵, Kamil Krakowski⁶, Daniel Stahl⁷, Nikolaos Koutsouleris⁸, Philip McGuire⁹, Paolo Fusar-poli¹⁰, Dominic Oliver⁹

¹*Kings College London*, ²*Royal Holloway University of London*, ³*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁴*Institute of Psychiatry, Psychology and Neuroscience*, ⁵*BRC Nucleus, South London and Maudsley NHS Foundation Trust*, ⁶*Department of Brain and Behavioural Sciences, University of Pavia*, ⁷*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁸*Ludwig-Maximilian-University*, ⁹*University of Oxford*, ¹⁰*King's College London and University of Pavia*

Background: Modelling the prodrome to severe mental disorders (SMD), including unipolar mood disorders (UMD), bipolar mood disorders (BMD) and psychotic disorders (PSY), should consider both the dynamics of symptoms and substance use (prodromal features), and their interactions over time. This need can be addressed by employing a network analysis, where each prodromal feature is a node and the connections (edges) between nodes indicate the predictive strength of these features over time. The centrality of nodes – their interconnectedness – could reveal insights into which symptoms most strongly predict the onset of disorders and identify potential intervention targets. We aimed to construct a global transdiagnostic SMD network, capturing the temporal relationships among 65 prodromal features. Our secondary aim was to compare diagnosis-specific sub-networks using permutation analysis.

Methods: We analysed a cohort from the South London and Maudsley NHS Foundation Trust (SLaM) Electronic Health Record (EHR) who were diagnosed with an SMD. Using validated natural language processing (NLP) algorithms, we extracted the occurrence of 65 prodromal features every three months from two years before to six months before SMD onset. To construct temporal networks of prodromal features, we employed Generalized Vector Autoregression (GVAR) panel analysis, adjusting for age, gender, ethnicity, and medication at diagnosis, and the frequency and length of EHR entries at each follow-up point. In each network, the strength of connections between features (edge weights) was estimated as correlation coefficients (z), and categorised into 3 types: autocorrelative (node predicts itself in the next time point), unidirectional (node predicts another, without reciprocation) and recursive (mutual prediction between two nodes). Centrality was calculated as the sum of edge weights leaving (out-centrality, c -out) or entering (in-centrality, c -in) a node. To assess if there were statistically significant differences in the edge weights across the three sub-networks (UMD, BMD, PSY) we conducted a permutation analysis, with p -values adjusted for multiple comparisons.

Results: The final sample consisted of 7,049 individuals (UMD:2,306, BMD:817, PSY:3,926). The global SMD network showed the strongest autocorrelation for tearfulness ($z=.10$), unidirectional positive relationships for irritability-agitation ($z_{12}=.03$) but not in the opposite direction ($z_{21}=.01$), mood instability-tearfulness ($z_{12}=.03$, $z_{21}=.01$) and irritability-aggression ($z_{12}=.03$, $z_{21}=.01$). Concerning recursive edges, positively recurring pairs were observed for aggression-hostility ($z_{12}=.04$, $z_{21}=.03$), delusions-hallucinations ($z_{12}=.04$, $z_{21}=.03$) and aggression-agitation ($z_{12}=.03$, $z_{21}=.03$). The most central features included aggression (c -out=.082) and tearfulness (c -in=.124). From the PSY network, positive psychotic symptoms were involved in the strongest unidirectional (hallucinations-disturbed sleep, $z_{12}=.04$, z_{21} LESS THAN 0.05) and recursive (delusions-hallucinations, $z_{12}=.04$, $z_{21}=.03$) edges, whilst agitation (c -out=.117) and aggression (c -in=.139) were highly central. From the permutation analysis, PSY showed few significant differences in edge weights compared to UMD (0.04%) and BMD (0.02%).

Discussion: This study represents the most extensive network analysis to date on the dynamic interplay of prodromal features in SMD. Our findings support the potential of transdiagnostic early detection services, provide potential targets for future interventions and underlines the importance of understanding dynamic symptom changes.

T111. DISORGANIZATION INDEX: MEASURING THE LOSS OF NARRATIVE COMPLEXITY DUE TO NEGATIVE SYMPTOMS

Marina Ribeiro*¹, Bárbara Malcorra², Tamara Meletti², Luísa Jensen², Natália Mota³

¹*Federal University of Rio Grande do Nortmarin*, ²*Mobile Brain*, ³*Federal University of Rio de Janeiro*

Background: In the past decade, the use of natural language processing tools has helped track language oddities under psychosis, but the use for clinical practice needs to understand and disentangle confounding factors, such as access to formal education. Word-recurrence graphs could map the increased narrative complexity during typical development, with an essential input of formal education. By mastering grammar and syntax rules from the academic use of the language, narratives change from a short-range recurrence to a long-range recurrence pattern. Still, in the course of psychosis, there is an abrupt decrease in this connected pattern (mainly a decrease in long-range recurrences). Here, we aim to verify how we can use word-recurrence graphs applied to emotional narratives to define predictive indexes considering typical development (weighted by years of education) and atypical development (weighted by severity of negative symptoms).

Methods: We interviewed a diverse sample of 232 participants: 65 with psychotic symptoms, 167 without psychosis, spanning from 2 to 60 years old, and none to more than 20 years of education. They narrated emotional stories (such as dreams or stories based on affective pictures) that were recorded and transcribed to be represented as a word-recurrence graph (each word was considered a node, and directed edges represented the sequence). We used sliding windows of 30 words to control for verbosity differences, with a 50% overlap between windows. We then calculated the number of Nodes (proxy to lexical diversity), repeated edges – RE (or short-range recurrence), nodes inside the largest strongly connected component – LSC (connectedness or long-range recurrence), average shortest path – ASP (graph size), and their similarities to a random graph distribution of graphs (by shuffling the word trajectories 100 times per window). Narrative complexity (NC) was defined as a multilinear correlation between word-recurrence graph attributes and years of formal education (proxy of typical development of language in contact with written language), and a multilinear correlation with the total of negative PANSS subscale defined Disorganization Index (DI). Then, we defined a normative curve by years of education for NC and severity in the negative PANSS subscale for DI, returning a comparative index in percentiles. We used a Naive Bayes classifier to find a cutoff of loss of narrative complexity (related to formal education) to predict the risk of psychosis, using both information from NC and DI as predictors. We also studied the association between both indexes and descriptive comparisons between groups.

Results: As predicted, there was a significant association between word-recurrence graph attributes and the severity of negative symptoms (Multilinear Regression: $R^2 = 0.34$, $p = 0.0088$). Using the percentiles of NC and DI, we found a cutoff: A narrative complexity (NC) below the 20th percentile was informative of the risk of psychosis with 75% accuracy, with more than 90% sensitivity for the group under psychosis. NC and DI also had a negative association (Spearman correlation: $Rho = -0.31$, $p \text{ LESS THAN } 0.0001$).

Discussion: As initially predicted, under psychosis, the narrative complexity drops below what was expected by years of formal education. These results point to a loss of narrative complexity associated with symptomatology (the more the impact of negative symptoms in narratives (the higher disorganization index), the lower the narrative complexity). This allows for measuring the impact of symptoms in communication patterns, which is clinically helpful for follow-up patients in psycho-social recovery.

T112. MACHINE LEARNING APPLICATIONS FOR THE IMMUNE PROFILING AND STRATIFICATION OF FIRST EPISODE PSYCHOSIS

Paolo Enrico^{*1}, Giuseppe Delvecchio², Nunzio Turtulici², Marcella Bellani³, roberto furlan⁴, Paolo Brambilla⁵

¹University of Milan, ²IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, ³Section of Psychiatry, Azienda Ospedaliera Universitaria Integrata Verona, ⁴San Raffaele Hospital, ⁵University of Milan

Background: Psychosis onset is a transdiagnostic event that leads to a range of psychiatric disorders, which are currently diagnosed through clinical observation. The integration of multimodal biological data could reveal different subtypes of psychosis onset to target for the personalization of care. In this study, we tested the existence of subgroups of patients affected by first-episode psychosis (FEP) with a possible immunopathogenic basis.

Methods: To do this, we designed a data-driven unsupervised machine learning model to cluster a sample of 127 FEP patients and 117 healthy controls (HC), based on the peripheral blood expression levels of 12 psychosis-related immune gene transcripts. To validate the model, we applied a resampling strategy based on the half-splitting of the total sample with random allocation of the cases. Further, we performed a post-hoc univariate analysis to verify the clinical, cognitive, and structural brain correlates of the subgroups identified.

Results: The model identified and validated two distinct clusters: 1) a FEP cluster characterized by the high expression of inflammatory and immune-activating genes (IL1B, CCR7, IL12A and CXCR3); 2) a cluster consisting of an equal number of FEP and HC subjects, which did not show a relative over or under expression of any immune marker (balanced subgroup). None of the subgroups was related to specific symptoms dimensions or longitudinal diagnosis of affective vs non-affective psychosis. FEP patients included in the balanced immune subgroup showed a thinning of the left supramarginal and superiorfrontal cortex (FDR-adjusted p-values LESS THAN 0.05).

Discussion: Our results demonstrated the existence of a FEP patients' subgroup identified by a multivariate pattern of immunomarkers involved in inflammatory activation. This evidence may pave the way to sample stratification in clinical studies aiming to develop diagnostic tools and therapies targeting specific immunopathogenic pathways of psychosis.

T113. MODELLING DECISION-MAKING IN A TRANSDIAGNOSTIC SAMPLE TO INVESTIGATE DISEASE SPECIFIC AND DISEASE GENERAL ALTERATIONS

Pritha Sen^{*1}, Franziska Knolle², Adam Culbreth³, Kathrin Koch², Felix Brandl⁴

¹Technische Universitat Munchen, ²Technical University of Munich, ³Maryland Psychiatric Research Center, University of Maryland School of Medicine, ⁴Department of Psychiatry and Psychotherapy, Technical University of Munich, School of Medicine

Background: Alterations in decision-making have been suggested to underlie different psychiatric illnesses, such as schizophrenia, depressive disorder (MDD), and obsessive-compulsive disorder (OCD). Studies report overlapping and divergent alterations in individuals diagnosed with those disorders and have been linked to symptoms of the respective disorders. As these disorders often co-occur, it is crucial to disentangle alterations in decision-making that are unique to specific disorders, from those that occur across diagnostic boundaries. Recent developments in computational modelling enable a

mechanistic deconstruction of decision-making processes, facilitating the identification of disease specific and disease general alterations. Therefore, to understand how decision-making alterations relate to disease specific as well as symptoms that occur across a range of psychiatric disorders (such as anhedonia, depression), we conducted a transdiagnostic study using two computational modelling approaches to a two-step Markov decision task combining individuals diagnosed with schizophrenia, OCD and MDD.

Methods: In this study, three patient groups—schizophrenia (in remission) (n=27), OCD (n=25), MDD (n=23)—and healthy controls (n=25) completed a behavioral two-step reinforcement learning task distinguishing habitual (model-free) and goal-directed (model-based) decision-making. We used two computational modelling methods hierarchical logistic regression, capturing independent contributions of choices at the subject level; and hierarchical Bayesian modelling where we employed four differently complex models exploring different parameters underlying model-free and model-based belief updating. The winning model, selected based on the lowest leave-one-out information criterion, featured six parameters, allowing investigation of learning rate, inverse temperature (decision-noise) at both stages, perseverance (repetitiveness), and model-based weight (model-based relative to model-free behavior).

Results: The results revealed an overall reliance on model-free decision-making behavior across all groups compared to healthy controls. Additionally, schizophrenia patients exhibited the lowest learning rate in stage one and the highest switching rate (lowest perseverance) compared to other groups. were more random in their response profiles than controls in stage two, with schizophrenia patients showing the highest levels of randomness, while OCD patients were additionally more random in stage one compared to controls and MDD patients. Importantly, the findings indicated a correlation between increased model-free behavior and elevated depressive symptoms, while more model-based choices were associated with lower levels of anhedonia across all patients.

Discussion: This study demonstrates significant disease-specific and general decision-making alterations in individuals with MDD, OCD, and schizophrenia, with the most pronounced deficits observed in schizophrenia. Completely random choice behavior on the two-step task may serve as a useful indicator for schizophrenia patients in remission, though further exploration is needed. Additionally, the results suggest that impaired decision-making behaviors are linked to depressive and anhedonia symptoms across all patient groups, indicating a shared behavioral mechanism as a potential starting point for behavioral interventions. Taken together, this underscores the potential of transdiagnostic studies to identify important avenues for interventions in psychiatric disorders.

T114. ONLINE X OFFLINE INTERVIEWS: FEASIBILITY OF REMOTE NLP-BASED ASSESSMENTS ON SSD

Renato Piccolo^{*1}, Matheus Carvalho¹, Diego Augusto Soares², Ana Clara Accioly³, Natália Bezerra Mota²

¹Federal University of Rio de Janeiro, Faculty of Medicine, ²Federal University of Rio de Janeiro; Research Department at Mobile Brain, ³Columbia University

Background: Psychosis is a common psychiatric syndrome shared by many mental disorders, of which Schizophrenia is the most prevalent. Its symptoms vary greatly and are characterized by but not limited to altered perception of reality, emotional disturbance, disorganized thought, impaired insight, and disruption in social functioning. The diagnosis of psychotic disorders are often difficult, resource, and time-consuming, often demanding long-

term observation of the condition's evolution, making its treatment hard especially in remote or impoverished communities. Computational psychiatry has emerged as a new tool to facilitate the diagnosis of Schizophrenia and other psychiatric conditions through word recurrence graph analysis (speech-graphs) of standardized interviews yet in development. In addition, conducting such interviews at a distance could make extending specialized psychiatric care to remote locations easier. The present study aims to investigate possible differences in the word-recurrence graph connectedness of the discourse of patients under psychosis obtained in remote (Online) and in-person (Offline) settings, which could be a significant limitation to the use of telemedicine in computational psychiatry.

Methods: We interviewed 20 patients with a diagnosis of chronic psychosis in SSD (7 females) in two conditions: offline (face-to-face interview) and online (remote interview through Google Meet), in a random order. In both conditions, the interviewer asked the participants to report affective narratives (such as dreams reports, as well as stories based on positive affective pictures), and non-affective reports (such as daily activities). All the reports were orally recorded, transcribed, and represented as word-recurrence graphs (nodes represented different words, and directed edges represented word sequence in a narrative). To control for verbosity differences, we used sliding windows of 30 words.

Results: Neither affective nor non-affective reports presented significant differences in narrative connectedness related to different conditions (online or offline interviews). Although not significant, dream reports showed a trend: higher connectedness related to lexical diversity (nodes in LCC) in offline interviews (face-to-face) compared to online conditions (Google Meet interview) (Offline LCC 23.12 ± 0.02 , Online LCC 22.28 ± 0.02 , $p = 0.0583$), different from affective image reports (Offline LCC 22.85 ± 0.02 , Online LCC 22.10 ± 0.02 , $p = 0.0835$) and daily reports (Offline LCC 24.06 ± 0.01 , Online LCC 23.42 ± 0.01 , $p = 0.4566$).

Discussion: The results point to a feasible solution that allows for a remote assessment of oral narratives. It is important to consider that the small sample size is an important limitation in this cohort, and to possible differences related to the nature of the narrative topic. However, in low-income countries, digital mental health solutions could add to the increment of mental health assessment in isolated locations, reducing the burden of not having mental health specialists to cover larger and remote areas.

T115. "ASK" VS. "INQUIRE": QUANTIFYING LEXICAL COMPLEXITY IN PSYCHOSIS USING WORD ETYMOLOGIES

Matthew Cotter^{*1}, Alessia McGowan¹, Zarina Bilgrami², Cansu Sarac³, Johanna Bayer⁴, Jessica Spark⁵, Marija Krcmar⁴, Melanie Formica⁵, Kate Gwyther⁴, Jessica A Hartmann⁵, Sophia Shuster¹, Alexandria Selloni¹, Jai Shah⁶, Shaynna Herrera¹, Patrick McGorry⁵, Alison Yung⁷, Barnaby Nelson⁵, Romina Mizrahi⁶, Guillermo Cecchi⁸, Stephen Heisig¹, Cheryl Corcoran¹, Agrima Srivastava¹

¹Icahn School of Medicine At Mount Sinai, ²Emory University, ³Long Island University, ⁴University of Melbourne, ⁵Orygen Youth Health Research Centre, ⁶McGill University, ⁷Deakin University, ⁸IBM Research

Background: Individuals with psychotic symptoms have less complex language. This deficit may be related to greater use of short, common words of Proto-Germanic origin (eg, “ask,” “old”) vs. more formal Old French/Latinate words (“inquire,” “ancient”). We hypothesized that individuals with early course psychosis (ECP) possess less lexical diversity and use

relatively more words with Proto-Germanic etymology and fewer with Old French/Latinate etymology, and that these features are related. We expected that those at clinical high risk for psychosis (CHR) would have findings intermediate between that of healthy comparisons (HC) and those with ECP.

Methods: We studied a cohort of 92 individuals with ECP, 144 CHR individuals, and 173 HC subjects, similar in demographics. The data were collected as part of an R01 that aimed to assess group differences and population variance in coherence and complexity of spoken language during open-ended interview. Interviews were transcribed and pre-processed using standard measures, including lemmatization, the conversion of different word inflections to the same basic inflection (e.g. “is”, “am” both become “be”). Only nouns, adjectives, verbs and adverbs were retained for analysis as etymology of filler words or articles such as “the” was not a focus. For etymology, we used both Etymonline and Wiktionary, ultimately focusing on Wiktionary as both its Germanic and Old French etymology were highly correlated with one another ($r = 0.99$), and because Wiktionary data was more structured in its presentation and more reliable to parse. To assess associations of speech etymology with lexical diversity, we also calculated Brunet and Honore statistics from transcripts, which are calculated using the number of unique words spoken and the total length of speech elicited. Brunet’s Index uniquely includes the number of words spoken exactly once in its calculation. Linguistic metrics of etymology were also evaluated for associations with demographics, including IQ.

Results: Our main hypotheses were supported in analyses that adjusted for age, sex, recruitment site and education. Namely, individuals with ECP used fewer words of Old French origin ($p < .01$) and more words of Germanic origin ($p < .01$), as compared with HC. Interestingly, the same pattern was found for CHR individuals as compared with HC, with fewer words of old French origin ($p < .01$) and more words of Germanic origin ($p < .01$). Further, these comparisons remained ($p < .01$) for Germanic and Old French for both ECP and CHR individuals) even when adjusting for IQ in the subset ($n = 270$) of individuals who had IQ testing available. Additionally, IQ had a positive correlation with old French word use ($r = 0.2$, $p < .02$), and a negative correlation with Germanic word use ($r = -0.3$, $p < .01$). Lexical diversity was also reduced in both ECP and CHR individuals, as compared with HC, using both Honore’s Statistic and Brunet’s Index (all p ’s $< .05$). Like IQ, lexical diversity had a positive correlation with Old French use (e.g., Honore: $r = 0.33$, $p < .01$) and a negative correlation with Germanic word use ($r = -0.35$, $p < .01$).

Discussion: Lower rates of Old French word use may indicate less use of sophisticated words and may be related to differences in intended speech formality. Also, CHR individuals were more similar to ECP than HC in terms of speech etymology content and lexical diversity. Speech etymology may be a trait marker of psychosis risk, and this may indicate that lexical features have utility for predicting risk for symptom worsening. For future directions, we hope to examine the specificity of this finding to schizophrenia and how speech etymology content may vary in different speaking contexts.

T116. COGNITIVE MODELLING OF THE INTRA-EXTRA DIMENSIONAL SET SHIFT TASK IN CHILDREN AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

Arndis Simonsen*¹, Oskar Hougaard Jefsen², Nicoline Hemager³, Ditte Lou Gantriis⁴, Birgitte Klee Burton⁵, Ditte Ellersgaard⁶, Kerstin J. Plessen⁷, Anne A.E. Thorup⁸, Jens Richardt Møllegaard Jepsen⁹, Merete Nordentoft¹⁰, Ole Mors¹¹, Aja Neergaard Greve¹², Riccardo Fusaroli¹³

¹Psychosis Research Unit, Aarhus University Hospital, ²Psychosis Research Unit, Aarhus University Hospital, Central Denmark Region, ³Research Unit at Mental Health Center and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ⁴The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Psychosis Research Unit, Aarhus University Hospital, ⁵Child and Adolescent Mental Health Centre, Copenhagen University Hospital, ⁶Copenhagen Research Centre for Mental Health (CORE), Mental Health Centre Copenhagen, Copenhagen University Hospital, ⁷Research Unit at Child and Adolescent Mental Health Center and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ⁸Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre and The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, ⁹Copenhagen Research Center for Mental Health – CORE; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); Child and Adolescent Mental Health Center, University of Copenhagen; Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) and Center for Neuropsychiatric Schizophrenia Research (CNSR), ¹⁰Mental Health Services - Capital Region of Denmark, Mental Health Centre Copenhagen, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, University of Copenhagen - Faculty of Health and Medical Sciences, ¹¹The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); Psychosis Research Unit, Aarhus University Hospital, ¹²Psychosis Research Unit, Aarhus University Hospital Psychiatry, ¹³Department of Linguistics, Semiotics and Cognitive Science, The Interacting Minds Center - Institute of Culture and Society,

Background: Deficits in executive functions have been suggested as intermediate phenotypes of schizophrenia and bipolar disorder. The Intra-Extra-Dimensional Set Shift task (IED) is widely used to measure executive functioning, in particular cognitive flexibility. However, traditional performance measures of the IED conflate general learning and attention shifting. Explicit cognitive modelling formalizing different cognitive processes at stake can help disentangle potential impairments. This is crucial to get a better understanding of the cognitive underpinnings of these mental disorders.

Methods: In this study, we investigated cognitive flexibility in children of parents with schizophrenia or bipolar disorder. We relied on data from the Danish High-Risk and Resilience Study VIA7, a multisite population-based cohort of 7-year-old children extracted from the Danish registries. Participants included 186 children at familial high risk of schizophrenia (FHR-SZ), 114 children at familial high risk of bipolar disorder (FHR-BP) and 196 population-based controls. Learning and attention shifting were assessed with the IED. We implemented Bayesian multilevel versions of two sequential learning models in Stan based on Talwar et al. (2021) and Yearsley et al. (2021), with partial pooling only within group. The first model considers each feature separately and includes a simple learning rate applied to each of them. The second model includes separate learning rates for positive and negative feedback, as well as a measure of attention shift between dimensions as a function of feedback. Model comparison relied on estimated Leave-One-Out out-of-sample predictive error.

Results: The model including learning rate from positive and negative feedback, and extra-dimensional attention shift was reliably the best model across all three groups. Extra-dimensional attention shift was generally low (circa 0.01) and not reliably different across groups (ERs LESS THAN 3 and GREATER THAN 0.3). Children generally learned more from negative (circa 0.4) than from positive feedback (circa 0.03). FHR-BP children presented reliably higher learning rates than the two other groups, albeit the effect was more reliable for learning from positive (0.02, se = 0.01, credibility: 0.91, ER= 10) than negative feedback (0.02, se = 0.03, credibility: 0.75, ER= 3). FHR-SZ children were not reliably distinguishable from population-based controls (ERs LESS THAN 3 and GREATER THAN 0.3).

Discussion: The results suggest that impairments in attention shifting, as measured with IED, are not identifiable at an early age in children at FHR-SZ or FHR-BP. However, the identified alterations in learning in children at FHR-BP, in particular positive feedback learning, may be related to symptoms such as impulsivity. The next step will be to identify whether the model-based parameters are related to relevant symptoms.

T117. REWARD-ORIENTED BEHAVIOR AND AMOTIVATION IN PATIENTS WITH EARLY PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

Vivian Shi Cheng Fung¹, Joseph Ching Yui Chan¹, Sandra Chi Yiu Wong¹, Corine Sau Man Wong¹, Wing Chung Chang^{*2}

¹The University of Hong Kong, ²University of Hong Kong

Background: Negative symptoms refer to deficits in motivation, experience of pleasure and/or emotional expression. It is a key target in early intervention among psychosis patients but remains to be an unmet therapeutic need. Experience sampling methodology (ESM) provides an opportunity to investigate momentary symptoms over time and their associated contextual factors. Although it has been shown to be a promising approach in measuring negative symptoms, including diminished motivation, it has rarely been applied to patients in early psychosis. The present study aimed to examine early psychosis patient's everyday experience of motivation and reward-oriented behaviors by comparing to that among healthy controls.

Methods: The ESM assessment lasted for 6 consecutive days, with 10 signals emitted each day. At each signal, participants were asked to complete a brief questionnaire that assessed momentary affect, current activity and social engagement, and their respective appraisals on pleasantness. Passive leisure activities such as watching TV, reading, browsing social media, and doing nothing or resting were considered as passive activities. All items were examined using multiple-choice questions and 7-point Likert scales. Prior to the start of the ESM assessment procedure, a short training session was held to explain the study procedures and to complete a practice survey. A total of 75 participants were recruited and provided ESM data. All patients were clinically stabilized and within 3 years of treatment in early intervention services for first-episode psychosis. Seven patients were excluded due to a low response rate (i.e., fewer than 20 valid responses). The final sample consisted of 33 early psychosis patients and 35 demographically matched healthy controls.

Results: Between-group comparison on the time spent in passive activities revealed a significantly increased engagement in passive activities among patients ($t=-5.09$, p LESS THAN 0.001). Reward-oriented behaviour was operationalized as the interaction between enjoyment and engagement for current activity at previous signal (i.e., $t-1$) was predictive of engagement in current activity at the present (i.e., t). Our results showed that engagement x

enjoyment at t-1 interaction was significant ($\beta=1.01$, $p < 0.001$) but no group differences were found in reward-oriented behaviour ($\beta=1.00$, $p=0.235$). The interaction effects remained unchanged after adjusting for educational attainment and employment status.

Discussion: We found that patients engaged in more passive activities compared to their matching controls. Our results suggest apparently intact activity-related reward-oriented behavior in early psychosis. Further research is required to verify our preliminary findings. Future investigation clarifying whether there is impairment in reward-oriented behavior in social contexts among patients with early psychosis.

T118. AN EXAMINATION OF RISK AND RESILIENCE FACTORS INFLUENCING PARANOIA ENDORSEMENTS ACROSS BLACK AND WHITE AMERICANS

J Wolny^{*1}, Jake Isenman², Alexandra Moussa-Tooks², Allen Bailey³, Angus MacDonald, III⁴, Joshua Mervis⁵, William P. Hetrick²

¹Indiana University, ²Indiana University-, ³Harvard Medical School/McLean Hospital, ⁴University of Minnesota, Department of Psychology, ⁵Temple University

Background: Paranoia has been demonstrated to be consistently elevated amongst Black Americans (e.g., Combs et al., 2002; Wolny et al., under review) with researchers positing that such elevations may reflect culturally compelled (i.e., adaptive) responses to systematic racial oppression and marginalization (Grier and Combs, 1980; Mosley et al., 2017). Researchers propose that such elevations may signify adaptive responses to systemic racial oppression and marginalization (Grier and Combs, 1980; Mosley et al., 2017). Despite this, there exists a notable dearth of quantitative research delving into the mechanisms underpinning these elevations, particularly within contemporary dimensional paranoia measures. The present investigation aims to address this gap by (i) exploring whether racial discrimination serves as a key explanatory factor driving the substantial increases in self-reported paranoia among Black Americans compared to their White counterparts, and (ii) investigating whether racial identification—a recognized protective factor among minority groups—may mitigate the potential relationship between racial discrimination and paranoia specifically among Black Americans.

Methods: A total of 921 individuals, self-identifying as either ‘Black/African American’ or ‘White,’ were recruited through Amazon’s Mechanical Turk (MTurk) using demographic filtering. The final analytical sample comprises 400 non-Hispanic White and 396 non-Hispanic Black participants who completed the R-GPTS, provided complete demographic data, and passed rigorous quality control checks. Research has shown that participants recruited through the MTurk platform are more demographically diverse and closely representative of the true American population compared to undergraduate samples (Buhrmester et al., 2011).

Results: Data analysis is currently underway, with the hypothesis that self-reported experiences of discrimination will partially mediate the relationship between race and self-reported paranoia. This supports the idea that experiences of discrimination act as a pivotal explanatory factor for the observed elevated levels of self-reported paranoia among Black Americans. Additionally, it is anticipated that racial identification will moderate the relationship between discrimination and paranoia among Black, but not White Americans, suggesting that high racial identification serves as a protective factor for Black Americans specifically.

Discussion: This research is poised to offer a more comprehensive and socioculturally informed exploration of paranoia across and within Black and White Americans. Such work is imperative for advancing equity in the conceptualization and measurement of the psychosis spectrum in ethnoracially diverse individuals.

T119. THE RELATIONSHIP BETWEEN SEXUAL DYSFUNCTION, SYMPTOMS, AND PSYCHOTROPIC SIDE EFFECTS AMONG INDIVIDUALS WITH SCHIZOPHRENIA

Pernille Kølbæk^{*1}, Ida Borg Hansen¹, Jonas Amstrup Riess¹, Marie Gamborg¹, Charlotte Hauge¹, David Dines¹, Yoon Fredriksen¹, Søren Dinesen Østergaard¹

¹*Psychosis Research Unit, Aarhus University Hospital - Psychiatry*

Background: Adverse sexual effects such as decreased libido, orgasmic dysfunction, and sexual arousal difficulties often accompany schizophrenia and are associated with reduced quality of life, which may contribute to reduced treatment adherence. Sexual dysfunction in this context may stem from the mental disorder itself (e.g., delusions with sexual content) and the use of psychotropic medications (e.g., prolactin-raising antipsychotics). Unfortunately, clinicians often under-recognize sexual dysfunction, and its investigation in clinical trials remains limited. The study aims to examine the relationships between sexual dysfunction and (i) positive and negative symptoms and (ii) side effects of psychotropic medications among individuals with schizophrenia.

Methods: A total of 80 participants will be recruited from the psychiatric outpatient clinics and bed units in the Central Denmark Region. Participants will be at least 18 years old, meet the ICD-10 diagnostic criteria for schizophrenia (F20.x), understand written and spoken Danish, and provide written informed consent. Patients will be ineligible to participate if they are subjected to coercive treatment measures, have an organic mental disorder or mental retardation or are under the influence of any substances of abuse. Participants will complete the Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction Measure, the 5-item World Health Organization Well-being Index, the Aarhus Side effect Assessment Questionnaire, and the Trauma History Questionnaire. Subsequently, a trained clinician will interview and rate participants on the 6-item Positive And Negative Syndrome Scale and the Udvalg for Kliniske Undersøgelser psychotropic side effect scale. Finally, the temporal relationships between reported adverse sexual effects, symptoms, and psychotropic side effects will be evaluated through a semi-structured interview.

Results: The study is ongoing, with results expected in January 2024 and presentation at the SIRS 2024 conference.

Discussion: This study holds promise for advancing our understanding of the complex relationship between sexual dysfunction, symptoms, and psychotropic side effects in individuals with schizophrenia. The findings may provide insights for developing more comprehensive treatment approaches and enhancing overall quality of life.

T120. INVESTIGATING THE OVERLAP: AN OBSERVATIONAL STUDY ON AUTISM SPECTRUM DISORDER AND PSYCHOSIS IN ADULTS

Martina Pelle*¹, Yael Sonnino², Michele Ribolsi³, Federico Fiori Nastro², Damiano Elisa², Esposto Eleonora², Prosperi Porta Davide², Giuliano Albergo³, Di Lorenzo Giorgio², Corinto Fernando²

¹*Tor Vergata University of Rome*, ²*Tor Vergata University of Rome, Rome*, ³*Psychiatry Unit, Campus Bio-Medico University*,

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction, communication, and restricted, repetitive patterns of behavior, interests, or activities. ASD exists on a continuum of clinical severity. Diagnostic criteria, initially formulated with a focus on childhood presentations, do not fully capture the nuanced manifestations in adults with ASD. Recognizing and identifying ASD requires a comprehensive understanding of the spectrum's diverse presentation across different age groups. Moreover, individuals with ASD frequently develop several comorbid psychiatric disorders, including psychotic disorders, which can impact the individual's quality of life, health, and prognosis. While traditionally viewed as discrete entities, emerging evidence suggests an intriguing intersection between ASD and psychosis; however, the overlap is not yet fully understood. This study aims to explore the interplay between ASD and other psychopathological dimensions in an adult clinical sample.

Methods: Data from 24 patients who accessed the psychiatry outpatient service of the University Campus Bio-Medico of Rome were collected. All patients were 18 years or older, and informed consent was obtained from all participants. Anamnestic interviews were conducted with the patients and their parents, when present and available. Additionally, all subjects underwent a battery of self-administered tests to investigate the presence of various psychopathological dimensions and comorbidities (BDI-II, PQ-16, ASI, LCB, SCL-90-R, CAPE, and AQ). Trained clinicians and researchers administered the Autism Diagnostic Observation Schedule (ADOS-2) Module 4 for adults to ascertain the diagnosis.

Results: The sample consists of 15 males (62.5%) and 9 females (37.5%) with a mean age of 28.2 years old (SD ± 8.33). Thirteen (54.2%) subjects fulfilled a diagnosis of ASD based on ADOS-2. A correlation matrix was performed to analyze and establish the relationship between measured variables, providing valuable insights into their interdependence and associations. Significant inverse correlations were observed between the 'Communication' dimension of ADOS and both the 'depressive frequency' and 'depressive distress' dimensions of CAPE ($r = -0.455$, $p = 0.044$, and $r = -0.460$, $p = 0.041$).

Discussion: This study presents preliminary data from ongoing research. Primary results show a statistically significant correlation between inadequacy in communication, observed by clinicians, and the frequency and distress of depressive manifestations, reported by patients with ASD. The recognition of psychosis in patients with ASD still represents a complex challenge even for expert psychiatrists, mostly due to phenotypical overlap between schizophrenia negative symptoms and autistic symptomatology. In this sense, a deep qualitative investigation of the subjective experience in ASD subjects and the investigation of the subjective feeling of depression might represent a valuable next step in achieving greater diagnostic accuracy. The small sample size, representing a major limitation, may affect the significance of the results. Further longitudinal studies are needed to expand the study's sample size and to follow up on the observed trends over an extended period, providing a more comprehensive understanding of the phenomena under investigation.

T121. NEGATIVE SYMPTOMS $\nrightarrow$ LOW SOCIAL FUNCTION

Rasmus Handest*¹, Ida-Marie Mølstrøm², Carsten Hjorthøj³, Mads Gram Henriksen⁴, Julie Nordgaard⁵

¹University of Copenhagen, ²Mental Health Center Amager, ³Copenhagen University Hospital, Mental Health Center Copenhagen, ⁴Mental Health Center Amager, Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Denmark, ⁵Mental Health Centre Amager, Denmark. Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Denmark

Background: Impaired social functioning in patients with schizophrenia is a crucial focus in psychiatry. The modern notion of recovery emphasizes both clinical and social remission, but the relationship between these two domains in patients with schizophrenia remains insufficiently explored. The prevailing model suggests that negative symptoms exert the most significant impact on social functioning. However, the empirical support for this hypothesis is uncertain. This study conducts a systematic review and meta-analysis to investigate the relationship between psychopathology and social functioning.

Methods: This systematic review and meta-analysis assessed cross-sectional data to examine the association between psychopathology and social functioning. We categorized social functioning into overall scores and subdomains (Socially useful activities, Personal and social relationships, and Self-care). We divided psychopathology outcomes into overall scores and subdomains (Positive symptoms, Negative symptoms, General symptoms, Disorganized symptoms, and Depressive symptoms). Univariate meta-regression was computed to examine the moderating effects of patient age or gender.

Results: We included 36 of 1,288 screened studies, comprising 4,742 patients with a mean age of 38.4 years, and 66.8% were men. All psychopathological domains exhibited a significant association with social functioning. No moderating effects of patient age or gender were observed.

The analysis of the association between overall social functioning and overall psychopathology revealed a negative correlation of -0.51 (95% CI [-0.63; -0.37]). All five psychopathological subdomains showed significant negative correlations ($P < .01$) with overall social functioning. Exploration of the association between subdomains of social functioning and psychopathology indicated that "Personal and social relationships" demonstrated associations with overall psychopathology ($P = 0.02$), positive and negative symptoms (both $P < 0.01$), but no association with depressive symptoms. "Socially useful activities" correlated with negative symptoms ($P < .001$), while "Self-care" showed associations with positive and negative symptoms (both $P < 0.01$).

Interpretation of the literature should be approached cautiously due to heterogeneity in results and measurement methods publication bias, and overlapping measures of psychopathology and social functioning. High heterogeneity was observed in results and measurement methods, with 13 different scales used to measure psychopathology. The study also indicated potential publication bias in the association between positive symptoms and overall social function. Measures of psychopathology and social functioning often overlapped, particularly for negative symptoms and general psychopathology.

Discussion: Contrary to the assertion that negative symptoms are the most significant symptom group regarding social functioning, our findings suggest that all examined symptom domains are significantly associated with social functioning. A possible interpretation is that the affected social functioning is not a consequence of a specific group of symptoms but

rather an integral part of the disease itself for some patients, akin to other symptom groups on par with the classical descriptions of autism by Bleuler or Minkowski.

T122. SOCIAL DEPRIVATION AS A SOURCE OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: A SYSTEMATIC REVIEW

Silvia Monari^{*1}, Silvia Bolano², Matthias Kirschner², Stefan Kaiser², Michel Sabé²

¹*Division of Adult Psychiatry, University Hospitals of Geneva*, ²*Division of Adult Psychiatry, Department of Psychiatry, University Hospitals of Geneva*

Background: Schizophrenia is a persistent and disabling disorder characterized by positive, negative and cognitive symptoms. Negative symptoms treatment remains an unmet challenge. While primary negative symptoms are inherent to the disease, secondary negative symptoms can arise from various factors, including residual positive symptoms, antipsychotic side-effects, substance abuse, depression, and social deprivation. There is a lack of a systematic review exploring the association between social deprivation (or its perception, such as loneliness) and secondary negative symptoms. This study aims to fill this gap by investigating the relationship between social deprivation and negative symptoms in individuals with schizophrenia.

Methods: Following PRISMA guidelines (CRD CRD42022259295), we conducted a systematic search using keywords and MeSH terms such as 'schizo*', 'social isolation,' 'social withdrawal,' and 'social deprivation.' We included cross-sectional, case-control, clinical trials, and longitudinal studies involving adults with schizophrenia spectrum disorders.

Results: The systematic search yielded 1,104 references. After title, abstract, or trial protocol screening, 285 articles remained. Of these, 29 studies with various designs were retained. The findings highlight the multifaceted nature of social deprivation, involving both external and internal factors that contribute to the complexity of negative symptomatology in individuals with schizophrenia. Common external factors included institutionalization, deinstitutionalization, forced social isolation (e.g., during the COVID-19 pandemic), stigma, and rejection from primary caregivers. Noteworthy outcomes included positive effects associated with deinstitutionalization, such as improved quality of life and reduced alogia, while motivational deficits were prevalent in institutionalized settings. Internal factors, such as depressive symptoms, experienced stigma, loneliness, impaired social cognition, and residual positive symptoms, also played significant roles in social deprivation.

Discussion: The systematic review sheds light on the limited but critical research on the role of social deprivation as a causative factor for secondary negative symptoms in schizophrenia. The findings underscore the multifaceted nature of social deprivation, encompassing both external and internal factors that contribute to the complexity of negative symptomatology in individuals with schizophrenia. In addition, the increase attempt to digitally phenotype negative symptoms by means of biobehavioral is discussed as an unprecedented opportunity for tracking, understanding and treating social deprivation within schizophrenia.

T123. EXPLORING VIRTUAL REALITY-ASSISTED THERAPY FOR AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA SPECTRUM DISORDERS THROUGH THE LENS OF PHENOMENOLOGY

Lisa Charlotte Smith*¹, Mariegaard Lise¹, Ditte Lammers Vernal², Gry Jørgensen¹, Annette Gosvig Christensen³, Fatime Zeka⁴, Nikolai Albert⁵, Julie Midtgaard⁶, Neil Thomas⁷, Carsten Hjorthøj⁸, Louise Birkedal Glenthøj⁹, Merete Nordentoft⁵

¹Copenhagen Research Center for Mental Health - CORE, VIRTU Research Group, ²Aalborg University Hospital, Psychiatry, Research Unit for Child and Adolescent Psychiatry, Aalborg, Denmark, ³Esbjerg Psychiatric Hospital, Region of Southern Denmark, Denmark, ⁴Copenhagen Research Center for Mental Health - CORE, VIRTU Research Group, University of Copenhagen, Department of Psychological Sciences, ⁵Copenhagen Research Center for Mental Health-CORE; Mental Health Center Copenhagen, Copenhagen University Hospital, Denmark, ⁶Centre for Applied Research in Mental Health Care (CARMEN), Mental Health Center Glostrup, University of Copenhagen, Copenhagen, Denmark; Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, ⁷Brain and Psychological Sciences Research Centre, Swinburne University and Monash Alfred Psychiatry Research Centre, Melbourne, Australia, ⁸CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; University of Copenhagen, Section of Epidemiology, ⁹Copenhagen Research Center for Mental Health (CORE), VIRTU Research Group, Mental Health Center Copenhagen, University of Copenhagen, Faculty of Social Sciences, Department of Psychology,

Background: In a currently active randomised controlled clinical trial (CHALLENGE), the efficacy of a novel virtual reality (VR)-assisted psychotherapy for persistent auditory verbal hallucinations (AVH, i.e. hearing voices) is tested. The patients enrolled in the trial are suffering from schizophrenia spectrum disorders. Based on an analysis of qualitative data from a smaller experimental sub-study (N=15), the focus of this oral presentation is on presenting phenomenological aspects of participants' experiences with VR-assisted therapy. The experimental sub-study's primary aims are to improve therapy effectiveness through minor software modifications, meanwhile also conducting an in-depth qualitative exploration of participants' experiences with VR-assisted therapy.

Methods: During the VR-assisted therapy, participants create an avatar that corresponds to their visual perception (or imagination) of the source of their most dominant voice. Additionally, and with the use of a software program the voice of the therapist is transformed into sounding like the voice heard by the participant. Part of therapy is conducted in VR as roleplay with the therapist taking on the role of the avatar. The focus of therapy is on gradually altering the relationship between the participant and the avatar with the avatar becoming less dominant. In the current sub-study, all participants were interviewed after finishing therapy. The semi-structured interviews covered themes such as 'acceptability', 'effectiveness', and 'transferability'. Broad, open-ended questions were asked to capture participants' immediate experiences. For this oral presentation the interviews were analyzed with the use of phenomenological and postphenomenological theory to capture how subjectivity and intersubjectivity may be experienced and transformed in VR-assisted therapy through the situated mediations occurring within the virtual world (user-environment relations) and outside VR (human-world relations).

Results: Themes of different types of realities emerged in the data: 1) the private psychotic reality, 2) our shared social (and physical) reality, and 3) virtual reality. Phenomenological similarities between psychotic experiences and VR were identified, especially pertaining to perception and language. The very real relationship between participants and their voices (AVH) are apparent in the interviews – with voices experienced as being present in therapy with a subjectivity of their own. During the course of therapy, the realities of VR and

psychosis occasionally merged, e.g. creating illusions of the VR avatar being the dominant voice from the psychotic reality. For participants who achieved a better relationship with their voices, possibilities of the self to perform particular activities (e.g. reading books, participating in social events) were regained, hence creating a larger field of opportunities for the self in the world (i.e. outside VR). Additionally, creating and sharing the avatar as a simulation of the most dominant voice enabled participants to communicate perceptual aspects of their auditory hallucinations to the therapist and relatives, thus possibly enhancing intersubjectivity regarding previously private experiences.

Discussion: This study highlights potential points of action that arise from the particular situatedness of participants positioned in this type of individualized VR environment. The dialogue with the avatar (embodied by the therapist) encompassed verbal acts constituting a possibility for change in the self and in the relationship with the dominant voice. Preliminary quantitative findings indicate that the method of conducting therapy with the use of an avatar in VR is promising. Understanding phenomenological aspects of psychosis and VR is key if we are to improve therapeutic methods that employ VR in the treatment of schizophrenia spectrum disorders.

T124. DISABILITY CASES COMPLICATED BY PSYCHOSIS AND SCHIZOPHRENIA SPECTRUM DISORDERS

Brad Booth*¹, Sarah Mamane², Dominique Bourget³

¹*University of Ottawa Faculty of Medicine*, ²*Royal Ottawa Hospital, Department of Schizophrenia*, ³*Royal Ottawa Mental Health Hospital*

Background: Independent medical evaluations (IMEs) are often sought by third parties to clarify psychiatric issues relevant to criminal or civil law. In criminal law, this might include determination of criminal responsibility, fitness to stand trial, or risk. In civil law, this might include determination of eligibility for disability benefits, fitness to work, and civil litigation for psychological damages. At times, individuals with obvious or subtle psychosis present in the context of these IMEs. Employed stable patients with psychotic disorders may have a relapse; alternatively, a new onset of psychosis can occur, causing them to be disabled and potentially qualifying them for disability insurance. They might also be sent for fitness for work or to clarify causality from accident or trauma. The current study reviews psychosis and schizophrenia spectrum disorders in IMEs for disability claimants.

Methods: The authors have completed a retrospective chart review of approximately 705 consecutive disability independent medical examinations (IMEs) dating back to 2010 drawn from forensic work by BDB. Data was extracted for patients who consented to research where a primary psychotic disorder was likely or suspected. For the current review, other medico-legal issues such as fitness to work and psychological harm, were excluded.

Results: Out of the approximately 705 consecutive IMEs, 27 (3.8%) were found to have a likely psychotic element to their presentation, such as schizophrenia spectrum diagnosis. Of this sample, 23 consented to use of their data in research. Nearly all were diagnosed with a new-onset psychotic disorder. There were 13 men (56.5%) and 10 women (43.5%). The average age was 45. Of the 23 patients, 7 had a previous disability leave with the average time from current leave from work to assessment being 864 days. In the study, the average patient had 2.5 comorbid DSM diagnoses suggesting high comorbidity. Diagnoses in descending frequency were: GAD, Depressive disorders, Social phobia, Substance use

disorders, and ADHD. For those with substance use disorders, 6 were using more than one substance; 8 were using cannabis, 5 were using alcohol, and 2 were using stimulants. Evaluatees had high baseline deficits in attention and impulsiveness at baseline and at the time of assessment as measured by the ASRS. Their PHQ-9 scores showed moderate depression and GAD-7 showed mild anxiety. Their BPAQ scores suggested average levels of aggression, anger, and hostility. They showed self-esteem deficits on the Rosenberg Self Esteem Scale and impression management on the PDS. The AUDIT and DAST suggested no issues with alcohol and substances. Lastly, the WHODAS-2.0 suggested mild-mod impairment overall. Evaluatees listed stressors contributing to the onset of illness/disability, with the most common workplace stressors being problem with supervisors and bullying. The most commonly reported personal stressors were death/illness in relatives and physical health.

Discussion: Experts involved in IMEs and other forensic evaluations must be aware of the potential of unrecognized/subtle psychotic signs. In approximately 3.8% of a large disability sample, psychosis was the likely cause of disability. Many had not been recognized as being psychotic and were not on appropriate treatment. Once the correct diagnosis of a schizophrenia spectrum disorder is made, the clinician can comment on the potential for improvement over a predictable course. The expert will be in a position to offer recommendations, such as pharmacological treatment, psychiatric and psychological follow-up, and other relevant advice.

T125. PREDICTING THE DIFFERENTIAL COURSE OF EVERY-DAY LIFE PSYCHOTIC EXPERIENCES ACROSS THE PSYCHOSIS LIABILITY SPECTRUM

Frederike Schirmbeck*¹, Uli Reininghaus², Mathias Zink³, GROUP Investigators⁴, Inez Myin-Germeys⁵

¹Central Institute of Mental Health, University of Heidelberg, ²Central Institute of Mental Health, Mannheim, ³Central Institute of Mental Health, Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, ⁴GROUP, ⁵Department of Neuroscience, KU Leuven- Leuven University,

Background: Over the last decades, extensive research has been conducted to identify predictors for the development and prospective course of psychotic symptoms. Prospective cohort studies mainly focused on categorical outcome over a longer period of time, whereas experience sampling methods (ESM) investigated potential predictors of moment-to-moment fluctuation in everyday life psychotic experiences. Interestingly, both cohort studies, as well as ESM studies have highlighted the impact of experienced stressful events and affective disturbances on the prospective course of psychotic symptoms. Some authors have even hypothesized an affective pathway to psychosis. Both study designs come with specific limitations, large assessment intervals in cohort studies and the focus on categorical outcome (transition, remission, relapse rates), might overlook relevant variation and cannot rule out unmeasured confounding effects, on the other hand very small assessment intervals in moment-to-moment (hour-to-hour) investigations might be too small to observe relevant changes.

To further unravel potential mechanisms in the course of psychotic experiences we choose an ‘in-between’ window of observation (day-to-day) and broadened our perspective of potential predictors. We aimed to identify and predict differential trajectories of day-to-day change in

psychotic experiences over a period of one week, focussing on the predictive validity of experienced events, coping strategies and affective disturbances on identified trajectories.

Methods: Analyses were conducted using ESM data from subjects across the psychosis liability spectrum, who previously took part in the INTERACT or GROUP study. The combined sample (n=340) included patients with psychotic disorder in a later illness stage, first episode patients (FEP) with psychosis and subjects at clinical high risk for psychosis (CHR-P). Latent class mixed model analysis (LCMM) were used to identify and visualize clusters of participants with similar distinct outcome trajectories of every-day life psychotic experiences. In a subsequent step, the prognostic validity of risk and resilience factors on these unconditional trajectories and within-subject day-to-day changes were explored by multilevel regression analyses.

Results: LCMM resulted in a 5-class solution. Mean class probabilities were moderate to high (0.70- 0.88), suggesting individuals had a 70-88% probability to be correctly assigned to one of the five latent classes. After visual inspection, identified trajectories could be defined as: (i) low (n=83), (ii) middle (n=142), (iii) high (n=78), (iv) decreasing (n=26), and (v) increasing (n=11) psychotic experiences. Compared to persistently low psychotic experiences, exploratory analyses showed that higher baseline stress and more negative affect increased the likelihood to belong to the high or middle trajectory, whereas higher levels of daily life self-esteem was associated with a lower likelihood for the increasing trajectory.

Discussion: Findings suggest that daily-life experienced stress and affective disturbances may have a negative effect on the subsequent course of experienced (subthreshold) psychotic symptoms over the course of one week. In contrast positive self-esteem might represent a protective factor for symptomatic increase.

T126. PRECISION PSYCHIATRY FOR SCHIZOPHRENIA SPECTRUM DISORDERS: PREDICTING PREDICTABILITY

Edwin van Dellen*¹

¹UMC Utrecht

Background: Precision psychiatry is an emerging field that aims to provide individualized approaches to schizophrenia spectrum disorders. Multivariate analysis and machine learning are used to create outcome prediction models based on clinical data such as demographics, symptom assessments, genetic information, and brain imaging. While much emphasis has been placed on technical innovation, the complex and varied nature of mental health presents significant challenges to the successful implementation of these models.

Methods: A review of ten challenges of precision psychiatry applications in schizophrenia spectrum disorders.

Results: Current datasets used to train precision prediction models do not reflect real-world populations and fail to incorporate realistic clinical outcome definitions. Treatment-related factors such as placebo effects and non-adherence to prescriptions are not considered. Fairness, prospective validation in comparison to current practice and implementation studies of prediction models are other key issues that are currently understudied.

Discussion: A shift is proposed from retrospective studies based on linear and static concepts of disease towards prospective research that considers the importance of contextual factors and the dynamic and complex nature of mental health in patients with schizophrenia spectrum disorders.

T127. RELIABILITY AND VALIDITY STUDY OF TURKISH VERSION OF SCHIZOPHRENIA COGNITION RATING SCALE (SCORS) WHICH ASSESS COGNITIVE IMPAIRMENT IN THE DAILY LIFE OF SCHIZOPHRENIA PATIENTS

Nedim Özak¹, Emine Iğın Hosgelen^{*2}, Bilge Targıtay Öztürk³, İ. Tolga Binbay³, Berna Binnur Akdede³, Köksal Alptekin³

¹M.D., Private Office, Balıkesir, ²Dokuz Eylül University, Institute of Health Science, ³Dokuz Eylül University, School of Medicine, Department of Psychiatry

Background: Schizophrenia is characterized by significant dysfunction in cognitive domains including memory, attention, processing speed, executive functions, and language skills. Despite its crucial role in clinical appearance and prognosis, cognitive assessments are difficult to perform in an outpatient setting due to the time-consuming nature of neurocognitive assessments. A scale named SCoRS “Schizophrenia Cognition Rating Scale” developed by Keefe et al (2006) provides a concise cognitive evaluation tool by obtaining information from the patient, informant, and interviewer in approximately 12 minutes. SCoRS also exhibits sensitivity to treatment effects (Keefe et al, 2015). This study aimed to establish the validity and reliability of the Turkish version of the “Schizophrenia Cognition Rating Scale” (SCoRS-TR) in schizophrenia patients.

Methods: The study’s sample comprised a total of 170 volunteers, including 130 schizophrenia patients (SchP) who met DSM-V criteria for schizophrenia and 40 healthy controls (HC). After gathering the sociodemographic data, the clinical characteristics of the patients were evaluated by using the Positive and Negative Syndrome Scale (PANSS). Structured Clinical Interview for DSM-V (SCID) was conducted for HCs to screen mental disorders. The Schizophrenia Cognition Rating Scale-Turkish Version (SCoRS-TR) was administered to both SchP and HC groups. Neurocognitive test battery which included Rey Auditory Verbal Learning and Memory (RAVLT), Trial Making A and B Forms (TMT-A and B), Stroop Color and Word Test (SCWT), Digit Symbol, Digit Span test, Category Fluency, Controlled Oral Word Association Test (COWA), and Wisconsin Card Sorting Test (WCST) was used to assess the correlation between SCoRS-TR and neurocognitive domains. For assessing the reliability of this new scale, internal consistency, test-retest, and interrater reliability analyses were conducted. The validity of the scale was assessed with similar scale validity, factor analysis, and differential validity methods.

Results: We found significant evidence for the reliability and validity of SCoRS for the Turkish population in our study. Conducted factor analysis shows SCoRS is structured with 4 factors (memory, attention/vigilance, executive functions, psychomotor activation subscales) which defined %63,4 of overall variance and has an acceptable internal consistency (for patient form $r=0.937$, for informant $r=0.940$, for interviewer form $r=0.937$). We also determined high interrater reliability (patient form $r=0.90$, informant $r=0.95$, for interviewer form $r=0.98$), high test-retest reliability (patient form $r=0.990$, informant $r=0.977$ and interviewer form $r=0.976$) and high differentiation capacity between patients and healthy volunteers ($p < 0.001$). We indicated similar scale validity between SCoRS-TR and neurocognitive tests. There were significant correlations between SCoRS subdomains (patient, informant, and interviewer) and RAVLT late recall (ranging $r:-0.46 - r:-0.51$), TMT-B (ranging $r:0.34 - r:0.37$), Verbal Fluency test ($r:-0.42 - r:-0.47$), and WCST (ranging $r:-0.35 - r:-0.39$) scores.

Discussion: In this study SCoRS-TR has demonstrated significant reliability and validity scores that may be useful in evaluating cognitive dysfunction in patients with schizophrenia.

Schizophrenia Cognition Rating Scale Schizophrenia (SCoRS) may contribute to determine severity of neurocognitive impairments evident in schizophrenia patients and trace progression of cognitive impairments during follow-up in clinical studies.

T128. REAL-ENVIRONMENT BASED VIRTUAL REALITY INTERVENTION PROGRAM FOR PSYCHOSOCIAL FUNCTIONING IN INDIVIDUALS DIAGNOSED WITH SCHIZOPHRENIA

Emine Ilgın Hosgelen*¹, Markus Berger², Faik Kartelli², Fatma Şimşek³, Berna Binnur Akdede⁴, Köksal Alptekin⁴

¹Dokuz Eylul University, Institute of Health Science, ²Dokuz Eylul University Faculty of Fine Arts Department of Film Design Animation Film Design and Directing, ³Department of Psychiatry, Community Mental Health Center, Bakırçay University Education and Research Hospital, ⁴Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry

Background: Virtual Reality (VR) presents a promising intervention method for psychosocial impairments in schizophrenia. In this study, we aimed to study the effect of a real-environment-based VR in improving psychosocial functioning in schizophrenia. Here we present preliminary findings of an ongoing study.

Methods: The data was obtained from the patients who were registered at Bakırçay University Çiğli Regional Education Hospital, Community Mental Health Center (CMHC). The study included 19 individuals who were diagnosed with schizophrenia based on the diagnostic criteria outlined in the DSM-V. The study was conducted with two groups: one experimental group that received VR sessions (VRG, n=11) and a control group (CG, n=8) with non-interventional face-to-face sessions, once a week for 12 weeks. Participants were randomly assigned to the study. The severity of schizophrenia symptoms of the patients was evaluated by using the Positive and Negative Syndrome Scale (PANSS). Psychosocial functioning was evaluated by using the Personal and Social Performance Scale (PSP) and Social Functioning Scale (SFS). Social cognition was evaluated by using Dokuz Eylul Theory of Mind Index (DEZIKO), Facial Emotion Identification (FEIT), and Facial Emotion Discrimination (FEDT) tests, and Reading Mind in the Eyes (RMET). Additionally, the Turkish version of the Observable Social Cognition–A Rating Scale (OSCARS-TR) was used to evaluate social cognition by caregivers of the patients. Neurocognition was evaluated by using the Turkish version of Screen for Cognitive Impairment In Psychiatry (SCIP). The assessments were conducted at both baseline and post-test stages. Socio-demographic variables and baseline assessments were compared using the Mann-Whitney U test. The hypothesis was tested using repeated measures ANOVA.

Results: The mean age was for VRG 37.27±9.95 and CG 40.75±7.96. The mean for total education years was for VRG 11.27±4.00, and CG 10.12±3.04. There was no difference in terms of age (p=.34) and education (p=.30) between the groups. There was also no significant differences between PANSS (p=.46), PSP (p=.65), DEZIKO (p=.30), FEIT (p=.74), FEDT (p=.93), OSCARS-TR (p=.13), and SCIP (p=.32) at the baseline assessments. However, there was a significant difference in SFS (p=.030), and its two subscales, interpersonal skills (p=.21) and prosocial activities (p=.016), at baseline between groups. The main effect of time was significant indicating that PSP [F(1,17)=39.38, p LESS THAN .001], SFS [F(1,17)=10.22, p=.005], DEZIKO [F(1,17)=13.58, p=.002], SCIP global [F(1,17)=15.21 p=.001] score significantly increased and PANSS [F(1,17)=85.91, p LESS THAN .001] score significantly decreased. However, there was no time x group interaction in these assessments.

The main effect of time and time x group interaction was not significant as following, respectively; for OSCARS-TR [$F(1,15)=.78$, $p=.39$; $F(1,15)=1.95$, $p=.18$], FEIT [$F(1,17)=0.20$, $p=.90$; $F(1,17)=2.16$, $p=.16$], FEDT [$F(1,17)=.22$, $p=0.64$; $F(1,17)=1.51$, $p=.78$], RMET [$F(1,17)=1.80$, $p=.18$; $F(1,17)=0.16$, $p=.70$].

Discussion: While VR is a promising tool for psychosocial skills training, these preliminary findings of this study did not strongly support this hypothesis of VR improvement in psychosocial functioning. Instead, individuals diagnosed with schizophrenia showed a significant increase in psychosocial functioning when engaged in weekly appointments over a 12-week period.

T129. INVESTIGATING THE CONCORDANCE BETWEEN DIFFERENT MEASURES OF FORMAL THOUGHT DISORDER SEVERITY

Georgia Zamperoni¹, Philip Sumner², Susan Rossell³, Eric Tan*⁴

¹*Centre for Mental Health and Brain Sciences, School of Health Sciences, Swinburne University of Technology, Melbourne,* ²*Centre for Mental Health and Brain Sciences, School of Health Sciences, Swinburne University of Technology,* ³*Centre for Mental Health and Brain Sciences, School of Health Sciences, Swinburne University of Technology, Department of Psychiatry, St Vincent's Hospital, Melbourne, Australia.,* ⁴*National University of Singapore*

Background: Disorganized speech, or formal thought disorder (FTD), is a core symptom of psychosis, with various measures and rating scales being used in both clinical and research settings. These range from general to more comprehensive measures, leading to significant heterogeneity in mechanistic and prognostic investigations of FTD. To date, how these different measures relate to each other, and thus the salience of this heterogeneity, has yet to be assessed. This study thus aimed to examine how different FTD measures rated the severity of FTD symptomatology using a single sample of speech. In particular, this study focused on assessing the agreement between measures (scale of measurement), as opposed to construct validity.

Methods: Speech recordings from 21 individuals diagnosed with DSM-5 schizophrenia-spectrum disorder or bipolar disorder were rated using 5 published measures of disorganized speech: the Thought Language and Communication (TLC) scale Global score, the FTD subscale from the Scale for the Assessment of Positive Symptoms (SAPS), the alogia subscale from the Scale for the Assessment of Negative Symptoms (SANS), items P2 Conceptual Disorganization and N6 Lack of Spontaneity and Flow of Conversation from the Positive and Negative Syndrome Scale (PANSS), and the Communication Disturbances Index (CDI) overall score. Agreement was assessed using the Bland-Altman plots procedure, where the relationships between two measures were graphically depicted and linear regressions used to test for proportional bias in the respective ratings. These were done only for measures that showed significant positive Spearman's correlations, which were used to confirm construct validity between two different measures.

Results: Our results suggested strong agreement between the TLC Global score and both SAPS FTD and SANS alogia, the TLC Global and PANSS P2 but not PANSS N6, SANS alogia and both PANSS P2 and N6, and SAPS FTD and PANSS P2. No significant agreement was found between the CDI and any other measure.

Discussion: Our findings demonstrate the interconnectedness of various assessment tools quantifying FTD, with strong relationships between selected comprehensive measures like

the TLC, and more general assessments like PANSS P2, SAPS and SANS, but not PANSS N6. This could contribute to a unified framework in FTD evaluation across diverse clinical and research contexts. For example, our data suggests that these measures could be used interchangeably, pending on context of usage, without significant differences in assessment outcomes. Until a consensus approach to FTD assessment is achieved, the current findings will go some way to improving interpretations across studies.

T130. INCREASED MORTALITY AMONG PATIENTS WITH SUBSTANCE INDUCED PSYCHOSIS (SIP) IN SCANDINAVIA

Eline Rognli¹, Carsten Hjorthøj², Anette Erlangsen³, Heidi Taipale⁴, Pihla Sassi⁵, Solja Niemelä⁶, Ina Heiberg⁷, Jørgen Bramness^{*8}

¹*Oslo University Hospital*, ²*Copenhagen University Hospital, Mental Health Center Copenhagen*, ³*Copenhagen Research Center for Mental Health – CORE, Mental Health Center Copenhagen*, ⁴*Karolinska Institutet*, ⁵*Department of Psychiatry, University of Turku*, ⁶*Department of Psychiatry, University of Turku, Turku, Finland*, ⁷*UiT - Arctic University of Norway*, ⁸*Norwegian Institute of Public Health*

Background: People with substance induced psychosis have a disorder that in some contexts is considered neither a drug use disorder nor a “proper” psychiatric disorder. There are almost no guidelines informing its treatment and most often stopping substance use is considered to the best (and only) way forward. Still as many as one in three people with SIP receive a diagnosis of schizophrenia in the time following a SIP-diagnosis, indicating that SIP is a serious disorder.

Methods: In this study we utilize data from Norway, Sweden, and Denmark to investigate the mortality of SIP. Data were taken from national patient registries in the three countries and involved all patients admitted with a diagnosis of SIP (ICD-10 F1x.5) from the first possible date using ICD-10 in each country (from 2008-2020) for patients age 18-79. Figures on total and cause-specific causes of death will be presented as standardized mortality ratios (SMRs). Cause specific mortality will include a) suicides, b) poisonings, c) accidents, d) cancer, e) cardiovascular and f) respiratory organs.

Results: Data are collected currently, and all data will be analyzed in January 2024.

Discussion: Initial preliminary findings indicate a 10-20 times increased mortality per year compared to age and gender matched controls. Detailed, but still preliminary findings will be reported at SIRS.

T131. THE JOHNS HOPKINS SCHIZOAFFECTIVE DISORDER PRECISION MEDICINE CENTER OF EXCELLENCE: AN APPROACH TO REDUCING THE HETEROGENEITY OF SCHIZOPHRENIA AND RELATED DISORDERS BASED ON TREATMENT RESPONSE

Russell Margolis^{*1}, Frederick Nucifora¹, Yifan Mo¹, Andor bodnar¹, Claire Mcaulley¹, Leslie Nucifora¹, Peter Zandi¹, Christopher Ross¹, Vidya Kamath¹, Tilak Ratnanathar¹, Gayane Yanokyan¹, Elizabeth Gerber¹, Hanna Jaaro-Peled¹, Allison Brandt¹

¹*Johns Hopkins*

Background: The heterogeneity of schizoaffective disorder (scz-aff), here defined broadly to include schizophrenia with and without extensive affective symptoms, has been recognized since the construct of schizophrenia was first developed in the late 19th and early 20th Century. We hypothesize that heterogeneity can be reduced by defining three subtypes of scz-aff based on treatment response: response to conventional antipsychotics (non-treatment resistant), response only to clozapine (treatment resistant), and lack of response to any antipsychotic medicine (ultra-treatment resistant). The goals of our program are therefore: 1) To develop methods that distinguish these subtypes prior to the onset of treatment, as a guide to choosing among current treatments. 2) To determine the neurobiological underpinnings of the subtypes, using a strategy to identify those factors in common to all subtypes, and those factors that distinguish each group. 3) To use health system data to understand and change clinical practice.

Methods: We propose to achieve these goals through 6 aims. In Aim 1, we will intensely study the large clinical population of patients with scz-aff disorder treated at Johns Hopkins to establish the phenotypes of the three scz-aff subtypes. Analyses will include detailed cross-sectional and longitudinal assessments of clinical symptoms, cognition, olfaction, function. In Aim 2, we will examine the patients and control with novel imaging techniques and ultra-high field (7 Tesla) technology to determine structural, connectivity, and neurovascular signature of each of the scz-aff subgroups. In Aim 3, we will generate iPSCs and induced neurons from individuals from each subtype of scz-aff and controls. Cells will be examined at different stages of differentiation, and compared to iPSCs engineered to contain rare mutations associated with high risk of scz-aff. Blood samples will be obtained for genetic analyses and to explore extracellular vesicles. In Aim 4, we will use mouse models to explore recently discovered genetic risk factors for scz-aff, and which may shed light on subtype specific pathophysiology. In Aim 5, we will determine EEG differences among scz-aff subtypes with an emphasis on sensory gating and attentional parameters. In Aim 6, we will take advantage of Hopkins EMR data, and eventually other data sets, to determine factors associated with the use and lack of use of clozapine, and the extent of treatment response to clozapine.

Results: Preliminary efforts have now demonstrated the feasibility of all 6 aims. Preliminary results will be detailed in other posters.

Discussion: If successful, our efforts, combined with the efforts of many others working on related projects, will lead to 1) increase in the use of clozapine, 2) targeting of clozapine to the correct patients at the correct time, 3) improved patient stratification in pharmacological trials for scz-aff treatment, 4) development of new therapeutic targets. This work was supported by the Abramson Fund, the ABCD Chairtable Trust, the NIMH, and Johns Hopkins inHealth.

T132. RESEARCH PRIORITIES FOR THE AUSTRALIAN EARLY PSYCHOSIS COMMUNITY

Joanna Fitzsimons^{*1}, Andrew Thompson², Karine Fernandez³, Eleanor Brown², Isabel Zbukvic², Deanna De Cicco³, Patrick McGorry², Kelly Allott², Stephen Wood²

¹University of Melbourne, ²University of Melbourne and Orygen, ³Orygen

Background: Although psychosis is a low prevalence disorder, the burden of disease is substantial, with considerable individual, community and societal costs and the need for innovation to prevent and treat mental health problems has never been greater. The Australian Early Psychosis Collaborative Consortium (AEPCC) has been established with

Wellcome Trust funding to drive national collaboration across the research, clinical and lived experience sector, to build a Clinical Trials and Translation Network, Clinical Quality Registry and Lived Experience Network, nationally. A key priority activity for Clinical Trials Networks (CTNs) is the development of research priorities for the sector, driven by all relevant stakeholder groups. CTNs can then facilitate national research collaboration, broad clinical service participation and ensure meaningful and purposeful involvement of lived experience communities, which in turn result in improved funding success rates, as funding bodies are clear the proposed large scale clinical trial proposal have been developed from real-world engagement, are more likely to success in reaching recruitment targets and build bridges across research-clinical-lived experience silos to ensure the questions being investigated are important to the whole sector and the findings will more likely be translated back in to clinical settings, should the findings be positive.

Methods: AEPCC set out to identify the most important research questions for the Australian early psychosis community. The AEPCC Scientific Committee reviewed and endorsed the proposed methods. A variety of methodologies were employed across an 18 month period including scoping of previous priority setting activities, online survey, online and in-person facilitated consultations, ranking survey and a final poll where participants were asked to pick the 2 most important questions, from a list of 10. Thematic analysis was conducted on the transcribed data.

Results: Across the multiple consultations, more than 600 responses were collated. In person or online consultations involved over 100 people from across all Australian States and Territories. More than 500 people participated in online surveys or polls. Data from the scoping surveys and in-person consultations were transcribed and thematic analysis conducted to identify key themes. An initial in-person forum was held in Melbourne, Australia to begin an early identification process of important clinical trial ideas based on 5 key priority themes (1) Causes and risks associated with developing early psychosis, 2) Models of care for early psychosis, 3) Comorbidity and complexity in early psychosis (e.g. physical health and early psychosis, trauma and early psychosis), 4) Diagnosis and treatment of early psychosis, and 5) Impact and long-term outcomes of early psychosis). This process demonstrated the need for further refinement and subsequently a poll was developed in consultation with research, clinical and lived experience community members where participants results of the poll will be discussed, highlighting differences between research, clinical and lived experience community priorities.

Discussion: Research priority setting is an important and challenging process for a sector to undertake, however the rewards in listening to and understanding the views and priorities of different stakeholders is a valuable reward that can result in better outcomes for lived experience members, as well as increased engagement in clinical trials. These benefits and challenges will be discussed along with the next steps that AEPCC will undertake with the sector to refine the trial questions and facilitate the development of a truly collaborative, national clinical trial based on the priorities identified in partnership.

T133. THE AUSTRALIAN EARLY PSYCHOSIS CLINICAL QUALITY REGISTRY - DEVELOPMENT AND IMPLEMENTATION IN REAL WORLD CLINICAL SETTINGS

Andrew Thompson^{*1}, Jo Fitzsimons², Karine Fernandez¹, Carolyn Sanderson¹, Yehudi Saling¹, Deanna De Cicco¹, Patrick McGorry²

¹Orygen, ²University of Melbourne and Orygen

Background: Over the last few decades research into early psychosis has increased dramatically. Early Intervention services have been established in an increasing number of countries internationally including clinical services for those at high risk of developing a psychotic disorder. However, the quality of service delivery is often not adequately monitored, data collection not systematized and the understanding of long term outcomes outside of research settings is lacking. Clinical Quality Registries (CQR's) are tools for monitoring the quality of care delivered to a specific diagnostic group or procedure. They are widespread in Australian healthcare outside of mental health. They involve the collection of minimum clinical and service data on a wide number of individuals in real-world clinical settings with opportunities for wider linkage to other routinely collected health care data such as mortality and prescribing. In this sense they fulfill the criteria of a learning health care tool. As part of the recently established Australian Early Psychosis Collaborative Consortium initiative we are establishing a CQR for early and emerging psychosis (FEP and UHR) Australia wide.

Methods: We describe the process of establishing the Minimum Dataset (MDS) and the CQR infrastructure. A series of panel discussions with an establishment of committee of clinicians' research and lived experience experts has guided the development of the MDS and implementation of the CQR in diverse services across the country.

Results: The current state of the national CQR infrastructure and the challenges in implementing this in the 5 demonstrator sites will be discussed.

Discussion: The establishment of a national CQR for early psychosis is the first of its kind for mental health in Australia. The CQR will lead to an improved collection of minimum data on outcomes, establish and improve risk profiling in practice, allow services benchmarking and improve quality and also understand long term outcomes in early psychosis.

T134. EXAMINING EARLY FUNCTIONAL RECOVERY AND SYMPTOM REMISSION RATES IN FIRST EPISODE SCHIZOPHRENIA

Joseph Ventura^{*1}, Felice Reddy², Kenneth Subotnik³, Gerhard Hellemann⁴, Keith Nuechterlein⁵

¹*UCLA*, ²*University of North Carolina at Chapel Hill*, ³*University of California, Los Angeles Psychiatry and Behavioral Sciences*, ⁴*University of Alabama, Birmingham*, ⁵*UCLA Semel Institute for Neuroscience and Human Behavior*

Background: Schizophrenia is no longer thought of as necessarily chronically disabling or as inevitably a deteriorating condition. Advances in pharmacological treatment and psychosocial interventions have increased expectations for positive outcomes including early functional recovery and symptom remission. Functional remission, a key component of early recovery, focuses on restoring and individual's ability to engage in daily activities, maintain employment, and build meaningful relationships. Negative symptoms, characterized by deficits in emotional expression, motivation, and social engagement, pose specific challenges to recovery in the early phases of schizophrenia. Addressing negative symptoms is integral to achieving comprehensive recovery and improving overall quality of life. Ongoing investigations seek to refine our understanding of early recovery processes to promote innovative interventions tailored to the unique functional and symptoms reduction needs of individuals experiencing their first episode of schizophrenia.

Methods: Participants were sixty-two young individuals with FES (psychosis onset LESS THAN 2 years at study entry) from the UCLA Aftercare Research Program enrolled in a 12-

month comprehensive early intervention program who had complete 12-month data. Treatment included medication management, weekly case management and individual supportive therapy, and psychoeducation for individuals and families. Using a longitudinal measurement approach, the patients were administered measures by raters trained to reliability to assess daily functioning using the Global Functioning Scale: Social 1= Extreme Social Isolation and 10=Superior Social/Interpersonal Functioning and Role 1= Extreme Role Dysfunction and 10= Superior Role Functioning. Symptoms were assessed with the SANS (Expressive and Experiential Domains) and SAPS Positive Symptom domains (Hallucinations and Delusions combined) where ratings of 0=none and 5=severe. Assessments were conducted at Baseline and subsequently every 3 months for one year. Baseline assessments were administered shortly after study entry. Our control sample was comprised of n=91 age- and demographically-matched healthy controls. Definition of Functional Recovery was determined by an analysis of the healthy control data showing that at study entry a large majority met the recovery criteria on the GFS Social (91%) and Role (92%) rating of 7 or above out of 10. Regarding negative and positive symptoms, we used the SANS and SAPS remission criteria (Andresen et al 2005) where remission is defined as a rating of mild = 2 or below out of 5.

Results: Regarding social functioning, we found that 43% of our sample either met recovery from the Baseline point or recovered within 3 months and maintained recovery for 12 months. Whereas 11% were slow in recovering, 5% did not maintain recovery criteria, and 55% never achieved full social recovery. For role functioning, we found that 29% of the sample met recovery from Baseline or recovered within 3 months and maintained recovery for 12 months. Whereas 18% were slow in recovering, 8% did not maintain recovery criteria, and 45% never achieved full social recovery. Regarding expressive negative symptoms, we found that 29% met remission criteria from Baseline or remitted within 3 months and maintained remission for 12 months. Whereas 17% were slow in remitting, 8% did not maintain remission criteria and 32% never achieved full expressive symptom remission. For experiential negative symptoms, we found that 21% met remission criteria from baseline or remitted within 3 months and maintained remission for 12 months. Whereas 10% were slow in remitting, 6% did not maintain remission criteria, and 64% never achieved full experiential symptom remission. Regarding positive symptoms (hallucinations and delusions combined), we found that 45% met remission criteria from Baseline or remitted within 3 months and maintained remission for 12 months. Whereas 8% were slow in remitting, 19% did not maintain remission criteria (mostly likely due to a positive symptom relapse), and 29% never achieved full positive symptom remission.

Discussion: This longitudinal analysis of essential elements of functional recovery and symptom remission criteria in an urban first episode sample of young individuals with schizophrenia sheds light on meaningful cut-offs and recovery and remission percentages. This information could be used in clinical trials and clinical settings to identify treatment targets and clinically meaningful changes in response to treatment interventions. We believe that the proportion of patients meeting recovery criteria is reduced when experiential negative symptoms are included, and this sheds light on exactly what those levels of negative symptoms may be that portend regarding better or worse functional outcomes.

T135. ENGAGING STAKEHOLDERS IN THE DEVELOPMENT OF STANDARDS FOR A CANADIAN RAPID LEARNING HEALTH SYSTEM IN EARLY INTERVENTION SERVICES FOR PSYCHOSIS: A CONSENSUS DEVELOPMENT CONFERENCE

Manuela Ferrari*¹, Amal Abdel-Baki², Emmanuelle Seery³, Jai Shah⁴, Marc-André Roy⁵, Phil Tibbo⁶, Ridha Joober⁷, Donald Addington⁸, Lili Zeng⁹, Gabriel Julien², Andrea Legros⁹, Francois Leblanc⁹, Elissa Zavaglia⁹, Hope Burko⁹, Megan Davies¹⁰, Sahar Fazeli⁴, Srividya Iyer¹⁰

¹McGill University and Douglas Mental Health Institute, ²Centre Hospitalier de l'Université de Montréal, ³Ministère de la Santé et des Services Sociaux, ⁴McGill University, ⁵Université Laval Faculty of Medicine, ⁶Dalhousie University, Department of Psychiatry, ⁷McGill University, Douglas Mental Health University Institute, ⁸University of Calgary, ⁹Douglas Hospital Research Institute, ¹⁰McGill University and Douglas Hospital Research Institute

Background: Psychotic disorders have profound personal and social impact. Consensus has emerged over three decades that early intervention services (EIS) providing high-quality care and reduced treatment delay may improve outcomes, especially in the first episode of psychosis. In Canada, four provinces have led EIS policy development and support strong EIS networks: Ontario (EPION), British Columbia (EPI APP), Québec (AQPEP), and Nova Scotia (NSEPP). Currently, 131 EIS operate in Canada. EIS guidelines identify elements and evidence-based standards of care essential to sustain high-quality services. Yet despite superior outcomes, multidisciplinary research has identified gaps between evidence-based guidelines, best practices, and the actual implementation of EIS. Use of a Rapid Learning Health System (RLHS) may provide a remedy, as the RLHS promotes rapid data gathering in routine clinical practice, a culture of shared clinician-patient responsibility, as well as engagement by patients, clinical teams, and managers in training and dissemination of evidence. Successful implementation of a RLHS in EIS also demands standards that ensure safety, accountability, evidence-based practice, and quality care, while fostering competitiveness and innovation. Building on the knowledge and experience of a multi-stakeholder team, this presentation describes the processes used to develop guidelines and acceptable practices in: 1) selecting indicators and competencies for rapid learning, and 2) identifying guidelines for creating a culture of rapid learning and improvement in a Canadian RLHS in EIS for psychosis.

Methods: To advance this multi-phase, multi-stakeholder project, we organized a Consensus Development Conference (CDC) in Montreal on Nov. 30-Dec. 1, 2023, inspired by a model from the U.S. National Institute of Health used by many countries in developing consensus statements to shape practices in medical disciplines. CDCs convene stakeholders (citizens, decision-makers, topic experts) to address specific issues, present scientific evidence to a panel/jury and generate joint recommendations. At least one program per Canadian province was invited to our CDC, 2-3 programs in larger provinces, ensuring diversity (e.g., urban and rural areas).

Results: Multi-stakeholder group aggregated to act as CDC panelists (11 people). Canadian EIS sent a delegation of service users, families, clinicians, researchers, and policymakers. A total of 114 attended the pre-conference activities (webinars on a Delphi survey), and 110 participated at the CDC, including seven peer support workers, eight service users and 11 family members. We used arts-based methods to enhance participant engagement (11 video capsules showcasing many participating EIS and three short movies made by former service users). The event was co-facilitated by two former service users and two family members. Formal presentations by Canadian EIS experts (researcher and peer-researchers) were

featured, and two small consensus workshops (10 working groups) met to discuss two key topics: quality of life and recovery; and service engagement and program satisfaction, then developed recommendations on how to implement RLHS in various provincial jurisdictions, maintaining provincial/program identity (e.g., in selecting indicators, assessments) while initiating a shared culture of continuous learning and improvement.

Discussion: This initiative in standards development supports provincial and federal decision-making on healthcare monitoring, system integration, communities of practice, and multicenter research while, crucially, ensuring better operationalization of the RLHS in EIS. The work accomplished at this CDC and new knowledge may inform similar international initiatives to bridge evidence-practice gaps in EIS for psychosis globally.

T136. THE PSYCHS: POSITIVE SYMPTOMS AND DIAGNOSTIC CRITERIA FOR THE CAARMS HARMONIZED WITH THE SIPS: A RESEARCH INSTRUMENT FOR THERAPEUTICS DEVELOPMENT IN CLINICAL HIGH RISK FOR PSYCHOSIS PSYCHOMETRIC EVALUATIONS OF THE PSYCHS INTERVIEW

Catalina Mourgues-Codern^{*1}, Paolo Fusar-Poli², Jai Shah³, Scott Woods¹

¹*Yale University*, ²*King College of London*, ³*McGill University*

Background: The PSYCHS (Positive SYmptoms and diagnostic criteria for the CAARMS Harmonized with the SIPS) is a new semi-structured clinical diagnostic interview and set of rating scales intended to ascertain clinical high risk for psychosis (CHR-P) and measure the severity of attenuated positive psychotic symptoms over time. It has been constructed carefully harmonizing the Comprehensive Assessment of At-Risk Mental States (CAARMS 2015) and Structured Interview for Psychosis-risk Syndromes (SIPS, version 5.6.1). Both of these existing instruments have well-established validity and reliability. Psychometric properties of the PSYCHS, however, should be established independently.

Methods: Two ongoing projects are being conducted to investigate criterion validity of the PSYCHS against two gold-standard interviews. One project is being undertaken against the SIPS at ten different sites, while the other is being conducted against the CAARMS at another ten. The study population consists of individuals between the ages of 12 and 35, with an expected female/male ratio of 1:1. Participants with medical, substance abuse, or communication disorders that could interfere with accurate patient evaluation are excluded from the study. Each participant undergoes two interviews conducted by two separate certified interviewers, not more than two weeks apart. In the SIPS-PSYCHS project, one interviewer conducts a SIPS interview while the other conducts a PSYCHS interview. In the CAARMS-PSYCHS project, one interviewer conducts a CAARMS, while the other conducts a PSYCHS. Interviewers remain blinded to each other's findings. The order of interviews for each project is randomly assigned within each site. The main analysis will determine raters' agreement between PSYCHS-SIPS and PSYCHS-CAARMS considering three diagnostic groups: psychosis (20%), CHR-P (40%), and neither (40%) as quantified by intraclass kappa coefficient. The proportion for each group was selected to represent the expected proportion of patients in a typical referred sample. An estimated sample size of 100 participants for each project was calculated by the kappaSize (V1.2) to yield 95% confidence to obtain agreement between two raters that is at least very good (lower bound of kappa=0.60 and target kappa=0.79). SIPS and CAARMS interrater reliability will be obtained to ensure consistency within gold standard assessment. For validity of symptom ratings against the gold standard, intraclass correlations will be used to assess agreement. The proposed samples will be

sufficient to yield 95% confidence (two-tailed) to obtain an agreement between two raters that is at least moderate (ICC GREATER THAN .74) with a power of .80. Convergent and divergent validity of the PSYCHS will be investigated using measures internal to the Accelerating Medicines Partnership® -Schizophrenia (AMP® SCZ) data collection. A third project will be conducted with another group of 10 sites and 100 participants to assess test-retest reliability for the PSYCHS. The sample size was estimated using the same specifications as the validation study. The percentage of agreement and kappa coefficient is expected to be at least very good (95% confidence to exceed kappa=0.60) for both validity projects and the test-retest project. Symptom agreement is expected to be at least moderate (ICC GREATER THAN .74). Group differences and correlations between the PSYCHS and other measures will show differences and associations in the expected direction for convergent and divergent validity.

Results: Eight participants have been studied (CHR-P = 5, Psychotic = 1, neither = 2) to date as part of Study 1. The absolute agreement for ascertainment between PSYCHS and SIPS was 100%. Additional available psychometric data will be presented.

Discussion: Early returns from criterion validation study 1 suggest that SIPS CHR ascertainment as determined by the PSYCHS is similar to SIPS CHR ascertainment as determined by the SIPS, supporting use of the PSYCHS to derive SIPS criteria for clinical trials entry and for other studies when indicated. Additional available psychometric data will be presented.

T137. BLINDED REMOTE RATINGS OF SITE BASED PANSS INTERVIEWS ADDRESS FUNCTIONAL UNBLINDING IN A STUDY OF ACUTE EXACERBATION OF PSYCHOSIS IN SCHIZOPHRENIA

Steven Targum^{*1}, William P Horan², Sharon Sawchak², Inder Kaul², Stephen K Brannan², Steven M Paul²

¹*Signant Health*, ²*Karuna Therapeutics*

Background: KarXT (xanomeline and trospium chloride) is an oral M1/M4-preferring muscarinic agonist in development for the treatment of psychiatric disorders. Trospium blocks the peripheral cholinergic effects associated with xanomeline (e.g., nausea, vomiting, diarrhea, sweating) but permits its central effects to persist. The possibility that cholinergic-related treatment emergent adverse events (TEAEs) might occur during KarXT treatment and allow functional unblinding was investigated in 2 previously reported studies of KarXT in acutely psychotic people with schizophrenia (EMERGENT-1 and -2). In both studies, remote raters blinded to TEAEs replicated the significant site-based PANSS scores favoring KarXT-assigned participants over placebo and obviated concerns about functional unblinding. EMERGENT-3 was the third study of KarXT in schizophrenia to compare scoring differences between live interviews and remote ratings derived from audio recordings of site-based interviews.

Methods: EMERGENT-3 was a phase 3 efficacy and safety study of KarXT in acutely psychotic hospitalized adults with DSM-5 schizophrenia experiencing an acute exacerbation of psychosis (NCT04738123). Eligible participants had total PANSS scores between 80-120, scores 4 on at least 2 key positive symptom items, and a CGI-S score 4 at screening and baseline. Enrolled participants were randomized to oral KarXT or placebo (1:1 ratio) for 5 weeks and flexibly titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg BID based on tolerance. Site-based raters administered PANSS interviews at every study visit and remote raters scored audio-digital recordings of these interviews. We compared paired total

PANSS scores and subscales including the Marder negative symptom factor (NSF). No data points were imputed in these analyses. Treatment response was defined as $\geq 30\%$ total PANSS score improvement from baseline using available pairs from the baseline and endpoint visits. Statistical analysis included ANOVA, paired t tests, and chi square analyses.

Results: Paired PANSS scores across all study visits (n=982) were highly correlated ($r=0.915$). 210 paired PANSS scores were available at the baseline and endpoint visits. KarXT-assigned participants had significantly greater improvement than placebo on both site-based and paired remote ratings for total PANSS scores ($p=0.0005$ and 0.0017 respectively) and the positive subscale (both $p < 0.0001$); site-based scores were significant on the negative subscale and Marder NSF whereas remote ratings yielded non-significant trends. Both site-based and remote ratings yielded significantly more KarXT treatment responders than placebo ($p < 0.004$ and < 0.04 respectively) with a total predictive value of 89.5%. A bi-directional pattern of scoring deviations was observed for the total PANSS and all subscales such that site-based scores were significantly higher than remote scores when site-based scores were symptomatically high but significantly lower when scores were low.

Discussion: Remote ratings of audio-recorded PANSS interviews replicated site-based ratings and confirmed for the third time (EMERGENT -1, -2, and -3) that remote raters with no knowledge of TEAEs can replicate the significant therapeutic benefit of KarXT over placebo for participants with schizophrenia. The findings obviate concerns that site-based raters were functionally unblinded by knowledge of TEAEs. Remote raters matched the significant findings of KarXT over placebo on the total PANSS and PSS and yielded non-significant trends favoring KarXT for negative symptoms. Lacking visual observation, the audio-recording method may limit remote raters' ability to fully assess negative symptoms.

T138. UNDERSTANDING THE INFLUENCE OF CHILDHOOD ADVERSITY ON PATHWAYS TO CARE DURING FIRST EPISODE PSYCHOSIS

Sheri Oduola*¹

¹*University of East Anglia*

Background: The link between childhood adversity (physical, sexual abuse, neglect, parental separation trauma) and the incidence of psychosis is established. However, there is limited research on the influence of childhood adversity (CA) on help-seeking and pathways to care (PtC) during first episode psychosis (FEP). In this study, we addressed two aims: (a) the associations between PtC characteristics, sociodemographic characteristics and reports of childhood adversity, and (b) the associations between the number of childhood adversities and PtC characteristics in a FEP sample.

Methods: We used data from the Clinical Record Interactive Search-First Episode Psychosis (CRIS-FEP) study. The study was conducted at the South London and Maudsley NHS Trust between 2010 and 2012. Descriptive statistical tests were used to determine associations between sociodemographic, PtC and childhood adversity. We performed multivariable logistic regression to assess the associations between a report of CA and PtC characteristics. We used multivariable negative binomial regression to examine the relationships between the number of CAs and PtC characteristics. In both regression analyses, we controlled for a priori confounders (age and gender).

Results: We identified 558 FEP patients. Of these, 218 (38.3%) patients had experienced childhood adversity, of whom 34.8% had at least two CA recorded. Patients were more likely to have experienced CA if they were female, younger, had an insidious onset of psychosis,

had a longer duration of untreated psychosis (DUP) and had used services before the onset of FEP. Among the patients that experienced CA, there was substantial evidence that they were more likely to be women (adj. OR=1.56; 95% CI=1.17 – 2.26) and had a longer DUP (adj. OR= 1.21; 95% CI=1.02 – 1.40). In terms of the relationships between the number of CA and PtC characteristics, we found evidence that patients with a long DUP (adj. IRR= 1.10; 95% CI 1.03 – 1.16), insidious onset of psychosis (adj. IRR= 1.65; 95% CI 1.21 – 2.25), and those with previous service use history (adj. IRR=1.29; 95% CI 1.02 -1.64) were more likely to experience multiple CA. Conversely, we observed that patients with family involvement in their help-seeking were less likely to report multiple CA (adj. IRR= 0.79; 95% CI 0.63 - 1.00).

Discussion: Our findings provide evidence of a link between childhood adversity and pathways to care during the first episode of psychosis. Experiences of CA are associated with longer DUP and are more prevalent in young people and women being female. There was strong evidence that patients with longer DUP, insidious onset of psychosis and previous service use are more likely to report multiple CA. Our findings are relevant to policymakers, clinicians, patients and carers.

T139. COURSE OF PSYCHOTIC DISORDERS AND CANNABIS USE: RESULTS FROM A 5-YEAR LONGITUDINAL STUDY

Giuseppe D'Andrea*¹, Amal Abdel-Baki²

¹Bologna University, ²Centre hospitalier de l'Université de Montréal

Background: Since their introduction, early-intervention services for psychosis (EIS) have proven to be more effective than standard care in reducing the long-term burden. Nevertheless, the course of psychotic disorders is highly heterogeneous and some individuals will not recover. Cannabis use, which is strongly associated with psychosis onset, might also be a key contributor to poorer outcomes.

Methods: We used a group-based dual trajectory modelling approach on a sample of first-episode psychosis (FEP) referred to two EIS located in the urban centre of Montreal to identify distinct trajectories of psychotic disorders and cannabis use and assess their relationship over a 5-years period. Both severity of psychosis and cannabis use were assessed yearly using, respectively, the Clinical Global Impression scale and the Drug Use Scale. The associations between the identified trajectories and baseline socio-demographic and clinical variables of interest were tested using multinomial logistic regression.

Results: A total of 392 individuals were included. We identified four trajectories of cannabis use: non-users (40.6%), quitters (11.6%), decreaseers (20.0%), and chronic users (27.8%). We also found four distinct trajectories of psychosis: early remission (11.5%), late remission (5.2%), partial remission (51.4%), and persistence (31.9%). Chronic cannabis users had 61% of probability to be in the group with persistent symptoms. However, non-users still had 23% of probability of non-remitting. Male sex and lower education were associated with non-remission of psychosis, whereas second-generation migrants were more likely to achieve symptoms remission compared with non-migrants. Lower social occupational functioning and diagnosis (non-affective v. affective) at baseline predicted worse long-term outcomes. Similar associations were found between predictors and cannabis use trajectories. Male sex and lower education were associated with chronic use of cannabis. Migrants were also more likely to be non-users. Lower social occupational functioning was associated with chronic use while there was no evidence of a relationship with the clinical diagnosis.

Discussion: Cannabis use persistence is associated with poorer outcomes even in EIS settings and needs appropriate intervention. Further research is needed to better identify the factors associated with persistence of cannabis use in order to reduce the burden of psychotic disorders.

T140. LINGUISTIC CORRELATES OF SUICIDAL BEHAVIOR IN INDIVIDUALS ON PSYCHOSIS SPECTRUM

Alessia McGowan^{*1}, Matthew Dobbs², Francesca Serio³, Matthew Cotter², Sophia Shuster¹, Alexandria Selloni², Cansu Sarac⁴, Zarina Bilgrami⁵, Shaynna Herrera¹, Guillermo A. Cecchi⁶, Marianne Goodman¹, Cheryl Corcoran⁷, Agrima Srivastava²

¹*Icahn School of Medicine at Mount Sinai*, ²*Icahn School of Medicine At Mount Sinai*, ³*Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA*, ⁴*Department of Health Sciences, University of Milan, Milan, MI 20122, Italy*, ⁵*Icahn School of Medicine at Mount Sinai and Long Island University*, ⁶*IBM, Thomas J. Watson Research Center*, ⁷*Icahn School of Medicine At Mount Sinai, James J. Peters VA Medical Center*

Background: Suicidal ideation and behavior are prevalent among individuals at clinical high-risk for psychosis (CHR) and individuals with psychosis. Natural Language Processing (NLP) provides an efficient method to identify linguistic markers of suicidality in these individuals. Our prior work has demonstrated that decreased use of modals (e.g., “could”, “should”) and increased use of words with semantic similarity to “anger” are correlated with suicidal ideation in CHR individuals. This study is the first to use NLP analyses of spoken language to identify linguistic correlates of prior suicidal behavior (SB) among individuals on the psychosis spectrum. We hypothesize that individuals on the psychosis spectrum with a history of SB will use language related to impulsivity at higher rates than those who have not. Further, we test whether semantic similarity to anger or modal use may also differentiate individuals on the psychosis spectrum with and without suicidal behavior.

Methods: The sample includes 62 individuals on the psychosis spectrum without SB, 19 CHR with SB, and 29 healthy controls. SB was measured using the Columbia-Suicide Severity Rating Scale. NLP methods include part-of-speech (POS) tagging, a GoEmotions-trained BERT (Bidirectional Encoder Representations from Transformers) Model, and Zero-Shot Text Classification. Impulsivity was modeled by iteratively comparing the semantic similarity of sentences from open-ended speech samples to items on the Barratt Impulsiveness Scale (BIS) using a BERT-based model. All analyses were done with adjustment for demographics.

Results: Individuals with psychotic symptoms with a history of SB used more words related to “anger” compared to those without SB ($s=0.05$; $p < 0.001$) and healthy controls ($s=0.09$; $p < 0.001$). Modal use was not significantly different between the groups. However, individuals on the psychosis spectrum, both with SB ($s=0.43$; $p < 0.01$) and without SB ($s=0.42$; $p < 0.01$) used more words related to the sentence “I act on impulse” compared to healthy controls. There was no significant difference between individuals on the psychosis spectrum with and without SB. The same pattern of results was found for “I do things without thinking”, “I make my mind up quickly”, “I have racing thoughts”, “I don’t pay attention”, and “I say things without thinking”. Thus, for impulsivity, there were no significant differences between those with and without a history of suicidal behavior, only between each of these groups and the healthy controls.

Discussion: As anger is not characteristic of psychosis or psychosis-risk, and anger in language relates to both SI and SB, findings have implications for the consideration of subthreshold anger in suicide risk assessment. However, increased spontaneous use of impulsivity-related speech does not separate individuals with and without histories of SB in this cohort, unlike other cohorts without psychotic symptoms. These findings are similar to what we found previously for use of 1st person pronouns, which typically differentiates individuals with and without SI, but did not do so in a cohort of individuals on the psychosis spectrum. Likely, this is because these individuals already have increased impulsivity and focus on self, as compared with healthy individuals. As NLP is scalable, these language markers may improve suicide screening and prediction.

T141. EMPLOYING SERVICE USER DATA TO IMPROVE EARLY PSYCHOSIS CARE: EPI-CAL'S REAL WORLD IMPLEMENTATION OF DATA DRIVEN CARE

Sabrina Ereshefsky^{*1}, Mark Savill¹, Kathleen E. Nye¹, Regina Gemignani¹, Valerie L. Tryon¹, Madison J. Miles¹, Chelyah Miller¹, Katherine Pierce¹, Merissa Kado-Walton², Amanda P. McNamara², Khanh Linh H. Nguyen¹, Nitasha Sharma¹, Briana Sepulveda¹, Maliha Safder², Lindsay M. Banks¹, Yi Zhang¹, Laura M. Tully¹, Rachel Loewy³, Christopher Hakusui¹, Viviana Padilla¹, Stephania L. Hayes¹, Daniel J. Shapiro¹, Karina Muro¹, Khalima A. Bolden-Thompson¹, Renata M. Botello¹, Rebecca Grattan¹, Andrew Padovani¹, Adam B. Wilcox⁴, Joy Melnikow¹, Daniel Tancredi², Bonnie Hotz¹, Donald Addington⁵, Sonya Gabrielian⁶, Steven R. Lopez⁷, Lisa Dixon⁸, Cameron S. Carter¹, Tara A. Niendam¹

¹University of California, Davis, ²University of California, San Diego, ³University of California, San Francisco, ⁴Washington University St. Louis, ⁵University of Calgary, ⁶University of California, Los Angeles, ⁷University of Southern California, ⁸New York State Psychiatric Institute

Background: Research supports the benefits of collecting service user (SU) outcomes data to longitudinally track treatment progress and symptom fluctuations in a range of medical and psychopathology conditions, including psychosis-spectrum disorders. The field could still benefit from greater understanding on how to translate this data into clinical practice. More information about clinicians' decision-making using SU data and the subsequent impact to SU outcomes, particularly in early psychosis (EP) spaces, is needed.

Methods: Data-driven decision-making is a core goal of Beehive, EPI-CAL's (<https://epical.ucdavis.edu>) data collection and visualization platform for SU, primary support person, and clinic data. Beehive was designed with community partners for California EP programs participating in a learning healthcare network/EPI-NET. EP staff participate in a 3-part Beehive training series, which includes multiple sessions on how to view data and use it in care. Providers use of data in care is captured in multiple ways: 1) SU's assigned clinician views of the individual's data are tracked – each 10 visits the clinician receives a popup, “How was this data used as part of care?” and clinicians “select all that apply” of potential actions they took; 2) Providers are responsible for resolving “urgent clinical notifications” when SU responses to key survey questions indicate risk to self (RTS) or others (RTO), being unhoused, and plans to stop taking medications by indicating their response in the “action list”; and 3) Beehive tracks SU lead clinician's views of any data. To better understand successes and challenges with implementation, and specific questions of using data in care, qualitative “barriers and facilitators” interviews were conducted with clinic staff/providers.

Results: 18 California EP community and university clinics who have been actively implementing Beehive for at least 6 months were included (2021-2023). SU participation varied between 0 and 60 months. 67 responses were received to the data use in care item, and 326 urgent clinical alerts were triggered. The top 3 actions clinicians took after viewing their client's data included "did not change current plan" (19%), provided psychoeducation (16%), and illustrated progress towards specific goal (12%). Approximately 97% of urgent clinical issues were resolved, with a median response time of 2 days. A majority of alerts were for RTS (~58%) and the most frequent RTS/RTO action was "conducted risk assessment" (67%). Compared to the extremely high clinician actions to urgent clinical alerts, for SUs with at least 2 time points (~100), only around 50% of their lead clinicians viewed any data, which is lower than anticipated. There were no effects of clinician viewing behavior on longitudinal SU data outcomes: symptoms (MCSI), process of recovery (QPR), life satisfaction (PWI), shared decision-making, and treatment satisfaction. Around 30 barriers and facilitators interviews with staff/providers suggest several benefits to Beehive — increased opportunity to discuss treatment goals, visualize data, and pull information helpful for reports — as well as challenges — additional training needed, acuity of clients, and collecting the data in general as initial barriers.

Discussion: Innovative approaches to collecting and using data in EP care has shown implementation successes as well as challenges. There are still several challenges to true measurement-based care implementation efficacy, as higher adoption is needed and it is difficult to view outcomes when use is so low. Clinician behavior change is also a significant potential moderator, as data-driven care may be new for many of our community-based clinicians. Together, these data suggest clinicians are responsive with external prompts (such as emails or pop-ups), find these features useful, and collect important information related to interventions with EP service users. However, when the impetus is on the clinician, we have more work to do.

T142. OPEN BOARD

T143. WHY DO SOME PEOPLE WITH PSYCHOSIS RISK SYMPTOMS SEEK PROFESSIONAL HELP AND OTHERS DO NOT?

Tecelli Dominguez^{*1}, Daniel Pech Puebla², Tamara Sheinbaum¹, Lourdes Nieto¹, Ana Fresán¹, Rebeca Robles¹, Steven. R López³, Neus Barrantes-Vidal⁴, César Celada¹, Mauricio Rosel¹, Ricardo Saracco¹, Maria del Carmen Lara⁵, Camilo de la Fuente-Sandoval⁶, Karina Franco-Paredes⁷, Felipe Díaz-Reséndiz⁷

¹*Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"*, ²*Comisión Nacional de Salud Mental y Adicciones*, ³*University of Southern California*, ⁴*Universitat Autònoma de Barcelona*, ⁵*Benemérita Universidad Autónoma de Puebla*, ⁶*Instituto Nacional de Neurología y Neurocirugía*, ⁷*Universidad de Guadalajara*

Background: Despite early detection and intervention efforts, many individuals with the first signs of psychosis still spend between one and two years without seeking adequate treatment. Help-seeking barriers differ according to the cultural context and country-specific mental healthcare systems. Research in this field has been mostly conducted in Western developed countries, where pathways toward care, availability, and accessibility of mental health resources differ from those of low and middle-income countries (LAMIC). Understanding

barriers to help-seeking in LAMIC, where early psychosis programs are still scarce, is important for improving strategies focused on reducing the duration of untreated psychosis. The current study aimed to explore differences in help-seeking barriers, perceived social support, and clinical and functional characteristics between two groups of Mexican young adults reporting psychosis risk symptoms, one currently receiving mental health treatment and the other not (MHT and without MHT). Furthermore, we explore predictors of using mental health services.

Methods: The sample comprised 481 Mexicans (mean age=27.2 years) reporting psychosis risk symptoms (according to the PQ-B cut-off), of which 53% (n=255) were not receiving mental health treatment. Participants responded to self-reported questionnaires through an online survey between March 2022 and October 2023. All participants provided informed consent.

Results: Findings of comparisons between groups showed that those without MHT reported higher barriers of self-reliance ($t(452)=5.2$, p LESS THAN 0.001), lack of time ($t(452)=5.8$, p LESS THAN 0.001) and money ($t(452)=3.4$, p LESS THAN 0.001), embarrassment ($t(452)=4.9$, p LESS THAN 0.001), concern about the family finding out ($t(452)=3.8$, p LESS THAN 0.001), and lack of clinician confidentiality ($t(452)=3.6$, p LESS THAN 0.001). The group receiving MHT showed significantly higher perceived social support and higher severity in all the clinical (except for depression) and functional variables than the group without MHT. The factors associated with an increased probability of using mental health services were: older age (OR=1.0, IC 95%: 1.02-1.07; p LESS THAN 0.001), a higher education level (OR=1.3, IC 95%: 1.1-1.5; p LESS THAN 0.01), higher socioeconomic status (OR=1.8, IC 95%: 1.2-2.6; p LESS THAN 0.01), greater distress associated with psychosis risk symptoms (OR=1.02, IC 95%: 1.01-1.03; p LESS THAN 0.01), higher severity of personality disorder (OR=1.0, IC 95%: 1.0-1.1; p LESS THAN 0.05) and anxiety symptoms (OR=1.2, IC 95%: 1.1-1.5; p LESS THAN 0.01), poor social functioning (OR=1.1, IC 95%: 1.0-1.1; p LESS THAN 0.0001), greater perceived cognitive impairment (OR=1.03, IC 95%: 1.01-1.05; p LESS THAN 0.01), fewer help-seeking barriers (OR=0.94, IC 95%: 0.9-1.0; p LESS THAN 0.001), self-reported mental health problems (OR=13.1, IC 95%: 8.5-20.4; p LESS THAN 0.001) and higher perceived social support (OR=1.02, IC 95%: 1.0-1.02; p LESS THAN 0.05).

Discussion: As far as we know, this is the first study exploring barriers to help-seeking in Mexican young adults with psychosis risk symptoms. Findings support previous studies indicating that stigma toward psychosis constitutes a major problem for contact with health services that may delay early identification and increase the duration of untreated psychosis. Regarding the Mexican context, the lack of preventive programs and community public services makes accessibility difficult and increases barriers for those with fewer economic resources. Findings provide relevant information that may help us understand why some of the Mexicans at-risk for psychosis are not using mental health services, which is useful for designing more effective strategies to improve help-seeking, early identification, and timely treatment delivery in Mexico.

T144. EXPLORING PATIENT PERSPECTIVES ON ANTIPSYCHOTIC MANAGEMENT FOLLOWING REMITTED FIRST EPISODE PSYCHOSIS: A QUALITATIVE STUDY

Laurent Bechard*¹, Elizabeth Anderson², Charles Massé³, Mina Gabriel-Courval³, Charles Desmeules³, Maxime Huot-Lavoie³, Olivier Corbeil⁴, Sébastien Brodeur³, Marc-André Roy³, Sophie Lauzier⁴, Marie-France Demers⁴

¹University Laval, ²School of Psychology, Université Laval, ³Université Laval Faculty of Medicine, ⁴Pharmacy Faculty, Laval University

Background: The management of antipsychotic treatment post-remission of a first-episode psychosis (FEP) remains contentious, with concerns about adverse effects and recovery outcomes. Guidelines advise using shared decision-making (SDM), yet its implementation is still limited. Patient perspectives on the treatment decision-making process are underexplored. Understanding these perspectives is crucial for optimizing SDM in clinical practice. We aim to describe the perception of service users on pros/cons of antipsychotic discontinuation after post remission of FEP.

Methods: This qualitative descriptive study involved semi-structured interviews with service users with remitted FEP at two early intervention clinics in the province of Québec, Canada. Data were thematically analyzed to discern user perspectives on the continuation or discontinuation of antipsychotic medication.

Results: Twelve service users (average age 26; 7 males, 5 females) participated, with a median follow-up of 30 months. Of these, 7 chose to continue antipsychotics, 2 were in the process of stopping, 2 intended to discuss cessation, and 1 had already stopped. Perceived advantages reported by the participants for long term antipsychotic maintenance were well-being, reduced psychotic symptoms, improved social functioning, and a reduced risk of relapse. All participants associated potential discontinuation with a heightened risk of relapse, none stated the specific percentage risk of relapse, nor the known efficacy of long-term antipsychotic use in preventing relapse in FEP as evidenced by current research. Some participants also viewed positively the fact that antipsychotic intake increased appetite, improved performance in hobbies, and gave emotional stability. However, continued long-term use was not without its perceived cons; notably, side effects were the most frequently cited concern, highlighted by half of the participants. Financial burden, dependency, and potential long-term health implications were also mentioned. Misconceptions about long-term medication risks, such as liver damage with lithium or renal damage with antipsychotics, were reported. Conversely, the choice of potentially stopping medication was seen as a way to improve well-being, reduce adverse effects, and a regain sense of self. Opinions on medication's role in achieving well-being or normalcy varied significantly; some viewed ongoing treatment as essential for stability, while others saw discontinuation as key to regaining autonomy.

Discussion: This study highlights the deeply personal and complex nature of decision-making regarding long-term antipsychotic management following FEP. Information reported by participants on the disadvantages of continued medication seemed to stem more from personal experiences rather than clinical counseling, which may reveal information needs. Although the risk of relapse is well recognized, the significance of such relapse varied extensively, with few service users reflecting on its potential impact on their lives. This underscores the need for clinicians to engage with service users more comprehensively, balancing the discussion of benefits and potential adverse effects, as experienced and perceived by the patient. Such engagement should aim to align treatment plans with each patient's values and preferences. Additionally, the complexity observed in these decision-making processes highlights the need for a decision aid tool, specifically designed to assist stakeholders in deciding whether to continue or not antipsychotic. This tool could significantly enhance the SDM process by providing personalized, evidence-based information tailored to individual needs.

T145. CANNABIS AND ALCOHOL MISUSE IN A COHORT OF PATIENTS WITH FIRST-EPISODE PSYCHOSIS: DIFFERENT TRAJECTORIES OF SUBSTANCE ABUSE AND IMPACT ON CLINICAL OUTCOMES

Carolina Spanevello*¹, Luis Alameda², Alessandra Solida³, Philippe Golay¹, Philippe Conus⁴

¹*Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Switzerland,* ²*Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Switzerland - Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Switzerland,* ³*Department of Psychiatry- Lausanne University Hospital (CHUV)- CH,* ⁴*Service of General Psychiatry, Department of Psychiatry, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland*

Background: Substance use disorder (SUD) is common in first-episode psychosis (FEP) and linked to poorer clinical and functional outcomes. Previous studies on the subject were mostly cross-sectional or had short-term follow-ups, leaving clinical impact of SUD course still unclear. Our main aim in this study was to (A) group patients on the base of different trajectories of SUD course along a 3-year follow-up period and to (B) explore any consistent association with baseline characteristics and clinical outcomes.

Methods: A total of 457 FEP subjects were included from our early-intervention program. First, we performed a latent class analysis on substance abuse indicators (alcohol and cannabis) during the 3-years program and defined groups based on different trajectories of SUD course. Thereafter, we adjusted for confounding factors and compared these groups for sociodemographic, clinical and outcome data through a series of logistic regressions.

Results: First we observed that cannabis and alcohol users formed two quite distinct groups of patients with few overlapping subjects, thus outlining different consumer profiles. As a supporting evidence, latent class analysis showed that SUD evolution was different in these groups, with lack of decreased consumers in the alcohol one (abuse, abstinent or light) and three profiles for cannabis (abstinent or light, decreased and persistent). Furthermore, logistic regression showed significantly better outcomes in patients who were abstinent compared to the persistent ones. Subjects decreasing cannabis use had better functional outcomes, but less clinical improvement than expected.

Discussion: Findings in this first-episode cohort support previous evidence that substance abuse has negative impact on clinical outcomes and functioning. Comparing to previous studies, decreased SUD was less significantly associated with clinical improvement.

T146. LITERATURE REVIEW ON THE IMPACT OF PHARMACISTS IN PSYCHOTIC AND BIPOLAR DISORDERS: A SCOPING REVIEW

Nadia Akliouat*¹, Elizabeth Anderson², Charles Desmeules³, Laurent Bécharde¹, Olivier Corbeil¹, Frédéric Bergeron⁴, Marc-André Roy⁵, Marie-France Demers¹

¹*Pharmacy Faculty, Laval University,* ²*School of Psychology, Laval University,* ³*Faculty of Medicine, Laval University,* ⁴*University Laval,* ⁵*Université Laval Faculty of Medicine*

Background: Previous studies have shown pharmacists in mental health. No studies have been conducted to describe the role of pharmacists in the early intervention of psychotic or

bipolar disorders. This population is more prone to side effects from the treatments they receive. Lower adherence to antipsychotic medications is a challenge in treating patients with these disorders. A low adherence is linked to a greater risk of hospitalizations.

Methods: The study aims to conduct a scoping review of the literature on the impact of pharmacists on individuals with psychotic or bipolar disorders in the literature. The searched database includes Ovid MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science without any date limitation. Data were extracted according to population, study design, country, impact of the pharmacist in the study, and study results. We included articles discussing psychotic and bipolar disorders. The articles must present the impact of clinical pharmacists. We also included retrospective cohort studies, longitudinal and observational studies, and quality improvement projects.

Results: 1676 studies were identified, and 1399 articles have been screened. The results of the study are going to be presented. A preliminary overview of the studies evaluated underlines the possible contribution of pharmacists on adherence, tolerability issues and care coordination. The pharmacist helps improve the efficacy of treatments and reduce polypharmacy.

Discussion: Pharmacists play a significant role in the care given to people with psychotic and bipolar disorders. The findings contribute to a deeper understanding of the current state of knowledge surrounding the implication of pharmacists in severe mental illnesses and help define opportunities on how to improve patients' access to the best possible care. This study also sheds light on the nuanced impact of pharmacists in optimizing outcomes for individuals with psychotic and bipolar disorders, signaling a call for further research and strategic interventions in early intervention.

T147. GLOBAL DISRUPTIONS IN WHITE MATTER INTEGRITY IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

Lara Bolte^{*1}, George Gifford², Mauricio Serpa³, Michiel Cottaar⁴, Paola Dazzan⁵, Arijia Maat⁶, Lieuwe De Haan⁷, Benedicto Crespo Facorro⁸, Birte Glenthøj⁹, Stephen M. Lawrie¹⁰, Colm McDonald¹¹, Oliver Gruber¹², Therese Van Amelsvoort¹³, Celso Arango¹⁴, Tilo Kircher¹⁵, Barnaby Nelson¹⁶, Silvana Galderisi¹⁷, Rodrigo Bressan¹⁸, Jun Soo Kwon¹⁹, Mark Weiser²⁰, Romina Mizrahi²¹, Gabriele Sachs²², Matthias Kirschner²³, the PSYSCAN Consortium²⁴, Rene Kahn²⁵, Philip McGuire²⁶

¹University of Oxford, ²Department of Psychiatry, University of Oxford, ³Institute of Psychiatry, University of Sao Paulo, Brazil, ⁴Nuffield Department of Clinical Neurosciences, University of Oxford, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁶University Medical Center Utrecht, NL, ⁷AMC Amsterdam, ⁸Hospital Universitario Virgen del Rocío. CIBERSAM. Universidad de Sevilla, IBiS, Sevilla, ⁹University of Copenhagen Center for Neuropsychiatric Schizophrenia Research, ¹⁰University of Edinburgh, ¹¹National University of Ireland, Galway, ¹²University of Heidelberg, ¹³Maastricht university, ¹⁴Hospital General Universitario Gregorio Marañón, ¹⁵Philipps-University Marburg, Department of Psychiatry, ¹⁶Orygen Youth Health Research Centre, ¹⁷University of Campania Luigi Vanvitelli, ¹⁸Universidade Federal de Sao Paulo - UNIFESP, ¹⁹Seoul National University College of Medicine, ²⁰Sheba Medical Center At Tel Hashomer, ²¹McGill University, ²²Department of Psychiatry and Psychotherapy, Medical University of Vienna,

Vienna, Austria, ²³University of Zurich, ²⁴The PSYSCAN Consortium, ²⁵University Medical Center Utrecht, ²⁶Department of Psychosis Studies, IoPPN, King's College London, UK

Background: Disruptions in white matter integrity have been reported across all stages of psychosis. However, findings have not been consistent, and it remains unclear whether these abnormalities precede disease onset or whether they occur downstream of disease progression. A major limiting factor of previous research has been the use of modest sample sizes. This study aims to overcome this limitation by involving multiple centres and to investigate white matter integrity at an early stage of the disease.

Methods: As part of the large-scale multi-centre PSYSCAN project, 207 (aged 25.64 ± 5.43 years; 134 male) participants with first-episode psychosis (FEP) and 113 (aged 23.67 ± 4.48 years; 66 male) age and sex-matched healthy controls (HC) completed the baseline assessment. T1-weighted and diffusion-weighted images were acquired using 3T scanners at all 18 scanning sites. Tract-Based Spatial Statistics was used to analyse fractional anisotropy. Participants also completed further scans and tests at baseline and additional time points.

Results: Relative to the HC participants, fractional anisotropy was significantly lower ($p < .05$) in FEP in multiple major white matter tracts, including the forceps minor, corticospinal tract, anterior thalamic radiation, inferior and superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and hippocampus. FEP subjects displayed no brain areas of significantly increased fractional anisotropy in comparison with HC.

Discussion: This study provides empirical support that white matter integrity is disrupted during the early stages of psychosis. This disruption is not exclusive to one region but affects the brain globally. Heterogeneity in the neuropathology of psychosis, neurodevelopmental abnormalities, and factors affecting the white matter microstructure such as inflammation may contribute to the observed widespread disruption. Future research focused on underlying mechanisms is needed.

T148. LATENT TRAJECTORIES OF FUNCTIONAL AND CLINICAL OUTCOMES FOLLOWING EARLY INTERVENTION SERVICES FOR FIRST EPISODE PSYCHOSIS

Olivier Percie du Sert^{*1}, Joshua Unrau², Ridha Joobar², Ashok Malla², Delphine Raucher-Ch  n  ², Martin Lepage²

¹Douglas Mental Health University Institute, ²McGill University

Background: From the very first episode, the course of psychosis is marked by substantial heterogeneity. This heterogeneity poses significant challenges in accurately diagnosing individuals, predicting treatment response, as well as prognosticating outcomes. While systematic and meta-analytical reviews have demonstrated the effectiveness of early interventions services (EIS) for first-episode psychosis (FEP), not all individuals derive equal benefits. The heterogeneity of functional and clinical trajectories within the context of EIS remains poorly understood. This study aimed to identify latent trajectories of functional, and clinical outcomes in a representative sample of FEP individuals undergoing EIS during the critical period. Additionally, we examined the inter-relationship between trajectories and investigated the association of trajectory membership with baseline characteristics and distal outcomes.

Methods: The Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) is a 2-year, high-fidelity, catchment area-based, EIS for FEP. Between 2003 and 2018, PEPP-Montreal provided services to 689 drug-na  ve individuals aged 14-35 years old, with

schizophrenia or another psychotic disorders. A comprehensive longitudinal assessment conducted at baseline, 1, 2, 3, 6, 12, 18 and 24 months yielded a detailed characterization of participants on multiple dimensions including sociodemographic, cognition, psychopathology, and functioning. Longitudinal latent growth modelling was used to identify trajectories of functioning, positive and negative symptoms. Covariates were investigated following a manual three-step approach. Multinomial logistic regressions were performed to identify predictors of latent class membership among baseline characteristics. Wald chi-square tests were used to test for differences in distal outcomes.

Results: Two trajectories of social-occupational functioning were identified: serious to slight impairment (57%) and major to serious impairment (43%). Positive symptoms exhibited two trajectories: high and decreasing (68%) and low and decreasing (32%). Negative symptoms displayed three trajectories: persisting (44%), decreasing (41%) and fluctuating (15%). Trajectories may differ in terms of the initial level of outcome and the rate of change over time. Individuals with lower symptom trajectories tended to follow a more favorable trajectory of functioning, while those with higher symptom trajectories were more likely to have an impaired trajectory of functioning. Additionally, early treatment response consistently and strongly predicted membership in better trajectories (OR = [4-14], while significant differences in clinical remission and functional recovery were found between trajectories at the end of EIS.

Discussion: While individual trajectories were heterogeneous and highly variable, these results confirm the existence of identifiable patterns and distinct courses of outcomes. Although precision psychiatry is still an emerging concept, our findings offer insights into clinically meaningful subgroups of individuals that could inform the development of individually tailored EIS and prognosis models for individuals experiencing FEP. Ultimately, the early identification of individuals who could benefit from more intensive and targeted care becomes crucial in optimizing treatment efficacy.

T149. SOCIAL ANHEDONIA IN CLINICAL HIGH RISK FOR PSYCHOSIS AND FIRST EPISODE PSYCHOSIS: ASSOCIATIONS WITH SOCIAL COGNITION AND DEPRESSIVE SYMPTOMS

Nahrie S Kim¹, Tae Young Lee¹, Aram Im¹, Diane Gooding*²

¹*Pusan National University Yangsan Hospital*, ²*University of Wisconsin-Madison*

Background: Characterization of social anhedonia in individuals at risk for, or in the early phases of, psychosis is essential in terms of better understanding clinical needs and enhancing precision medicine. Prior work has suggested the association between elevated levels of social anhedonia and poorer clinical outcomes. The high comorbidity of major depressive disorder in some individuals at clinical high risk for psychosis (CHR-P) further complicates the presentation. Because impairments in social cognition may lead to disruptions in reward processing, one study goal was to examine the association between social cognitive task performance and self-reported levels of social anhedonia. We also sought to investigate further the relationships between social anhedonia, depression, and other psychopathological features.

Methods: The participants included 51 CHR-P individuals, 29 first-episode psychosis (FEP) patients, and 92 matched healthy controls (HC). We administered the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) to measure social anhedonia, the Reading the Mind in the Eyes Test (RMET), and the Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions (MSCEIT-ME) to assess social cognition, and the

Montgomery-Asberg Depression Rating Scale (MADRS) to evaluate depressive symptom severity. Group comparisons and correlation analyses examined the relationship between the ACIPS and the RMET, MSCEIT-ME, and MADRS.

Results: Both the CHR-P and FEP groups demonstrated significantly lower ACIPS scores, indicating greater social anhedonia, than the HC group ($p < .001$). Within the CHR-P group, 21 individuals had comorbid major depressive disorder. The ACIPS scores of the CHR-P group with comorbid depression were significantly lower than those without comorbid depression ($p < .05$). The MADRS score in the CHR-P group was correlated with ACIPS scores at a trend level. The ACIPS scores of FEP patients were significantly correlated with MSCEIT-ME scores but not with RMET accuracy. In contrast, neither the CHR-P nor HC groups exhibited any correlation between the ACIPS and either social cognitive task (MSCEIT-ME or RMET).

Discussion: These data converge with earlier studies indicating that CHR-P individuals exhibit pronounced social anhedonia before psychosis onset. The findings extend the literature by suggesting potential variations in the mechanisms underlying the manifestation of social anhedonia within the psychosis spectrum. The significant association of social anhedonia with concurrent depression observed within a subgroup of CHR-P individuals may indicate a particularly at-risk group or may be predictive of a distinct diagnostic trajectory within the CHR group. Further investigation from a transdiagnostic perspective should be conducted on CHR-P individuals. These additional characterizations may help inform early identification and treatment efforts.

T150. INTRODUCING A VALUABLE RESEARCH TOOL: THE HEALTHCARE-INTEGRATED RESEARCH DATABANK

Anne-Marie Essiambre^{*1}, Chantale Thériault¹, Maxime Huot-Lavoie², Colombe Claveau³, Olivier Corbeil⁴, Laurent Béchar⁴, Sophie Chabot¹, Elizabeth Anderson⁵, Marie-France Demers⁴, Roy Marc-André⁶

¹CERVO Brain Research Centre, ²Faculty of Medicine, Laval University, ³Psychology School, Laval University, ⁴Pharmacy Faculty, Laval University, ⁵School of Psychology, Université Laval, ⁶Department of Psychiatry, Laval University

Background: Clinique Notre-Dame-des-Victoires is a first episode psychosis (FEP) clinic, based in Québec, Canada. The clinic provides clinical support for youth who have undergone a FEP, featuring a diverse team of clinicians from various health fields dedicated to enhancing their long-term recovery. Complementing the clinical team, the clinic also houses healthcare-integrated research team, the Équipe de recherche RAPPsoDIS (Recherche Axée sur la Personne et le Psychose: Démarche Intégrée aux Soins, i.e. the Person-Centered Research and Psychosis: Integrated Approach to Care). A databank has been developed to address identified clinical needs and research questions posed by graduate students or researchers, aiming to enhance knowledge in the field of FEP. More specifically, the primary objectives include: 1) enhancing comprehension of FEP patients' experiences; 2) identifying mental and physical comorbidities and their correlations with various FEP aspects; 3) defining the relationship between psychosis-associated factors and functional levels; 4) evaluating the impact of diverse treatments; 5) measuring the influence of overall health on functioning; 6) documenting treatment response and contributing factors; and, 7) advancing understanding of the evolution of FEP.

Methods: Ethical approval has been obtained before establishing the healthcare-integrated research databank. The platform employed for the databank is RedCap (Research Electronic Data Capture), a secure web software designed for constructing and overseeing projects, including databases and surveys. Access to a patient's clinical data requires written consent. Following this, a research team member collects and inputs data into the databank. Consequently, the databank's population aligns with admission criteria for the FEP clinic: patients must exhibit symptoms or a diagnosis of a psychotic disorder, be aged between 18-35, and either have not been treated for psychosis or have received treatment for less than 12 months.

Results: The structure of the databank was inspired by the clinical monitoring of patients admitted to the FEP clinic. Observation spans from admission to the clinic and recurs every six months until the end of follow-up. Diverse databank forms capture metabolic, demographic, pharmacological, and clinical data. For instance, blood tests measure health indicators such as blood sugar, prolactin, cholesterol levels, and metabolic syndrome risk. Sociodemographic details include socio-professional status, marital status, education, legal status, diagnoses, comorbidities, family history (mental and physical), psychological trauma history, and psychiatric hospitalization. Ongoing records of psychotropic medications encompass type, dosage, and treatment duration. Additionally, data from various clinical scales widely used in the FEP field is collected.

Discussion: The continual advancement of technologies, including secure web software, presents a significant advantage for mental and physical health research. It offers compelling options to enhance understanding in FEP. Utilizing a databank such as the Healthcare-integrated Research Databank is one of these valuable options. The great variety of data in this databank renders it exceptionally unique and holds promise for addressing research questions and clinical needs. In the near future, we aim to enhance data management through the implementation of artificial intelligence. This approach has the potential to streamline databank management, benefiting various research projects. Looking ahead, clinicians and patients may also reap the rewards of these advancements.

T151. UNDERSTANDING CAFFEINE IMPACT ON SUSTAINED ATTENTION IN EARLY PHASE PSYCHOSIS: UNVEILING COGNITIVE INSIGHTS THROUGH THE USE OF EEG

Ashley Francis^{*1}, T-Jay Anderson², Katie McKearney³, Philip Tibbo⁴, Derek Fisher⁵

¹*Dalhousie University Faculty of Medicine*, ²*Department of Psychology, Dalhousie University*, ³*Department of Psychology, Mount Saint Vincent University*, ⁴*Dalhousie University, Faculty of Medicine*, ⁵*Department of Psychology, Mount Saint Vincent*

Background: Caffeine is commonly consumed for its purported positive effects on alertness, mood, and cognition. Cognitive impairment, including the domain of attention, stands out as a notable feature of schizophrenia (SZ). Those diagnosed with SZ often consume high levels of caffeine, commonly exceeding 550 mg daily, but how caffeine influences cognition in individuals with SZ, especially in the early stages of the illness, remains understudied. Electroencephalography (EEG)-derived event-related potentials (ERPs) provide a means to explore these cognitive effects at the neural level. This study aimed to investigate how acute caffeine intake affects individuals with SZ using a double-blind, placebo-controlled design.

Methods: Our study involved individuals from the Nova Scotia Early Psychosis unit who were within the first five years of their SZ diagnosis (n = 11) and healthy controls (n = 14), all between the ages of 20 – 38 (HC: M = 22.5, SZ: M:28.18), participants significantly

differed in age with individuals with SZ being significantly older than HCs. There were no other differences between groups on any other demographic information.

Results: Our findings revealed that, regardless of the drug condition, individuals with SZ consistently showed smaller P300 amplitudes than HCs throughout AX-continuous performance task (AX-CPT). Individuals with SZ also tended to have faster P300 latencies, possibly indicating incomplete processing within this group. There were no main effects found for the behavioural findings, however, some interesting interactions were found. One interesting interaction revealed that there was a relationship between the accuracy of responses, drug condition and group, such that HCs ($M = 93.96$, $SE = 1.66$) in the caffeine condition were outperforming individuals with SZ ($M = 87.79$, $SE = 2.19$; $p = .05$). We also found the expected results, which suggested that the caffeine significantly improved the performance of HCs on the behavioural findings. Interestingly, our study suggested that the relationship between caffeine and SZ might be influenced by symptom profiles. Specifically, higher negative symptoms were linked to longer latencies while amplitude appeared to be more influenced by positive symptoms, suggesting an increase in positive symptoms correlated with a decrease in P300 amplitude, however, this was only true when caffeine was present.

Discussion: Our research suggests that acute caffeine intake did not enhance sustained attention in individuals with early-phase schizophrenia, at either the neural or behavioural level. Future studies should consider using caffeine doses equivalent to or higher than participants reported daily intake as we found that compared to previous reports the usage reported by our participants was abnormally low. The relatively low caffeine use in our SZ sample could serve as a limitation to the study and may be a distinct feature of an early-phase sample, however, this relationship would need to be further explored.

T152. EARLY PSYCHOSIS PROGRAM SERVICE USER SELF-REPORTED EDUCATION, EMPLOYMENT, AND SOCIAL ACTIVITIES AND THE RELATIONSHIP TO OVERALL LIFE SATISFACTION: PRELIMINARY DATA FROM THE CALIFORNIA EPI-CAL PROJECT

Valerie Tryon^{*1}, Kathleen E. Nye², Nev Jones³, Leigh Smith⁴, Mark Savill⁵, Sabrina Ereshefsky⁶, Daniel Shapiro⁷, Katherine M. Pierce⁵, Chelyah Miller⁸, Madison J. Miles², Amanda P. McNamara⁹, Merissa Kado-Walton¹⁰, Khanh Linh H. Nguyen², Nitasha Sharma², Christopher Hakusui⁸, Viviana Padilla⁴, Maliha Safdar¹¹, Rachel Loewy¹², Laura M. Tully¹³, Yi Zhang⁵, Lindsay Banks⁸, Stephania L. Hayes², Karina Muro⁸, Khalima A. Bolden-Thompson⁸, Renata M. Botello², Rebecca Grattan⁴, Andrew J. Padovani¹⁴, Adam B. Wilcox¹⁵, Joy Melnikow¹⁴, Daniel J. Tancredi¹⁶, Bonnie Hotz⁴, Donald Addington¹⁷, Sonya Gabrielian¹⁸, Steven R. Lopez¹⁹, Lisa Dixon²⁰, Cameron S. Carter⁴, Tara A. Niendam⁴

¹UC Davis Medical Center, ²University of California, Davis, School of Medicine, ³University of Pittsburgh, ⁴Department of Psychiatry and Behavioral Sciences, University of California Davis, ⁵University of California Davis, ⁶University of California, Davis, ⁷UC Davis Dept. Psychiatry and Behavioral Sciences; Early Psychosis Programs, ⁸Department of Psychiatry and Behavioral Sciences, University of California-Davis, Sacramento, CA, ⁹University of California at San Diego, ¹⁰Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, ¹¹University of California, San Diego, ¹²Department of Psychiatry, Weill Institute for Neurosciences, University of California - San Francisco, ¹³Department of Psychiatry and Behavioral Sciences, University of California,

Davis, School of Medicine, Sacramento, CA 95820, USA, ¹⁴Center for Healthcare Policy and Research, University of California-Davis, Sacramento, CA, ¹⁵Washington University in St. Louis, ¹⁶Department of Pediatrics, University of California Davis, ¹⁷Department of Psychiatry, University of Calgary, ¹⁸Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, ¹⁹Department of Psychology, University of Southern California, ²⁰NYSPI/Columbia University Medical Center

Background: California's EPI-CAL project (<https://epical.ucdavis.edu>) joined several university- and community-based early psychosis (EP) programs to create a learning health care network and contribute to the NIMH EPINET database. People receiving EP care consistently identify obtaining occupational success and high-quality social relationships as important goals. Satisfaction with vocational roles and social relationships can contribute to overall quality of life. The objective of the current study was to summarize education and employment-related activities for services users in EPI-CAL, to examine if they are satisfied with their current occupational and educational roles in life and their relationships, and whether this was related to overall satisfaction with life as whole.

Methods: Service users across EPI-CAL clinics completed self-report surveys about outcomes related to their life and mental health treatment. Surveys are administered at enrollment in the EP program and every 6 months thereafter. Descriptive analyses summarize the demographic and outcomes data collected related to service users' self-reported functioning, including survey responses regarding life outlook, social relationships, employment, and education. Chi-square analysis was used to examine age group differences between education and employment activities. A linear regression was run to examine the effect of role satisfaction and social relationships on overall life satisfaction as measured by the Personal Wellbeing Index (PWI).

Results: To date, 287 service users across 20 EPI-CAL clinics have completed surveys on life outlook, education, employment and related activities, and social relationships. Services users received diagnoses associated with a first episode psychosis (FEP; $n = 208$, 72%), clinical high risk (CHR; $n = 65$, 23%), or FEP/CHR status not confirmed ($n = 14$, 5%). Ages ranged from 11 to 36 ($M = 20.01$ years, $SD = 4.7$). School and work attendance was examined across age groups with 137 individuals (48%) reporting school attendance only (part-time or full-time), 49 individuals (17%) in work only, 34 individuals (12%) in both school and work, and 49 individuals (17%) engaged in neither school nor work. As expected, there was a significant effect of age on the type of activities that individuals were engaged in ($\chi^2(9)=127.75$, $p < 0.001$), with younger people proportionally participating in only school to a higher degree than other roles and older adults (26+ years) were engaged in only work or neither work nor school to a higher degree than other age groups. When asked whether they were engaged in as much work, volunteering, or school as they wanted, 115 (40%) service users either agreed or strongly agreed and 101 (35%) disagreed or strongly disagreed. Social relationships (belonging to a group of people that share attitudes and beliefs), role satisfaction (feels that current role will help them reach their long-term goals), and participation in education and/or employment activities significantly predicted overall satisfaction with life as a whole (R^2 for overall model 23.1%; $F(5, 238) = 14.27$, $p < 0.001$).

Discussion: In the current study, work and school engagement varies widely across service users in EP programs as the individuals in these programs represent a diverse group that are at different developmental stages in their life. Self-reported social relationship satisfaction, role satisfaction, and work and/or school engagement were significantly related to overall life satisfaction. Therefore, EP service providers must focus on occupational, educational, and

social relationship satisfaction as recovery goals for individuals receiving early intervention services.

T153. EVALUATING AN EARLY-STAGE PSYCHOSIS TRAINING PROGRAM FOR INTERDISCIPLINARY MENTAL HEALTH TRAINEES: A MIXED-METHODS PILOT STUDY

Joseph DeLuca^{*1}, Julie Berrett-Abebe¹, Michelle Pagnotta¹, Reese Ranno¹, Lennart Mierow¹, Margaret McClure¹

¹*Fairfield University*

Background: Early-stage psychosis (EP) refers to youth at clinical high risk for psychosis (CHR) or those experiencing first-episode psychosis (FEP). Early identification is critical, since a longer duration of untreated psychosis (DUP) is consistently associated with poorer recovery outcomes. However, many mental health (MH) providers do not receive training in EP screening/referral and few studies have focused on training MH trainees – a critical population of future leaders in the field who are very likely to work with young people experiencing psychosis during their training. The aim of this study was to pilot test an EP training program for interdisciplinary MH trainees.

Methods: We conducted this ~75-minute in-person training in December 2023 with interdisciplinary MH trainees (graduate and undergraduate) at a US university. A mixed-methods approach was used, with a pre-test (N=33) and immediate-post-test (N=37). The presentation was co-developed and co-presented by an EP expert (licensed clinical psychologist) and two experts in interdisciplinary healthcare (licensed social worker and licensed counselor). The interactive presentation included ~15 minutes of foundational content on interdisciplinary healthcare best practices, followed by ~60 minutes of EP content (e.g., prevalence and spectrum of psychosis, CHR v. FEP, case study and video, stigma, screening/referral, Q and A). Primary outcome variables included clinical comfort in treating someone with psychosis; intended clinical behavior regarding screening, seeking supervision/consultation, and speaking with caregivers about psychosis; clinical self-efficacy regarding knowledge and skills; public stigma (social distance, negative stereotypes); psychosis knowledge and perceived barriers to implementing knowledge/skills (open-ended questions); and feasibility/acceptability (satisfaction).

Results: Matched participant data were analyzed (N=21). This matched sample was primarily white (81%), graduate students (76%), female (67%), and aged 18-34 (81%). There was a relatively even distribution of trainees from psychology, social work, counseling, psychiatric nursing, and marriage/family therapy. Paired-samples t-tests revealed significant pre/post changes in all outcome domains: clinical comfort ($p=.021$), intended clinical behavior (likelihood of screening [$p=.005$] and speaking with caregivers [$p=.002$]; seeking supervision/supervision [$p=.340$]), clinical self-efficacy (knowledge [$p \text{ LESS THAN } .001$] and skills [$p \text{ LESS THAN } .002$]), public stigma (social distance [$p \text{ LESS THAN } .001$] and negative stereotypes [$p=.002$]), and feasibility/acceptability (satisfaction $M=9.2/10.0$, $SD=1.3$, and GREATER THAN 95% agreed the training was useful and could be incorporated into their clinical work). One-third of participants reported limited psychosis knowledge at pre-test, and preliminary qualitative analyses suggested improvements in psychosis knowledge at post-test. Barriers to implementing knowledge from the training into clinical practice included structural barriers (e.g., too many screeners at intake, reimbursement) and lack of confidence due to limited clinical experience.

Discussion: This brief, interdisciplinary training program on EP demonstrated acceptability, feasibility, and initial effectiveness. Interdisciplinary MH trainees reported improvements in their clinical development, reductions in stigma, and high satisfaction with the training. Participants also identified perceived barriers to using new knowledge and skills. Future research will further explore barriers and facilitators, as well as survey participants longitudinally to explore trainees' retention and use of training skills.

T154. EARLY PSYCHOSIS INFORMATICS INTO CARE [EPICARE]: A CO-DESIGNED FRAMEWORK FOR IMPLEMENTING AND EVALUATING A NATIONAL INTEGRATED DIGITAL REGISTRY AND CLINICAL DECISION SUPPORT SYSTEM WITHIN EARLY INTERVENTION IN PSYCHOSIS SERVICES

Sian Lowri Griffiths^{*1}, Graham Murray², Sophie, M Allan³, Sonia Johnson⁴, Richard Drake⁵, Sarah Sullivan⁶, Megan Pope¹, John Ainsworth⁵, Pauline Wheelan⁵, Ben Green⁵, Mohammad Zia Katshu⁷, Yanakan Logeswaran⁸, Matt Machin⁹, Justin Waring¹, Rachel Upthegrove¹, James Kirkbride⁸

¹University of Birmingham, ²Department of Psychiatry, ³University of East Anglia, ⁴University College London, ⁵University of Manchester, ⁶University of Bristol, ⁷Nottingham University, ⁸UCL, ⁹University of Manchester

Background: Early Intervention in Psychosis (EIP) services in England are mandated to provide multidisciplinary care to people experiencing First Episode Psychosis (FEP). Despite UK National Health Service (NHS) investment in EIP, people from historically underserved populations may have unequal access to high quality services, and only 30-40% achieve full recovery. In other disease areas, including stroke and dementia, national digital registries coupled with clinical decision support systems have revolutionised delivery of equitable, evidence-based interventions to transform patient outcomes and reduce population-level disparities in care and prognosis. Given psychosis is ranked the third most burdensome mental health condition by the World Health Organization, it is essential that we achieve the same parity of health improvements. We have co-designed an evidence-based, stakeholder-informed framework for the build, implementation, and evaluation of a national integrated digital registry and clinical decision support system for psychosis, known as EPICare (Early Psychosis Informatics for Care).

Methods: Using a participatory co-design framework, we engaged key stakeholders (N~40-50) across four meetings to establish the parameters and essential features of EPICare and identify factors likely to influence adoption and implementation into routine practice. Stakeholders consisted of organisational, clinical, academic, and patient and public contributors. In collaboration with National Health Service (NHS) informatics teams, we identified how to retrieve key data items from Electronic Health Records and subsequently design the software architecture and data model to create an infrastructure plan for future implementation.

Results: Guided by Normalisation Process Theory, data synthesised from observations of stakeholder meetings and individual interviews (n=10) were subject to interpretative qualitative analysis. A co-designed set of guides were produced to allow for the build, implementation, and evaluation of EPICare in a larger, future study. The results of which will be presented in this talk, along with the next steps for the future deployment and evaluation of EPICare within EIP in the UK.

Discussion: With the enormous pressures facing our health systems, leveraging data from routine practice, to learn and provide real-time actionable insights, will be vital to improve real-world outcomes, identify and prevent inequalities in care, and ensure individuals receive the most appropriate treatments at the right time to promote recovery and maximise life chances.

T155. PITUITARY VOLUME AND STRESSFUL LIFE EVENTS IN ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

Mireia Solerdelcoll*¹, Adriana Fortea², Daniel Ilzarbe³, Elena de la Serna⁴, Emma Muñoz⁵, Inmaculada Baeza⁶, Gisela Sugranyes⁶

¹Institute of Neuroscience, Hospital Clínic de Barcelona, ²Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic of Barcelona, Spain, ³Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic of Barcelona, Barcelona, Spain, ⁴Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic of Barcelona, Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain, ⁵Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS), Barcelona, Spain, ⁶Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic of Barcelona, Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain. Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Background: Identifying biomarkers of transition to psychosis in individuals at clinical high risk for psychosis (CHR-P) is essential to understanding the mechanisms underlying the disease. Pituitary volume (PV) abnormalities, which are thought to index hypothalamic-pituitary-adrenal (HPA) axis dysregulation, have been observed in the early stages of psychosis. PV enlargements have been identified in CHR-P samples and are more pronounced among those who later develop psychosis. Adolescence is an important period for understanding brain changes associated with the onset of psychosis and coincides with developmental maturation of the HPA axis, however, no studies so far have examined PV changes in adolescents at CHR-P. We aimed to compare PV in adolescents at CHR-P and healthy controls at baseline.

Methods: A longitudinal study (CAPRIS) was performed in adolescents (aged 10-17 years) at CHR-P and healthy controls (HC). At baseline, socio-demographic data were collected, and a comprehensive clinical assessment was performed on all participants, including the Structured Interview for Prodromal Symptoms, and the Scale of Prodromal Symptoms (SIPS/SOPS) and the Stressful Life Events Schedule (SLES). Structural images were acquired at baseline. Images were processed with FreeSurfer. Between-group differences in PV were examined.

Results: A total of 67 scans (30 CHR-P and 37 HC) were included in the analysis. There were no significant differences in sex, age, or cannabis use between groups, but there were differences in the use of pharmacological treatment ($p < .001$). A higher number of Stressful Life Events (SLE) in the CHR-P compared with HC was found ($p < .001$). CHR-P individuals had significantly larger PV relative to healthy controls ($823,9 \pm 132,9$ vs. $757,1 \pm 135,8$ mm³, $p = 0,047$), however, between-group differences after controlling for the use of antipsychotics, were not maintained ($p = 0.223$). There was a strong,

positive correlation between PV and psychosocial stress, $r = .82$, $p < .001$, with a greater number of SLE associated with larger PV.

Discussion: The phase before the onset of psychosis in a sample composed of exclusively children and adolescents is associated with a larger PV, possibly reflecting stress-related HPA axis hyperactivity. We propose that PV together with a combination of criteria that focus on complementary aspects of the clinical features, such as the role of stress and hormonal stress response can increase our ability to predict the occurrence of a first episode of psychosis, thus allowing specific and targeted preventive strategies. Preventing or reducing the stress response in the prodromal phase could potentially alter the trajectory to psychosis.

T156. SEX DIFFERENCES IN WORKING MEMORY IN EARLY PSYCHOSIS: A TRANSLATIONAL STUDY IN RATS AND HUMANS

Itziar Montalvo¹, Antonio Armario², Joan Visa², Silvia Fuentes², Roser Nadal², Meritxell Tost¹, Francesc Estrada¹, Ángel Cabezas³, Elisabet Vilella³, Javier Labad^{*4}

¹*Department of Mental Health. Parc Tauli University Hospital. Institut d'Investigació i Innovació Parc Taulí (I3PT). CIBERSAM. Sabadell, Barcelona. Spain,* ²*Institut de Neurociències, Universitat Autònoma de Barcelona, Spain.,* ³*Hospital Universitari Institut Pere Mata, IISPV, Universitat Rovira i Virgili. Reus, Spain.,* ⁴*Consorci Sanitari del Maresme, Mataró*

Background: Working memory deficits in schizophrenia are present as impairments in the temporary storage and manipulation of information, significantly impacting cognitive functions and overall daily functioning. These cognitive deficits occur at early stages of the disease, even before the onset of psychotic symptoms. Previous research in both humans and rats (using the maternal immune activation [MIA] model of schizophrenia) suggest that there are sex differences in working memory deficits. In general, most human studies suggest a better performance in working memory in males, although other studies point to a poorer working memory in women with a history of childhood trauma. Some animal studies report poorer working memory in males. The main aim of our study was to test whether there were sex differences in working memory in rats and humans.

Methods: The animal study used a MIA model with the viral mimic polyinosinic-polycytidylic acid (poly IC). Long-Evans male and female rats from Janvier (France) were used. On days GD15 and GD17 pregnant rats were given vehicle (saline) or received 5 mg/kg (1 ml/kg) poly I:C in saline through the tail vein, while gently restrained. The influence of prenatal treatment in pups on working memory was evaluated in adulthood with the T-maze (working memory, 5 days including habituation and pretraining). Pre-pulse inhibition of the startle response (PPI, a single day, as a measure of sensorimotor gating) was also measured. The human study included 44 patients with clinical-high-risk for psychosis (CHR), 113 first-episode psychosis (FEP) and 49 healthy controls. Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ). The Weschler Memory Scale-III-Edition Spatial Span (WMS-III-SS) was used to assess visual working memory with a translational approach (compared to the T-maze). Statistical analyses were conducted with SPSS v. 25.0 (IBM Corp, USA). General mixed models were used in rats to compare the effects of treatment (Poly IC vs saline) and sex on working memory. Multiple linear regression analyses were used in humans to explore the relationship between sex, diagnoses and childhood trauma on working memory, adjusting for age and education status, and testing potential interactions (sex by

diagnosis, sex by childhood trauma). Only significant interactions were found in the final equation. Significance was set as $p < 0.05$.

Results: Poly IC did not exert a statistically significant effect in the T-maze working memory test, but tended to induce opposite effects in males (decreasing) vs females (increasing). In addition, control females showed a reduced PPI and lower number of correct responses in the T-maze, in comparison to control males. In humans, CHR diagnosis (Beta= -0.220, $p = 0.015$) but not FEP diagnosis was associated with poorer working memory. Sex and childhood trauma were not associated with cognitive performance, nor significant interactions between sex and diagnoses or childhood trauma were found.

Discussion: While the MIA model with poly I:C in rats suggests opposite effects by sex—decreasing in males and increasing in females—the clinical implications of these findings remain uncertain. In humans, the association between clinical high-risk for psychosis (CHR) diagnosis and poorer working memory highlights the presence of cognitive impairments in people at risk of psychosis and the need for early intervention. However, the absence of significant influences related to sex or interactions with diagnoses and childhood trauma in humans suggests the need to explore other contributing factors. Our results emphasize the importance of conducting comprehensive investigations into sex-specific cognitive vulnerabilities in schizophrenia.

T157. WEIGHT CHANGES AT 12 WEEKS IN DRUG-NAIVE, FIRST-EPIISODE PSYCHOSIS PATIENTS ATTENDED IN A REAL-WORLD SETTING

Paula Suárez-Pinilla^{*1}, M^a Carmen Flor-Gómez², Clementina González-Rubial³, Susana Viota-Mañanes⁴, Rocio Perez-Iglesias⁵, Jose Antonio Cortés-Fernández², Guillermo Isidro-García², Jorge Romay-González⁵, Beatriz Voces-Gutierrez², Javier Vazquez-Bourgon⁶

¹University Hospital Maqués de Valdecilla, Santander, ²Hospital Universitario Marqués de Valdecilla, ³Hospital Comarcal de Laredo, ⁴Hospital Comarcal Sierrallana, Spain, ⁵University Hospital Marques de Valdecilla, ⁶Department of Psychiatry, University Hospital Marqués de Valdecilla, Institute of Biomedical Research Valdecilla (IDIVAL), Santander, Spain. CIBERSAM

Background: Second-generation antipsychotics often leads to weight gain even in first-episode psychosis patients, showing a rapid and continuous weight gain in the first few weeks. This study examined the weight changes induced by antipsychotic treatment in a cohort of first-episode drug-naive subjects.

Methods: We audited all the patients consecutively admitted to the Early Intervention (EI) Clinical Program for Psychosis (ITP-Can-Santander), in Spain, from January 2020 to July 2023. Inclusion criteria were: aged from 17 to 65, and being affected by a drug-naïve FEP (affective or non-affective). Exclusion criteria were: suffering from a severe neurological disease or traumatic brain injury, severe intellectual disability or/and psychosis directly induced by illicit substances. Participants were treated with very low dose of antipsychotic medication in monotherapy, CBT, and physical health interventions, which started within the first two weeks of contact with services. For this study, we investigated changes at 12 weeks in body weight.

Results: A total of 163 patients were included. Fifty-five percents were female ($n=89$). The mean age was 37 years old. Fifty three percent of the cohort ($n=87$) had more than 35 years at first contact with services, particularly women (64,1%). The mean daily dose of antipsychotics (in chlorpromazine equivalents) was 195.04 (SD=97.16) mg. The mean

baseline weigh was 65.9 (SD=14.3) kg, although the mean ‘usual’ weigh was 67.8 (SD=14.9) kg. This could mean a weight loss of 1.9 kg with respect the ‘usual’ weight at the onset of psychosis.

At week 12, 148 patients were evaluated (91% adherent to EI program). The average weight at endpoint was 71.2 (SD=13.6) Kg, meaning a weight gain of 4.9 (SD=5.6) Kg with respect the baseline mean weigh, but only 2.6 (SD=8.6) Kg when considering the mean ‘usual’ weigh. Outcomes associated with significant weight gain after 12 weeks were: tobacco consumption, cannabis use, being male and being under 35 years-old (all $p \geq 0.025$). Interestingly, being inpatient at baseline resulted in higher weight gain after 12 weeks compared to those subjects treated in the outpatient setting since onset, although this difference was not statistically significant ($t=1.89$; $p=0.061$). Finally, there were not a significant correlation between antipsychotic doses (in chlorpromazine equivalents) and weight increase after 12 weeks (Pearson’s coefficient=-.099; $p=0.316$).

Discussion: Weight gain is common in drug-naïve patients after the first 12 weeks of treatment, even with very low doses of atypical antipsychotics. However, a plausible previous weight loss before psychosis onset may be considered when quantifying the ulterior weight gain. Periodical assessments of weight along with interventions promoting physical exercise and healthy lifestyle should be part of the clinical management in EI real-world settings.

T158. STRATIFICATION OF INDIVIDUALS IN SOCIAL COGNITIVE TRAININGS: INVESTIGATING DIFFERENCES ACROSS DATA-DRIVEN BRAIN SUBGROUPS IN RECENT ONSET PSYCHOSIS

Julian Wenzel^{*1}, Öznur Bastürk¹, Dominic Dwyer², Shalaila Haas³, Paolo Brambilla⁴, Stephen J. Wood², Rachel Upthegrove⁵, Stefan Borgwardt⁶, Rebekka Lencer⁷, Eva Meisenzahl⁸, Raimo K. R. Salokangas⁹, Christos Pantelis¹⁰, Alessandro Bertolino¹¹, Nikolaos Koutsouleris¹², Joseph Kambeitz¹, Lana Kambeitz-Ilankovic¹

¹University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinic for Psychiatry and Psychotherapy, ²Orygen, Melbourne, Australia, ³Icahn School of Medicine at Mount Sinai, New York, USA, ⁴University of Milan, Milan Italy, ⁵University of Birmingham, Birmingham, United Kingdom, ⁶University of Luebeck, Luebeck, Germany, ⁷University of Muenster, Muenster, Germany, ⁸Heinrich-Heine University Duesseldorf, Duesseldorf, Germany, ⁹University of Turku, Turku, Finland, ¹⁰University of Melbourne and Melbourne Health, Melbourne, Australia, ¹¹University of Bari, Bari, Italy, ¹²Ludwig-Maximilian-University, Munich, Germany

Background: Cognitive abilities critically affect real-life social and professional functioning [1] and are frequently impaired in psychiatric conditions including psychosis [2]. Social cognitive training (SCT) has shown small to medium effect sizes on cognition and real-world functioning within the psychosis spectrum [3]. Despite a large proportion of patients benefitting from the training, considerable heterogeneity in SCT response is present [4]. SCT effectivity might depend on individual differences in the brain’s susceptibility to neuroplastic changes and therefore stratification of individuals based on their brain structural characteristics might offer opportunities for personalization of SCT.

Methods: 97 individuals (age in years [sd] = 27.4 [6.49], female in % = 40.2) with recent-onset psychosis (ROP) from a multi-site cohort were randomized to either 10h of SCT or treatment as usual (TAU). We split individuals into relatively impaired and relatively

preserved brain subgroups which were derived from their individual brain structural characteristics using a data-driven clustering approach published previously [5]. Cognitive performance including social cognition, attention, verbal learning, speed of processing, working memory and global cognition as well as social and role functioning scales were assessed pre- and post-intervention to evaluate SCT effects.

Results: We found a significant improvement in Global Functioning (GF) role scores for the SCT as compared to the TAU group ($F(1,89) = 4.9, p = .03$). Among individuals of the SCT arm, individuals in the relatively preserved brain subgroup showed a significantly increased performance in the (untrained) domain of attention at the cognitive assessment post-intervention, whereas individuals assigned to the relatively impaired brain subgroup showed a decline in performance in this domain ($F(1,92)=1.7, p = .017$). Unfortunately, both effects did not survive false discovery rate correction.

Discussion: SCT has shown effectivity in improving cognitive and real-world functioning in psychosis. However, our findings show a trend that taking into account individual characteristics on the neurobiological level one might be able to identify individuals who are particularly profiting from SCT. Future studies should pinpoint more specific neurostructural and -functional targets for stratification in order to nurture this potential avenue for personalization of SCT.

T159. RISK OF RELAPSE ASSOCIATED WITH SPECIFIC ANTIPSYCHOTICS IN PERSONS WITH FIRST-EPISODE PSYCHOSIS AND CO-OCCURRING CANNABIS USE DISORDER

Heidi Taipale^{*1}, Alexander Denissoff², Jari Tiihonen³, Marta Di Forti⁴, Ellenor Mittendorfer-Rutz³, Antti Tanskanen³, Antti Mustonen⁵, Solja Niemelä²

¹Niuvanniemi Hospital, University of Eastern Finland, ²University of Turku, ³Karolinska Institutet, ⁴King's College London, ⁵Tampere University

Background: Cannabis use is associated with an increased relapse rate in persons with psychosis and in general, antipsychotic medications are effective in reducing relapses in psychosis. There is a lack of research on the effectiveness of antipsychotics regarding patients with concomitant cannabis use and psychosis, and regarding comparative effectiveness of specific antipsychotics. We studied real-world effectiveness of antipsychotics for preventing psychosis relapses among persons with first-episode psychosis and co-occurring cannabis use disorder.

Methods: Swedish nationwide registers were utilized to identify persons with first-episode psychosis and co-occurring cannabis use disorder (first-time diagnosis of psychosis as ICD-10 F20-F29, with concomitant recording of F12) during the years 2006-2021. Association between use of specific antipsychotics (oral vs. long-acting injectable, LAI, forms) and risk of hospitalization due to psychosis relapse was investigated in within-individual design where each person acts as his/her own control to minimize selection bias, analyzed with stratified Cox models.

Results: The cohort included 1820 patients (85% men, mean age 26.8, SD 8.3). Of them, 81.9% used antipsychotics during the follow-up and 63.6% were re-recorded with a cannabis use-related diagnosis, indicating persistent use. During the follow-up, 61% (N=1111) of the cohort experienced psychosis relapse. Compared with non-use, use of any antipsychotic was associated with a 33% decreased risk of relapse (aHR 0.67, 95%CI 0.60-0.72). The lowest risk of relapse was found for risperidone-LAI (0.40, 0.22-0.71), aripiprazole-LAI (0.42, 0.27-0.65), clozapine (0.43, 0.29-0.64), paliperidone-LAI (0.46, 0.30-0.69) and antipsychotic

polytherapy (0.60, 0.51-0.70). Of oral non-clozapine antipsychotics, aripiprazole was associated with the lowest risk of relapse (0.61, 0.45-0.83). Relatively similar results were observed regarding the risk of any psychiatric hospitalization and substance use-related admissions.

Discussion: Antipsychotics are effective in relapse prevention in patients with first-episode psychosis and co-occurring cannabis use disorder. These findings support the use of long-acting injectable formulations of second-generation antipsychotics in relapse prevention in these patients.

T160. FIRST-EPISODE PSYCHOSIS AND GAMING DISORDER: IMPROVING SCREENING AND PATIENT'S EVOLUTION

Maxime Huot-Lavoie^{*1}, Olivier Corbeil², Laurent Béchard³, Sébastien Brodeur⁴, Charles Desmeules¹, Chantale Thériault⁵, Anne-Marie Essiambre⁵, Colombe Claveau⁶, Lauryann Bachand⁷, Joelle Rodrique¹, Amélie M Achim⁸, Amal Abdel-Baki⁹, Isabelle Giroux¹⁰, Yasser Khazaal¹¹, Marie-France Demers¹², Marc-André Roy¹³

¹Université Laval Faculty of Medicine, ²Faculty of Pharmacy, Université Laval, ³Pharmacy Faculty, Laval University, ⁴Faculty of Medicine, Laval University; IUSMQ, CIUSSS-CN, ⁵CERVO Brain Research Centre, ⁶Psychology School, Laval University, ⁷School of Psychology, Université Laval, ⁸Département de psychiatrie et de neurosciences Université Laval; VITAM - Centre de recherche en santé durable; Centre de recherche CERVO, ⁹Centre hospitalier de l'Université de Montréal, ¹⁰School of psychology, Laval University, ¹¹Université de Lausanne, ¹²Faculté de pharmacie de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, ¹³Faculté de médecine de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec

Background: With the recent addition of gaming disorder (GD) in the 11th international classification of disease (ICD-11), there has been a growing interest in understanding the impact of video games among people with severe mental illnesses. Although clinicians widely recognize the frequent comorbidity of GD and psychotic disorders (PD), little is known about the consequences of this addiction in such vulnerable populations.

Considering the significant impact of addictions such as substance abuse on patients' recovery, there is an impetus to better comprehend the association between PD and GD, particularly in young adults suffering from first-episode psychosis (FEP) given their increased use of video games. To this end, our research program aims to: 1) summarize the available knowledge on the comorbidity between GD and PD, including FEP; 2) determine the prevalence of GD in patients with FEP; 3) identify the consequences of GD on these patients' outcomes.

Methods: First, we realized a scoping review to summarize the depth and breadth of the literature regarding comorbid PD with GD and to identify knowledge gaps. Secondly, we conducted a prospective cohort study including all patients admitted to an adult early intervention program for FEP between November 1st, 2019, and October 31st, 2022. All patients were systematically screened for GD using the Nine-Item Internet Gaming Disorder scale (IGDS9-SF) at admission and every 6 months thereafter for up to 3 years. Diagnosis of GD was confirmed by the treating psychiatrist based on the ICD-11 criteria. The severity of

the patients' psychopathology and their functioning were rated by the treating psychiatrist using the Positive and Negative Symptom Scale (PANSS) and the Social and Occupational Functioning Assessment Scale (SOFAS), respectively, at admission and every 6 months for the duration of the follow-up.

Results: Literature concerning comorbid PD with GD is limited to only a few case reports. Little evidence suggests that excessive video game play or abrupt gaming disruption may trigger psychosis. However, there have been no empirical study conducted to support these hypotheses. Among 285 patients treated at the FEP program during the 3-year study period, 31 (10.9%) displayed an excessive gaming behaviour. Among those patients, 14 were diagnosed with GD based on the ICD-11 criteria, for a prevalence of 4.9%. Main preferences for video game types were massively multiplayer online role-playing games (MMORPGs), strategy games, solo-role playing, action-adventure games, and sports games. Trajectory analysis showed a significant association between GD and patients' symptomatology and functioning, as measured by the PANSS (chi-square = 0.035) and the SOFAS (chi-square = 0.007), respectively.

Discussion: There is a paucity of data regarding GD and comorbid PD; it is plausible that psychotic symptoms may lead or exacerbate video gaming behaviours, and the other way around, but this remains to be further explored. The preliminary results of our cohort study highlight an increased prevalence of GD in FEP patients compared to the general population. Most importantly, these findings suggest that GD may significantly interfere with patients' recovery, which underscores the need for greater clinical and research attention to this comorbidity.

T161. SUPPORTING EDUCATION IN YOUNG PEOPLE FACING A FIRST EPISODE PSYCHOSIS: THE EXPERIENCE OF A RECOVERY-ORIENTED SUMMER SCHOOL

Amelie Pavard^{*1}, Tasneem Pichori², Anne-Laure Krikorian³, Benjamin Garnier⁴, Malgozarta Pousthomis⁴, Mathilde Rozet⁴, Louis Volle⁴, Marjorie Coquery⁴, Romain Tabone⁴, Annabelle Boudou⁴, Nathalie Perez⁴, Quentin Litaudon⁴, Frederic Haesebaert⁵

¹CH Le Vinatier, Lyon, ²Abt Brain, Lyon (France), ³Université Claude Bernard, Lyon (France), ⁴CH Le Vinatier, Lyon (France), ⁵PSYR2 Team, INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, Université Claude Bernard Lyon 1, Lyon, France, Lyon, France.

Background: Students represent a vulnerable population: nearly 75% of mental health disorders begin before age 24 (Kessler et al., 2007). Young adults are bound to face an important amount of changes in different areas of their lives (corporal, emotional, hormonal, environmental, and economical dependance), and even more so as students (geographical distance from family, cognitive mobilization, examination stress...). Despite this high level of vulnerability that requires greater mental health care, we observe less resources and less healthcare seeking in this population (Morvan and Frajerma, 2021).

Due to cognitive impairment and residual symptoms, students experiencing a first psychotic episode (FEP) are particularly at risk of dropping out. The literature shows that accessing cognitive remediation therapy and transferring the acquired knowledge into daily life (bridging) is difficult for FEP users. To improve cognitive abilities and bridging, several studies highlight the need to develop integrative and ecological approaches that promote

active experimentation strengthening self-determination (Versace et al., 2021; Masson, 2022; Haesebaert, 2023). Supporting FEP students in an integrative way in and with their environment, therefore represents a challenge.

Methods: According to Romainville (2000), three main important factors can promote adaptation to higher education: personal factors (motivation, self-esteem, coping skills, learning strategies, self-construction, managing daily-life, lifestyle and physical activity, self-determination), pedagogic factors (self-documentation and teaching methods), and environmental factors (familial dimension and resource people at school).

Based on these factors, we co-built a 4-days “summer school” with healthcare professionals and academics (physical activity educator, occupational therapist, neuropsychologist, case managers, psychologist, psychiatrists and peer helpers).

The objectives were to provide a daily rhythm, information about school arrangements, concrete and simple tools to integrate into students’ daily lives (e.g. stress regulation tools, cognitive management...), and to help identify resource people available during the school-year to avoid dropouts. Everyday included mindfulness practises, physical activity, as well as a psychoeducation sessions and active experimentation on a target topic.

Results: We carried out two sessions in summers 2023 (S1) and 2024 (S2). We observed good user attendance: 67% (S1) and 80% (S2) participants attended the entire summer school. Participants indicated that the summer school was useful (78%), and that they felt comfortable contacting one of the speakers in the future (76%). Post-summer schools, users were significantly more confident about their studies ($p=.05$) and the balance between studies, leisure, and social life ($p=.05$), compared to pre-summer schools. Six months post-summer schools, 57% (S1) and 87% (S2) of the students were still in school. We plan to organise a 2-day-boosting session in February 2024 after the exams, to support the students’ motivation. This short session will also rely on the student adaptation questionnaire to university (QAEU, Carayon and Gilles, 2005), as a complementary measure of effectiveness.

Discussion: The summer school offers an integrative and ecological approach in school university environment, and promotes active experimentation to strengthen self-esteem and motivation. It appears to be an interesting way of promoting social functional recovery and reducing school dropouts for FEP students.

T162. ROLE OF CLINICAL INSIGHT AT FIRST MONTH IN PREDICTING RELAPSE AT THE YEAR IN FIRST EPISODE OF PSYCHOSIS (FEP) PATIENTS

Mirjana Selakovic*¹, Ilias Vlahos², Irene Ralli², Alexandros Hatzimanolis², Lida- Alkisti Xenaki², Stefanos Dimitrakopoulos², Rigas- Filippou Soldatos², Stefania Foteli², Nikos Nianiakos², Ioannis Kosteletos², Pedagogiotissa Stefanatou², Ageliki- Aikaterini Ntigridaki², Theoni- Fani Triantafyllou², Marina Voulgaraki², Vassiliki Ermilou², Leonidas Mantonakis², Konstantinos Kollias², Nikos C. Stefanis²

¹*GH Sismanogleio*, ²*1st Department of Psychiatry, National and Kapodistrian University of Athens, Eginition Hospital*,

Background: Clinical insight constitutes a useful marker of the progress and outcome of First Episode of Psychosis (FEP) and lack of insight has been associated with more severe psychopathology, treatment non-adherence and re-hospitalization/relapse. In this study, we aimed to further investigate the possible role of insight as predictor of relapse, its relation to

diagnosis (non-affective vs affective psychosis) and to other parameters of positive psychotic symptomatology namely delusions, hallucinations and suspiciousness.

Methods: 88 patients of the Athens FEP study were examined at three different time points (baseline, month, year). Their scores in the relevant items of the Positive and Negative Syndrome Scale (PANSS) were compared (G12 for insight; P1 for delusions, P3 for hallucinations, P6 for suspiciousness) and were further associated to diagnosis (non-affective vs affective psychosis) and outcome of the year (remission/relapse).

Results: According to G12, 16.1% of the participants had insight at baseline, 69% at one month and 86.9% at one year. Subjects with absence of insight at one month and one year according to G12 had significantly greater P1, P3 and P6 at one month and one year, respectively. Patients with relapse at one year had greater score on G12 at one month and one year, while the median change of G12 from baseline to one year was lower in those with relapse. At one month, P1 and P6 were significantly higher in patients diagnosed with non-affective psychosis compared to those diagnosed with affective psychosis ($p < .001$).

Discussion: Lack of insight based on G12 at one month may serve as predictor of relapse at one year. Delusions and suspiciousness (based on P1, P6) at one month relate to the diagnosis of non-affective psychosis.

T163. COMPARING FUNCTIONAL OUTCOMES BETWEEN TWO COORDINATED SPECIALTY CARE AT 6- AND 12-MONTHS: THE ROLE OF DUP

Hadar Hazan*¹, Bin Zhou², Fangyong Li³, Maria Ferrara⁴, John Cahill⁵, Emily Kline⁶, Toni Gibbs-Dean⁷, Silvia Corbera Lopez⁸, Sneha Karmani⁷, Sarah Riley⁹, Sumeyra Tayfur⁷, Cenk Tek⁷, Matcheri Keshavan¹⁰, Vinod Srihari¹¹

¹Yale Medical School, ²Yale university, ³Yale centre for analytical sciences, ⁴Institute of Psychiatry, University of Ferrara, Italy, ⁵Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, ⁶Boston University School of Medicine, ⁷Yale University School of Medicine, ⁸central Connecticut state university, ⁹Yale university medical school, ¹⁰Harvard University, ¹¹Yale Department of Psychiatry, New Haven, CT

Background: Aim: This study aimed to investigate whether patient outcomes differ between Coordinated Specialty Care (CSC) clinics and determine how the Duration of Untreated Psychosis (DUP) explains these differences.

Methods: A quasi-experimental design compared functional outcomes from two CSC clinics: one implementing early detection (ED) strategies (STEP, $n = 147$) and the other using standard detection methods (PREP, $n = 75$). Linear regression assessed associations between DUP (total, demand, supply) and outcome measures (global, occupational, and social functioning and quality of life) at baseline, 6, and 12 months. Analysis of Variance (ANOVA) compared outcomes between sites, and Sobel's test assessed DUP's mediation role.

Results: Patients at STEP showed more significant improvement in overall functioning (measured by GAF- Δ) at both 6 and 12 months compared to those at the PREP clinic. DUP-total, and specifically the DUP-supply when considering QoL, accounted for some of the differences in overall functioning (GAF- Δ) and QoL scores between the two sites at 6 months. DUP did not explain the differences at the 12-month mark.

Discussion: Conclusions: DUP reduction may improve functional outcomes in the early stages of CSC treatment. However, long-term effects are less clear, and other service

elements at each clinic may also influence outcomes. Future research should explore underlying mechanisms and compare different CSC models.

T164. BASELINE ANTIPSYCHOTIC PRESCRIPTION AND SHORT-TERM OUTCOME INDICATORS IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS: RESULTS FROM A 1-YEAR FOLLOW-UP INVESTIGATION IN A REAL-WORLD CARE SETTING.

Lorenzo Pelizza*¹, Alessandro Di Lisi¹, Emanuela Leuci², Emanuela Quattrone², Marco Menchetti¹

¹Bologna University, ²AUSL di Parma

Background: The prognostic prediction of outcomes in individuals at clinical high-risk for psychosis (CHR-P) is still a significant clinical challenge. Among multiple baseline variables of risk calculator models, the role of ongoing pharmacological medications has been partially neglected, despite meta-analytical evidence of higher risk of psychosis transition associated with baseline prescription exposure to antipsychotics (AP) in CHR-P individuals. The main aim of the current study was to test the hypothesis that ongoing AP need at baseline indexes a subgroup of CHR-P individuals with more severe psychopathology and worse prognostic trajectories along a 1-year follow-up period.

Methods: This research was settled within the ‘Parma At-Risk Mental States’ program. Baseline and 1-year follow-up assessment included the Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF). CHR-P individuals who were taking AP medications at entry were included in the CHR-P-AP+ subgroup. The remaining participants were grouped as CHR-P-AP-. In between-group comparisons, categorical variables were examined using the Chi-square test, while the Mann–Whitney U test was used to compare continuous parameters. Logistic regression analyses with dichotomized 1-year outcome parameters (previously showing statistically significant differences in inter-group comparisons) as dependent measures and sociodemographic and clinical characteristics as independent variables were also performed.

Results: Hundred and seventy-eight CHR-P individuals (aged 12–25 years) were enrolled (91 CHR-P-AP+, 87 CHR-P-AP-). Compared to CHR-P AP-, CHR-P AP+ individuals had older age, greater baseline PANSS ‘Positive Symptoms’ and ‘Negative Symptoms’ factor subscores and a lower GAF score. At the end of our follow-up, CHR-P-AP+ subjects showed higher rates of psychosis transition, new hospitalizations and urgent/non-planned visits compared to CHR-P- AP- individuals.

Discussion: In agreement with increasing empirical evidence, also the results of the current study suggest that AP need is a significant prognostic variable in cohorts of CHR-P individuals and should be included in risk calculators. In particular, AP prescription at presentation can be considered as an indicator of poorer short-term outcome (such as psychosis transition, new hospital admission, and urgent/non-planned visits).

T165. RETROSPECTIVE STUDY OF PHARMACOGENETIC ANALYSES OF A COHORT OF PATIENTS WITH ULTRA-TREATMENT RESISTANT SCHIZOPHRENIA

Alexandre Carpentier*¹, SPR Team², Noémie Roudil³, Mickaël Naassila⁴, Marie-Cécile Bralet⁵

¹Clermont de l'Oise Psychiatric Hospital, ²Pôle PRERPS-Centre Hospitalier Isarien-EPSM Oise, ³Service Pathologies Résistantes (SPR), Clermont de l'Oise Psychiatric Hospital, ⁴GRAP INSERM UMR 1247, ⁵CRISALID CHI Clermont de l'Oise/institut de Psychiatrie/GRAP INSERM UMR 1247/ UPJV Amiens/CESP INSERM UMR 1018 Paris

Background: Antipsychotic medications serve as the primary treatment for schizophrenia. There exists considerable variation among individuals in how they respond to antipsychotics, encompassing both the effectiveness of the treatment and the occurrence of adverse effects. Although the exact source of this interindividual variability in antipsychotic response remains incompletely understood particularly in case of treatment resistant schizophrenia or ultra-treatment resistant schizophrenia, genetics emerges as a significant contributing factor. The ongoing research effort to identify pharmacogenetic markers that can predict both the efficacy and adverse reactions to antipsychotics is a rapidly advancing field. This research has the potential to replace the current trial-and-error approach to selecting schizophrenia treatments with a personalized medicine approach.

Furthermore, in instances of ultra-treatment-resistant schizophrenia, each successive intervention may exacerbate poor tolerance attributed to the frequent utilization of antipsychotic polypharmacy. The objective of our study was to conduct a retrospective analysis of pharmacogenetic assessments within a cohort of patient with ultra-treatment-resistant schizophrenia. The goal was to identify any pharmacogenetic specificities that could substantiate the hypothesis of a distinct phenotype associated with ultra-treatment-resistant schizophrenia.

Methods: A retrospective analysis was conducted to investigate the pharmacogenetic profiles of a cohort of 8 patients with ultra-treatment-resistant schizophrenia. The study spanned a specified time frame, examining historical data and pharmacogenetic information from patient records. Additional analyses conducted after October 2023 will be included in results presented on the poster.

Results: Analyses focused on the following cytochromes: CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2B6. One patient underwent a pharmacogenetic exome sequencing after the discovery of two rare variant of the CYP2B6. All patients demonstrated hypermetabolism of CYP1A2, and 50% of them displaying hypermetabolism of CYP2C19. Conversely, 50% of the patients demonstrated complete or partial hypometabolism of CYP2D6 and/or CYP2B6. Two highly rare variants in the LRP1B and GNB3 genes were identified during exome analysis but could not be interpreted."

Discussion: These preliminary results will be further supplemented for the poster presentation, but they already reveal specificities related to some cytochromes. Additionally, discovery of rare variants is noteworthy, further exposing a patient to antipsychotic side effects and a poor response to clozapine.

T166. THE SHARED GENETIC BASIS OF CANNABIS USE AND PSYCHOSIS: A CROSS-POPULATION GENETIC PATHWAY ANALYSIS

Isabelle Austin-Zimmerman*¹, Emma Johnson², Giulia Trotta³, Edoardo Spinazzola³, Zhikun Li³, Diego Quattrone⁴, Robin Murray⁵, Pak Sham⁶, Evangelos Vassos⁴, Marta Di Forti⁵

¹King's College London, ²Washington University School of Medicine, ³Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁴Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK, ⁶The University of Hong Kong

Background: The causal direction of the correlation between cannabis use and psychosis has been a subject of ongoing interest across fields of psychiatric medicine, epidemiology, addiction science, and genetics. This paper presents an in-depth genetic analysis aiming to elucidate the causal associations and underlying mechanisms explaining the observed association between cannabis use and psychosis.

Here, we build upon the existing literature by meta-analysing recent schizophrenia and bipolar disorder GWAS to create a broad psychosis phenotype. We combine this with recent data from the largest GWAS of cannabis use disorder (CUD) to conduct local genetic correlation analysis and pathway analyses to identify the specific regions and pathways across the genome that may explain the shared genetic liability for the two traits. Previous work in this field has focused almost solely on data from participants of European (EUR) ancestry. In this study we utilise data from African (AFR) ancestry participants in the Genomic Psychiatry Cohort (GPC) to facilitate cross-population analyses, enhancing the generalisability of our findings.

Methods: We used METAL to conduct a cross-disorder fixed effect meta-analysis using data from the recent GWAS of schizophrenia and bipolar disorder. Given the aim of capturing the full breadth of genomic associations with both psychotic disorders, we did not filter out variants that were only present in one of the input studies. We used Linkage Disequilibrium Score Regression (LDSC) to calculate a SNP-based heritability and establish the genome-wide genetic correlation between our psychosis phenotype and CUD. We also investigated the local genetic correlation using Supergnova, to identify the specific regions driving this genome-wide correlation. We used multiple methods, including PASCAL and MAGMA, to identify significantly enriched genetic pathways that are either trait-specific or overlapping. Finally, we used Mendelian Randomisation (MR) analyses to identify putatively causal associations between these pathways and cannabis-associated psychosis.

Results: We identify 517 genome-wide significant loci for psychosis in EUR subjects. We calculate a SNP-based heritability estimate for this broad psychosis phenotype of 0.14 (0.004, $p=6.3 \times 10^{-251}$). The genetic correlation between psychosis and CUD is 0.35 ($p=2.53 \times 10^{-67}$). We identify three regions of significant local genetic correlation on chromosomes 1, 2, and 12. Genes within these regions play a role in intracellular signalling, neuronal development, and have been linked to a range of neuropsychiatric and cardiometabolic traits in previous genomic studies.

We identify 75 traits significantly associated with CUD, and 196 pathways significantly associated with psychosis. Of these, 32 are common between the two traits, which is greater than the overlap expected by chance ($p=2.2 \times 10^{-7}$). These overlapping pathways have a range of biological functions, including signal transduction, platelet production and activation, opioid signalling, neurotransmission, insulin secretion, GABAergic activation and signalling.

Discussion: The identified pathways provide insights into the potential biological mechanisms linking cannabis use and psychosis and highlights several areas of key future research. This is one of very few studies in this field to include to AFR data. Additional studies with increased diversity remain essential across the field of psychiatric genetics to ensure findings are offering value to the full patient population.

T167. ANALYSIS OF THE INFLUENCE OF GENETIC LOAD FOR SCHIZOPHRENIA RESILIENCE ON SUBCLINICAL DISORDER-RELATED TRAITS IN THE GENERAL POPULATION

Patricia Mas-Bermejo^{*1}, Sergi Papiol², Pilar Torrecilla³, Valeria Lavín³, Jackie Nonweiler³, Monika Budde², Thomas R. Kwapil⁴, Urs Heilbronner², Neus Barrantes-Vidal³, Thomas G. Schulze², Araceli Rosa⁵

¹*Secció de Zoologia i Antropologia Biològica, Universitat de Barcelona; Institut de Biomedicina de la Universitat de Barcelona,* ²*Institute of Psychiatric Phenomics and Genomics, Ludwig Maximilian University,* ³*Universitat Autònoma de Barcelona,* ⁴*University of Illinois at Urbana-Champaign,* ⁵*Universitat de Barcelona*

Background: Most people at elevated risk for a mental disorder will never develop it. This has led to the investigation of plausible protective mechanisms in these individuals that would help them remain healthy despite their genetic burden. Recently, a genome-wide association study (GWAS) for schizophrenia resilience was developed capturing the protective effect of common genetic variants that presumably reduce the penetrance of risk loci for schizophrenia. Here, we aimed to leverage this GWAS to study the effect of such genetic resilience for schizophrenia in the context of subclinical disorder-related traits expressed as a continuum in the general population.

Methods: The samples analyzed in this study included two cohorts comprising 228 and 941 nonclinical college students from the Barcelona Longitudinal Investigation of Schizotypy studies (BLISS-1 and BLISS-2, respectively) and a cohort comprising 389 subjects from the general population in Germany (PsyCourse). Psychotic-like experiences were assessed in the three samples with the Community Assessment of Psychic Experiences (CAPE). Schizotypy was assessed with the Wisconsin Schizotypy Scales in BLISS-1 and the Multidimensional Schizotypy Scales in BLISS-2. These variables were dichotomized using a median split approach to define high versus low scores. Polygenic scores for schizophrenia resilience (resilience-PGS) were computed for each participant using the PRS-CS method based on the recent schizophrenia resilience GWAS. Associations between resilience-PGS and the psychometric variables were tested with logistic regressions and the obtained results were meta-analyzed applying an inverse variance method with random effects models.

Results: The meta-analyses of the associations between resilience-PGS and the positive, negative and depressive dimensions of psychotic-like experiences revealed no significant results. However, a trend towards an association was observed for the CAPE depressive dimension, where subjects with higher resilience-PGS scored lower on this variable (OR = 0.84; 95%-CI = 0.69 - 1.03; P = 0.09). Regarding schizotypy, the meta-analyzed results showed no significant associations between resilience-PGS and neither the positive nor the negative dimension of schizotypy.

Discussion: Our results suggest that although this resilience-PGS has been previously used successfully to discern between affected and unaffected individuals with similar schizophrenia genetic load, it might not be able to capture with such precision the subtle differences in subclinical traits at the nonclinical end of the continuum. Nevertheless, considering the trend towards significance found, it could be possible that our analyses still lack some statistical power to capture its effects. In any case, further investigations in this area should be carried out to gain more knowledge on how resilience variants keep us from developing a disorder. Understanding these mechanisms would represent a sound step toward more effective early interventions.

T168. GENETICS OF SCHIZOTYPY: REVIEW OF CURRENT LITERATURE AND NOVEL INSIGHTS FROM DEEP PHENOTYPING

Tina Meller^{*1}, Clara Lundberg¹, Carlo Maj¹, Andreas Forstner², Igor Nenadic³

¹*Philipps University Marburg*, ²*University of Bonn*, ³*Philipps-Universität Marburg / UKGM*

Background: Schizotypy, a multifaceted personality construct, is a stable phenotypic indicator of psychosis proneness and an established dimensional marker of psychosis risk, while psychotic-like experiences (PLE), describe more state-like occurrences of (prodromal) symptoms. Still, the genetics of subclinical psychosis remain less clear: Initial studies indicated an involvement of single schizophrenia risk variants in schizotypy, but findings on associations with polygenic risk scores (PRS) are inconsistent.

In the current study, we combine deep phenotyping with multiple schizotypy instruments as well as psychotic-like experiences (as state markers, considering both frequency and related distress) to test their associations with polygenetic schizophrenia risk and a novel polygenic score of resilience to schizophrenia. In addition to direct associations, we also test interactions of schizotypy facets with each other and PLE, as recent behavioral and brain imaging studies indicate the relevance of relative dimension patterns rather than levels of single facets. We contrast our findings with those of our recently published analysis of two large nonclinical samples.

Methods: In N=367 healthy young adults (mean age=23.85, SD=3.79), we assessed prodromal symptoms and related distress (PQ-16) and three complementary schizotypy inventories (SPQ-B, OLIFE, MSS) that were aggregated into facet-level composite scores for positive, negative, and disorganized schizotypy. In our previously published analysis, we tested associations between schizotypy (SPQ-B) and a schizophrenia PRS in N=623 (231 male, mean age=32.62, SD=12.47) psychiatrically healthy adults and N=1133 (516 male, mean age=44.63, SD=12.85) blood donors.

DNA was extracted from whole blood samples and genotyped using standard quality control procedures. PRS for schizophrenia and resilience to schizophrenia were calculated based on GWAS summary statistics. Cryptic relatives ($\pi\text{-hat} \geq 0.125$) and outliers in ancestry components (distance from the mean of GREATER THAN 6SD) were excluded. We tested bivariate associations (Spearman's rho) and linear regression models with interaction terms in R, including sex and ancestry components as covariates in all analyses and applying false discovery rate (FDR) correction to control for multiple comparisons.

Results: We found positive associations between the schizophrenia PRS and PQ-16 symptom number ($\rho=0.16$, $p=0.003$, $p_{\text{corr}}=0.018$) and level of distress ($\rho=0.14$, $p=0.009$, $p_{\text{corr}}=0.027$) as well as a nominally significant association with the positive schizotypy score that did not remain after FDR-correction ($\rho=0.11$, $p=0.041$, $p_{\text{corr}}=0.082$). While none of the interactions between schizotypy scores were associated to either of the two PRS, we found a significant interaction between schizophrenia PRS and the disorganized schizotypy score on PQ-16 distress ($b=-0.10$, $p=0.004$, $p_{\text{corr}}=0.048$), with a positive relationship between PRS and distress under low disorganized schizotypy and a negative relationship between the two under high disorganized schizotypy.

Our previous analysis did not find significant correlations between the polygenic score for schizophrenia and schizotypy dimensions in either of the two cohorts. This was confirmed by meta-analysing the p-values of each sample.

Discussion: Our study is the first to provide an analysis of both trait-level (schizotypy) and state-level (PLE) indicators of psychosis risk and their association to polygenic markers of both risk for and resilience to schizophrenia.

We confirm polygenic risk for schizophrenia to be associated with both frequency of and subjective distress to PLE in non-clinical subjects, but only find a nominally significant association with positive schizotypy. Concurrent with recent studies, our results thus indicate a greater overlap between polygenic schizophrenia risk and prodromal symptoms and PLE as well as the distress related to those symptoms. While our results - concurrent with our own and other previous analyses - do not support a direct association between polygenic schizophrenia risk and schizotypy, we show that schizotypy modulates how polygenic risk is expressed and experienced in state-level psychotic phenomena. Importantly, this also highlights the divide between frequency versus distress markers of PLE, which is in line with recent imaging studies implicating different regional brain structural effects, depending on whether prodromal symptoms or PLE are just frequent or subjectively distressing.

Our findings also shed a light on the apparent paradoxical phenomenon that schizotypy (an established risk phenotype) can also act protectively and lead to decreased subjective distress, especially in cases where only a single schizotypy facet is elevated. These findings help extend our understanding of the genetics of schizophrenia by including full spectra (such as subclinical phenomena) and multi-dimensional variation across different facets (positive, negative, and disorganised). Our interpretation of the current findings as well as our own recent meta-analytical analysis allow us to sketch a model of how schizophrenia risk genes might operate across the non-clinical and clinical spectrum as well as across diagnostic categories.

T169. PREVALENCE, CORRELATES AND CLINICAL RELEVANCE OF PSYCHOTIC EXPERIENCES IN THE DUTCH GENERAL POPULATION

Wim Veling^{*1}, Vera Brink¹, Catheline van Driel¹, Stynke Castelein², Hannah Jongsma³

¹University Medical Center Groningen, ²Lentis Research of Lentis Psychiatric Institute and Rob Giel Research Center of University Medical Center Groningen, ³Center for Transcultural Psychiatry 'Veldzicht'

Background: In people with mental health problems, psychotic experiences (PEs) may represent the milder end of the psychosis continuum. In such samples, PEs have been associated with an increased risk for developing psychotic disorder, and with more severe psychopathology in general. The meaning and clinical relevance of PEs in the general population is less clear. As PEs occur infrequently, studies predominantly investigated lifetime prevalence, and could explore only a limited set of potential correlates. Large population-based studies are needed to study prevalence of more recent PEs and test a broad range of potential correlates of PEs in the general population.

Methods: This study used cross-sectional Lifelines data, a large longitudinal cohort study that includes over 167,000 participants (10%) from the northern population of the Netherlands. 48,652 adults participated in the third wave, that included the Psychosis Screening Questionnaire (PSQ), assessing PEs in the past year. For the current study, participants aged GREATER THAN 18 were included if they had complete data on the screening question of all five PSQ items. 12-month prevalence of PEs was calculated. A broad range of potential sociodemographic, behavioral, environmental, premorbid, family,

health related, functioning and cognitive correlates of PEs was tested in logistic regression analyses.

Results: 48,286 people (99.2% of the eligible Lifelines sample) had complete data on the 12-month PSQ items. One third endorsed at least one of the five screening items, 10 percent two items, 4.3 percent three or more items. The prevalence of thought interference in the past year was 13.2%, paranoid ideations were reported by 10.2%, hallucinations by 3.2%. The regression analyses are ongoing.

Discussion: Psychotic experiences in the past year are not uncommon in the adult general Dutch population, with four percent reporting at least three PEs. The proportions of PEs are similar to those in some other countries. Discussion of correlates and interpretation of the meaning and clinical relevance of PEs in the general population will be presented at the conference.

T170. PERINATAL VARIATION IN ENVIRONMENTAL LIGHT ASSOCIATED WITH INCREASED RISK FOR SCHIZOPHRENIA - AN EXPLORATORY ANALYSIS OF COMBINED SAMPLES

Digby Qusted*¹, Ayse Kurtulmus², Aynur Gormez³, Rashmi Patel⁴, Akeem Sule⁵, Srivasan Thirumalai⁶, Andrew McQuillin⁷, Michaela Otis⁸

¹Oxford Health NHS Foundation Trust, ²Istanbul Medeniyet University Goztepe research and training Hospital, Department of Psychiatry, Istanbul, Turkey., ³Istanbul Medeniyet University, Department of Psychiatry, Istanbul, Turkey, ⁴Department of Psychosis Studies, IoPPN, King's College London, UK, ⁵Essex Partnership University NHS foundation Trust; Dept. of Psychiatry, Cambridge University, UK (Hon), ⁶Marlborough House MSU, Milton Keynes Oxford Health NHSFT, ⁷Molecular Psychiatry Laboratory, Division of Psychiatry, Faculty of Brain Sciences, University College, London, ⁸Multimorbidity and Mental Health Theme; Department of Primary Care and Public Health, Imperial College, London, United Kingdom

Background: Studies have shown associations between perinatal light variability with case register incidence rates and of vitamin D deficiency in schizophrenia suggesting the possible relevance of peri-natal sunshine to schizophrenia genesis. Early post-natal solar insolation level has also been positively associated with age of onset in bipolar disorder ((Bauer et al; 2015; J. of Psychiatric Research; 64; 1-8). We investigated further an original hypothesis (Qusted DJ. 1996 - Med. Hypotheses. Mar;46(3):233-8) that perinatal variation in environmental light (EL) exposure could be associated with the condition, in a model incorporating familial risk and gender, and present here the outcome of the exploratory analysis of data from two combined samples.

Methods: In study (1) Schizophrenic patients (n=89) were diagnosed according to SADS-L while a healthy control (HC) version was used for the comparator group (n=174). Fields included place and date of birth, family psychiatric history (FPH) with pedigree information as well as personal history. In Study (2) a primary care self-report dataset was used where those with a personal history of mental illness were excluded. Measures of variation of perinatal environmental light (EL) exposure were divided into 9 pre-and 6 post-natal trimesters. Sunshine EL exposure for each individual was calculated from MET Office UK data in sunshine hours per day by month and then grouped into trimesters, as a difference from the historic means for England and Wales, or Scotland, with these monthly sunshine means subtracted from the individual's data. The historic means used were a 63 year set for

Study (1) and 50 years for Study (2). Logistic regression was used to estimate the effect of EL variation on schizophrenia risk by fitting a two way interaction term with EL and FPH, adjusting for gender.

Results: In the combined dataset including 89 (60 M; 29 F) schizophrenic patients and a total of 449 (171 M; 278 F) healthy controls, mean daily sunshine variations in the three month trimester groupings showed a significant effect of low EL on the risk of schizophrenia in the post-natal (OR=3.49, 95%CI=1.72-7.09, P=0.001) and mid-foetal trimesters (OR=3.09, 95%CI: 1.50-6.35, P=0.002) as an interaction effect with positive FPH in first degree relatives and adjustment for gender. Above average levels of sunshine were protective, even with a positive FPH for the first post-natal trimester but not in the mid-foetal trimester. In a stratification cohort using only those with FPH an interaction effect with low EL was seen for both genders in the post-natal trimester but an effect in males in the mid-foetal trimester was non-significant.

Discussion: The above findings show an association between the EL variable and risk for schizophrenia analysed as an interaction with family history in a combined dataset where the number of healthy controls was substantially enlarged by the inclusion of a self-report primary care sample. This finding therefore suggests that if peri-natal sunshine variation is relevant to schizophrenia then a factor linked with development is being influenced by a fluctuation in the number of sunshine hours per day as a difference from the historic monthly means. However, in a previous analysis of the schizophrenia sample in study (1) findings also suggested that the mean total of daily sunshine hours per month is associated with schizophrenia risk. The present finding continues to be limited by the schizophrenia patient number, although the HC group was substantially increased in this combined exploratory analysis. A further limitation is the assumption that geographical relocation did not occur during the analysed phases of gestational and post-natal development. The previously analysed variability in total daily sunshine hours by trimester will therefore need to be investigated in further studies with larger sample sizes, including both healthy controls and schizophrenic patients with well characterised family histories and the inclusion of an aetiopathogenetic mechanism.

T171. DIAGNOSIS AND MANAGEMENT OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA: REAL-WORLD EVIDENCE FROM A CROSS-SECTIONAL SURVEY OF PSYCHIATRISTS

Theresa Cassidy*¹, Artak Khachatryan², Stephanie Read²

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Evidence and Access, Certara, London, UK

Background: Cognitive impairment (CI) associated with schizophrenia is a core feature of the disorder and is associated with reductions in quality of life and independent living. Current treatments for schizophrenia, such as antipsychotics, are effective at reducing positive symptoms, but do not improve cognitive outcomes. Despite the established negative impact of CI in schizophrenia, it is unclear to what extent practicing physicians recognise, diagnose, treat and manage the condition. This study aimed to understand and characterise physician attitudes and practice regarding how schizophrenia patients with CI are assessed, monitored and treated in routine clinical care.

Methods: A bespoke online survey was developed and administered to 121 psychiatrists across the United States (US), United Kingdom (UK) and Germany in December 2022. Psychiatrists were identified via a third-party panel and were eligible for inclusion if they had

been practicing for ≥ 36 months (including ≥ 12 months in the US, UK or Germany) and treated ≥ 5 patients with schizophrenia annually.

Results: 121 psychiatrists completed the online survey (US: n=41; UK: n=40; Germany: n=40). This sample of experienced psychiatrists (45.5% had ≥ 15 years practice) estimated a mean (standard deviation [SD]) of 51.0% (28.0%) of schizophrenia patients exhibit signs of CI; of these patients, psychiatrists diagnosed CI in a mean (SD) of 34.8% (29.7%). The most common instruments to assess CI were the Montreal Cognitive Assessment and the Mini-Mental State Examination, with 62.0% and 81.8% of psychiatrists respectively reporting their use. When assessing CI in patients, psychiatrists ranked deficits in executive function (38.0%), reduced attention (19.0%) and deficits in reasoning/ problem solving (16.5%) as the most important signs of impairment. Psychiatrists ranked working/studying (48.8%), managing finances (16.5%) and taking prescribed medications (11.6%) as the most disrupted activities of daily living for patients with CI. If patients exhibited CI, 91.7% of psychiatrists recorded it in the patients' medical charts, with terms such as cognitive impairment (81.0%), attention deficit (47.1%) and communication deficit (43.8%) most commonly noted. For treatment of CI, psychiatrists reported implementing a watch-and-wait strategy for 46.5% of patients. Almost half of psychiatrists (48.8%) reported that CI increased the frequency of patient follow-up visits. A large proportion (59.5%) of psychiatrists did not administer medications, however, 52.9% prescribed cognitive behavioural therapy to manage CI. There was no consensus on the effect of anti-psychotic treatments, with 52.9% of psychiatrists indicating improvement and 46.3% of psychiatrists indicating a negative impact on the severity of CI symptoms.

Discussion: These data contribute to the understanding of physicians' attitudes and practices towards CI in schizophrenia. Considering the large proportion of schizophrenia patients affected by CI, the considerable variation in diagnosis, treatment and management practices reported by psychiatrists highlights the need for clearer guidance in the management of CI to improve treatment outcomes and quality of life for patients.

T172. OBJECTIVE BURDEN AMONG PRIMARY AND SECONDARY CAREGIVERS FROM COGNITIVE IMPAIRMENT SYMPTOMS OF PATIENTS WITH SCHIZOPHRENIA

Corey Reuteman-Fowler¹, Sebastien Tulliez², Matthew Ridley³, Katja Rudell³, Alessandra Girardi³, Christoph Correll^{*4}, Richard Keefe⁵, Abraham Goldring⁶

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Boehringer Ingelheim International GmbH, ³PAREXEL International Corp., ⁴, ⁵Duke University Medical Center, Professor of Psychiatry and Behavioral Sciences, ⁶Clinical Trial Media

Background: Cognitive impairment associated with schizophrenia (CIAS) is highly burdensome and the severity of such symptoms can impact the burden of care. The chronic nature of schizophrenia incurs substantial burden to the caregiver - whether family or professional (social workers, case manager etc) - from the shift of burden of care from inpatient hospital services, with four main areas of burden being identified in the literature: daily "hassles", and financial, emotional, and physical burden. Recent guidance/standards, including clinical, Health Technology Assessment (HTA e.g., NICE), are beginning to recognize the value of evidence demonstrating the alleviation of carer provision for patients with a medical condition (e.g., for decision making), particularly those with neurological and psychiatric conditions that arguably impose the greatest burden on caregivers. However, existing research focuses mostly on primary (i.e., family) caregivers as opposed to secondary

caregivers (i.e., professionally trained). The present study therefore aimed to provide a preliminary overview of objective caregiver burden experiences (defined in the literature as the effects on the caregiver in respect of daily tasks) from CIAS symptoms among both primary (family, informal) and secondary (professional, formal) caregivers.

Methods: In a COA content validation interview study, a question asking about the caregivers' experiences of the cognitive functioning issues they had observed in the patient, elicited spontaneous data pertaining caregiver's experience of burden. Subsequently, a secondary, qualitative, inductive thematic analysis was conducted on this burden-focused data.

Results: Findings revealed two overarching themes: 1. Caregiver difficulty (Subthemes: Hard to continue care, Hard to improve their quality of life, Constant additional and extra work[load], Hard to teach/unable to learn, Difficult to communicate with patient, and Blame [in the firing line]), and 2. Caregiver necessity (Subthemes: 'Without my care they wouldn't get things done', and Financial budgeting – reminders and remedials). Our analysis demonstrates both caregiving difficulty and necessity to be high across the dataset and irrespective of whether a primary or secondary caregiver was interviewed.

Discussion: Consistent with the literature, the requirement for the assumption of extra work and role responsibilities was central to the high level of caregiving difficulty and necessity found among both primary and secondary caregivers of patients with schizophrenia. Financial impacts were described as a necessity. Experience of frustration was mentioned by one caregiver and no further evidence emerged regarding the emotional, or the physical aspects of caregiving. To be able to present adequate evidence in accordance with the contemporary HTA guidance, further work is warranted inclusive of subjective caregiver burden experiences (defined in the literature as the extent to which the caregivers perceive the burden of care) associated with CIAS. Moreover, due to the multidimensional nature of caregiver burden, additional facets need to be incorporated in future studies, including incidence of financial costs, depression, time of work, shame, embarrassment, guilt, self-blame, gender, ethnicity, and culture. A noted limitation is the secondary analysis nature of this study, conducted on data acquired from a study with a different objective. Nevertheless, this research highlights the importance of incorporating caregiver burden experiences in schizophrenia, and the need for further work to acquire richer caregiver burden data.

T173. OUTCOMES OF SCHIZOPHRENIA PATIENTS RECEIVING COMMUNITY MANAGEMENT SERVICE IN URBAN CHINA

Jiali Wang*¹, Jinghua Su², Xiaohua Sun³, Xiaofei Hou⁴, Haidong Song³, Guangming Xu⁴, Liang Zhou²

¹The University of Chicago, ²Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China, ³Affiliated Mental Health Center Zhejiang University school of Medicine, Hangzhou Seventh People's Hospital, Hangzhou, China, ⁴Mental Health Center of Tianjin Medical University, Tianjin Anding Hospital, Tianjin, China

Background: To provide integrated community-based mental health care for patients with serious mental illness, China launched the Community-based Program of Management and Treatment for Serious Mental Illness in 2004, known as the Community Management Service. Patients receive telephone or face-to-face follow-up management delivered by community mental health professionals. Over 70% of service recipients are schizophrenic patients. Although Community Management Service has been implemented for nearly two

decades and has covered the whole mainland China, the efficacy of the Community Management Service on patient-level outcomes remains unknown. The study aimed to estimate potential effects of the Community Management Service on patient-level outcomes, including symptoms, social function, outpatient service utilization, and medication compliance.

Methods: We conducted a single-blind, multi-centered cohort study. The exposed group was patients receiving management. We matched unmanaged patients with two patients receiving management according to city, gender, and age due to the limited number of unmanaged patients. Baseline data were from patients' medical records in 2019. Sociodemographics, age of onset, DUP, and outcomes were collected via face-to-face interviews from March 2022 to January 2023. The primary outcome was symptom assessed with PANSS. Multivariate regression models were used to estimate the potential effects. Propensity score matching and adjustment were performed as sensitivity analysis. Analyses were conducted using Stata 17.0, with statistical significance set at 0.05.

Results: A total of 259 patients were included in the cohort study, including 93 unmanaged patients and 166 patients receiving management. Mean age was 38.5 (12.3), and 59.5% were female. PANSS score in patients receiving management was significantly higher (58.0 (45.0, 70.0) vs. 49.5 (38.5, 64.0), $P=0.004$). The multivariate linear regression showed no statistically significant difference in PANSS between patients receiving management or not ($b=0.015$, 95%CI=-0.076, 0.106). Results of sensitivity analysis were consistent with main analysis. However, we found significant interactions between continuous education and management status ($P=0.010$). Among patients with primary school or below educational level, those receiving management were observed to have fewer symptoms ($b=-0.401$, 95%CI=-0.710, -0.092). Patients receiving management had more outpatient visits (IRR=1.140, 95%CI=1.005, 1.293), and higher odds of regular outpatient visits (OR=1.972, 95%CI=1.096, 3.551). Social function deficits were higher in patients receiving management ($b=1.234$, 95%CI=0.001, 2.466). But among patients with lower educational level, those receiving management tended to have better social function ($P=0.011$). There were no significant associations between Management and medication compliance.

Discussion: Although the Program has established China's first community-based mental health system, our findings suggested limited improvement in patient-level outcomes. Therefore, in the future, intensive intervention services, such as psychosocial intervention and intervention targeting medication adherence, should be considered based on existing services. Besides, given the limited resources of community mental health services, future research should further identify patients who are more sensitive to the services to promote the rational allocation and utilization of resources and to optimize the Program. Finally, more comprehensive evaluations are needed.

T174. EFFECT OF PUBLIC SMOKING RESTRICTION PRECAUTIONS ON THE SCHIZOPHRENIA PATIENTS' SMOKING PREVALANCE AND AMOUNT OF SMOKING CONSUMPTION

Eldem Güvercin*¹, Bilge Targıtay Öztürk², Tolga Binbay², Berna Binnur Akdede³, Köksal Alptekin³

¹Dokuz Eylul University, Faculty of Medicine, Izmir, ²Dokuz Eylul University, School of Medicine, Department of Psychiatry, Izmir, Turkey, ³Dokuz Eylul University Department of Neuroscience, Dokuz Eylül University, School of Medicine, Department of Psychiatry, Izmir

Background: In 2008, Türkiye has introduced a law for preventing smoking and its harmful effects. It has brought serious restrictions on advertisements and sponsorships encouraging smoking, and smoking was banned in common public areas, public offices and all kinds of public transportation vehicles. These restrictions taken throughout the country generally yielded results, and in the first 5 years of legal regulations, smoking prevalence decreased by 13.4% across Türkiye. Smoking is more common among patients with schizophrenia than in general population. It has been reported that tobacco smoking is 1.5 times more frequent in patients with schizophrenia, compared to general population. Reducing smoking in patients with schizophrenia may contribute to reducing morbidity and mortality in these individuals.

Methods: In this retrospective study, we evaluated 435 individuals diagnosed with schizophrenia who applied to the outpatient clinic at the Dokuz Eylül University Hospital, İzmir, Türkiye. Participants divided into two groups: First group (n=236) consist of the patients, applied to the outpatient clinic before the endorsement of smoking restriction laws (at the year of 2008 and before). Second group (n=199) including the patients, who have applied the outpatient clinic after the year of 2008. Their smoking habits and cigarettes consuming per day were analyzed with independent samples T-test.

Results: Both the cigarette consumption frequency (t (433): -2.05; p LESS THAN 0.05) and the number of cigarettes smoked per day (mean: 11.23; SD: 14.48 vs mean: 13.45; SD: 17.33; p LESS THAN 0.05) were found to be significantly lower in individuals who were followed up at the outpatient clinic after 2008 compared to individuals who were evaluated before 2008.

Discussion: The current legal restrictions for smoking have significant effects in patients with schizophrenia, both the smoking habit and the average number of cigarettes consuming per day have decreased in these patients. Reducing smoking in patients with schizophrenia is a realistic and desirable goal and it is important to ensure the continuity of the precautions. We hope that the encouraging decrease in the prevalence and amount of smoking in patients with schizophrenia under the influence of legal regulations, will provide additional measures and public health policies to additional smoking reduction in patients with schizophrenia.

T175. CONTENT CONFIRMATION OF THE SCHIZOPHRENIA COGNITION RATING SCALE (SCORS): A QUALITATIVE STUDY WITH PRIMARY AND SECONDARY CAREGIVERS

Corey Reuteman-Fowler¹, Sebastien Tulliez^{*2}, Maggie Heinrich³, Katja Rudell³, Alessandra Girardi³, Christoph Correll⁴, Richard Keefe⁵, Abraham Goldring⁶

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Boehringer Ingelheim International GmbH, ³PAREXEL International Corp., ⁴The Zucker Hillside Hospital; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Charité - Universitätsmedizin Berlin, ⁵Duke University Medical Center, ⁶Clinical Trial Media

Background: Cognitive impairments associated with schizophrenia are burdensome with detrimental effects on patients' everyday life. The Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item interview-based clinical reported outcomes assessment of cognition-related functioning in patients with schizophrenia. The assessment requires input from patients, caregivers, or clinicians. Although the SCoRS demonstrated good psychometric properties in several publications, further confirmation of its content with the informant population, in particular, primary caregivers who spend more time with the patient during the day is needed. This study sought to assess the content confirmation of the instrument and its

understanding and clarity with caregivers who cared for a patient with a diagnosis of schizophrenia.

Methods: A qualitative cross-sectional non-interventional study was conducted in the United States. Interviews were conducted with primary caregivers (PC; unpaid), and secondary caregivers (SC; professionally trained). Two discussion guides were developed: one for the primary informants, and one for the secondary informants. Interviews lasted approximately 90 minutes and included three parts: 1) caregiver and patient characteristics; 2) concept elicitation; and 3) cognitive debriefing.

Results: Altogether, 40 caregivers were interviewed, n=20 in each group. The majority of caregivers were females (PC: 85%; SC:60%). The mean age at the time of interviews was 51 years (range=28-82) for PCs and 41 years (range 22-60) for SCs. Half of the PCs were parents of the patient with schizophrenia, 40% relatives and 10% partners. The SC group included 25% therapists, 15% clinical research coordinators, 10% sub-investigator psychometric raters, 5% registered nurse and 5% director of non-profit organization. Most caregivers accurately interpreted questions, items and response options (70%-100%). Ease of response selection across items appeared overall slightly lower for primary caregivers, typically due to the clinical profile of some patients (e.g., rare or no social relationships, no change of routine) or the uncertainty concerning what the patient is really thinking/understanding (e.g., no overt manifestations), rather than the scale properties. Most items were endorsed by the majority of informants in both groups. However, they did not observe much language difficulties in two items: leading to conversational confusion and attention in conversation (n items = 2, endorsed by LESS THAN 30% of caregivers). Nevertheless, these two items were well understood by most caregivers in both groups, response options were easy to select and the examples provided were considered useful. Additionally, all domains were endorsed by at least 50% of caregivers in both groups. Certain concepts were seen to be highly relevant to patients with schizophrenia. Particularly Attention and Problem-solving were endorsed by 95% of caregivers living with the patients. Memory and Working Memory were endorsed by all SCs.

Discussion: The content and usability of the SCoRS were confirmed with both informal and professionally trained caregivers. However, caregivers did not observe patients' conversations in group settings or with new individuals and therefore could not assess these activities. This data further highlights that cognitive issues are frequently present in patients with schizophrenia, and thus need addressing to improve the patients' quality of life.

T176. GLOBAL DISTRIBUTION OF ENVIRONMENTAL RISK STUDIES FOR SCHIZOPHRENIA

Evangelos Vassos*¹, Sarah Tosato²

¹King's College London, ²Section of Psychiatry, Department of Neurological, Biomedical and Movement Sciences, University of Verona, Italy

Background: There is a substantial body of literature on genetic and environmental risk factors associated with schizophrenia. Genetic research has largely been conducted in Europe and North America, with little representation of the rest of the world. Indeed, previous reviews of twin and genome-wide association studies show that European ancestry populations are over-represented, with middle- and low-income countries having little or no participation in the current body of genetic research. Concerns have been raised that this

preferential representation of Europeans may exacerbate health disparities between different ethnic/ancestral groups. However, there is no systematic evaluation of similar disparities of studies focusing on environmental exposures. For this reason, we performed a systematic review of studies evaluating environmental risk factors for schizophrenia, recording where they were conducted and then by linking our findings with publicly available data, we tried to identify correlates with the uneven global distribution.

Methods: Using Pubmed and PsycINFO electronic databases, we performed a systematic review of studies reporting on exposure to established environmental risk for schizophrenia (e.g. migration, urbanicity, childhood trauma, cannabis etc) and subsequent onset of incident schizophrenia spectrum disorders. We plotted the number of studies and of recruited cases by the country where studies were conducted. Then we downloaded publicly available data on population size, measures of wealth (e.g. GDP), measures of medical provisions (number of doctors), measures of research investment (R and D spending, number of researchers), and of quality research outputs (number of papers published, number of Nobel laureates in science) per country. We performed univariable and multivariable regression analyses of each predictor with the number of studies and recruited cases per country identified through our literature search.

Results: In total we identified 308 publications of 342 studies fulfilling our inclusion criteria, including 445,000 cases with schizophrenia spectrum disorders. The majority were conducted in northern Europe (most studies from the UK; N=53) and North America. Very few studies were conducted in South America, South Africa and East Asia, with large parts of the world totally unrepresented. In the associations between the number of environmental risk studies for schizophrenia with potential predictors, we found that neither population nor wealth or research investment of countries were strong predictors of research outputs in the field. Interestingly, the stronger correlations were found for number of researchers per population and for indicators of high-quality research, such as number of Nobel laureates per country.

Discussion: Our results demonstrate a gap of knowledge due to the under-representation of environmental risk studies of incident schizophrenia in large parts of the world. This has implications in the generalisability of any findings from studies conducted in the Northern hemisphere but also in our ability to progress in efforts to make causal inferences about biological pathways to schizophrenia. As an example, if migration or urbanicity, which are considered as ‘proxy’ for unmeasured underlying risk factors, act only in industrialised communities and not in low-income countries, we should invest in research on differences between these environments, which could shed a light on the actual causal pathways to schizophrenia.

Our conclusion is that emphasis needs to be given to enabling and expanding schizophrenia research to parts of the world currently under-represented. This will enable generalisation and a more equitable utilisation of research findings but will also progress research on causal pathways to schizophrenia.

T177. A PRELIMINARY STUDY ON THE FACTORS AFFECTING THE RECOVERY OF INPATIENTS IN PSYCHIATRIC HOSPITALS-FOCUSING ON RECOVERY PRACTICES IN WHO QUALITY RIGHTS

Narae Jeong¹, Yu Sang Lee^{*2}

¹Department of Clinical Psychology, Yongin Mental Hospital, Yongin, Republic of Korea,

²*Yongin Mental Hospital*

Background: Recovery-based practice has been gradually receiving attention in the Korean psychiatric settings, but there is still a lack of research on factors and applications related to recovery. World Health Organization QualityRights(WHO, 2019) is a comprehensive package of educational and instructional materials based on a human rights based approach and recovery, starting with efforts to ensure mental health and well-being. Based on this direction, Korean psychiatric settings need to actively devise ways to promote recovery-oriented practical activities. Therefore, this study aimed to systematically identify the factors influencing the attitude towards recovery targeting those receiving inpatient treatment in a psychiatric hospital.

Methods: A total of 100 inpatients at Yongin Mental Hospital in Korea completed self-report questionnaires assessing demographic characteristics, illness duration and history, social support, stigma, and attitudes towards recovery and human rights sensitivity. All data were converted into continuous and categorical variables and analyzed through hierarchical regression analysis.

Results: Based on the analysis of 80 responses, excluding data with numerous missing values and insincere answers, it was observed that the duration of illness and the number of hospitalizations significantly influenced attitudes toward recovery. Additionally, self-perceived social support emerged as a potential factor influencing recovery attitudes. Social support was found to moderate the relationship between disease duration and recovery.

Discussion: The study suggests that the duration of illness and the number of hospitalizations impact the attitudes toward recovery among psychiatric inpatients, with higher perceived social support associated with more positive recovery attitudes. In other words, as the psychiatric problem becomes chronic, the attitude to recover decreases, but social support and interest seem to be able to buffer their relationship. There is a need to gradually expand recovery-centered approaches in Korean psychiatric settings, and it is necessary to prepare specific measures to support this. Finally, the significance and limitations of the studies were discussed.

WHO QualityRights; Psychiatric inpatients; Social Support; Recovery oriented approach.

T178. A VAGAL INFLUENCE ON SCHIZOPHRENIA? RESULTS OF TWO SWEDISH NATIONWIDE RETROSPECTIVE COHORTS

Cornelia Richter^{*1}, Skibicka Karolina², Urs Meyer¹, Sabine Rohrmann³, Jean-Philippe Krieger⁴

¹University of Zurich, Institute of Veterinary Pharmacology and Toxicology, ²Pennsylvania State University, Department of Nutritional Sciences; University of Gothenburg, Institute of Neuroscience and Physiology, ³University of Zurich, Epidemiology Biostatistics and Prevention Institute, ⁴University of Zurich, Institute of Veterinary Pharmacology and Toxicology; University of Gothenburg, Institute of Neuroscience and Physiology

Background: The vagus nerve is a major bidirectional route of communication between the brain and the body. Several lines of evidence suggest that impaired vagal communication may be a potential risk factor for the development of schizophrenia. First, meta analyses indicated that heart rate variability, a proxy measurement for vagal activity, is consistently lower in patients with schizophrenia compared to healthy controls and mirrors the progression of psychotic symptoms. Second, preclinical studies in rats demonstrated that the lesion of subdiaphragmatic vagal afferents is sufficient to induce a schizophrenia-like behavior. Longitudinal evidence in humans is, however, lacking. Hence, the objective of this

study was to test whether disrupted vagal communication impacts the subsequent risk to develop schizophrenia in humans. For this, we studied individuals with vagotomy, the surgical resection of the vagus nerve once commonly performed to treat peptic ulcers.

Methods: We applied a retrospective cohort approach using nationwide data from the Swedish National Patient Registry from the period 1970-2010. First, we compared the risk to develop schizophrenia between vagotomized patients (n = 16 231) and non-vagotomized individuals matched for age and sex randomly sampled from the registry (n= 162 310; “general population cohort”). In a second analysis, we took into account that peptic ulcer was the main indication for vagotomy and therefore compared vagotomized patients (n= 7 625) with individuals matched for age, sex, and history of peptic ulcer disease (n= 38 125; “ulcer cohort”). For both cohorts, the association between vagotomy and schizophrenia was investigated using Cox proportional hazards models, including death as competing risk.

Results: Both analyses found no significant change in the risk to develop schizophrenia following vagotomy overall (hazard ratio [HR] = 1.25 [95% confidence interval [CI] 0.78, 2.01] in the “general population cohort” and HR = 0.90 [0.27, 3.15] in the “ulcer cohort”). These results however, hide a disparity between different vagotomy surgeries: truncal vagotomy was associated with an 8.6-fold increase in the risk to develop schizophrenia in the “general population cohort” (HR: 8.56 [4.82, 15.20]), whereas selective vagotomy showed no significant effect (HR: 0.54 [0.27, 1.11]). The number of schizophrenia cases was too small to analyse vagotomy subtypes in the “ulcer cohort”.

Discussion: Our results partly support the idea that impaired vagal function can precipitate the development of schizophrenia. Notably, the finding that truncal but not selective vagotomy is associated with an increased risk of schizophrenia raises the possibility that the activity of non-gastric vagal branches may be of particular relevance for the development of schizophrenia. Future studies should aim at increasing the number of included patients to obtain better estimates, for example by combining registries from different nations.

T179. AN EXAMINATION OF FACTORS ASSOCIATED WITH POLICE STIGMA AND VIOLENCE TOWARDS BLACK INDIVIDUALS SUFFERING FROM MENTAL ILLNESS

Amy Weisman de Mamani^{*1}, Merranda McLaughlin², Salman Ahmad¹, Genesis Saenz-Escalante¹, Denise Chung-Zou¹

¹*U. of Miami*, ²*University of Washington*

Background: High-profile, police-induced deaths have disproportionately involved individuals with serious mental illness (SMI), particularly Black men (Dempsey et al., 2020; Frankham, 2018; Edwards et al. 2018). As such many black people with SMI report a hesitancy to call the police even when they are in dire need of police assistance (Altamirano and Weisman de Mamani, 2023). As prejudice and stigma are often precursors to aggression (Gilbert and Bushman, 2017), it is critical to identify factors associated with police stigma towards individuals with serious mental illness (SMI). In line with the frustration aggression hypothesis (Gilbert and ushman, 2017) which purports that that one’s own frustration and distress are often linked to prejudice and aggression towards others, we hypothesized that officers who experience more psychological distress and greater suicidal ideation would report holding more stigma towards individuals with schizophrenia. Qualitative data from police officers was also examined to help pinpoint ways to improve police officer interactions with individuals with SMI.

Methods: A mixed method design was used to conduct assessments with 107 police officers recruited through Qualtrics' online panels. The Depression Anxiety and Stress Scale-21 (DASS-21), The Suicidal Behavior Questionnaire, and the Modified Day's Mental Illness Scale were used to measure psychological distress, suicidal ideation and behaviors, and mental illness stigma respectively. Qualitative data from police officers was also derived from analogue studies using hypothetical vignettes of an encounter between a police officer and a black man with schizophrenia.

Results: As hypothesized, we found that officers who had poor mental health, assessed through both the DASS-21 ($r = .380$; $p < .001$) and the Suicidal Behavior Questionnaire ($r = .353$, $p < .001$), were more likely to hold stigmatizing attitudes toward people with SMI. Many interesting themes also emerged with respect to our qualitative data. For example, in one scenario officers were asked to describe their response to a hypothetical vignette depicting an interaction between a Black man with schizophrenia and a police officer that resulted in the officer shooting and killing the man. While some officers criticized the use of lethal force, the large majority of responses were in defense of the officers' actions (etc., "officers must do whatever it takes to effect an arrest", "...force is sometimes necessary.")

Discussion: Stigma toward others is a form of non-physical aggression that can be highly correlated with physical aggression (Vincent, Peterson and Parrot, 2016). Thus, our finding that police officer's own distress is linked to greater stigma towards individuals with SMI may offer indirect support for the frustration aggression hypothesis (Gilbert and Bushman, 2017). These findings suggest that efforts to bolster officers' own mental health may be one indirect way to reduce stigma and aggression toward people with SMI. Given that the most frequent theme to emerge for the escalation scenario was a defense of the officer's actions, our data suggest that police officers may be less willing to acknowledge the shortcomings of their role, because they feel laypeople/onlookers do not understand the full context of these situations (e.g., high stress, poor pay, newly trained officers put in high crime areas). Thus, future work that attempts to improve communication and understanding between police officers and the communities they serve (particularly the Black community), may assist in decreasing the likelihood of violent outcomes when these groups interact.

T180. GENETIC AND ENVIRONMENTAL INDUCED REDOX DYSREGULATION DURING EARLY DEVELOPMENT AFFECTS NEURONAL MATURATION/DIFFERENTIATION AND NKCC1/KCC2 SWITCH IN IPSC-DERIVED NEURONS OF EARLY PSYCHOSIS PATIENTS

Basilio Giangreco*¹, Daniella Dwir², Luca Bartesaghi³, Omar Alijevic⁴, Aline Monin², Ha Nam Nguyen⁵, Philipp S. Baumann⁶, Raoul Jenni², Martine Cleusix⁶, Michel Cuénod², Paul Klauser⁷, Philippe Conus⁶, Stephan Kellenberger⁴, Hongjun Song⁸, Roman Chrast³, Kim Q. Do², Nicolas Toni²

¹Center for Psychiatric Neuroscience, Lausanne University Hospital and University of Lausanne, ²Center for Psychiatric Neuroscience, Lausanne University Hospital and University of Lausanne, Switzerland, ³Departments of Clinical Neuroscience and Neuroscience, Karolinska Institutet, Stockholm, Sweden, ⁴Department of biomedical Sciences, University of Lausanne, Switzerland, ⁵Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, ⁶Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Switzerland, ⁷Center for

Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland, ⁸Department of Neuroscience and Mahoney Institute for Neurosciences, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Background: Excitatory/inhibitory (E/I) imbalance is a hallmark of schizophrenia (SZ) and may play a crucial role in the manifestation of the cognitive symptoms. These alterations may arise from abnormal maturation of the inhibitory system during early brain development, involving the NKCC1/KCC2 switch. This mechanism encompasses the switch of the GABAergic neurotransmission from excitatory to inhibitory, induced by a decrease in NKCC1 expression in parallel with an increase in KCC2 expression. The NKCC1/KCC2 switch was found to be involved in the maturation of the E/I balance but also in the proliferation and differentiation of neural progenitors during brain development. Moreover, some postmortem studies suggest impairments in NKCC1 and KCC2 expression in SZ. Based on the major role of oxidative stress (OxS) in the pathophysiology of SZ, we hypothesized that NKCC1/KCC2 alterations may be induced by a redox dysregulation, originating from the interaction between genetic and environmental risk factors. More specifically, we investigated, in both an animal model and in early psychosis (EP) patients, whether a redox dysregulation during early neuronal development affects the NKCC1/KCC2 switch, leading to neuronal maturation/differentiation impairments.

Methods: The animal study was conducted on a transgenic mouse model of GSH deficit (Gclm-KO), which has a SZ related phenotype. The Gclm-KO mice display increased OxS and decreased parvalbumin-expressing interneurons (PVI) in the ventral (VH) but not dorsal (DH) hippocampus. Proliferation of neural progenitors in the dentate gyrus (DG) of the VH and DH was quantified with BrdU injection followed by immunohistochemistry (IH) on WT and KO mice (N=5). NKCC1/KCC2 were evaluated by western blot on the microdissected DG.

For the human study, iPSC were induced from fibroblasts of EP patients (EPP) and healthy controls (HC), bearing or not a genetic polymorphism for OxS vulnerability, and enrolled in a multi-levels characterized cohorts. iPSC were differentiated into neural precursors cells (NPC, N=3-5) and followed during their differentiation into neurons (N=1).

Results: We found abnormal proliferation/survival of neural progenitors and altered NKCC1/KCC2 protein levels in the DG of the Gclm-KO as compared to the WT. This proliferation/maturation imbalance was further found in iPSC-induced NPC and neurons from EPP, as compared to HC, with increased Ki67 and decreased DCX levels by IH. Neurons from EPP exhibited an immature phenotype, characterized by a reduction in dendritic complexity (MAP2/Tuj1). The NKCC1/KCC2 switch was also altered during the differentiation of patient NPC into neurons. Moreover, EPP NPC had higher levels of Nrf2 during the early phase of differentiation, as compared to HC and were also more sensitive to a pro-oxidant environment, by increasing their antioxidant defenses (nrf2, gclc, gclm, gpx and gred gene expression). Interestingly, a pro-oxidant environment during the very early phase of maturation increased NKCC1 in both HC and EPP NPC, leading to a delay in the NKCC1/KCC2 switch. An additional OxS challenge in a pro-oxidant environment induced a long-term effect in the HC NPC, with decreased KCC2 expression.

Discussion: Altogether, our results suggest that redox dysregulation, induced by a genetic predisposition and/or a pro-oxidant environment, affects the NKCC1/KCC2 switch, which may lead to abnormal maturation of neurons. While these findings are preliminary and require additional confirmation, they remain highly significant for advancing our comprehension of the developmental changes in NKCC1/KCC2 during brain maturation, which could explain the cognitive symptoms associated with SZ.

T181. NAVIGATING DIVERSITY IN MATERNAL IMMUNE ACTIVATION PROTOCOLS: A COMPREHENSIVE REVIEW OF MAMMALIAN MODELS

Ali Shahbazi¹, Maral Khodaparast*¹, Dina Vagharimehr²

¹*Iran University of Medical Sciences*, ²*University of Pavia*

Background: After the historic realization of the impact of infectious disease outbreaks on next generation's psychiatric health, many different maternal immune activation (MIA) protocols have been designed in order to replicate some aspects of human psychiatric disorders in different animals extending from mice to non-human primates. These models make it possible to examine aspects of the pathomechanism of schizophrenia, autism and depression that were not accessible through any preceding replications of these disorders. MIA models have also become a useful medium to study the effect of a variety of interventions on prevention and reversal of psychiatric disease-related phenotypes. However, the variation of MIA protocols makes confusion when choosing the right model for a given objective and raises questions about method standardization and comparability of the widely available manuscripts that have used these protocols. The aim of this review is to help with designing maternal immune activation methodologies for a given research question.

Methods: The data presented in this review are derived from articles retrieved from PubMed and Scholar spanning 1990-2023, utilizing the following keywords: Prenatal Immune Activation, Maternal Immune Activation, Gestational Immune Activation, Schizophrenia, Autism, Depression, LPS, Poly I:C and MAM. Human, ex vivo and in vitro studies and animal neurodevelopmental studies that have used non-immune stimulating agents have not been included in this review.

Results: The data extracted from selected papers has been organized into comprehensive tables, encompassing details on experimental animals, MIA induction protocols, validation techniques, secondary interventions, and corresponding behavioral and molecular assessments.

In the analysis of diverse MIA protocols, studies were primarily categorized based on the experimental animals including rodents and primates, studies were then subcategorized using the immune mimetic agent (Poly I:C, LPS, direct use of virus, bacteria) and gestational stages of immune activation (early, mid, or late gestation). The administration details including: dosage ranges, routes, and durations, model validation (selected cytokines), study outcomes including: molecular assessments and behavioral evaluations and secondary interventions (both pharmacologic and nonpharmacologic) were then presented meticulously in separate tables.

Discussion: The comprehensive exploration of maternal immune activation (MIA) has provided valuable insights into the complex interplay of neurodevelopment and environmental factors contributing to neuropsychiatric disorders and also helped in developing relevant tools for preclinical drug research. However, the absence of uniformity in research methodologies makes it hard to design a study using these animal models. Recently a detailed guideline has been proposed for reporting MIA studies, which is an important aid in increasing the quality of the future research.

This review takes a step back and aims to help design MIA research methodologies. The data regarding protocol variations have been presented for each step of the experiment and help selecting proper MIA protocol for experiments via substantial summarization and classification of the available literature. We aim to facilitate standardization in experimental

design and interpretation, fostering a more cohesive understanding of MIA's impact on psychiatric disorders in animal models and addressing the gaps and future direction for studies in this field.

T182. NEUROPATHOLOGY OF COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA

Naomi Futhey*¹, Elizabeth Gregory¹, Belen Arranz², Josep Maria Haro³, Fidel Vila-Rodriguez¹, Mark S. Cembrowski¹, Veronica Hirsch-Reinshagen¹

¹*The University of British Columbia*, ²*Hospital Parc Sanitari Sant Joan de Déu*, ³*Parc Sanitari Sant Joan de Déu, CIBERSAM, Universitat de Barcelona, Barcelona, Spain*

Background: Cognitive impairment is a core tenant of chronic schizophrenia and can be as disabling as that experienced by patients with Alzheimer Disease (AD). Research shows impairment may present prior to the onset of positive symptoms and be exacerbated by aging, but a mechanism has never been elucidated. In AD, accumulation of abnormal proteins leads to chronic neurodegeneration and a characteristic neuropathological signature. Our pilot data, however, shows that cognitive impairment in chronic schizophrenia is only partially explained by neurodegeneration, suggesting the presence of a different neuropathological process specific to schizophrenia.

Methods: We have obtained clinical and demographic data for 55 patients with chronic schizophrenia that underwent autopsy in compliance with standard European ethical requirements. Clinical data includes psychiatric diagnoses, Global Assessment of Functioning (GAF) score, Clinical Global Impressions (CGI) measurement, pharmacological treatment history, and cause of death. A subset of 34 subjects has additional neuropsychological evaluations including Positive and Negative Syndrome Scale (PANSS) scores, Mini-Mental Status Examination (MMSE), Frontal Assessment Battery (FAB), Calgary Depression Scale for Schizophrenia (CDSS), and CERAD scores. Standard evaluation of neurodegenerative diseases was performed in all subjects using 15 tissue blocks per subject, including all lobes, white matter, limbic system, deep grey nuclei (basal ganglia and thalamus), brainstem, and cerebellum. Initial exploratory data analyses was performed to ascertain central tendency, dispersion, and data distribution, as well as whole group correlations between severity of neurodegenerative pathology with clinical and neuropsychological score scales.

Results: The mean (SD) age of death in our cohort was 78.2 (9.4), and the mean disease duration 53.9 (10.6) years. 14 patients (32.6%) had completed primary school or more, and 42 (81.1%) were heavy smokers. 37 (74.0%) were on antipsychotics, the mean GAF score was 30.7 (12.0) and mean CGI 4.4 (0.9). Mean total PANSS score was 100.3 (30.0), mean positive symptom score was 22.2 (9.2) and the mean negative score was 28.5 (9.8). The mean MMSE was 17.4 (8.3), CDSS was 1.9 (2.5) and FAB 7.6 (4.5). On autopsy, 25 patients out of 54 (47%) had neurodegenerative or cerebrovascular neuropathological findings of enough severity to explain cognitive impairment in non-schizophrenia patients. These included 17 (32%) cases with moderate or severe AD pathology, 5 (9%) with significant cerebrovascular disease, and 3 (6%) cases with severe non-AD neurodegenerative pathology. One patient had remote history of a lobectomy. However, neurocognitive test scores did not correlate with severity of neuropathological changes.

Discussion: This cohort represents a group of elderly patients with chronic schizophrenia with relatively low mean education level, high smoking rate, marked impairment in global

functioning and significant cognitive impairment. The latter two are not entirely explained by neuropathological changes typically associated with dementia.

T183. ALTERED RETINAL MICROSTRUCTURES AND ELECTROPHYSIOLOGY AND THEIR ASSOCIATION WITH CLINICAL PARAMETERS AND VISUAL BRAIN REGIONS IN SCHIZOPHRENIA SPECTRUM DISORDERS

Florian Raabe*¹, Emanuel Boudriot², David Popovic¹

¹Max-Planck Institute of Psychiatry, ²Department of Psychiatry, LMU Munich Germany

Background: Optical coherence tomography (OCT) and electroretinography (ERG) studies have revealed both structural and functional retinal alterations in patients with schizophrenia spectrum disorders (SSD). However, it remains unclear which retinal layers are affected in SSD and how retina, brain, and clinical symptomatology are interconnected.

Methods: OCT, ERG, and brain magnetic resonance imaging (MRI) were applied to comprehensively investigate the visual system in a cohort of 103 patients with SSD and 130 healthy control individuals. A sparse partial least squares algorithm was used to identify multivariate associations between phenotypic and biological data. To assess specific differences between the groups, covariate-adjusted case-control comparisons of OCT and ERG parameters were subsequently performed with generalized estimation equations. Additional post hoc analyses were conducted to explore the relationship between retinal parameters, clinical disease features, and MRI volumes in patients.

Results: The sparse partial least squares analysis yielded a phenotype-eye-brain signature of SSD in which greater disease severity and impaired cognition were associated with electrophysiological and structural retinal impairment ($p < 0.001$). In case-control comparisons, patients with SSD had lower macular thickness, thinner retinal nerve fiber and inner plexiform layers, less negative a-wave amplitude, and lower b-wave amplitude. In patients, post hoc analyses linked retinal features to clinical parameters, such as duration of illness, duration of untreated psychosis, and cognition.

Discussion: This study demonstrates microstructural and electrophysiological retinal alterations in individuals with SSD that are associated with clinically relevant outcome parameters. Assessment of retinal parameters might help for future stratification of patients and could support the way towards personalized treatment strategies.

T184. STATE-DEPENDENT MODULATION OF STRIATAL AND HIPPOCAMPAL GLUTAMATE FUNCTION BY TAAR1 AGONIST ULOTARONT

Nina Dedic*¹, Sung Min Yang¹, Ayan Ghoshal¹, Jeffrey Hubbard², Florian Gackière², Romain Teyssié², Stuart A Neale³, Seth C Hopkins¹, Kenneth S Koblan¹, Linda J Bristow¹

¹Sumitomo Pharma America, ²Neuroservices Alliance, ³Neurexpert Limited

Background: Aberrant dopaminergic and glutamatergic function, particularly within the striatum and hippocampus, has repeatedly been associated with the pathophysiology of schizophrenia. Supported by preclinical and recent clinical data, trace amine-associated receptor 1 (TAAR1) agonism has emerged as a potential new treatment approach for schizophrenia. While current evidence implicates TAAR1-mediated regulation of dopaminergic tone (i.e. presynaptic dopamine syntheses capacity and/or release) as the

primary circuit mechanism, little is known about the effects of TAAR1 agonists on the glutamatergic system and excitation-inhibition balance. Here we assessed the impact of ulotaront (SEP-363856), a TAAR1 agonist in Phase III clinical development for schizophrenia, on glutamate function in the mouse striatum and hippocampus.

Methods: Acute brain slices were obtained from *Drd1a*-tdTomato and C57Bl6/J mice for striatal and hippocampal experiments, respectively. Whole-cell patch-clamp (voltage-clamp mode) recordings in the dorsal striatum were performed to investigate the effects of TAAR1 agonists ulotaront and RO5166017 on synaptic transmission. Striatal medium spiny neurons (MSNs) were identified based on their electrophysiological properties, and classified as D1 (i.e. tdTomato+) or putative D2 (i.e. tdTomato-) MSNs. Extracellular recordings in the hippocampal CA1 region were performed to assess firing activity and synaptic transmission (either via a multielectrode array or glass micropipette).

Results: Ulotaront reduced spontaneous glutamatergic synaptic transmission and neuronal firing in striatal and hippocampal brain slices, respectively. Interestingly, ulotaront potentiated electrically-evoked excitatory synaptic transmission in both brain regions, with the striatal effect being specific to a subpopulation of D2 MSNs. Similar striatal effects were also observed with the TAAR1 agonist, RO5166017. Furthermore, ulotaront exhibited a significant effect on excitatory but not the inhibitory synaptic activity of MSNs, which suggests a modulatory effect on striatal excitation-inhibition balance.

Discussion: The ability of ulotaront to selectively potentiate evoked synaptic responses, while reducing spontaneous activity suggests state-dependent modulation of glutamatergic tone and the potential to enhance the signal-to-noise ratio. These findings expand the mechanistic circuit hypothesis of TAAR1 agonists, which may be uniquely positioned to normalize both, the excessive dopaminergic tone and regulate abnormal glutamatergic function associated with schizophrenia.

T185. A DIFFUSION TENSOR IMAGING STUDY COMPARING WHITE MATTER INTEGRITY IN FAMILIAL HIGH-RISK INDIVIDUALS FOR BIPOLAR DISORDER AND PSYCHOSIS WITH HEALTHY CONTROLS

Muhammed Demir*¹, Cemal Demirlek², Burcu Verim², Berna Yalincetin³, Berna Akdede⁴, Burak Baykara⁵, Nabi Zorlu⁶, Emre Bora⁷

¹*Institute of Health Sciences, Department of Neuroscience, Dokuz Eylul University,*
²*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey,* ³*Department of Neuroscience, Dokuz Eylul University, Izmir, Turkey,* ⁴*Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, Izmir, Turkey,* ⁵*Department of Child and Adolescent Psychiatry, Dokuz Eylul University Medical School, Izmir, Turkey,* ⁶*Department of Psychiatry, Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey,* ⁷*Dokuz Eylul University Department of Neuroscience, Dokuz Eylul University, School of Medicine, Department of Psychiatry*

Background: Within familial high-risk studies for bipolar disorder (FHR-BD) and psychosis (FHR-P), Diffusion Tensor Imaging (DTI) has become pivotal in exploring the intricacies of white matter microstructure in the human brain. By investigating individuals at familial high risk, this study aims to unveil subtle changes in white matter integrity that may precede clinical manifestations. Utilizing Tract-Based Spatial Statistics (TBSS) and the randomise tool in FSL, our analysis focuses on key DTI metrics—Fractional Anisotropy (FA), Radial Diffusivity (RD), and Axial Diffusivity (AD). The objective is to pinpoint specific white

matter irregularities associated with familial risk, offering valuable insights into early neurobiological indicators. These findings may pave the way for tailored interventions and preventative measures for individuals predisposed to bipolar disorder and psychosis.

Methods: In this study, we recruited a total of 56 participants, comprising 18 individuals at familial high risk for psychosis (FHR-P), 19 individuals at familial high risk for bipolar disorder (FHR-BD), and 19 Healthy Controls. Participants from familial high-risk groups were identified through patient records or outpatient settings at the Early Diagnosis and Intervention Department of Psychiatry at Dokuz Eylül University. All participants underwent MRI sessions using a 3 Tesla scanner. We conducted diffusion tensor imaging (DTI) analyses using FSL toolboxes. Voxel-wise statistical analysis was performed on Fractional Anisotropy (FA), Radial Diffusivity (RD) and Axial Diffusivity (AD) values using the Tract-Based Spatial Statistics (TBSS) toolbox. FA, RD and AD values were compared between healthy controls and familial high-risk groups separately. T-test comparisons were carried out using the randomise tool in FSL, with multiple comparison corrections performed using threshold-free cluster enhancement (TFCE). The statistical maps revealed significant tracts, identified by thresholding the p-value below 0.05.

Results: Investigating whole-brain Fractional Anisotropy (FA) and Radial Diffusivity (RD) comparisons revealed no significant clusters across all groups. Additionally, whole-brain Axial Diffusivity (AD) comparisons between the Familial High Risk for Psychosis (FHR-P) and Healthy Control (HC) groups did not show any significant clusters. However, in the comparison between Familial High Risk for Bipolar Disorder (FHR-BD) and HC groups, significant clusters were identified in the body of the corpus callosum. Further analysis, using the randomise tool with the superior longitudinal fasciculus as a mask, revealed that the FHR-P group exhibited significant clusters characterized by lower FA values and higher RD values compared to the HC group.

Discussion: Our investigation revealed notable distinctions in white matter microstructure among familial high-risk groups for bipolar disorder and psychosis. Notably, the familial high-risk for bipolar disorder (FHR-BD) group exhibited significantly higher Axial Diffusivity (AD) clusters in the body of the corpus callosum, potentially indicative of compensatory mechanisms. Conversely, whole brain analyses showed no significant clusters for Fractional Anisotropy (FA) and Radial Diffusivity (RD) values, suggesting that these measures, unlike in chronic patients, may not be as informative in the context of familial risk groups. Further analyses, particularly when employing a mask for the superior longitudinal fasciculus, revealed significant clusters. This outcome implies that the microstructural anomaly might be subtle, making it challenging to detect at the whole-brain level with stringent multiple comparison corrections, underscoring the importance of focused analyses on specific tracts.

T186. LONGITUDINAL CHANGES IN CORTICAL NETWORKS OF FIRST EPISODE SCHIZOPHRENIA PATIENTS

Peter Van Dyken^{*1}, Michael MacKinley², Ali Khan³, Lena Palaniyappan⁴

¹University of Western Ontario, ²London Health Sciences Centre, ³Robarts Research Institute, London, Ontario, ⁴Douglas Mental Health University Institute, Montreal, Quebec

Background: Patients with chronic schizophrenia have marked disruption of white matter connectivity as shown by diffusion MRI (Kelly et al., 2018). However, this disruption appears to be limited or absent in first episode psychosis (FEP) patients (Van Dyken, 2023, in review). Thus far, most studies of FEP have been cross-sectional or short-term follow-up on

treatment effects. This has precluded the disambiguation of two distinct issues that may explain the white matter disruption that characterized established illness: (1) a dynamic post-onset process of white matter-alterations in early phases of this illness vs. (2) a more severe extent of pre-onset white matter changes resulting in a chronic, intractable pattern of illness. Here, we investigate this issue in a longitudinal cohort of FEP patients and healthy controls to investigate the first possibility in this dichotomy: whether early phase of schizophrenia is characterised by ongoing changes in white matter diffusivity over time.

Methods: N=21 FEP patients and N=13 healthy controls (HCs) were recruited from an established cohort (TOPSY) in London, Ontario, Canada. Participants were scanned twice with follow-up 6-12 months after baseline. Baseline scans of patients were performed following initial diagnosis, before initiation of treatment. Data was acquired with 7T MRI using diffusion-weighted ($b=0,1000$; 64 directions; 2mm res) and T1-weighted (MP2RAGE; 0.75mm res) protocols. Diffusion data was preprocessed with and FSL pipeline (degibbs, susceptibility distortion correction with topup, motion and eddy current correction with eddy) and probabilistic tractography was performed with MRTrx using Constrained Spherical Deconvolution, the iFOD2 tracking algorithm, and Anatomically Constrained Tractography. Tract Based Spatial Statistics (TBSS) was used to measure voxel-wise decreases in fractional anisotropy (FA) and increases in mean, radial, and axial diffusivity (MD, RD, AD) between sessions. After defining structural connectivity matrices using the Brainnetome atlas, a graph theory-based clustering approach called the Network Based Statistic (NBS) was used to identify connections with significant increases in FA, and decreases MD, RD, and AD. For all analyses, data were fit to a mixed linear model, with subjects as a random effect and time by group as the fixed effect. Results were compared to a null distribution generated by 10,000 permutations.

Results: On average across the white matter, in FEP patients FA significantly declined between sessions ($z(73)$; $p = 0.017$), while MD ($z(73)$; $p \text{ LESS THAN } 0.01$) and RD ($z(73)$; $p \text{ LESS THAN } 0.001$) significantly increased. HCs had no change in these metrics, and the changes of MD ($z(73)$; $p \text{ LESS THAN } 0.01$) and RD ($z(73)$; $p \text{ LESS THAN } 0.05$) in FEP were significantly greater than that of HCs. Regionally, significantly lower FA and higher RD in the second scan was found in the left hemisphere in the genu of the corpus callosum and the centrum ovale. Connections with decreased FA and increased RD were found predominantly in the left hemisphere, particularly between the frontal, parietal, and temporal lobes. No regional or connectivity effects were seen in healthy controls, however, changes in FEP patients were not significantly different from changes in healthy controls.

Discussion: A change in diffusivity toward the patterns observed in chronic patients can be seen in FEP patients during the immediate aftermath of the first psychotic episode, however, it is unclear if this change is mediated by schizophrenia or an effect of physical, pharmacological, and social effects of a psychotic episode. Disruption localized in the left hemisphere may contribute to disruption of language networks.

T187. GLUCOSE-DOPAMINE INDEX: A PROMISING NEW METRIC FOR SCHIZOPHRENIA RESEARCH

Irena Dajic^{*1}, Ulrich Sauerzopf², Ana Weidenauer², Katharina Landesmann², Cornelia Diendorfer², Nicole Praschak-Rieder², Matthäus Willeit²

¹Medical University of Vienna, ²Department of Psychiatry and Psychotherapy, Medical University of Vienna

Background: Dysregulated dopamine signaling and altered energy homeostasis are well documented in schizophrenia (SCZ) and mounting evidence suggests that the two findings are closely connected. We have previously shown that blood glucose levels exhibit a positive association with specific binding of the selective D2/3 dopamine receptor agonist [11C]-(+)-PHNO in healthy volunteers (HV), and that this relationship is inversed in patients with SCZ (Sauerzopf et al. 2021). Here, we operationalize the glucose-dopamine relationship as a simple ratio of [11C]-(+)-PHNO binding to blood glucose (henceforth, GD index) and examine the utility of this new measure in capturing clinically relevant features of the disorder.

Methods: 27 HV (14m, 13f) and 15 patients with first-episode SCZ (10m, 5f) underwent baseline [11C]-(+)-PHNO PET scans as further described in Sauerzopf et al. (2021) and Weidenauer et al. (2020). Regional and voxelwise estimates of [11C]-(+)-PHNO specific binding (BPND) were derived using the simplified reference tissue model with cerebellar cortex serving as the reference region. The resulting BPND values were divided by blood glucose concentrations (mmol/L) measured prior to tracer injection using a hand-held device. Thus derived GD indices were compared between study groups using independent sample t-tests. Exploratory analyses examined the correlations between the indices and PANSS subscale scores, as well as individual PANSS items.

Results: GD indices were significantly lower in patients with SCZ as compared to HV in the caudate ($p=0.037$), putamen ($p=0.015$), and ventral striatum ($p=0.033$). Voxelwise analyses across basal ganglia structures provided concordant results in the form of large clusters extending bilaterally across the striatum (p LESS THAN 0.05, false discovery rate-corrected). Of the three compound symptom scores, only positive symptoms displayed associations with GD indices and these remained at trend-level (putamen: $r=-0.49$, $p=0.07$; globus pallidus: $r=-0.45$, $p=0.09$). However, we observed striking correlations of regional GD indices with several PANSS items, most notably blunted affect (ventral striatum: $r=0.84$, p LESS THAN 0.001) and somatic concern (hypothalamus and ventral striatum: $r=-0.68$, p LESS THAN 0.01).

Discussion: Regional GD indices proved apt in capturing group differences between patients with first-episode SCZ and HV as well as clinical correlations within the patient group that were not evident when baseline BPND values or glucose levels were evaluated separately (Weidenauer et al 2020). Based on these preliminary results, the GD index seems to be a promising metric for characterizing systemic disturbances in SCZ. Further studies are needed to corroborate and extend these findings.

Sauerzopf U, Weidenauer A, Dajic I, et al. Disrupted relationship between blood glucose and brain dopamine D2/3 receptor binding in patients with first-episode schizophrenia. *Neuroimage Clin.* 2021;32:102813. doi:10.1016/j.nicl.2021.102813

Weidenauer A, Bauer M, Sauerzopf U, et al. On the relationship of first-episode psychosis to the amphetamine-sensitized state: a dopamine D2/3 receptor agonist radioligand study. *Transl Psychiatry.* 2020;10(1):2. Published 2020 Jan 8. doi:10.1038/s41398-019-0681-5

T188. MORPHOLOGICAL DIFFERENCES IN DEEP BRAIN STRUCTURES BETWEEN COGNITIVE SUBTYPES OF SCHIZOPHRENIA

Jacob Holker*¹, Aaron Clouse², Jacob Jensen³, Sierra Jarvis², Samuel Johnson², Kennedy Madrid², Holly Paxton-Winiarski², Chase Junge⁴, Karteek Popuri⁵, M. Faisal Beg⁶, Matthew Smith⁷, John Csernansky⁸, Lei Wang⁹, Derin Cobia²

¹Brain Imaging and Behavior Lab at Brigham Young University Provo, ²Brigham Young University, ³University of Pennsylvania School of Medicine, ⁴University of Indiana, ⁵Memorial University, ⁶Simon Fraser University, ⁷University of Michigan, ⁸Northwestern University Feinberg School of Medicine, ⁹The Ohio State University Wexner Medical Center

Background: Cognitive deficits are a key aspect of schizophrenia, yet a broad spectrum of cognitive impairment is seen in the disorder, ranging from severe impairment to nearly normal functioning compared to healthy individuals. Research into brain structure integrity among cognitively differentiated subtypes of schizophrenia is growing, with the goal of pinpointing significant underlying factors for each distinct cognitive profile. This study focused on delineating the morphology of deep brain structures in a large multi-site sample of cognitive subtypes in schizophrenia through advanced brain mapping techniques. It was hypothesized that those with preserved cognitive abilities would show structural features akin to those of healthy subjects, contrasting with those in a more typically impaired subgroup.

Methods: Participant data was derived from the federated SchizConnect data sharing project. Schizophrenia participants were clustered into cognitive deficit (CD=99) and cognitively spared (CS=223) subgroups using a k-means algorithm; matched healthy comparison subjects were also included (CON=208). Neuropsychological functioning was assessed with a comprehensive battery, and MR scanning included T1-weighted images. Shape features of the caudate (CAUD), putamen (PU), globus pallidus (GP), nucleus accumbens (NA), thalamus (TH), hippocampus (HPC), and amygdala (AM) were derived using surface-based processing pipelines. Statistical analyses included vertex-wise contrast maps to test specific group differences in deep brain morphology corrected for multiple comparisons using random-field theory.

Results: Examination of vertex-wise contrast surface maps revealed significant abnormal shape in CS relative to CON in AM, HPC, TH, PUT, CAUD, and NA, with a prominent bilateral strip of inward deformation along dorsal aspects of the TH in CON-CS deformation maps. As for the CS-CD contrast, a significant outward deformation in the right amygdala was observed. Finally, examination of CON-CD contrasts revealed both significant inward and outward deformation in HPC, GP, and PUT.

Discussion: Findings generally, but not completely, endorse the concept of neurobiological diversity corresponding to the cognitive characteristics of empirically-defined schizophrenia subtypes. The cognitively spared subgroup exhibited atypical surface morphology across various brain structures relatively to CON, indicating a unique subcortical brain profile. The lack of notable abnormalities in the cognitively impaired subgroup points to different brain mechanisms influencing the clinical manifestation of the disorder. Distinct pathophysiological features might be active in each schizophrenia subgroup, suggesting either different variants of the disorder or the presence of biological protective elements that mitigate the severity of the condition.

T189. EXTRASTRIATAL DOPAMINE D2/3 RECEPTOR AVAILABILITY CONTRIBUTES TO CONDITIONED HALLUCINATIONS

Ulrich Sauerzopf^{*1}, Irena Dajic¹, Katharina Landesmann¹, Ana Weidenauer¹, Cornelia Diendorfer¹, Karsten Bamminger¹, Cécile Philippe¹, Lukas Nics¹, Nicole Praschak-Rieder¹, Matthäus Willeit¹

¹Medical University of Vienna

Background: Both, delusional perceptions as well as hallucinations can be conceptualized as faulty inference based on over-reliance on expectation in determining the presence or content of percepts. These psychopathological phenomena are commonly found in schizophrenia. The current dopamine hypothesis of schizophrenia comprises a role for both, striatal hyper-dopamergeria and cortical hypo-dopaminergia in the pathogenesis of schizophrenic psychosis. Previous studies have highlighted the role of enhanced striatal dopamine levels in mediating expectation-induced perceptual experiences in animals as well as human volunteers.

The aim of the present study was to ascertain whether extra-striatal dopamine D2/3 receptor availability, as measured by a highly sensitive and selective D2/3 receptor agonist radioligand [11C]-(+)-PHNO, could likewise be linked to susceptibility to auditory hallucinations induced by a cross-modal sensory conditioning task.

Methods: Ten healthy volunteers (2 male, 8 female), aged 19-28 (24±3), underwent a [11C]-(+)-PHNO positron emission tomography (PET) scan combined with an amphetamine challenge eliciting a hyper-dopaminergic state. The tracer was administered as a bolus followed by constant infusion (kbol=80). After tracer equilibrium was achieved, 0.3 mg/kg of d-amphetamine were administered i.v.. The conditioned hallucination (CH) task was performed after the PET scan was completed and within 111 ± 39 min of the amphetamine challenge. PET images were pre-processed in an in-house pipeline and regional time-activity curves were extracted using a detailed multimodal parcellation atlas. Pre- and post-amphetamine BPND values were calculated using the equilibrium approach, with the cerebellum as the reference region. The effects of post-amphetamine BPND values on CH frequency and associated confidence ratings were estimated using logistic and linear regression models, respectively. Logistic regression model fit was assessed using McFadden's pseudo R²; all p values were bonferroni corrected.

Results: CH frequency was associated with post-amphetamine [11C]-PHNO BPND values in a widely distributed set of cortical and subcortical regions. The strongest positive effects of BPND values on CH frequency were observed in the left parahippocampal gyrus, inferior frontal gyrus (BA47), inferior frontal sulcus, parts of the cingulate gyrus (BA 23 and BA 32) and the orbitofrontal gyrus (BA8) (pseudo R : 0.35-0.52, p-value LESS THAN 2.2e-16)). There was a negative association between mean confidence ratings and BPND in subsections of the superior frontal gyrus, posterior insula, and dorsal anterior cingulate cortex (adjusted R² GREATER THAN 0.85, p-value LESS THAN 0.05).

Discussion: Under hyper-dopaminergic conditions, the propensity to experience conditioned hallucinations was in general positively correlated with the [11C]-(+)-PHNO BPND indicating that these experiences were more likely if less dopamine was available in these brain areas. The confidence in these percepts was, though, negatively correlated with BPND. These findings are consistent with the hypothesis that dysregulations in prefrontal dopamine levels could be an important factor contributing to clinical hallucinations and the formation of delusions.

T190. DISSECTING NEUROANATOMICAL DISEASE TRAJECTORIES OF SCHIZOPHRENIA ACROSS THE LIFESPAN

Foivos Georgiadis^{*1}, Katerina Manoli², Stefan Kaiser³, Erich Seifritz¹, Sofie Valk², Paul Thompson⁴, Theo van Erp⁵, Jessica Turner⁶, Philipp Homan¹, Matthias Kirschner³

¹University Hospital of Psychiatry, University of Zurich, ²Max planck Institute for Human Cognitive and Brain Sciences, ³University Hospital of Psychiatry, University of Geneva, ⁴Imaging Genetics Center, University of Southern California, ⁵Psychiatry and Human Behavior School of Medicine, University of California Irvine, ⁶Department of Psychology, Georgia State University

Background: Schizophrenia is associated with widespread cortical abnormalities, with a demonstrated developmental onset. Aligning with a neurodevelopmental model, highest prevalence is between 18-25 years; however, later-onset (GREATER THAN =35) schizophrenia cases are well-documented, markedly, with differences in both symptomatology and outcomes. Studies comparing the neurobiological substrates of different age of onset remain hitherto scarce and limited by small sample sizes. Here, in the largest sample to date, we characterize and compare neuroanatomical patterns of typical (N=1035) and later-onset (N=214) schizophrenia patients and matched healthy controls (HC; N = 2867).

Methods: Using linear regression models, controlling for age and sex, and after adjusting for batch effects, we first compared cortical thickness of 68 regions between the entire HC cohort, vs. typical-onset schizophrenia and later-onset schizophrenia patients separately. In a next step, we directly compared the cortical thickness alterations of typical-onset compared to later-onset schizophrenia. To this end, we first regressed out age, age² and sex from subject-level cortical thickness data and compared the resulting residuals between typical-onset and later-onset schizophrenia individuals. Linear models with total cortical thickness and the similar covariates were used to confirm the convergent effect of the separate brain region models. To further examine cortical thickness as a singular phenotype, linear mixed models with brain region as a random effect in the case of the 68 brain regions, and laterality in the case of total cortical thickness models were implemented.

Results: Typical-onset schizophrenia patients showed widespread cortical thickness reductions compared to HC, with strongest effect sizes observed in occipital-parietal-temporal regions and the inferior frontal gyrus (t-values GREATER THAN 10; all pFDR LESS THAN .05), while only the bilateral pericalcarine cortex was not significantly different from HC. In later-onset schizophrenia, strongest cortical thickness reduction was observed in predominantly tempo-frontal regions (all t-values GREATER THAN 4; all all pFDR LESS THAN .05). In terms of topographical pattern, the cortical maps of typical-onset SCZ and later-onset SCZ show a high degree of topographical similarity (r=0.78, pspin LESS THAN .05). In a direct comparison later-onset SCZ patients show convergently lower effect sizes (Cohen's D) reductions in CT across all regions (MDCohen = 0.07 [0.05,0.09], pt-test LESS THAN .0001, V = 2199, pwilcoxon LESS THAN .0001). The lower region-specific disease-related reductions in later-onset patients is confirmed in a linear mixed model with brain region as a random effect ($\beta_{\text{stand}}=0.03$ [0.025,0.035], p LESS THAN 0.0001). Our total cortical thickness linear mixed model with laterality as a random effect further supports lower disease-related cortical thickness reductions in later- vs early onset schizophrenia patients ($\beta_{\text{stand}}=0.05$ [0.03,0.07], p = 0.0188). Very similar results are obtained when additionally controlling for total intracranial volume. Separate linear models for each region separately and for each side separately, in the case of total cortical thickness show convergent results with the linear mixed models.

Discussion: Altogether, our findings suggest high overall topographical similarity of cortical thickness reductions in typical-onset and later-onset schizophrenia and show in the largest sample size to date indications for stronger age-adjusted cortical thickness reduction in

typical-onset compared to later-onset schizophrenia patients. In addition, subtle variations of cortical alteration patterns were observed suggesting additional occipital, parietal, and temporal regions being affected in typical-onset schizophrenia, which are relatively spared in later-onset schizophrenia. These preliminary findings suggest shared neurobiological mechanisms underlying cortical thickness reduction in typical-onset and later-onset schizophrenia, and hint to a sparing effect of later schizophrenia onset on neuroimaging correlates of cortical thickness. These sparing effects appear to be more pronounced in occipital-parietal-temporal regions.

T191. VARIABILITY IN THE DEFAULT MODE NETWORK INCREASES FOLLOWING THE ONSET OF PSYCHOSIS

Ali Khatibi^{*1}, Majid Saveri², Sian Lowri Griffiths¹, Aaanya Malaviya¹, Paris Alexandros Lalousis³, Shalalia Haas⁴, Lana Kambeitz-Illankovic⁵, Stephen J. Wood⁶, Nicholas M Barnes¹, Katharine Chisholm⁷, Alexandra Stainton⁸, Junhao Wen⁹, Gyujoon Hwang¹⁰, Christos Davatzikos¹¹, Alessandro Bertolino¹², Stefan Borgwardt¹³, paolo brambilla¹⁴, Joseph Kambeitz¹⁵, Rebekka Lencer¹⁶, Christos Pantelis¹⁷, Stephan Ruhrmann¹⁸, Raimo K.R. Salokangas¹⁹, Frauke Schultze-Lutter²⁰, Andre Schmidt¹³, Eva Meisenzahl²¹, Dominic B. Dwyer²², Nikolaos Koutsouleris²³, Rachel Upthegrove¹, ... the PRONIA study group²⁴

¹University of Birmingham, ²Sick Kids Hospital, Toronto, Canada, ³Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁴Cahn School of Medicine at Mount Sinai, ⁵University of Cologne, ⁶Orygen, the National Centre of Excellence for Youth Mental Health, Melbourne, Australia, ⁷Aston University, ⁸Orygen, The National Centre of Excellence in Youth Mental Health, ⁹University of Pennsylvania, ¹⁰University of Pennsylvania, ¹¹University of Pennsylvania Perelman School of Medicine, ¹²University of Bari, ¹³University of Basel, ¹⁴University of Milan, ¹⁵Department of Psychiatry, University of Cologne, Germany, ¹⁶University of Muenster, ¹⁷Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, VIC, Australia, ¹⁸Dept. of Psychiatry and Psychotherapy, University of Cologne, ¹⁹Department of Psychiatry, University of Turku, Finland, ²⁰Heinrich-Heine University Düsseldorf, ²¹Department of Psychiatry and Psychotherapy, Heinrich-Heine University Düsseldorf, ²²Department of Psychiatry, Ludwig Maximilian University, Munich, ²³Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, ²⁴EU Consortium

Background: The default mode network (DMN) is a set of brain regions active during rest and self-referential thought. DMN abnormalities have been consistently found in schizophrenia. Some recent studies suggest that evaluating connectivity within the DMN can help us find those individuals at a higher risk of developing psychosis. We were interested to see if connectivity within 24 nodes within the DMN can help us differentiate individuals at risk (CHR) from those with recent onset psychosis (ROP).

Methods: Resting-state fMRI data acquired as part of the EU-FP7-funded PRONIA study have been used in this study. Based on Schaefer's local-global parcellation of the human cortex, masks have been used to extract the time series from 24 nodes linked to the DMN. Connectivity between these nodes compared between ROP and CHR.

Results: Our results suggest that differences in the connectivity between several nodes within the DMN are significant in comparing CHR and ROP. Most of these nodes, such as the Middle temporal gyrus and Inferior frontal gyrus, have higher connectivity in ROP than

CHR. However, some nodes, such as the Middle temporal gyrus and PCC, have lower connectivity in ROP than CHR.

Discussion: Our findings suggest that the development of pathology in psychosis is associated with increased variability in the resting state connectivity within the DMN. The next step in our analysis will be to explore the correlations with inflammatory markers and investigate their impact on the DMNS's connectivity.

T192. NEURAL DYNAMICS OF SOCIAL PERCEPTION IN SCHIZOPHRENIA

Daniel Vieira¹, Jessica Lee¹, Nicolas Foley¹, Gaurav Patel^{*2}

¹*Columbia University/NYSPI*, ²*Columbia University*

Background: Declines in social cognition lead to much disability in schizophrenia. We previously reported on how these social cognition changes relate to connectivity and functioning during naturalistic stimulation of the temporoparietal junction/posterior superior temporal sulcus (TPJ-pSTS). Here we present how connectivity changes with the type of stimulus, how the temporal dynamics of the neural activity relate to the viewing of the naturalistic stimulus, and how both these connectivity changes and dynamics differ in schizophrenia.

Methods: Participants watched a 12-minute audio/visual movie clip (22 healthy controls (HC) and 24 schizophrenia participants (SzP)), a 15-minute visual-only movie clip (27 SzP and 21 HC), or listened to a 7.5-minute audio-only story (23 HC and 20 SzP) while BOLD-fMRI data was collected. We first used weighted shortest path length (wSPL) from each region of interest (ROI) to either right A1 or V1 to quantify the stimulation-induced changes in network connectivity from rest. We then clustered (k-means) the audio/visual and visual-only movie-evoked BOLD time-courses into co-activation pattern (CAP) states. We examined the association of the time-course of each of these CAP states with both movie visual features and saccades recorded during the movie-viewing.

Results: Superior temporal sulcus (STS) ROIs demonstrated the largest change from rest in wSPL to A1 or V1 in both groups, and wSPL between unimodal sensory areas shortened more in SzP versus HC from rest ($p < 0.05$). Then, for both the visual and audio/visual clips, we found CAP states that involved all the TPJ-pSTS areas. These CAP states were significantly associated with the movie's visual motion intensity, degree of social engagement among characters, each individual's saccadic frequencies, the expression of sarcasm (audio/visual clip only), and the number of faces in peripheral vision (all $pFDR < 0.005$). SzP CAP states frequently diverged from HC when HC were in the TPJ-pSTS CAP states during both clips. These moments were associated with higher visual motion velocities in the visual-only clip, with the expression of sarcasm in the audio/visual clip, and with social interactions in both clips ($pFDR < 0.05$).

Discussion: These experiments highlight the role of the TPJ and STS areas in dynamic changes associated with aspects of social cognition, and how the functioning of these areas may differ in SzP. With these dynamic measures we plan to extend precision imaging methods to capture dynamics that can then be used for both diagnostic and treatment purposes.

T193. UNVEILING THE IMPACT OF SINGLE AND MULTI-CLASS TREATMENT WITH ANTIPSYCHOTICS ON RSEEG FUNCTIONAL CONNECTIVITY AND

NETWORK TOPOLOGY: A CROSS-SECTIONAL STUDY IN HOSPITAL-ADMITTED PSYCHIATRIC PATIENTS

Melissa Zandstra^{*1}, Hannah Meijs², Metten Somers¹, Cornelis Stam³, Bieke de Wilde⁴, Jan van Hecke⁴, Peter Niemegeers⁴, Jurjen Luykx¹, Edwin van Dellen¹

¹UMC Utrecht, ²UMC Utrecht, Maastricht University, ³VUmc, Amsterdam, ⁴Ziekenhuis Netwerk Antwerpen

Background: In the pursuit of delineating biomarkers for schizophrenia spectrum disorders, resting-state EEG (rsEEG) functional connectivity and network topology have emerged as promising avenues. However, medication use such as antipsychotics poses a potential confounding factor in biomarker research. We explored the impact of both single and multi-class antipsychotic treatments on rsEEG characteristics in a psychiatric population.

Methods: RsEEG was analyzed in a real-world cross-sectional sample of 900 hospital-admitted psychiatric patients. Patients treated with antipsychotics (AP) were compared to unmedicated patients and patients treated with antidepressants (AD), benzodiazepines (BDZ), and multi-class combinations of these treatments. To assess the associations between antipsychotic treatments and macroscale rsEEG characteristics, we employed a general linear model with post-hoc tests. Additionally, Spearman's rank correlation analyses were performed to explore potential dosage effects.

Results: Compared to unmedicated patients, single-class use of AP was associated with lower functional connectivity in both the delta and alpha bands. We also found correlations between AP dosage and functional connectivity in these frequencies. Importantly, we found evidence for cumulative or interaction effects of different classes of psychotropics on rsEEG characteristics: multi-class medication use was associated with differences in functional connectivity and network topology measures compared to single-class medication use. These effects were most pronounced for concomitant use of all three classes of psychotropics.

Discussion: Our cross-sectional study suggests small but significant associations between single and multi-class use of antipsychotics and macroscale rsEEG functional connectivity and network characteristics. These findings highlight the importance of considering the effects of antipsychotics, as well as their interaction with other psychotropics, when investigating rsEEG biomarkers in patients on psychotropic medication.

T194. NEURAL CORRELATES OF ANTICIPATION, DECISION MAKING AND FEEDBACK PROCESSING IN THE BALLOON ANALOGUE RISK TASK IN SCHIZOPHRENIA

Daniela Mier^{*1}, Alexander Wolber¹, Sarah Stumpp¹, Leonie Lipinski¹, Natascha Büchele¹, Michael Odenwald¹, Brigitte Rockstroh¹, Stephanie N.L. Schmidt¹

¹University of Konstanz

Background: Patients with schizophrenia are known to present impaired reward anticipation and decision making. These impairments are accompanied by aberrant activation and connectivity of fronto-parietal and fronto-striatal networks. However, previous tasks on risky decision-making were not suitable to separate reward anticipation from decision-making. Our novel variant of the Balloon Analogue Risk Task (BART) allows differentiating between reward anticipation and decision-making, as well as feedback processing in the context of risky monetary decisions.

Methods: In our preregistered study (<https://osf.io/rza63/>), 28 patients with schizophrenia and 31 healthy controls matched by age, gender and education, completed the novel BART variant during functional magnetic resonance imaging. In the BART, participants can inflate virtual balloons with increasing monetary gain going along with increasing risk of balloon explosion and with this increasing risk of losing money. Participants are informed about the increasing risk. Data was acquired with a 3 T Siemens Skyra Scanner and analyzed with SPM 12.

Results: Data collection has only recently been finished and analyses are ongoing, but current preliminary analyses across participants show strong activation in nucleus accumbens, insula and dorsolateral prefrontal cortex for all three decision making processes. Comparing patients with controls, patients behaved less risky with a lower number of adjusted pumps, and reduced activation in nucleus accumbens during anticipation, but not during decision-making or feedback of a monetary gain.

Discussion: Our preliminary findings replicate previous studies with the BART by showing involvement of frontal regions, the insula and the nucleus accumbens. In addition, they replicate reduced nucleus accumbens activation during reward anticipation, and risk averse behavior in the BART in schizophrenia. Final activation analyses, and results from additional connectivity analyses and parametric modulation, incorporating the influence of the riskiness of decisions are in progress and will be presented at the conference. These analyses will contribute to a differentiated understanding of impaired decision-making in schizophrenia.

T195. INVESTIGATING PREDICTIVE LANGUAGE PROCESSING IN INDIVIDUALS WITH PSYCHOTIC-LIKE SYMPTOMS – A MULTIMETHOD APPROACH

Elisabeth Sterner^{*1}, Lucy J. MacGregor², Verena Demler³, Christoph Mathys⁴, Franziska Knolle³

¹Klinikum Rechts der Isar, Technical University of Munich, ²University of Cambridge, ³Technical University of Munich, ⁴Interacting Minds Centre, Aarhus University

Background: Impaired language processing is a core symptom of psychosis and is critically involved in shaping positive (e.g., auditory hallucinations) and negative symptoms (e.g., social withdrawal). Predictive Coding accounts of psychosis suggest an imbalance in the weighting of prior beliefs and incoming sensory information as the underlying mechanism to drive symptom development. Due to its predictive nature, language processing offers an efficient way to test the interplay of prior information and sensory likelihood. Thus, the goal of this study was (I) to investigate the use of semantic prior beliefs relative to sensory information during predictive language processing as a trait marker for psychotic-like symptoms, (II) to examine whether an overreliance induces task-based hallucinations, and (III) to explore the underlying neurophysiological signatures of potential alterations.

Methods: 55 participants assessed for psychotic-like symptoms completed a predictive language paradigm while their brain activity was recorded with EEG. In the task, participants listened to sentences of varying predictability (e.g., high predictability: “The small dog was chewing on his ... bone”; low predictability: “The old man is sorting the ... coins”). The sentence-final word of each sentence (e.g., “bone” or “coins”) was degraded in clarity to different degrees, ranging from fully unintelligible to fully intelligible. Participants were asked to report the word they perceived to assess task-based hallucinations. To estimate the relative strength of semantic prior beliefs over the sensory input, we fitted a linear Bayesian

regression model. Additionally, we investigated the neurophysiological underpinnings of predictive language processing using EEG.

Results: Computational modeling showed that prior semantic knowledge relative to sensory information was overweighted with increasing psychotic-like symptoms. Interestingly, the overweighting of semantic prior beliefs was generally associated with experiencing more conditioned hallucinations. The EEG analysis revealed that increasing psychotic-like symptoms were linked to more negative N400 amplitudes – an ERP component that indexes lexico-semantic processing and has been discussed as a neurophysiological signature of a prediction error within the Predictive Coding framework.

Discussion: Our findings show that healthy individuals with enhanced psychotic-like symptoms more strongly rely on prior contextual information during predictive language processing. On a neurophysiological level, this is reflected in changes in the N400 component, indicating altered prediction error processing. Taken together, our findings provide initial evidence of how suboptimal predictive language processing gives rise to misperceptions and how these processing alterations are reflected on a neurophysiological level.

T196. FUNCTIONAL CONNECTIVITY PATTERNS ASSOCIATED WITH IMMUNE PROFILES IN PSYCHOSIS: PRELIMINARY RESULTS FROM THE UK BIOBANK DATABASE

Edward Palmer*¹, Jack Rogers², John Williams¹, Rachel Upthegrove³

¹*University of Birmingham*, ²*Institute for Mental Health, University of Birmingham*, ³*Institute of Mental Health, University of Birmingham, United Kingdom*

Background: There is a growing body of evidence showing that inflammation or changes in the immune system play a key role in certain mental health disorders, including psychotic disorders. In psychosis, pro-inflammatory states have been observed prior to the onset of illness and have been linked to specific symptoms, specifically negative symptoms such as anhedonia. The aim of this research is to explore the underlying neurobiological mechanisms that could inform different inflammatory profiles and identify immune-active subgroups that could help inform detection and targeted intervention. Evidence exploring different immune-active subgroups and alterations in brain structure has revealed differences in grey matter volume in the Middle temporal gyrus and hippocampus. In those with psychosis generally, decreased activity in the default mode network and increased activity in the salience network has been observed. However, less is known about the functional connectivity differences associated with inflammation as measured using resting-state functional MRI and whether these are mediated by negative symptoms.

Methods: Using data from the UK Biobank (UKBB, project number 92051), an open-access resource providing detailed characterisation of over half a million people aged 40–69 years and providing data on demographics, health records, genomics, clinical blood biomarkers and neuroimaging. We identified all participants with a Psychotic ICD10 diagnosis (F2XX|F302|F312|F315|F323|F333) from hospital admissions and for whom structural and resting state functional neuroimaging data was available (N=93). We then identified a group of matched healthy controls (HCs) based on age, gender, ethnicity and fluid intelligence. The images were pre-processed using FMRIB Software Library (FSL), with independent component analysis (ICA) and dual regression conducted using MELODIC (Multivariate Exploratory Linear Decomposition into Independent Component Analysis). Group-wise comparisons explored differences in functional connectivity between participants with a

diagnosis and HC, with further dimensional analysis exploring associations with measures of inflammation, notably the peripheral measure of CRP and negative symptoms such as mood, motivation and various cognitive measures.

Results: Using exploratory tensor ICA, 30 components were extracted representing group-average networks of brain regions. Three ICs were identified as representing networks of interest: the default mode network (DMN); the Central executive network (CEN) ; the salience network. Group-level comparison revealed a significant difference between cases and controls in the DMN and the CEN with dual regression analysis of functional connectivity (FC) revealing that the HCs showed greater FC in bilateral dorsal lateral prefrontal cortex compared to participants with a psychotic disorder. Differences in FC were also observed for those with high- versus low-level inflammation, with HC's showing increased FC within the left DLPFC and lateral posterior parietal cortex within the CEN compared to cases with high-CRP levels.

Discussion: Differences in resting-state neural FC provides important insight into the underlying neurobiological mechanisms linked to psychotic disorders. This work provides novel insight into neural connectivity changes in a large UK population database linked to different clinical and inflammatory profiles. This work could help refine prediction models that help identify immune-active subgroups linked to targeted intervention approaches and longer-term clinical and functional outcomes.

T197. AMYGDALO-FRONTAL CONNECTIVITY DISRUPTION AND EMOTION DYSREGULATION IN SCHIZOPHRENIA

Delfina Lahitou Herlyn^{*1}, Maite Aramburu², Deborah Pou², Araceli Lagostena³, Augusto Defelippe³, Elsa Costanzo³, Gabriela De Pino⁴, Mirta Fabiana Villareal⁵, Mariana Nair Castro⁶

¹CONICET, ²University of Buenos Aires - FLENI, ³FLENI, ⁴University of Buenos Aires - UNSAM, ⁵Instituto de Neurociencias FLENI - CONICET, ⁶Instituto de Neurociencias FLENI - CONICET - University of Buenos Aires

Background: Emotional regulation (ER), understood as the ability to influence one's own and others' emotions, is crucial for social functioning. Schizophrenia (SZ) is a highly prevalent disease, characterized by significant impairment of social skills. On the other hand, childhood is a critical period of neurodevelopment, highly susceptible to environmental changes. Therefore, adverse experiences during childhood (ACEs) increase the risk of psychopathology in adulthood, possibly by impairing circuits involved in ER and top-down processing. However, the relationship between functional brain connectivity and emotional dysregulation, as well as the impact of ACEs on the brain function of ER, remains unclear. This study aims to investigate brain connectivity and its relationship with difficulties in ER and ACEs exposure in patients with SZ.

Methods: Thirty participants (15 SZ and 15 healthy controls –HC–), aged between 18 and 60, were recruited. They underwent clinical evaluation using the Structured Clinical Interview for DSM-5 (SCID) to confirm the diagnosis or the absence of pathology in each case. Resting-state fMRI data were acquired using a GE Discovery MR750 3.0 T scanner. In addition to the PANSS (Positive and Negative Symptoms Scale), and the DERS (Difficulties in Emotion Regulation Scale), participants were also assessed using the Childhood Trauma Questionnaire (CTQ) to evaluate the presence of adverse childhood experiences (ACEs), processing and analysis of functional brain connectivity (FC) were performed utilizing FSL (FMRIB

Software Library v6.0), and statistical analysis was conducted using the R program (R Studio).

Results: A deficit in FC was observed between the right amygdala (rAMY) and three cortical clusters—left cerebellar hemisphere (p-value: 5.96e-08), bilateral frontal pole (p-value: 0.0395), and bilateral pre- and post-central gyri along with the precuneus (p-value: 0.0487)—in patients with SZ compared to HC. Interestingly, amygdalo-frontal hypoconnectivity was associated with difficulties in ER in daily life in SZ (p-value: 0.017). This association was primarily driven by dimensions related to impaired impulse control, limited ability to implement emotion regulation strategies, and a lack of emotional clarity. This FC disruption was also directly associated with the presence and severity of ACEs, particularly in sexual abuse (p-value: 0.049).

Discussion: The findings suggest a potential link between a key clinical feature of SZ, emotional dysregulation, and a disruption in fronto-amygdala connectivity. This neural pathway, involved in top-down mechanisms of emotion control, could underlie this association. In addition, the presence of ACEs, particularly sexual abuse, may significantly contribute to this connectivity deficit.

T198. STRUCTURAL ANOMALIES WITHIN THE THALAMUS OF EARLY PSYCHOSIS PATIENTS AND THEIR RELATIONSHIPS WITH PERIPHERAL REDOX/INFLAMMATORY MARKERS

Daniella Dwir¹, Gauvain Cung¹, Yasser Alemán-Gómez², Meritxell Bach-Cuadra³, Raoul Jenni¹, Patric Hagmann², Luis Alameda⁴, Kim Q Do¹, Philippe Conus⁴, Paul Klauser¹, Pascal Steullet*⁵

¹*Center for Psychiatric Neurosciences; Lausanne University Hospital (CHUV), Switzerland,*

²*Service of Diagnostic and Interventional Radiology, Department of Medical Radiology, Lausanne University Hospital (CHUV), Switzerland,* ³*Medical Image Analysis Laboratory (MIAL), Centre d'Imagerie BioMédicale (CIBM), Switzerland,* ⁴*Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Switzerland,* ⁵*Center for Psychiatric Neurosciences, Lausanne University Hospital*

Background: Thalamus-related anomalies are parts of the pathology associated with the emergence of psychosis. In a recent multimodal MRI study on early psychosis patients (Alemán-Gómez et al. Schizophr Bull. 2023;49:196-207), we found disparate alterations: widespread diffusion-related anomalies (i.e., increased intraneurite volume fraction, IntraVF) within the whole thalamus, but reduced gray matter concentration (GMc) only in medial and posterior thalamic subregions. The pathological mechanisms underlying such anomalies remain however unknown. In search for factors contributing to these anomalies, we have investigated the relationships with peripheral markers of redox regulation associated with the GSH system (GSH peroxidase, GPx; GSH reductase, Gred) and oxidative stress/inflammation (metalloproteinase-9, MMP9; soluble receptor for advanced glycation end products, sRAGE).

Methods: Participants were 97 early psychosis patients (EPP) from the Lausanne Psychosis Cohort and 97 age-, sex-matched healthy subjects for whom we had MRI data. MRI was performed on a 3-Tesla scanner with T1w and Diffusion Weighted Imaging (DWI) sequences. Local GMc was estimated from T1w images, and IntraVF was calculated from DWI images using the Spherical Mean Technique. Each thalamus was subdivided in 7 nuclei to compute the mean GMc and IntraVF inside those regions. Peripheral markers: GPx and

Gred activities were measured in blood cells, while sRAGE level and MMP9 activity were quantified in plasma.

Results: GPx activity was higher in women than in man irrespective of the group and was positively correlated with Gred, specially in women of both groups. sRAGE level was higher in EPP than in controls independently of the sex, but no group or sex differences were found for MMP9 activity. We observed no correlation between MMP9 activity and sRAGE level in any of the groups. Likewise, these two markers did not correlate with GPx and Gred activities in both controls and EPP. Linear models revealed sex-group interactions in the relationships between blood markers and structural thalamic parameters. GPX activity was negatively correlated with IntraVF in the whole thalamus and positively correlated with GMc in the whole thalamus in women controls, but not in EPP. The relationship between GPx and GMc was most prevalent in the pulvinar. By contrast, MMP9 activity showed positive relationships with GMc in posterior thalamic subregions (pulvinar and lateral posterior-ventral posterior group) in women EPP only.

Discussion: To summarize, we found a sex-specific regulation of the GPx/Gred system independently of the pathology, and higher sRAGE levels in EPP. Moreover, our results suggest that redox homeostasis and MMP9/RAGE-related pathways may impact or modulate the thalamus macrostructure organization in a complex manner that differs among sex and clinical groups. These data also suggest that the thalamic anomalies revealed by DWI (IntraVF) and T1wI (GMc) in EPP are affected by different pathological mechanisms.

T199. LOWER ARTERIOLAR CEREBRAL BLOOD VOLUME IN RECENT-ONSET SCHIZOPHRENIA COMPARED TO CONTROLS MEASURED BY INFLOW-BASED VASCULAR-SPACE-OCCUPANCY (IVASO) MRI

Andor Bodnár¹, Adrian Paez², Kia Ultz², Christopher Ross³, Jun Hua², Russell Margolis³

¹Johns Hopkins University School of Medicine, ²F. M. Kirby Center, Kennedy Krieger Institute, ³Department of Psychiatry, Johns Hopkins University School of Medicine

Background: Schizophrenia is a complex and heterogenous disease, prominently associated with metabolic and microvasculature abnormalities. Arterioles may be the most sensitive component of the microvasculature to metabolic disturbances. Based on our preliminary work and other findings, we hypothesize that arteriolar cerebral blood volume (CBVa) is diffusely decreased in schizophrenia, including in individuals with recent onset of schizophrenia.

Methods: To explore this hypothesis, differences in CbVa were examined by iVASO (noninvasive blood nulling approach) MRI, extended to 3D whole brain coverage at 7T, between recent onset schizophrenia patients (N = 16, duration of illness mean = 1.5 yrs, SD = 1.8 yrs) and healthy controls matched for age and sex (N = 12). CbVa was examined in 98 distinct brain regions. CbVa values of each voxel within each brain regions were average for each participant and then within each group.

Results: 16/24 subregions within the frontal lobes had significantly reduced CbVa in schizophrenia (ranging from 16.2-36.9% change; $\eta^2 = 0.15-0.39$). All 10 subregions of parietal lobes had significant decreases in CbVa in schizophrenia (21.1-31.8% change; $\eta^2 = 0.29-0.40$) along with 12/14 subregions of the temporal lobes (17.4-40.6% change; $\eta^2 = 0.17-0.29$). CbVa in the insular cortices, and cerebellum were also significantly reduced in schizophrenia (13.1-36.3% change; $\eta^2 = 0.15-0.26$) along with most occipital regions (6/10 regions; 18.3-24.2% change; $\eta^2 = 0.23-0.26$). Similarly, both anterior and posterior cingulate cortices had significantly reduced CbVa in schizophrenia (6/10 regions; 13.9-23.4% change;

$\eta^2 = 0.21-0.41$). The only cortical region with significant increased CBVa in schizophrenia was the left cuneus (13.4% change; $\eta^2 = 0.19$). CBVa was also reduced in subcortical regions, but reduction only reached significance in the thalamus, amygdala, and medulla oblongata likely due to a limited number of voxels.

Discussion: Taken together, these findings replicate and extend previous iVASO results in schizophrenia patients and establish that CBVa is diffusely decreased in almost all areas of the brain, even in patients with recent onset of diagnosable disease. These findings suggest that, rather than being localized to particular circuits, schizophrenia is a disease that affects the whole brain. The relationships between CBVa and longitudinal course of disease (including prodromal stages), treatment response, or treatment resistance, remains to be determined.

This work was funded by T32MH015330, R21MH107016, and ABCD Charitable Trust.

T200. ANALYSING RESTING-STATE FMRI CONNECTIVITY PATTERNS IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS: PRELIMINARY INSIGHTS

Chloe Clifford*¹, Elizabeth Farrow², Matthew R. Broome³, Charles Large⁴, Rachel Upthegrove³, Jack Rogers²

¹University of Birmingham, ²Institute for Mental Health, University of Birmingham, Birmingham UK and Centre for Human Brain Health, University of Birmingham, Birmingham UK, ³Institute for Mental Health, University of Birmingham, Birmingham UK, ⁴Autifony Therapeutics Limited

Background: Individuals with psychotic disorders, including those at clinical ‘high-risk’ for psychosis (CHR-P), exhibit wide-spread alterations in brain functional connectivity, which might contribute to the cognitive, emotional and perceptual symptoms associated with psychosis. Studies using resting-state functional magnetic resonance imaging (rs-fMRI) have revealed disruptions in functional connectivity patterns within and between neural networks in psychotic disorders. Specifically, aberrant connectivity patterns have been found in neural networks such as the default mode network (DMN), which is important for self-referential processing, the salience network (SN), which is involved in task-switching and prioritising relevant information and the frontoparietal network (FPN), important for cognitive and executive functioning. These disruptions may contribute to distorted perceptions, difficulties distinguishing relevant information and deficits in cognitive and emotional processing that are associated with psychosis. However, research into the different connectivity patterns observed in the CHR-P population is limited, with the underlying neurobiological mechanisms linked to CHR-P and transition to a psychotic disorder unclear.

Methods: Preliminary analysis has investigated rs-fMRI connectivity patterns in young people at CHR-P compared to matched healthy controls (HC). The MATLAB-based CONN toolbox (RRID:SCR_009550) was used for anatomical and functional imaging pre-processing, denoising and first- and second-level connectivity network analysis. Whole-brain resting-state functional connectivity networks were analysed for all participants, with region-of-interest (ROI)-to-ROI connectivity applied to explore whether network functional connectivity differed between CHR-P and HC.

Results: Findings are considered in relation to previous studies showing disrupted functional connectivity in CHR-P. Abnormal connectivity patterns are shown within various neural networks including the DMN, SN and FPN in CHR-P individuals compared to HC. Weaker

connectivity between brain regions within these networks, including the posterior cingulate cortex and frontolateral prefrontal regions, were found in CHR-P young people compared to HC.

Discussion: The identification of differences in resting-state neural functional connectivity provides important insight into the underlying neurobiological mechanisms that could inform prognosis and early detection of CHR-P individuals. Specifically, this work provides insight into neural connectivity changes that occur before the onset of positive and negative psychotic symptoms and helps address heterogeneity in CHR-P research. Additionally, research into functional connectivity is important for developing prediction models that could help facilitate understanding of the progression of psychotic disorders and decrease longer-term clinical and functional outcomes. Overall, this research contributes to growing research on neural correlates of CHR-P and further provides specific brain regions and networks for future research.

T201. SEXUAL DIMORPHIC INFLUENCES ON AGE OF ONSET AND DURATION OF ILLNESS ON PATTERNS OF CORTICAL THICKNESS IN INDIVIDUALS WITH SCHIZOPHRENIA

Rachael Slate*¹, Aaron Clouse¹, Jacob Holker¹, Kaitlyn Greer¹, Barrett Humble¹, Madeleine Reading¹, Jacob Jensen¹, Kennedy Madrid¹, Sierra Jarvis¹, Seth Garrison¹, Stefan Ehrlich², Derin Cobia¹

¹Brigham Young University, ²Carl Gustav Carus of the Technische Universität Dresden

Background: Since the manifestation of schizophrenia varies across sexes (i.e., more mood symptoms and better overall functioning for women), the interaction between the diagnosis and sex is hypothesized to have a significant impact on morphology—making it an important contributor to schizophrenia’s neurological effects. Previous literature has yet to utilize high-dimensional brain mapping to assess how the brain morphology of men and women with schizophrenia differs as it pertains to age of onset (AOO)/duration of illness (DOI). Neuroimaging studies can provide evidence that brings the field closer to understanding whether later diagnosis among women may be due to prominent neurobiological features, thus excluding more sociological-leaning explanations. The purpose of this study was to utilize a sex-wise approach to examining cortical thickness alterations in men and women with schizophrenia, relative to healthy groups, and how it changes as a function of both AOO and DOI.

Methods: Participant data was derived from the federated SchizConnect data sharing project and the Human Connectome Project for Early Psychosis. Total samples included male schizophrenia (SCZ-M=273), female schizophrenia (SCZ-F=93), male healthy comparison (CON-M=247) and female healthy comparison subjects (CON-F=143). Whole brain vertex-wise cortical thickness was estimated from structural T1-weighted images using the FreeSurfer toolkit and compared between groups using SCZ-M/CON-M, SCZ-F/CON-F, CON-M/F, and SCZ-M/F contrasts. The relationship between whole brain cortical thickness and AOO/DOI variables were examined both separately and combined (interaction effects) per SCZ-M/SCZ-F groups by constructing vertex-wise correlation coefficients; age was included as covariate where appropriate, and all models were corrected for multiple comparisons.

Results: In the cortical thickness contrast between SCZ-M/CON-M, SCZ demonstrated significant thinning in the left isthmus cingulate region. For SCZ-F/CON-F contrast, significant thinning was noted in the left rostral anterior cingulate region for SCZ. There were

no significant findings noted for the CON-M/F contrast. For SCZ-M/F, SCZ-M demonstrated significant thinning in the left isthmus cingulate region. There were no significant findings observed across the AOO analyses for both SCZ samples. For DOI analyses, in SCZ-F there was a significant negative correlation with cortical thickness and the left entorhinal and the right superior frontal regions. Bilaterally, SCZ-M globally had a significant negative correlation against DOI. The SCZ-M/F interaction between cortical thickness and DOI differed in the left isthmus cingulate (negative correlation for males).

Discussion: Main findings from this study reveal more cortical thinning in SCZ-M compared to SCZ-F, especially within the left cingulate region. Additionally, DOI had a negative correlation with cortical thickness across patients, with females exhibiting negative thickness-DOI relationships in left entorhinal and right superior frontal regions, and males with bilateral global negative relationships between cortical thickness and DOI. These findings suggest DOI may have a more significant neurobiological impact on male patients, especially within cingulate regions. This may explain better overall functioning in female patients—thus, potentially leading to later diagnoses often observed in women compared to men with schizophrenia.

T202. A RETROSPECTIVE [11C]-(+)-PHNO PET DATA ANALYSIS ON THE CORRELATIONS BETWEEN SUBCORTICAL DOPAMINE SIGNALLING AND PERIPHERAL LIPID PROFILE IN SCHIZOPHRENIA

Katharina Landesmann^{*1}, Ana Weidenauer¹, Ulrich Sauerzopf¹, Irena Dajic¹, Cornelia Diendorfer¹, Nicole Praschak-Rieder¹, Matthäus Willeit¹

¹*Medical University of Vienna*

Background: One of the main reasons for the higher mortality rate among patients with schizophrenia is the increased risk of hyperlipidemia and its associated cardiovascular effects. It has been suggested that this co-occurrence may be due to shared underlying causes. This study aims to investigate the connection between subcortical dopamine signaling and peripheral metabolic indicators in both patients with schizophrenia (SZ) and healthy volunteers (HV).

Methods: Positron emission tomography (PET) imaging using [11C]-(+)-PHNO, an agonist radiotracer for dopamine D2/3 receptors, was employed to compare the neurochemical effects of amphetamine (AMPH), a dopamine-releasing agent, in HV and SZ. Additionally, the study examined the correlations between peripheral metabolic markers (list) and [11C]-(+)-PHNO binding (BPND) as well as amph-induced dopamine release.

Results: Opposing correlations were seen between [11C]-(+)-PHNO binding potentials (BPND) and metabolic markers in HV and SZ. Among HV, there was a positive correlation between both baseline and post-AMPH BPND and levels of total cholesterol (e.g. baseline globus pallidus (GP): $r=0.44$, $p=0.058$, GP post-AMPH: $r=0.53$, $p=0.023$) and LDL cholesterol (e.g. baseline GP: $r=0.49$, $p=0.038$, GP post-AMPH: $r=0.57$, $p=0.016$). Among SZ, negative correlations between BPND values and levels of total cholesterol (e.g. putamen post-AMPH: $r=-0.65$, $p=0.009$) and LDL cholesterol (e.g. putamen post-AMPH: $r=-0.69$, $p=0.0045$) were detected. Furthermore, HV displayed a negative correlation between BPND values and levels of HDL cholesterol (e.g. caudate after AMPH: $r=-0.71$, $p=0.0071$) while SZ demonstrated a positive correlation between subcortical BPND and HDL cholesterol levels (e.g. baseline ventral striatum: $r=0.61$, $p=0.02$). Lastly, HV displayed a positive correlation between amphetamine-induced dopamine release and levels of HDL cholesterol (e.g. SNVTA: $r=0.7$, $p=0.0081$), whereas SCZ displayed a positive correlation between

amphetamine-induced dopamine release and levels of LDL (Vstr: $r=0.71$ $p=0.003$) and total cholesterol (Vstr: $r=0.8$, $p=0.00038$).

Discussion: These findings indicate a physiological connection of subcortical D2/3 receptor availability and amphetamine-induced dopamine release with peripheral lipid markers. Additionally, PHNO's sensitivity to extracellular dopamine concentrations allows the interpretation of the correlations seen between BPND and peripheral lipid markers as correlations between subcortical dopamine concentration and peripheral lipid markers in opposing directionality. The results suggest that this relationship is altered in schizophrenia, as there are correlations with the same metabolic markers in patients, but in the opposite direction. Overall, the study suggests interactions between peripheral lipid metabolism and brain dopamine signaling, as well as potential pathological changes in dopamine-lipid interactions in individuals with schizophrenia.

T203. ASSOCIATIONS BETWEEN CEREBELLUM SUBREGION VOLUMES AND SEVERE VIOLENCE IN PSYCHOSIS PATIENTS AND NON-PSYCHOTIC VIOLENT OFFENDERS

Thomas Fischer-Vieler^{*1}, Jaroslav Rokicki², Milin Kim³, Esten Leonardsen⁴, Thomas Wolfers⁵, Christina Bell⁶, Gabriela Hjell⁷, Natalia Tesli⁸, Nina Bang⁹, Ingrid Melle¹⁰, Ole A. Andreassen⁶, Christine Friestad¹¹, Petter Andreas Ringen⁶, Unn K. Haukvik¹²

¹University of Oslo, Ulleral Hospital, ²SIFER Centre of Research and Education in Forensic Psychiatry, and NORMENT Norwegian Centre for Mental Disorders Research, Oslo University Hospital, Norway, ³NORMENT Norwegian Centre for Mental Disorders Research, Oslo University Hospital, Norway, ⁴NORMENT Norwegian Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital; Department of Psychology, Faculty of Social Sciences, University of Oslo, Norway; ⁵NORMENT Norwegian Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital; Department of Psychiatry and Psychotherapy, Tübingen, Center for Mental Health, University of Tübingen, Germany; German Center for Mental Health (DZPG), ⁶NORMENT Norwegian Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital, ⁷NORMENT Norwegian Centre for Psychosis Research, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Østfold Hospital Trust, Graalum, Norway, ⁸SIFER Centre of Research and Education in Forensic Psychiatry; NORMENT Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute for Clinical Medicine, University of Oslo, Oslo, Norway, ⁹Norwegian University of Science and Technology (NTNU), ¹⁰NORMENT, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital, ¹¹Department of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway, ¹²NORMENT, Norwegian Centre for Mental Disorders Research, Institute for Clinical Medicine, University of Oslo, Oslo, Norway; Department of Mental Health and Addiction,

Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway

Background: The cerebellum contains more than 50 % of the human brain's neurons and has shown to play an important role far beyond regulating motoric processes. Cerebellar grey matter volume decrease has consistently been reported in schizophrenia. Further, these volume differences in the cerebellum have been linked to rule-breaking behaviour. Particularly, damage to the cerebellar subregions vermis and posterior lobules was reported to contribute to blunting of affect, impulsiveness, and aggressive behaviour. Hence, the cerebellum may be a key node in the complex interplay of both structural and functional alterations in the processes leading to both schizophrenia and violent behaviour, with subregional differences in volumetric patterns that may guide the search for possible explaining mechanisms.

Methods: 3-T MRI scans were obtained from 107 non-violent patients with schizophrenia spectrum disorders (SSD-NV), 36 SSD patients with a history of severe violence (SSD-V), 20 non-psychotic violent offenders (NPV) who were sentenced to indeterminate detention, and 411 healthy controls (HC). All participants were males. Cerebellar subregion volumes were obtained with ACAPULCO, a cutting-edge cerebellum parcellation algorithm that relies on convolutional neural networks. Group differences in total and subregional volumes were analysed using MANCOVA and ANCOVAs, covarying for confounders and significance values adjusted using Bonferroni correction for multiple tests.

Results: Total cerebellar grey matter volume was significantly lower in both SSD-NV ($p < .001$, Cohen's $d = .49$) and SSD-V ($p = .014$, Cohen's $d = .64$) compared to HC. The cerebellar lobules in SSD-NV had lower volumes in left Crus I ($p = .010$, Cohen's $d = .32$), right Crus II ($p = .003$, Cohen's $d = .46$), Vermis VIII ($p = .028$, Cohen's $d = .40$), Vermis IX ($p = .003$, Cohen's $d = .42$), and Vermis X ($p = .010$, Cohen's $d = .39$) compared to HC. Furthermore, we found significant volume decrease in right Crus I ($p = .025$, Cohen's $d = .62$), and Vermis IX ($p < .001$, Cohen's $d = .81$) between SSD-V and HC.

There were neither significant differences between SSD-NV and SSD-V, nor between NPV and the other groups.

Discussion: We found decreased grey matter volumes in the posterior cerebellar hemispheres and the vermal regions in both schizophrenia groups independent of violence history, but with a different subregional pattern. Interestingly, lower volumes specifically in the vermal region IX and right Crus I have been reported in individuals with Autism spectrum diagnosis. Hence, our results may give support to hypotheses pointing at autistic features like impaired social processing and poor mentalizing as crucial factors for violence proneness in some individuals with schizophrenia spectrum disorders.

T204. SCHIZOPHRENIA-SPECTRUM PSYCHOPATHOLOGY AS COMPARED TO ALTERED MICROSTRUCTURE OF THE WHITE MATTER LANGUAGE CONNECTIVITY

Werner Surbeck¹, Noemi Dannecker¹, Anna Steiner¹, Robin Samuel², Allegra Gasser¹, Dominic Fabian¹, Niklaus Denier³, Tobias Bracht³, Peter Brugger¹, Philipp Homan¹

¹Psychiatric Hospital of the University of Zurich, ²University of Luxembourg, Esch-sur-Alzette, Luxembourg, ³Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern

Background: Schizophrenia-spectrum psychopathology appears to exist as a continuum in the general population, ranging from subtle, sub-clinical schizophrenia-like phenomenology in healthy individuals to overt schizophrenia. Language processing anomalies, clinically identified within formal thought disorders, are a core feature of schizophrenia-spectrum phenomenology. Pronounced structural changes in perisylvian cortical language areas have previously been associated with this phenomenon. Corresponding substrates in relation to white matter connectivity of language are far less well-characterized so far. Since semantic processing anomalies are crucially involved in the characteristic language disturbance of schizophrenia-spectrum psychopathology, and the left ventral language stream is increasingly associated with semantic processing anomalies, we postulate a pronounced microstructural change in ventral language connectivity.

Methods: Here we used Diffusion Tensor Imaging and applied manual fiber tractography to carefully reconstruct white matter fibers from individual brain scans. We included 40 individuals with early psychosis, 40 healthy individuals with high schizotypy, and 40 healthy individuals with low schizotypy. Schizotypy was assessed with the Oxford-Liverpool Inventory of Feelings and Experiences. For the ventral language stream, we assessed the inferior fronto-occipital fasciculus (IFOF), while the arcuate fasciculus (AF) was used as representative of the dorsal language stream. Since the corticospinal tract is not associated to language, it was used as control tract.

Results: With regard to the IFOF, early psychosis patients had lower MD than controls ($-.563$ standard deviation, 95% CI $[-.990, -.137]$, $t = -2.622$, $p = .010$) and high schizotypy controls had higher MD than low schizotypy controls ($.665$ standard deviation, $[.202, 1.129]$, $t = 2.849$, $p = .005$), as calculated by regression models of the two diffusivity measures FA and MD adjusted for age. Furthermore, the difference between early psychosis and high schizotypy was significantly greater than between early psychosis and low schizotypy ($F = 8.117$, $p = .002$). Although no significant results were found in relation to the AF per se, there were no significant differences of the MD measures between the IFOF and the AF. No significant group differences were found with regard to the corticospinal tract.

Discussion: Although the alteration of white matter microstructure in the IFOF differed significantly between early psychosis patients and healthy controls, there is no clear correlation between the severity of SS psychopathology and the microstructural changes (from low schizotypy to high schizotypy to early psychosis). Furthermore, the difference in white matter microstructure of the left IFOF, as manifested in the differences in MD measures, does not differ significantly from those observed with the AF. These results indicate an alteration of the entire perisylvian white matter language connectivity in early psychosis without a preference for its ventral parts.

T205. MULTIMODAL IMAGING OF NEUROINFLAMMATION IN EARLY-PHASE SCHIZOPHRENIA SPECTRUM DISORDERS

Shiral Gangadin^{*1}, Rene Mandl², Lot de Witte³, Neeltje Van Haren⁴, Maya Schutte⁵, Marieke Begemann², Rene Kahn⁶, Iris Sommer⁷

¹UMCG, ²University Medical Center Groningen, ³Department of Psychiatry, Icahn School of Medicine, Mount Sinai, NY, USA; Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, ⁴Erasmus Medical Centre, Rotterdam, Netherlands, ⁵Department of Neuroscience, UMC Groningen, ⁶Icahn School of Medicine at Mount Sinai, ⁷Department of Biomedical Sciences of Cells and

Systems and Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Background: Various lines of research suggest immune dysregulation as a potential therapeutic target for negative and cognitive symptoms in schizophrenia spectrum disorders (SSD). Immune dysregulation would lead to higher extracellular free-water (EFW) in cerebral white matter (WM), which may partially underlie the frequently reported lower fractional anisotropy (FA) in SSD. We aim to investigate differences in EFW concentrations - a presumed proxy for neuro-inflammation - between early-phase SSD patients (n = 55) and healthy controls (HC; n = 37), and to explore immunological and cognitive correlates.

Methods: To increase specificity for EFW, we study several complementary magnetic resonance imaging contrasts that are sensitive to EFW. FA, mean diffusivity (MD), magnetization transfer ratio (MTR), myelin water fraction (MWF) and quantitative T1 and T2 were calculated from diffusion-weighted imaging (DWI), magnetization transfer imaging (MTI) and multicomponent driven equilibrium single-pulse observation of T1/T2 (mcDESPOT). For each measure, WM skeletons were constructed with tract-based spatial statistics. Multivariate SSD-HC comparisons with WM skeletons and their average values (i.e. global WM) were not statistically significant.

Results: In voxel-wise analyses, FA was significantly lower in SSD in the genu of the corpus callosum and in the left superior longitudinal fasciculus (p LESS THAN 0.04). Global WM measures did not correlate with immunological markers (i.e. IL1-RA, IL-6, IL-8, IL-10 and CRP) or cognition in HC and SSD after corrections for multiple comparisons.

Discussion: We confirmed lower FA in early-phase SSD patients. However, nonFA measures did not provide additional evidence for immune dysregulation or for higher EFW as the primary mechanism underlying the reported lower FA values in SSD.

T206. NEGATIVE SYMPTOMS AND RSFC: LEVERAGING EMA AND INDIVIDUAL-SPECIFIC TECHNIQUES

Nada Dalloul*¹, Erin Moran¹, Deanna Barch¹

¹*Washington University in St. Louis*

Background: Motivational deficits have been well established in schizophrenia and have been shown to cut across psychotic and mood disorders. These deficits have been robustly associated with disability and distress. However, they are resistant to current treatments due to unknown underlying mechanisms. There are some indications that these motivational deficits are related to differences in resting state functional connectivity (RSFC). However, the findings are mixed in the literature – many studies report null relationships. These divergent results might be partly due to the limitations of traditional methods. First, most studies use clinical measures assessed at one time point which are limited in their ability to capture daily fluctuations in motivation. Second, traditional methods of determining RSFC use group-averaged data, which mask important inter-individual differences in functional connectivity. In contrast, ecological momentary assessment and individual-specific (IS-RSFC) techniques can account for intra-individual variability. By leveraging these methods, this study aims to elucidate the transdiagnostic relationships between motivational deficits and functional connectivity.

Methods: 144 participants (29 Schizophrenia/Schizoaffective Disorder; 38 Bipolar Disorder, 37 Major Depressive Disorder, 40 Controls) completed an EMA questionnaire on motivation and pleasure (MAP) for current and anticipated behaviors four times a day for 14 days.

Participants also completed two six-minute resting-state BOLD scans. Network connectivity matrices based on group-averaged parcels were created using the Gordon network parcellation. Individual-specific network connectivity matrices were calculated using an empirically validated template-matching technique. Averaged Fisher z-transformed pair-wise correlations within each network and averaged participation coefficient for six networks were assessed (Default Mode (DMN), Cingulo-Opercular (CON), Dorsal Attention (DA), Ventral Attention (VA), Salience (SAL), and Fronto-Parietal (FPN)). Bayesian hierarchical regression models assessed relationships between current and anticipatory MAP scores and RSFC metrics. These models included age and sex as covariates, as well as diagnosis and interactions between diagnosis and RSFC metrics to assess transdiagnostic relationships. IS-RSFC models will include average motion and number/size of parcels as additional covariates.

Results: The tests of effect presence produced mixed results for all twelve models. The 95% credible intervals indicated that within-network correlations and participation coefficients from the group-average parcellations of the six networks were not significantly related to anticipatory or current MAP when accounting for diagnosis, age, and sex. However, the probability of direction and region of practical equivalence tests revealed notable trends: MAP was negatively related to the participation coefficients for DMN, SAL, CO, and DA, positively related to the within-network correlations for SAL, DA, and VA, and negatively related to the within-network correlations for FPN (PD GREATER THAN 75%; ROPE LESS THAN 10%).

Discussion: The analyses partially supported relationships between RSFC derived from group-averaged parcellations and anticipatory and current MAP. While the credible intervals suggest no relationship, other tests indicate several non-zero effects. These results suggest small to null relationships between RSFC and MAP. However, they are limited by the use of group-averaged data, which might mask important inter-individual variability in functional connectivity. The planned analyses will address this by assessing the relationships of MAP with IS-RSFC.

T207. DISRUPTED NEURAL PROCESSING OF DYNAMIC NATURALISTIC STIMULI IN SCHIZOPHRENIA

Eric Reavis^{*1}, Yixuan Lisa Shen², Yasmeen Campos¹, Melodie Yen¹, Lourdes Concepción Esparza², Carolyn Parkinson²

¹*Semel Institute for Neuroscience and Human Behavior at UCLA*, ²*UCLA Department of Psychology*

Background: Schizophrenia (SZ) is associated with perceptual and cognitive impairments that are linked to poor functional outcomes. Extensive research has characterized such deficits using highly controlled laboratory tasks and neuroimaging. Yet, there have been few attempts to study stimulus processing in SZ under more dynamic and naturalistic conditions, leaving the field with little information about how perception and cognition might operate differently in SZ than in healthy samples under real-world conditions. The present study aims to bridge this knowledge-gap by using dynamic audiovisual stimuli and functional magnetic resonance imaging (fMRI) to investigate potentially aberrant naturalistic stimulus processing in SZ. In the current analyses, we focused on neural activity in regions of interest (ROIs) from the default-mode network (DMN). Specifically, we compared inter-subject correlation (ISC) measures of fMRI activity in SZ and healthy control (HC) participants for the medial

prefrontal cortex (MPFC), middle temporal gyrus (MTG), temporo-parietal junction (TPJ), and posterior cingulate cortex (PCC). These ROIs were selected a priori due to their importance in processing of naturalistic audiovisual stimuli in healthy samples.

Methods: An interim sample of 38 SZ and 38 HC participants completed a high-resolution T1 anatomical scan and fMRI as part of an ongoing study. Across three fMRI runs totaling about 40 minutes, participants viewed a set of naturalistic audiovisual clips in the same order. They were instructed to freely watch the videos as if they were watching television at home. MRI data were preprocessed and quality issues (e.g., excessive motion) were identified using a standardized pipeline (fMRIPrep). We used the Schaefer parcellation scheme, which divides the cortex into 200 regions based on neuroanatomical features of the T1, to define the DMN ROIs for each participant. We computed mean within-group ISCs for each participant in each ROI, quantifying the degree of similarity between the average activity in each region for each individual relative to all other members of the group. We then compared mean ISCs between the SZ and HC groups for each ROI using independent-samples t-tests.

Results: Seven SZ participants were excluded for excessive motion, leaving a usable sample of 31 SZ and 38 HCs. In each DMN ROI except MPFC, we found bilateral ISC reductions in SZ relative to HCs: right MTG [$t(67) = -3.38$, $p = 0.001$], left MTG [$t(67) = -3.45$, $p = 0.001$], right TPJ [$t(67) = -2.78$, $p = 0.007$], left TPJ [$t(67) = -3.02$, $p = 0.003$], right PCC [$t(67) = -3.03$, $p = 0.004$], and left PCC [$t(67) = -2.00$, $p = 0.0049$]. In MPFC, there was a significant group difference on the right [$t(67) = -2.82$, $p = 0.006$], but not the left [$t(67) = -1.85$, $p = 0.07$].

Discussion: The present results show that neural activity in DMN regions is aberrant in SZ while viewing naturalistic stimuli designed to approximate real-world perceptual experience. In particular, the results imply that stimulus processing in SZ tends to be more idiosyncratic than in HCs. This is consistent with prior research, which suggests that responses to perceptual stimuli tend to be more varied in SZ. However, the current results extend prior findings in a distinctly new direction, showing an effect under more naturalistic conditions, and providing a quantitative index of the degree to which individuals' perceptual experiences differ from an expected pattern. In future analyses with larger samples, we plan to investigate whether such indices relate to sociobehavioral functioning in SZ and determine whether they provide a basis for a novel biomarker of functioning in the disorder.

T208. DETERMINANTS OF CLOZAPINE AND NORCLOZAPINE PLASMA LEVELS IN A CHILEAN SAMPLE: NEW INSIGHTS FROM A MULTIVARIATE ANALYSIS

Maria De Los Angeles Herrera¹, Camila Diaz², Cristián Mena^{*3}, Alfonso Gonzalez-Valderrama⁴, Gabriela Barría-Santibañez⁵, Leticia Luna⁶

¹*Instituto Psiquiátrico Dr. José Horwitz, Santiago, Chile and School of Chemistry and Pharmacy, Faculty of Pharmacy, Universidad de Valparaíso, Chile.*, ²*Clozapine Pharmacovigilance Program, Instituto Psiquiátrico Dr. J. Horwitz Barak. Santiago, Chile.*,

³*Early Intervention in Psychosis Program at J. Horwitz Psychiatric Institute, Santiago; Finis Terrae University,* ⁴*Early Intervention in Psychosis Program at J. Horwitz Psychiatric Institute, Santiago, Chile and Finis Terrae University,* ⁵*Instituto Psiquiátrico Dr. José Horwitz, Santiago, Chile,* ⁶*School of Chemistry and Pharmacy, Faculty of Pharmacy, Universidad de Valparaíso, Chile.*

Background: Clozapine is the first-line antipsychotic drug for the management of treatment-resistant schizophrenia (TRS). It has a metabolism influenced by age, sex, smoking habit, and drug interaction with other medications. Variability in metabolism could be evidenced by clozapine and norclozapine plasma levels. Few studies in Latin American population have raised information regarding this therapeutic blood monitoring. Chile is the only country in South America with reported monitoring serum clozapine levels in tertiary attention centers. Considering this, we evaluate a sample treated at the largest Chilean clozapine clinic of the main national psychiatric hospital analyzing the plasma levels of clozapine/norclozapine in relation to the prescribed dose and other known factors that influence pharmacokinetics.

Methods: A retrospective observational study was carried out with information of clozapine users, over 15 years of age, who were treated at the Instituto Psiquiátrico Dr. José Horwitz (Santiago, Chile) between April 2022 and March 2023. Study variables included were gender, age at the sample moment, clozapine daily dose, weight (kg), height (m), body surface(m²), smoking status, other medications administrated (including daily doses) and plasma concentrations of clozapine (ng/ml) and norclozapine (ng/ml). Data analysis included a multivariate linear regression to evaluate together the linear relationship between plasma concentrations of clozapine and norclozapine with different variables of interest. Statistical significance was considered with a two-tailed p-value less than 0.05.

Results: We included 566 clozapine/norclozapine plasma levels from 333 clozapine users. Median age of patients was 40.9 years (IQR 29 – 53.3). Most samples were obtained from male patients (356 samples, 62.9%). 262 (46.7%) of samples were obtained in smoker patients. Daily doses of clozapine range from 75 to 800 mg/day (median 400 mg/day). Plasma concentrations of clozapine varied between 20.8 and 3461.4 ng/mL (median 278 ng/mL) and of norclozapine between 22.9 and 1287, 4 ng/mL (median 176.3 ng/mL). Smokers had concentrations 35% lower than non-smokers. In the multivariate analysis related to clozapine plasma levels we found a significative association with daily number of cigarettes (β -coefficient -0,152, t -3,703, p LESS THAN 0,001), gender (β -coefficient 0,154, t 3,655, p LESS THAN 0,001), age (β -coefficient 0,113, t 2,706, p LESS THAN 0,007) and fluoxetine dose (β -coefficient 0,116, t 2,905, p LESS THAN 0,001). We obtained a β -coefficient of 0,296 (t 7,209, p LESS THAN 0,001) for the overall correlation of clozapine plasma levels and clozapine dose adjusted for body surface, gender, age and fluoxetine dose. For norclozapine plasma levels we found significative association with daily number of cigarettes (β -coefficient -0,182, t -4,664, p LESS THAN 0,001), gender (β -coefficient 0,198, t 4,926, p LESS THAN 0,001), age (β -coefficient 0,115, t 2,887, p LESS THAN 0,004) and valproic acid dose (β -coefficient -0,116, t -4,291, p LESS THAN 0,001). The correlation β -coefficient was 0,393 (t 10,025, p LESS THAN 0,001) for the overall correlation of norclozapine plasma levels and clozapine dose adjusted for body surface, gender, age, and valproic acid dose.

Discussion: The present results provide valuable information to apply in the clinical context in order to optimize treatment and improve therapeutic goals for Latin American populations. More studies are necessary to improve clinical recommendations of the use clozapine/norclozapine plasma levels.

T209. CLOZAPINE AS A THERAPEUTIC CHOICE: LONGITUDINAL ANALYSIS OF POSITIVE AND NEGATIVE SYMPTOM SCALE SCORES IN A NATURALISTIC SETTING

Rachel Scheinberg¹, Zhirui Fu¹, Laura Scott¹, Arlene Cuerdo¹, Lilian Zhong¹, Chloe Bethany¹, Malaka Harper¹, Leslie Nucifora¹, Allison Brant¹, Russ Margolis¹, Gayane Yenokyan¹, Frederick Nucifora*¹

¹*Johns Hopkins School of Medicine*

Background: Treatment resistant schizophrenia (TRS) occurs in up to 35% of patients and leads to a substantial burden on patients, families and society. The only medication approved by the FDA for TRS is clozapine. Unfortunately, clozapine is dramatically underutilized due to rare but potentially severe side effects, and FDA REMS requirements that result in the need for regular blood draws and enrollment of patients, prescribers, and pharmacies in an associated registry. Increasing clozapine use could decrease symptoms and improve the quality of life for patients with TRS. However, while the value of clozapine for TRS has been well-established, the pattern of improvement on clozapine is less-well established, particularly in naturalistic clinical settings. Establishing this pattern could strengthen the case for clozapine utilization and provide practical guidance for prescribers. The objective of the current study is therefore to assess the symptom trajectories on clozapine using longitudinal data from a clinical setting with the goal of determining the time to improvement, the duration of improvement, the extent of improvement, and the particular symptom domains that improve.

Methods: The study population consisted of patients treated with clozapine at a specialty clozapine clinic of the Johns Hopkins Bayview Community Psychiatry Program. Each patient is assigned to a psychiatrist and a therapist, one therapist oversees clozapine REMS issues, and site nurses provide some assistance with managing side effects. Approximately 100 patients are treated in the clinic at any one point in time. This preliminary study focused on 28 patients started on clozapine after enrolling in the clinic. These patients had been designated treatment resistant based on standard criteria, and were at least moderately ill as defined by Positive and Negative Symptoms Scale (PANSS) scores of GREATER THAN 58 or by overall clinical presentation. PANSS symptoms were assessed approximately every 6 months while patients were enrolled in the clinic and taking clozapine, including prior to the onset of clozapine treatment. Patients were considered clozapine-responders if PANSS score declined to less than 58 or improved by 20%.

Results: PANSS scores of patients started on clozapine significantly improved during the first year of treatment. The improvement was generally sustained during subsequent treatment. All subdomains of the PANSS significantly improved during the course of the first year of treatment. Mean improvement for the PANSS total score within the first year was 13.9 [95%CI: -22.2, -5.6], and 3.6 [95%CI: -6.2, -1.0], 3.1 [95%CI: -6.4, 0.3] and 7.3 [95%CI: -11.6, -2.9] respectively for the positive, negative and general subdomains. 25% of patients who did not respond at 6 months responded at 12 months, and an additional 17% who had not responded at 12 months improved by their last PANSS assessment with the average duration of 6.64 years.

Discussion: These results suggest that treatment with clozapine is associated with improvement of symptoms across positive, negative and general domains of the PANSS in a naturalistic setting. Notably, in some individuals, improvement may take a year or more, justifying prolonged treatment with clozapine, particularly in the absence of established alternatives. The results further support the use of clozapine for patients with TRS.

T210. OPEN BOARD

T211. EFFECT OF ACUTE OLANZAPINE TREATMENT ON TRANSCRIPTOMICS IN THE HYPOTHALAMUS

Sandra Pereira*¹, Laura Castellani¹, Chantel Kowalchuk¹, Khaled Alganem², Xiaolu Zhang², William Ryan², Raghunath Singh¹, Sally Wu¹, Emily Au¹, Roshanak Asgariroozbehani¹, Sri Mahavir Agarwal¹, Adria Giacca³, Robert McCullumsmith², Margaret Hahn¹

¹*Centre for Addiction and Mental Health*, ²*University of Toledo*, ³*University of Toronto, Physiology*

Background: Antipsychotics dysregulate glucose metabolism and increase the risk of type 2 diabetes mellitus. We have reported that the antipsychotic olanzapine acutely impairs the ability of insulin or glucose administered into the brain (3rd ventricle) to maintain glucose homeostasis in rats. The hypothalamus, which is adjacent to the 3rd ventricle, plays a key role in the regulation of glucose metabolism throughout the body. In the current study, we assessed how acute administration of a clinically relevant dose of olanzapine per se affects transcription in the hypothalamus of rats. The objective of this study is to further understand the central pathways altered by olanzapine and to identify interventions to minimize its metabolic side effects.

Methods: Male Sprague Dawley rats underwent surgery to implant an intracerebroventricular (i.c.v., 3rd ventricle) cannula. Following recovery, catheters were inserted into the jugular vein and carotid artery for infusion and blood sampling, respectively. After 4-5 days, rats underwent a 2-hour pancreatic euglycemic clamp, which maintains basal (fasting) circulating concentrations of insulin and glucose. A single subcutaneous injection of olanzapine was administered immediately before the start of the clamp and therefore, the effects of olanzapine were investigated under controlled levels of insulin and glucose. The dose of olanzapine (3mg per kg of body weight) corresponds to clinically relevant occupancy of dopamine D2 receptors. Throughout the clamp protocol, i.c.v. saline was infused at the same rate as i.c.v. glucose, as per our previous publication on the effects of olanzapine on glucose sensing by the brain. At the end of the clamp, hypothalamus samples were collected, stored, and subsequently analyzed using RNA sequencing (RNA-seq). The effect of olanzapine on hypothalamic gene expression was assessed by comparing two groups: one that received olanzapine vs. another that received the vehicle for olanzapine. Both groups received i.c.v. saline. Full transcriptome pathway analysis was performed using fgsea R package. To identify compounds (perturbagens) that have the opposite (discordant) effects on gene expression compared to olanzapine, integrative LINCS was used.

Results: Olanzapine upregulates pathways associated with inflammation in the hypothalamus. In contrast, it downregulates hypothalamic pathways involved in protein folding. The latter is linked to endoplasmic reticulum (ER) stress, which occurs when there is a build-up of unfolded or misfolded proteins in tissues. Olanzapine also blocks the pathways of G protein-coupled receptors. Leading edge gene analysis identified genes driving these changes, for example the upregulation of inflammatory cytokines such as Tnf, Il1b, and Il6. Perturbagen analysis identified compounds that block inflammation and ER stress, such as radicicol, as agents that have the opposite effect compared to olanzapine on hypothalamic gene expression.

Discussion: Using RNA-seq, which is an unbiased approach, we found that olanzapine acutely stimulates inflammation and ER stress in the hypothalamus. In the literature, inflammation and ER stress are linked and both impair glucose homeostasis. Future studies should assess if anti-inflammatory agents or chemical chaperones, which reduce ER stress, can restore the ability of central insulin and nutrients to control glucose metabolism in the

presence of olanzapine. Since these compounds are used clinically for other disorders, the translational potential of such interventions in the context of olanzapine treatment is substantial.

T212. MUSCARINIC RECEPTOR AGONISTS AND POSITIVE ALLOSTERIC MODULATORS IN ANIMAL MODELS OF SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Nobuyuki Nomura*¹, Spyridon Sifakis², Malcolm R. MacLeod³, Johannes Schneider-Thoma², Irene Bighelli², Alexandra Bannach-Brown⁴, Sameer Jauhar⁵, Sridhar Natesan⁵, Anthony C. Vernon⁵, Sabine M. Höller⁶, Andrea de Bartolomeis⁷, Georgia Salanti⁸, Stefan Leucht²

¹*Section Evidence-Based Medicine, Technical University of Munich*, ²*Department of Psychiatry and Psychotherapy, Section Evidence-Based Medicine, Technical University of Munich, Munich, Germany*, ³*The University of Edinburgh, Edinburgh, Scotland, UK*, ⁴*Berlin Institute of Health at Charité Universitätsmedizin Berlin, CAMARADES, Berlin, Germany*, ⁵*Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK*, ⁶*Helmholtz Zentrum München Neuherberg, Germany*, ⁷*University of Naples, Naples, Italy*, ⁸*University of Bern, Bern, Switzerland*

Background: The current antipsychotics, all acting through dopamine D2 receptor occupancy, demonstrate efficacy in improving symptoms in acute schizophrenia and preventing relapses. However, they are associated with burdensome side effects and non-response rates of approximately 30%. Therefore, there is pressing need for non-dopaminergic antipsychotics. Recent findings from three phase III randomized controlled trials indicate that xanomeline (an M1/M4-preferring muscarinic receptor agonist) is efficacious in improving symptoms in acute schizophrenia. Additionally, numerous muscarinic medications with different mechanisms of action (e.g., emraclidine, an M4 positive allosteric modulator) are undergoing clinical or preclinical development. Given the urgency for novel antipsychotics and the promising findings for muscarinic receptor agonists, this study aims to conduct a systematic review and meta-analysis of muscarinic agonists in animal models of schizophrenia.

Methods: We employ a comprehensive search strategy, covering numerous databases including PubMed, MEDLINE, Web of Science, and preprint servers, to identify published and unpublished studies on muscarinic agonists in animal models of schizophrenia. Studies describing primary experiments using various methods for inducing psychosis-like behaviors in animals, including stimulant or NMDA antagonist-induced models of schizophrenia, were eligible for inclusion in the review. Two independent reviewers screen the records found in the search, extract data, and evaluate the risk of bias using the SYRCLE tool. Our primary outcomes are behavioral assays with predictive validity to identify antipsychotic effects in animal models of schizophrenia, i.e., locomotor hyperactivity and prepulse inhibition (PPI) impairment. Other behavioral outcomes are also analyzed as secondary outcomes. Data are aimed to be synthesized using multilevel multivariable meta-regression models with robust variance estimation. The confidence in the evidence is evaluated using the GRADE approach.

Results: The systematic review is ongoing, and we present our preliminary data at the conference.

Discussion: We expect that this review builds a body of evidence on the effects of muscarinic agonists in animal models of psychosis-like paradigm, which aims to provide

insights into the search for innovative molecular targets and the development of novel antipsychotics.

T213. CLOZAPINE AND LONG-TERM MORTALITY RISK IN PATIENTS WITH SCHIZOPHRENIA IN HONG KONG: EVIDENCE FROM THE CLINICAL DATA ANALYSIS AND REPORTING SYSTEM

Huiquan ZHOU^{*1}, Hao Luo¹, Jennifer Tang², Sherry Kit Wa Chan¹

¹*The University of Hong Kong*, ²*The Chinese University of Hong Kong*

Background: Schizophrenia patients experience a significantly elevated mortality risk, primarily attributed to suicide-related deaths. The impact of long-term clozapine use on mortality risk remains uncertain, as this medication has been associated with both increased infectious and cardiovascular mortality risks, as well as potential protective effects against suicidal behavior. Furthermore, it is hypothesized that continuous and discontinuous users of clozapine may exhibit distinct mortality risks. Hence, this study aims to comprehensively investigate the association between clozapine use and both all-cause mortality and suicide mortality risks in individuals diagnosed with schizophrenia.

Methods: Individuals with a schizophrenia diagnosis (ICD-9-CM 295) between January 1993 and March 2021 were retrieved from the Hong Kong Clinical Data Analysis and Reporting System (CDARS). The case group consisted of schizophrenia patients who initiated clozapine treatment between 2003 and 2012, with the index date set as the date of clozapine initiation. Controls were matched using propensity score matching in a 1:2 ratio, considering demographic factors and physical and psychiatric comorbidities, and were individuals who had never received clozapine during the follow-up period. Continuous clozapine users were differentiated from discontinuous users by two metrics: (1) having received a clozapine prescription within the last year, and (2) having been prescribed clozapine for more than 90% of the total follow-up duration. We applied accelerated failure time (AFT) models to estimate hazard ratios (HR) for all-cause mortality and suicide death comparing both discontinuous and continuous clozapine users to non-clozapine users. Any covariates with standardized mean difference (SMD) GREATER THAN 0.05 were adjusted for in the survival models.

Results: A total of 3,152 individuals using clozapine were identified, with 1,132 classified as discontinuous users and 2,020 as continuous users. Propensity score matching successfully matched 6,304 controls. Among the matched groups, imbalanced covariates included age (SMD: 0.29), schizophrenia duration (SMD: 0.21), and count of previous antipsychotics (SMD: 1.40). Using adjusted accelerated failure time models that controlled for the imbalanced covariates and accounted for Bonferroni Correction, the findings revealed that both continuous (HR: 0.38, 97.5% confidence interval [CI]: 0.23–0.62) and discontinuous (0.53; 0.31–0.90) clozapine users exhibited a lower risk of suicide mortality when compared to non-clozapine users. No significant associations were found between clozapine use and all-cause mortality risk.

Discussion: The findings of this study suggest that both continuous and discontinuous use of clozapine, compared to non-clozapine use, is associated with a lower risk of suicide mortality among individuals with schizophrenia. This indicates a potential protective effect of clozapine, especially continuous use in reducing the risk of suicide-related deaths in this population. However, it is essential to note that no significant association was also found between clozapine use and all-cause mortality. This highlights a potential trade-off between the benefits and risks of clozapine treatment. Healthcare providers should carefully consider

the patient's risk profile and weigh the potential benefits against other risks when making treatment decisions.

T214. COMPARATIVE EFFECTIVENESS OF ANTIPSYCHOTICS FOR RELAPSE PREVENTION AMONG 131,476 REAL-WORLD PATIENTS WITH A SCHIZOPHRENIA-SPECTRUM DISORDER

Aleksi Hamina*¹, Heidi Taipale², Johannes Lieslehto³, Markku Lähteenvuo⁴, Antti Tanskanen⁵, Ellenor Mittendorfer-Rutz⁶, Jari Tiihonen⁷

¹Niuvanniemi Hospital, ²Niuvanniemi Hospital, University of Eastern Finland, ³Niuvanniemi Hospital, Kuopio, Finland, ⁴University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland, ⁵Karolinska Institutet, ⁶Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, ⁷Niuvanniemi Hospital, University of Eastern Finland; Karolinska Institutet

Background: We aimed to compare the real-world effectiveness of antipsychotics, including recently marketed drugs, in relapse prevention among persons with schizophrenia-spectrum disorder.

Methods: Utilizing nationwide data, we identified all persons between the ages of 16-65 diagnosed with schizophrenia-spectrum disorder (ICD-10 F20-F29) from the registers of inpatient and specialized outpatient care, sickness absence and disability pension in Sweden (N=131,476). An incident cohort with first-episode psychosis was also identified (N=39,355). Twenty most common antipsychotic monotherapies were identified, and the risk of relapse, defined as hospitalization due to psychosis, was investigated in within-individual design to minimize selection bias, by adjusting for the temporal order of treatments, time since cohort entry and concomitant drugs. The follow-up covered the years 2006-2021.

Results: Mean age of the study cohort was 45.7 (SD 16.2) years and 53.3% were men. During the follow-up (max 15 years, mean 10.4, SD 5.7), 48.5% (N=63730) experienced relapse at least once. All specific antipsychotics were associated with decreased relapse risk compared with non-use of antipsychotics. Paliperidone 3-month long-acting injectable (LAI) (HR 0.39, 95%CI 0.30-0.51), olanzapine LAI (0.44, 0.40-0.48), aripiprazole LAI (0.46, 0.42-0.51) and clozapine (0.50, 0.48-0.52) ranked best in relapse prevention, followed by other LAIs including paliperidone 1-month LAI (0.54, 0.51-0.58). Quetiapine was associated with the highest risk of relapse. Of newer antipsychotics, cariprazine showed rather similar results as other non-clozapine second-generation orals, however, confidence intervals were wide. Antipsychotics showing significantly lower aHRs among incident cases compared to prevalent cases included olanzapine LAI, clozapine, oral paliperidone and oral aripiprazole.

Discussion: Antipsychotics, especially long-acting injectables, are effective in preventing relapses in real-world circumstances among persons with schizophrenia-spectrum disorders.

T215. UNDERSTANDING PATIENT, CAREGIVER, AND PRESCRIBER PREFERENCES FOR AN ANTIPSYCHOTIC REGIMEN ADMINISTERED ONCE EVERY 2 MONTHS FOR SCHIZOPHRENIA: A QUALITATIVE SINGLE-PERSON INTERVIEW STUDY CONDUCTED IN EUROPE AND THE USA

Stephanie Loomer¹, MURAT YILDIRIM*², Jessica Madera-McDonough³, Arun Micheelsen², Kristine Harrsen², Bolu Oladini³, Clodagh Beckham⁴, Soma Nag³, Dawn Bates¹, Xavier Guillaume¹, Pedro Such²

¹Oracle Life Sciences, ²H. Lundbeck A/S, ³Otsuka Pharmaceutical Development and Commercialization, Inc., ⁴Otsuka Pharmaceutical Europe Ltd.

Background: Schizophrenia is a chronic condition that requires consistent pharmacological treatment to maintain symptom control. Long-acting injectable (LAI) formulations of antipsychotics are associated with improved adherence compared with daily oral treatment. When selecting a treatment, prescribers should consider the preferences of patients and caregivers to ensure that treatment goals are met.

Methods: This ongoing, qualitative study will explore patient, caregiver, and prescriber preferences for LAI dosing frequency, and factors influencing preferences for an LAI administered once every 2 months for the treatment of schizophrenia. The study is being conducted in France, Germany, Italy, Spain, and the USA, and is recruiting adults aged GREATER THAN =18 years diagnosed with schizophrenia, caregivers, and prescribers. Data are being collected via web-assisted telephone in-depth interviews using a semi-structured discussion guide to harmonise conversation flow across stakeholder groups and countries. Thematic analysis of the data is being undertaken. The target sample size is 20 patients, 10 caregivers, and 10 prescribers, with data collection ongoing.

Results: Preliminary findings from interviews with 9 patients, 7 caregivers, and 10 prescribers are reported here. While patients and caregivers have mixed feelings on once-monthly LAIs, most mentioned treatment effectiveness as a benefit and value less-frequent administration and fewer medications to manage symptoms. Patients consider that an ideal treatment would offer flexibility of administration, while caregivers prioritise fewer/no adverse events (AEs). Factors influencing prescriber selection of an LAI are a history of low adherence, patient characteristics and preferences, caregiver involvement, and symptom severity. Some prescribers feel that LAIs may lessen “control” for patients (loss of autonomy) and clinicians (inability to change dose or address AEs).

Patients and caregivers have generally favourable views on an LAI with a 2-month dosing interval, as this would translate to less time spent attending appointments and on associated travel. Words like “freedom” and “serenity” were used to describe feelings on an LAI with a 2-month dosing interval, along with noting that it would mean less responsibility and being able to go on holiday. Some patients feel that less burden on their caregiver is most influential when considering a switch to an LAI administered once every 2 months. The primary concern of patients and caregivers is the medication wearing off before the next injection and the potential for more AEs. Remembering when they are due for an injection is seen as a challenge by some; others note they may forget the appointment.

Prescribers feel that fewer consultations with an LAI administered once every 2 months may benefit doctors and patients, and that patients may feel well for a longer period of time with a gradual-release medication. Perceived disadvantages include a potential need for supplemental oral antipsychotics; a concern with all LAIs, regardless of dosing interval, is an inability to alter dosing. Prescribers would be open to recommending an LAI with a 2-month dosing interval for patients stable on oral medication and desiring decreased dosing frequency.

Discussion: There may be acceptance for an LAI administered once every 2 months to treat schizophrenia, due to greater freedom and less burden. Critical factors for uptake are treatment effectiveness and duration of efficacy.

T216. FACILITATING ANTIPSYCHOTIC DRUG CHOICE WITH THE "SHARED DECISION MAKING ASSISTANT" APP

Stefan Leucht^{*1}, Natalie Peter², Spyridon Sifakis³, Katharina Müller⁴, Alessandro Rodolico¹, Peter Brieger⁴, Alkomiet Hasan⁵, Wolfgang Strube⁵, Ingrid Bauer⁵, Johannes Hamann⁶

¹*Technical University of Munich*, ²*Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, School of Medicine and Health, Technical University of Munich*, ³*Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, School of Medicine and Health, Technische Universität München*, ⁴*kbo IsarAmper Klinikum München*, ⁵*Department of Psychiatry, Psychotherapy and Psychosomatics, University of Augsburg*, ⁶*Klinikum Mainkofen*

Background: According to current estimates, it takes an average of 17 years for a scientific innovation to be put into practice. There are many reasons for this. On the one hand, it is certainly the case that clinicians do not have the time to read scientific journals. According to already outdated estimates, a general practitioner would have to read 19 articles every day, 365 days a year, to cover the articles relevant to him. Even if clinicians read that many articles, the scientific jargon and technical terms would make it difficult for them to understand them. Guidelines are a way of summarizing the evidence in a selected and condensed way. However, in situations such as antipsychotics for schizophrenia treatment, for example, there are so many drugs, with varying efficacy but above all so many different side effects, that guidelines can only present very rough selection criteria.

Methods: In this situation, digital applications in the form of visualisations or APPs for computers, tablets and smartphones are the solution of choice. With the Shared Decision Making Assistant, we have developed such a visualisation in which the efficacy and six different side effects are presented graphically based on the results of a current network meta-analysis. With one click, the antipsychotics can be sorted according to effectiveness or a specific side effect. Medications that are out of the question can be clicked away. One can also view the effectiveness and various side effects side by side. The app/visualisation is supported by the presentation of essential information about the individual antipsychotics "in a nutshell". It enables doctors to access information quickly and involve patients in the form of shared decision-making.

Results: The usefulness of the app has been tested in a randomized controlled trial which is currently analysed. We will present the results and briefly demonstrate the functions of the app/visualisation. It is freely available also here <https://ebmapp.org/de/tools/sdma-app>).

Discussion: Digital solutions are an important way to go to reduce the evidence-practice gap. Work is needed to better understand how results are best displayed, what is the most important for clinicians and patients, and in which circumstances such visualisations are most useful.

T217. DRUG ADHERENCE AND ATTITUDE TOWARDS MEDICATION DURING TREATMENT WITH LONG-ACTING INJECTABLE ANTIPSYCHOTICS VS. ORAL ANTIPSYCHOTICS: AN EXPLORATORY STUDY

Sofia Francesca Aprile¹, Pierfelice Cutrufelli^{*1}, Alessandro Rodolico¹, Ludovico Mineo¹, Antonino Petralia¹, Maria Salvina Signorelli¹, Filippo Caraci¹

Background: Inadequate adherence to pharmacological regimens in psychiatric treatment is linked to numerous adverse consequences, such as an increased risk of disease relapse, frequent hospital admissions, impaired daily functioning, overall decline in quality of life, and increased resistance to medications. While Long-Acting Injectable (LAI) antipsychotics are recognized for their efficacy in enhancing adherence, their connection with patients' overall attitudes toward antipsychotic drugs remains less explored. This study aimed to investigate the differences in adherence levels and therapeutic attitudes between patients administered LAI antipsychotics and those administered oral antipsychotic medications.

Methods: A cross-sectional study was conducted on patients receiving antipsychotic treatment. The study included 18 patients taking LAI antipsychotics and 20 taking oral antipsychotics. Compliance and therapy perception were assessed using the Drug Attitude Inventory (DAI-30) and adherence using the Brief Adherence Rating Scale (BARS), supplemented by monitoring delays or absences in LAI treatment; absences were noted when patients missed their treatment window; delays were recorded when administration exceeded the scheduled day but occurred within the adequate timeframe. Welch's t-test was used for statistical analysis to identify significant differences between groups in scales, subscale and individual items.

Results: Statistically significant differences were observed in both adherence and attitude. The LAI group showed significantly higher ($p < .001$) adherence rates (mean=97%, SD=0.04) than the oral group (mean=79%, SD=0.16). Conversely, the oral group scored significantly higher ($p = 0.009$) on the DAI-30 (mean = 19.8, SD = 6.01) than the LAI group (mean = 9, SD = 14.8). Additionally, the LAI group exhibited significantly lower scores on both DAI-30 subscales (subjective response to antipsychotics and attitude towards therapy) and on item 27 ($p < .001$), related to perceived control.

Discussion: The findings from this study highlight the significant differences in adherence and attitudes toward therapy between patients on LAI antipsychotics and those on oral antipsychotics. Notably, the higher adherence rate in the LAI group confirmed the effectiveness of LAI formulations in ensuring consistent medication intake. Conversely, the higher DAI-30 scores in the oral antipsychotic group suggest a more positive attitude toward therapy. Further research is needed to clarify this aspect and understand the causal relationship: whether it is the use of LAI antipsychotics that leads to a different attitude towards therapy or whether the preference for LAI over oral antipsychotics is influenced by a pre-existing variation in attitude, determining the directionality of the relationship between LAI use and patient attitudes towards their treatment. The lower scores on item 27 of the DAI-30 within the LAI group, reflecting a perceived lack of control, underscore the importance of this factor in future investigations, reinforcing the notion that perceived control could be a critical element in understanding patient attitudes towards LAI antipsychotics.

T218. SENSORY PROCESSING DEFICITS OF MK-801 RESPONDS TO RISPERIDONE ACROSS ASSR-EEG, PPI AND 5-CSRTT

Ashley Bernardo^{*1}, John Huxter², Lukasz Dlugosz¹, Cam MacMillan¹, Lauren Giggins², Guy Higgins¹

¹Transpharmation Ltd Canada, ²Transpharmation Ltd. UK

Background: A common characteristic of untreated symptoms in Schizophrenia (SZ) is difficulty processing sensory information. Auditory Steady State Response (ASSR) is an

electroencephalography (EEG) based response reflecting ones ability to integrate auditory sensory information by cortical networks. Pre-Pulse Inhibition (PPI) similarly considers cortical processing efficiency by using auditory sensory information and the resulting reflex motor output. 5-Choice Serial Reaction Time Task (5-CSRTT) uses sensory stimuli to elicit a learned response and specifically considers processing related to attention and impulse control. The NMDA antagonist MK-801, modulates the rats response and performance across all assays (ASSR, PPI and 5-CSRTT). Atypical antipsychotics such as risperidone aim to overcome processing impairments by primarily targeting the serotonin (5-HT) system.

Methods: Sprague Dawley rats were used in all studies. ASSR: N=7 (crossover design), PPI: N=12 (parallel design), 5-CSRTT: N=32 (crossover design). In these assays, the dose response of MK-801 (0.01-0.3 mg/kg) was established followed by reversal effects of either risperidone. ASSR: Animals were implanted to DSI telemetry devices and presented with click-train stimuli. PPI: Startle response was quantified as %PPI following trial types including, startle pulse alone, startle pulse plus pre-pulse, pre-pulse alone. 5-CSRTT: Animals were trained to perform a nose poke into an illuminated aperture to receive a food reward. During testing, a 5s intertrial interval was used over 100 trials.

Results: ASSR: In a dose response manner, MK-801 reduced ASSR, significantly enhanced 50-100 Hz high-gamma power and suppressed frequencies below 30Hz. Risperidone was able to partially reverse the MK-801 ASSR deficit (p LESS THAN 0.001) and reversed the increased high-gamma dose dependently (p LESS THAN 0.001). PPI: MK-801 reduced % PPI in a dose dependent manner (p LESS THAN 0.001). 5-CSRTT: MK-801 increased premature (p LESS THAN 0.001) and perseverative responding (p LESS THAN 0.001) relating to increased impulsivity and compulsivity respectively. Risperidone reversed premature responses (p LESS THAN 0.001) and perseverative responding (p LESS THAN 0.001).

Discussion: The sensitivity of different sensory processing assays varies such that ASSR-EEG and 5-CSRTT are highly sensitive and require low doses of MK-801 to produce a change in response and behavioral. PPI however requires higher doses of MK-801 to elicit a change in behavioral output. In conclusion, MK-801 impairs processing of environmental stimuli across multiple assays including ASSR-EEG, PPI and 5-CSRTT. Risperidone improves some aspects of sensory processing across ASSR-EEG, PPI, and 5-CSRTT.

T219. HYPERCLOZAPINEMIA: CLINICAL IMPLICATIONS AND THE RISK OF MISINTERPRETING PSYCHOTIC SYMPTOMS

Sharon Taub¹, Noa Menkes-Caspi², Shiri Kamhi-Nesher¹, Amir Krivoy*²

¹Geha Mental Health Center, ²Geha Mental Health Center, Petach Tikva

Background: The consensus regarding the therapeutic threshold for clozapine blood level is between 350-600 µg/L and blood levels above 1000 µg/L are associated with an increased risk of developing CNS- related side effects. Hyperclozapinemia refers to elevated blood levels of clozapine, which may result from factors like drug interactions, metabolic changes, or overdose. Elevated clozapine levels can potentially lead to various symptoms ranging from mild anticholinergic effects to various psychopathological manifestations, altered consciousness states, and serious complications such as myocarditis, respiratory depression, and seizures. However, it is often the case that high clozapine levels may appear as psychotic exacerbation, which in turn may lead to a wrong clinical decision to increase dose, rather than decrease, thus resulting in full intoxication.

Methods: We examined the clinical presentation and management of four cases of misdiagnosed clozapine intoxication. Clozapine serum level test has been available in Israel since 2017. We were able to link clinical data from hospitals and community from the database of Clalit Health Services (CHS) the largest health maintenance organization in Israel (N=4.8 million members, 53% of Israel's population). We extracted all cases with serum clozapine levels from 2017 to 2023 and focused on individuals with levels of 1000 ng/ml or higher (hyperclozapinemia). We further explored factors that might be associated with hyperclozapinemia such as dosing, blood laboratory and concomitant medications. Finally, we assessed the clinical management following the detection of hyperclozapinemia with regard to dose adjustments, consecutive serum level measurement, and utilization of medical services.

Results: Among the four clinical cases of clozapine intoxication, two were associated with concomitant fluvoxamine treatment, one with concomitant cytotoxic chemotherapy and one had a seizure that was misdiagnosed as idiopathic epilepsy and due to what was misdiagnosed as psychotic exacerbation resulted in clozapine dose gradually increased. Maximum clozapine blood levels of the cases ranged between 2000-3621 ng/ml. management eventually was based on detecting hyperclozapinemia, reducing clozapine dose, adjusting by further blood tests, and stopping fluvoxamine.

Between the years 2017-2023, 1362 patients had been tested for clozapine serum level, among the CHS members. This is a rate of 24.8% (out of 5524 patients purchasing clozapine during this period). Of them 200 (14.6%) had a maximal clozapine level of 1000-1500 ng/ml (42.5% women, mean age 42.4 ± 14 years) and 94 (6.9%) had a maximal level of 1500 ng/ml and above (52.1% women, mean age 44.3 ± 13.2 years), of them 58 (61.7%) were detected on their first test. Two people had levels above 3000, maximum level was 3621. Compared with lower levels, hyperclozapinemia (level above 1000 ng/ml) was associated with higher mean dose (450.8 mg/d 415 mg/d for level of GREATER THAN 1500 and 1000-1500, respectively), being women, lower smoking rate, and older age. There were significant associations between higher clozapine levels and lower red cell indices (hemoglobin, hematocrit and RBC count), decreased eosinophils count, and an increase in neutrophil count. Extreme hyperclozapinemia was associated with a higher proportion of concomitant use of fluvoxamine (12 out of 94, 12.8%, compared to 0.9%-3% in the other groups, $p < 0.0001$). There was no association between hyperclozapinemia and other blood tests (lipids, chemistry, liver functions tests, CRP, prolactin, CPK, HbA1c) as well as diagnoses of diabetes mellitus, ischemic heart disease, epilepsy, EEG testing, using concomitant valproic acid or death rate. In most cases, following maximal clozapine level above 1000 ng/ml, there was dose reduction (by a mean of -15 mg/d) and retesting clozapine blood level (in 90% of cases), however, this still resulted in mean high levels (1332 ng/ml and 954 ng/ml for above 1500 and 1000-1500 groups, respectively). There was no difference in rates of general hospital admissions, however higher rates of emergency department referrals (17% and 13% for above 1500 and 1000-1500 groups, respectively) between groups of clozapine levels.

Discussion: Hyperclozapinemia (levels of 1000-1500 ng/ml) and extreme hyperclozapinemia (GREATER THAN 1500 ng/ml) are not usually associated with a specific clinical syndrome (even not with a higher rate of seizures), and can easily be mistaken for psychotic exacerbation, potentially leading to dangerous dosage increases. However, clozapine intoxication is a severe clinical situation with potential fatal consequences. A heightened suspicion for intoxication is crucial when there is concomitant fluvoxamine treatment or a drop in red blood cell indices and eosinophils in combination with neutrophilia. Management typically involves discontinuation or dose reduction of clozapine based on the severity of

symptoms, and retesting clozapine level to confirm therapeutic level. Monitor vital signs closely. For severe intoxication, admission to an intensive care unit may be necessary.

T220. EFFECT OF GLUTAMATE MODULATOR JNJ-46356479 AND CLOZAPINE ON GLUTAMATE AND GABA BRAIN-LEVELS IN A POSTNATAL KETAMINE MOUSE MODEL OF SCHIZOPHRENIA

Albert Martínez-Pinteño^{*1}, Natalia Rodríguez², David Olivares Berjaga², Santiago Madero³, Llucia Prohens², Constanza Morén⁴, Alex Gonzalez-Segura¹, Irene Martínez-Serrano⁵, Sergi Mas⁶, Eduard Parellada⁷, Patricia Gassó⁸

¹University of Barcelona, ²Department of Basic Clinical Practice, University of Barcelona, ³Department of Psychiatry, Hospital Clinic, Neuroscience Institute, Barcelona, Spain, ⁴Hospital Clinic of Barcelona - IDIBAPS-CIBERER, ⁵University of Barcelona, Hospital Clinic, ⁶Department of Basic Clinical Practice, University of Barcelona, IDIBAPS, CIBERSAM, Spain., ⁷Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. University of Barcelona. CIBERSAM, IDIBAPS. Barcelona, Spain, ⁸University of Barcelona-IDIBAPS-CIBERSAM

Background: Alterations in glutamatergic neurotransmission have been postulated to be a key pathophysiologic mechanism of schizophrenia (SZ) [1]. Given the lack of efficacy of antipsychotics in treating negative and cognitive symptoms, glutamate (GLU) inhibitors could represent a promising pharmacological strategy to ameliorate these symptoms. Positive allosteric modulators (PAM) of the mGlu receptor 2, such as JNJ-46356479 (JNJ), inhibit the presynaptic release of GLU. We have previously reported that JNJ treatment during a critical period of neurodevelopment mitigates neuropathological impairments in a postnatal ketamine (KET) mouse model [2]. Dealing with GLU storm during the early stages of SZ may be particularly effective in preventing the onset of the disease or slowing its progression and the clinical deterioration of patients.

Aim: To evaluate the efficacy of an early JNJ treatment in reversing neuropathological deficits induced in a postnatal KET mouse model of schizophrenia. We investigated the immunofluorescence-based quantification of vesicles labeled with GLU transporter (VGLUT) and GABA transporter (GAD65/67) as markers of glutamatergic and GABAergic neurotransmission, respectively.

Methods: A total of 36 C57BL/6J pups were exposed to KET (30mg/kg) on postnatal days (PND) 7, 9, and 11 to disrupt NMDAR function. Subsequently, mice were treated daily with subcutaneous injections with 10mg/kg of JNJ-46356479 (JNJ) or clozapine (CLZ), as a clinical antipsychotic of reference, during the adolescent period (PND 35-60). On PND 120, mice were perfused with phosphate buffer saline 1X followed by 4% paraformaldehyde. Coronal sections of the prefrontal cortex (PFC) and hippocampus (HPC) were prepared for immunofluorescent double labeling with antibodies for Vglut1 and GAD65-67. Confocal images were automatically analyzed using ImageJ software to quantify the number of GLU and GABA vesicles.

Results: Due to sex differences in immunofluorescence-based quantification of GLU and GABA vesicular transporters, we conducted a multivariate analysis of variance. The analysis revealed significant differences in the number of GLU vesicles among the HPC subregions across treatment groups (CA1 (F (11,30) = 5,39, p LESS THAN 0.001), CA2 (F (11,30) = 2,23, p = 0.049 and CA3 (F (11,30) = 5,39, p LESS THAN 0.001)). Post-hoc test indicated a

significant increase in the number of GLU vesicles between the KET group and vehicle (VEH) group, particularly in the CA3 region ($p = 0.012$). Although the difference between the groups in GLU levels in CA1 did not reach statistical significance ($p = 0.056$), a notable trend was observed. The administration of JNJ treatment in the KET mice model significantly reduced the levels of GLU in both CA1 and CA3 regions ($p = 0.004$ and $p = 0.001$, respectively), whereas no effect was observed with CLZ treatment. While we observed differences in GABA levels in the CA3 region, these differences did not reach statistical significance according to the post-hoc test. No significant differences were found in GLU and GABA vesicular levels in the dentate gyrus and PFC regions.

Discussion: These findings indicate the effectiveness of JNJ treatment in attenuating GLU dysregulation in both CA1 and CA3, suggesting its potential as a therapeutic approach for mitigating GLU-related pathology in SZ. Comparatively, JNJ appears to exert a more pronounced effect than clozapine.

T221. PREVENTION, DETECTION, AND MANAGEMENT OF CLOZAPINE-INDUCED MYOCARDITIS

Mishal Qubad*¹, Gabriele Dupont², Martina Hahn², Simon S Martin³, Valentina Puntmann⁴, Eike Nagel⁴, Andreas Reif², Robert A Bittner²

¹Goethe University Frankfurt, University Hospital, ²Goethe University Frankfurt, University Hospital, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Germany,

³Goethe University Frankfurt, University Hospital, Department of Radiology, Germany,

⁴Goethe University Frankfurt, University Hospital, Department of Cardiology, Institute for Experimental and Translational Cardiovascular Imaging, Germany

Background: Approximately one-third of patients diagnosed with schizophrenia develop treatment resistance (treatment-resistant schizophrenia, TRS). Currently, clozapine remains the most effective and only approved drug for TRS. Clozapine-induced myocarditis (CIM) ranks among the most important side-effects necessitating immediate clozapine termination. This often results in its permanent discontinuation. Overall, the scarcity of sufficient alternative treatment approaches warrants concerted efforts to minimize permanent discontinuation.

Methods: In this narrative review, we provide a critical literature review of relevant aspects of CIM including pathophysiology, risk factors, prevention, timely detection, and management strategies as well as post-CIM re-challenge approaches. We based our research on a MEDLINE and Google Scholar search for all publications addressing CIM and post-CIM re-challenges. We included both relevant clinical studies as well as meta-analyses and reviews. We selected all articles that were published until November 2023. We searched for articles addressing the following MeSH terms: treatment-resistant schizophrenia, schizoaffective disorder [AND] treatment resistance, bipolar disorder [AND] treatment resistance, clozapine [AND] xx, with xx reflecting the topic we aimed to focus at, at that time point (e.g., myocarditis, re-challenge [AND] myocarditis, pharmacokinetics).

Results: Slowing clozapine titration rates and early routine use of therapeutic drug monitoring (TDM) can reduce the risk of dangerously fast increases in plasma clozapine levels which constitutes an established risk factor for CIM. Prescribers should also consider the pharmacokinetic effects of concomitant medication including valproate, olanzapine, and altered clozapine metabolism related to changes in CYP1A2 enzyme activity due to inflammation. Additionally, stringent CIM screening and management ensure timely

detection of CIM thus increasing patient safety and the chance for a restitutio ad integrum. In this context, a central issue arises from the widely different clinical practices regarding clozapine use in different psychiatric healthcare systems. Such differences comprise diverging titration rates and monitoring regimes respectively. These issues are illustrated with a special focus on the relevance of C-reactive protein, troponin, N-terminal-pro-hormone-and-brain-natriuretic-peptide, TDM, and cardiac magnetic resonance imaging. Moreover, recent findings indicate that the efficacy of clozapine re-initiation is superior compared to alternative approaches including treatment with olanzapine, long-acting injectable antipsychotics, and electroconvulsive therapy. Therefore, post-CIM clozapine re-challenges gain increasing attention. Success rates have been estimated at 60 %. Such a re-challenge requires considerable slow titration regimes and intensified monitoring.

Discussion: Permanent clozapine discontinuation can be associated with a detrimental course of illness. In this narrative review, we illustrate systematic CIM prevention strategies considering CIM pathophysiology and established risk factors. We highlight how the use of stringent screening methods allowing a timely CIM detection can facilitate a successful clozapine re-challenge. Moreover, while we focus on schizophrenia, we also discuss the relevance of CIM for treatment resistance in related disorders such as schizoaffective and bipolar disorder. Notably, these strategies should also reduce clozapine underutilization.

T222. METABOTROPIC GLUTAMATE RECEPTORS IMMUNODENSITIES IN SCHIZOPHRENIA SUBJECTS BRAIN AND IN A TWO-HIT MOUSE MODEL OF SCHIZOPHRENIA

Jon Ander Santos^{*1}, Oihane Martínez-Peula², Jon DelaCuesta-Barrutia², Amaia M Erdozain³, Benito Morentin⁴, Javier González-Maeso⁵, Luis Felipe Callado⁶, J Javier Meana⁶, Alfredo Ramos-Miguel⁶, Guadalupe Rivero⁶

¹University of the Basque Country (UPV/EHU), ²Department of Pharmacology, University of the Basque Country (UPV/EHU), Spain, ³Department of Pharmacology, University of the Basque Country (UPV/EHU) and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain, ⁴Basque Institute of Legal Medicine and Biobizkaia Health Research Institute, Spain, ⁵Department of Physiology and Biophysics, Virginia Commonwealth University School of Medicine, United States, ⁶Department of Pharmacology, University of the Basque Country (UPV/EHU), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) and Biobizkaia Health Research Institute, Spain

Background: Postmortem brain studies showed reduced densities of class II metabotropic glutamate receptors (mGluR2/3) in the dorsolateral prefrontal cortex (DLPFC) of schizophrenia (SZ) subjects. These alterations were exacerbated (mGluR2) or reversed (mGluR3) by antipsychotic (AP) medication. mGluRs have been tested as targets for novel AP drugs, and some mGluR polymorphisms have been associated with genetic susceptibility to SZ. Thus, this work aimed to study the regulation of class I mGluR1 and 5 and class III mGluR4 and 7 in postmortem DLPFC of subjects with SZ, and class I, II and III mGluRs in a two-hit mouse model of SZ combining poly(I:C)-induced maternal immune activation (MIA) and Grm2 genetic deficiency.

Methods: Human cohort was comprised of 21 pairs of SZ and control subjects, matched by age, sex and postmortem delay. DLPFC specimens were obtained at autopsies in the Basque Institute of Legal Medicine. Standard plasma toxicological assays were used to separate SZ cases who were (AP-positive; n=10) or were not (AP-free; n=11) taking APs by the time of

death. The two-hit murine model was generated by administration of poly(I:C) (5 mg/kg, i.p.) or saline to pregnant dams at gestational day 9.5. The offspring (n=48) were divided in 12 groups according to sex, MIA exposure and Grm2 genotype, and were sacrificed at postnatal day 84. Western blot (WB) analysis with selective antibodies evaluated the cortical expression of mGluR1, 4, 5 and 7 in human samples, and mGluR1, 3, 4, 5 and 7 in samples of mouse origin. Data were analyzed by paired t-test (human study) and or three-way ANOVA (mouse study).

Results: WB experiments in human and murine brain extractions detected specific monomeric immunoreactive bands for mGluR1 (~150 kDa), mGluR3 (~100 kDa), mGluR4 (~100 kDa), mGluR5 (~150 kDa) and mGluR7 (~90 and ~100 kDa). mGluR4 ~100 kDa expression was significantly lower in SZ subjects (-27.8%, p LESS THAN 0.05), but this effect could not be specifically attributed to AP-free or AP-positive SZ subjects. mGluR7 ~90 kDa expression was significantly lower in total SZ (-63.9%, p LESS THAN 0.001) and AP-positive subjects (-70.5%, p LESS THAN 0.001), compared to control subjects. Similar downregulation was observed for mGluR7 ~100 kDa immunodensity in SZ samples (-31.3%, p LESS THAN 0.05), which could also be attributed to AP-positive cases (-43.3%, p LESS THAN 0.05). No alteration in mGluR1 or 5 ~150 kDa expression was found in SZ subjects compared to controls. Mice study showed that Grm2 deficiency was not associated with compensatory effects on other mGluRs. Indeed, mice that were partially and totally deficient in Grm2 displayed lower cortical amounts of mGluR7 ~90 kDa (-18%, p LESS THAN 0.05). MIA exposure had a sex-dependent effect on ~150 kDa mGluR5 expression (p LESS THAN 0.05), so that its brain immunodensities increased in females, while decreased in males.

Discussion: Similar to class II (mGluR2 and 3), class III (mGluR4 and 7) but not class I (mGluR1 and 5) mGluRs were reduced in cortical samples from subjects with SZ. The two-hit model did not completely reproduce the alterations in class II and III mGluR densities observed in DLPFC samples of SZ subjects, but altered mGluR5 sex-dependently. In addition, lower cortical levels of mGluR2 were associated with mGluR7 downregulation in both humans and mice. The present results suggest that SZ-associated cortical downregulation of class II and III mGluR densities may be specific to human pathology or AP treatment.

This work was supported by grants PID2022-137848OB-I00 (MCIU/AEI/FEDER) and IT1512/22 (Basque Government). Santas, J.A. is a recipient of a predoctoral fellowship from the Basque Government.

T223. ARGENTINE CONSENSUS-STATEMENT ON MANAGEMENT TREATMENT-RESISTANT SCHIZOPHRENIA: UP-TO-DATE

Alejo Corrales^{*1}, Federico Rebok², Manuel Vilapriño³, Carlos Benavente Pinto⁴, Cristian Garay⁵, Ricardo Corral⁶, Pedro R. Gargoloff⁷, Anibal Goldchuk⁸, Guillermo Hönig⁹, Fabian Lamaison¹⁰, Gabriela Jufe¹¹, Eduardo Leiderman¹², Carlos Morra¹³, Pedro Damian Gargoloff¹⁴

¹Argentine National University UNT, ²Hospital "Dr. Braulio A. Moyano", Servicio de Emergencia, Buenos Aires, Argentina., ³Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo UNC., Departamento de Neurociencias., Mendoza, Argentina.,

⁴Residencia Psiquiátrica Teresa de Calcuta., Servicio de Admisión, Tandil, Argentina.,

⁵Universidad de Buenos Aires UBA., Psychiatric department, Buenos Aires, Argentina,

⁶Hospital "José T Borda", Docencia e Investigación., Buenos Aires, Argentina., ⁷Hospital

Neuropsiquiátrico Dr. A. Korn- Melchor Romero., Asesor/colaborador, La Plata, Argentina,
⁸*Universidad de Buenos Aires UBA, Departamento Salud Mental, Buenos Aires, Argentina.,*
⁹*Hospital J. T. Borda, Jefe de Servicio 25 B, Buenos Aires, Argentina,* ¹⁰*Universidad Nacional de la Plata UNLP., Psychiatric department, La Plata, Argentina.,* ¹¹*Asociación de Psiquiatras Argentinos APSA., Instituto Superior de Formación de Posgrado., Buenos Aires, Argentina.,* ¹²*Universidad de Buenos Aires UBA, Facultad de Medicina y Facultad de Psicología., Buenos Aires, Argentina.,* ¹³*Universidad Nacional de Cordoba UNC., Posgrado de Psiquiatría, Cordoba, Argentina.,* ¹⁴*Hospital Alejandro Korn, Psychiatric department, La plata, Argentina.*

Background: Approximately 30 % of people with schizophrenia fail to respond to antipsychotic treatment which impacts the burden of the disease. Treatment-Resistant Schizophrenia (TRS) denotes patients with failure to respond to at least two adequate trials of different antipsychotics. Clozapine is a unique drug approved for treating treatment schizophrenia resistant, however 1/3 of patients fail to respond to clozapine. Even though different strategies have been proposed for treating clozapine-resistant treatment, the evidence is very limited, unclear, and of poor quality. The expert consensus statement in diagnostic and treatment of TRS is the result of experts from the main national scientific societies under the organization of the Argentine Association of Biological Psychiatry.

Methods: A formal literature search was conducted and then, panel members were asked to complete 35 questions addressing different aspects of TRS. The modified Delphi method was used to unify expert opinions and obtain a consensus [4]. The panel achieved consensus statements after two rounds of discussion. The scope of the consensus statement included: definition, diagnosis, pseudo-resistance, comorbidities, risk factors., neurobiology aspects, measurement instrument, cognitive function, psychosocial intervention and management of TRS.

Results: Ten statements on TRS reach a consensus, that focused on the following high-yield. TRS was defined as, no response to at least two antipsychotics, one of second-generation antipsychotics (SGA), either at doses equivalent to 600 mg chlorpromazine or full doses of second-generation antipsychotics, for at least six weeks each. SGA with a long-acting formulation must be considered when nonadherence occurs. Pseudo-resistance, comorbidities such as substance abuse, and no-adherence to pharmacological treatment should be assessed before considering TRS. Measurement instruments (e.g. PANNS, CGI-S) should be used for monitoring the treatment response, symptoms severity, and illness progress. Psychosocial intervention, psychoeducational and CBT augmentation approaches are recommended. Although distinctive underlying neurobiological mechanisms of TRS have been proposed, more studies are needed to address this issue. Male gender and the early onset are most prominent risk factor in TRS. TRS patients show greater cognitive impairments compared to no treatment-resistant schizophrenia patients and this may be associated with poor outcomes. Clozapine is primely recommended for treatments TRS. The evidence for augmentation strategies is limited. Despite the reported benefits being modest, some augmentation strategies have been mentioned in this paper for clozapine-resistant schizophrenia. Further augmentation strategies studies are needed to improve treatments and outcomes for those patients. Electroconvulsive therapy may be a possible treatment as an augmentation strategy for patients with clozapine-resistant schizophrenia.

Discussion: This is the first TRS consensus in Argentina. In this consensus report, we provide a comprehensive literature review as well as a lengthy debate on TRS. As a result of this work, we developed recommendations. The recommendations are based on evidence and expertise and, are aligned with international consensus. This report will be of interest to anyone involved in the management of patients with TRS.

T224. SYNDROME METABOLIC INDUCED BY ANTIPSYCHOTICS AND HEMATOLOGICAL ABNORMALITIES

Alejo Corrales*¹, Pedro Damian Gargoloff², Tomas Maresca³, Federico Rebok⁴

¹Argentine National University UNT, ²Hospital "Dr. Alejandro Korn", Servicio de Subagudos Hombres., La Plata, Argentina, ³Institute of Biological Psychiatric. IPBI, Pharmacology, Buenos Aires, Argentina., ⁴Hospital "Dr. Braulio A. Moyano", Servicio de Emergencia, Buenos Aires, Argentina.

Background: increased in cardiovascular diseases risk. The component of the syndrome include, hypertension, central obesity, dyslipidemias (high triglycerides and low high density lipoprotein cholesterol HDLc) and impaired glucose tolerance. MS is well known to be highly prevalent among individuals affected by psychosis. Part of this increased risk is attributable to the use of antipsychotic medications, especially second-generation antipsychotics. Independent studies suggest that about 50% of patients treated with APs develop metabolic complications. Metabolic Syndrome is also well recognized as being associated with an increased cardiovascular risk resulting mortality. The link between antipsychotics and venous thromboembolisms is known. It is estimated that the risk of venous thromboembolism is twice that of the general population. Atypical antipsychotics have different effects than typical antipsychotic. But the biological mechanism are still unknown. To date there are few evidence of hematological changes (platelets and cross fibrin mesh) in metabolic syndrome caused by psychotropic agents.

Objective: To determinate whether metabolic syndrome caused by antipsychotic drugs produce changes in hematological system (in particular platelets and cross fibrin mesh) and increase risk of thromboembolism and explore at the relationship between hematological changes and cardiometabolic side effect.

Methods: We elaborate a Rabbit model of syndrome metabolic induced by antipsychotics. We feed a rabbits with normal diet and rabbits with high fat diet (cholesterol 1%) plus olanzapine 0,25 mg/kg/day during 5 week. Blood samples were collected from the two rabbits groups. The blood was centrifugate for 20 minutes then platelet rich plasma (PRP) was collected. We compare the ultrastructure of rabbits platelet (morphology) and cross-linking fibrin mesh, by scanning electron microscopy (SEM), between two groups. Haemostatic profile (activated partial thromboplastin time, Thrombin Time, platelets count) was analyzed as well.

Results: We found morphologic differences between two groups. The platelets of rabbits with metabolic syndrome show many pseudopods (that means platelets activations) We found disorganized and less strained cross-linking fibrin mesh among rabbits with cardio metabolic syndrome (CMS). The fibrin fiber diameter was increased in MCH compared to controls CD (P LESS THAN 0.05). Haemostatic profile differences between the two groups were not observed (P GREATER THAN 0.05)

Discussion: Ours findings demonstrated premature platelet activation (as a result of the chronic inflammation) and this trigger morphological alteration of cross-linking fibrin mesh. This condition would predispose to protrombotic state. The future investigation must put particularly focus on 1- the association between metabolic syndrome induce by antipsychotics and protrombotic state 2- whether this condition could, in part, mediate cognitive deficit in schizophrenia. Even though more studies are needed to validate this

finding, psychiatrists should be aware of the potentials platelets activations and morphological alteration of cross-linking fibrin mesh caused by of antipsychotics.

T225. CBD ALTERS SENSITIVITY TO THC IN PEOPLE WITH PSYCHOSIS AND COMORBID CANNABIS USE DISORDER

Edward Chesney^{*1}, Dominic Oliver², Ananya Sarma¹, Doga Lamper¹, Ikram Slimani¹, Millie Lloyd¹, Irma Gasparini-Andre¹, Michael Welds³, Natavan Babayeva³, Will Lawn¹, Matilda Kråkström⁴, Alex Dickens⁴, Matej Orešič⁴, Tom P Freeman⁵, Amir Englund¹, John Strang¹, Philip McGuire²

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*University of Oxford*, ³*South London and Maudsley NHS Foundation Trust*, ⁴*University of Turku*, ⁵*University of Bath*

Background: Cannabidiol (CBD) is a candidate novel treatment for both psychotic disorders and cannabis use disorder. Experimental studies in healthy volunteers suggest that pre-treatment with CBD can reduce the acute adverse effects of delta-9-tetrahydrocannabinol (THC). We investigated whether oral CBD can reduce the effects THC in people with psychosis and a comorbid cannabis use disorder.

Methods: We recruited people with schizophrenia or schizoaffective disorder (mean age 40 years) who also had a cannabis use disorder (n=30). All participants were regular and heavy cannabis users (mean use = 5 days/week; 1.1 g/day). Participants were studied on two occasions, in a double-blind, randomised, placebo-controlled, within-subjects crossover trial. In one session, participants received cannabidiol (1000 mg, oral) 3 hours before administration of 20 mg THC via a vaporiser. In the other session, pre-treatment was with a placebo. Primary outcomes were change in Positive and Negative Syndrome Scale-Positive subscale (PANSS-P), and delayed verbal recall on the Hopkins Verbal Learning Task-Revised. Blood samples were collected for measurement of plasma THC, CBD and their metabolites at six timepoints. The statistical analysis plan was pre-registered. Linear mixed models were used to assess the effect of CBD on continuous outcomes, including arm and visit order as fixed effects and participant as a random effect. McNemar's test was used to compare categorical outcomes.

Results: Following pre-treatment with CBD, the mean change in PANSS-P after administration of THC was +5.0, compared to +2.9 following placebo (mean difference [MD] = 2.1 [95% CI: 0.60 to 3.7]; p = 0.011). A PANSS-P increase of ≥ 9 was evident in seven experiments following CBD, but not in any following placebo (p = 0.0000045). PANSS scores on conceptual disorganisation (MD = 0.65 [95% CI: 0.17 to 1.1]; p = 0.012) and suspiciousness/persecution (MD = 0.55 [95% CI: 0.15 to 0.95]; p = 0.012) were higher following CBD than after placebo. Delayed verbal recall following CBD pre-treatment was 3.5 words, compared to 4.8 words following placebo (MD = -1.3 [95% CI: 0.61 to 2.0]; p = 0.0011). Pharmacokinetic analyses indicated that CBD pre-treatment had no effect on plasma THC levels (Cmax: +6.6 ng/ml; p=0.43; AUC0-90 = +481 ng*min/ml, p=0.22).

Discussion: In people with psychosis and a cannabis use disorder, pre-treatment with CBD increased sensitivity to the effects of THC on psychotic symptoms and cognition. This effect was not attributable to a pharmacokinetic interaction between CBD and THC. Cannabis use disorder is associated with alterations in brain CB1 receptor density, which might account for

the results. Further studies are needed to clarify whether this effect of CBD is evident in people with psychosis that are occasional cannabis users.

T226. BEHAVIORAL EFFECTS OF SUB-CHRONIC KETAMINE ADMINISTRATION IN ADULT ZEBRAFISH

Matheus Gallas Lopes*¹, Daniela V. Müller¹, Thailana Stahlhofer-Buss¹, Leonardo M. Bastos¹, Sofia Z. Becker¹, Samara M. Bruck¹, Angelo Piato¹, Ana P. Herrmann¹

¹*Universidade Federal do Rio Grande do Sul*

Background: Ketamine (KET), a glutamatergic NMDA-receptor antagonist, is used to recapitulate schizophrenia-related behavioral phenotypes in model animals. Despite the focus on the use of rodents in this field, the zebrafish (*Danio rerio*) is a model organism that, given its potential to mitigate species-specific biases arising from employing specific strains or species, is on the rise in the neurosciences, showing a highly conserved genetic and physiological background when compared to humans. However, behavioral assays relevant to the neurobiology and the symptoms of schizophrenia are not well-established and validated in this species. The aim of this study was to evaluate the effects of sub-chronic exposure to KET on the behavior of adult zebrafish in the Social Preference Test (SPT) and the Open Tank Test (OTT).

Methods: We used 128 4-month-old wild-type zebrafish, with an equal distribution of males and females (ethics committee 35525/2019). Following block randomization procedures, animals were allocated to one of four experimental groups: control, KET 10 mg/L, KET 20 mg/L, or KET 40 mg/L (n = 32). Zebrafish were exposed to water or KET for 20 min in groups of 4 for 5 consecutive days; after a washout period on day 6, animals were re-exposed on day 7 to the same treatment. Behavioral tests were performed on experimental days 1, 5, and 7 immediately after the treatments. Animals were sequentially subjected to the SPT and OTT individually. Social preference (as measured by the time spent near a stimulus shoal) and locomotor parameters were automatically scored using ANY-Maze software. Experiments were run in two batches and the pooled data were analyzed by two-way ANOVA with the experimental group and the experimental day as factors. This project was preregistered in the Open Science Framework (<https://osf.io/r7xdy>).

Results: In the SPT, subchronic exposure to KET reduced the time fish spent in the interaction zone ($F(3,362) = 54.94$, p LESS THAN 0.0001) and increased the total distance traveled ($F(3,362) = 97.54$, p LESS THAN 0.0001), maximum speed ($F(3,362) = 30.55$, p LESS THAN 0.0001), and line crossings ($F(3,362) = 123.0$, p LESS THAN 0.0001). Total distance traveled by animals decreased over the experimental days in the SPT ($F(2,362) = 3.36$, $p=0.0357$). In the OTT, KET treatment also increased the total distance traveled ($F(3,362) = 50.14$, p LESS THAN 0.0001), maximum speed ($F(3,362) = 15.48$, p LESS THAN 0.0001), and rotations ($F(3,362) = 11.40$, p LESS THAN 0.0001). A significant effect of the experimental day was observed for the distance traveled ($F(2,362) = 19.24$, p LESS THAN 0.0001), maximum speed ($F(2,362) = 7.90$, $p=0.0004$), and rotations ($F(2,362) = 9.85$, p LESS THAN 0.0001) in the OTT, indicating a reduction of these behaviors over time. No interactions between group and experimental day were observed.

Discussion: In general, KET treatment induced behavioral alterations that recapitulate schizophrenia-related phenotypes in every experimental day. Our findings also show a higher effect size and reproducibility of KET in recapitulating such phenotypes in zebrafish when compared to our own experience with MK-801. Unlike experiments conducted with rodents, there was no sensitization or tolerance in the response to KET exposure throughout the days.

Our data also corroborate previous observations of context-dependency regarding the hyperlocomotor effects of NMDA antagonists, as the presence of a social stimulus led to hyperlocomotion in all KET concentrations in the SPT, while only the highest KET concentration induced hyperlocomotion in the OTT. Further studies are still needed to assess the long-lasting effects of KET treatment in zebrafish.

T227. SWITCHING PATIENTS WITH SCHIZOPHRENIA TO TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA), FROM RISPERIDONE MICROSPHERES (R064766): AN EXPLORATION OF POPULATION PHARMACOKINETIC (POPPK)–BASED STRATEGIES

Itay Perlstein¹, Jonathan Meyer², Ziqi Yue³, Joel Owen³, Vijay Ivaturi³, Kelli R. Franzenburg⁴, Mark Suett⁵, Rolf Hansen⁶, Avia Merenlender Wagner⁷, Rajendra Singh⁸, Rolf Hansen III^{*9}

¹*Magic Wand Research LLC, Philadelphia, PA United States*, ²*Department of Psychiatry, University of California, San Diego, CA, United States*, ³*Pumas-AI Inc., Annapolis, MD, United States*, ⁴*Teva Branded Pharmaceutical Products R and D, Inc., West Chester, PA, United States*, ⁵*Teva UK Limited, Harlow, United Kingdom*, ⁶*Teva Branded Pharmaceutical Products R and D, Inc., Parsippany, NJ, United States*, ⁷*Teva Pharmaceutical Industries Ltd., Netanya, Israel*, ⁸*Teva Branded Pharmaceutical Products R and D, Inc., West Chester, PA, United States*, ⁹*Teva Pharmaceutical Industries, Ltd.*

Background: Differences in pharmacologic properties between various long-acting injectable antipsychotics (LAIs), combined with a lack of clinical studies on switching between them, represents a large data gap in psychiatry. Data on such switches are necessary to help inform clinicians who transition patients between LAI products. The objective of this analysis was to use PopPK modeling to characterize dosing conversions and switching strategies from R064766 (an intramuscular [im] LAI formulation of risperidone microspheres administered once every 2 weeks [q2w]; Risperdal Consta®) to TV-46000 (a LASCA formulation of risperidone administered once monthly [q1m] or once every 2 months [q2m]).

Methods: Total active moiety (TAM; risperidone + 9-OH risperidone) concentration-time profiles were simulated based on published PopPK models for R064766 (Gefvert O, et al. *Int J Neuropsychopharmacol.* 2005; 8:27–36) and TV-46000 (Perlstein I, et al. *Schizophrenia International Research Society*; May 11–15, 2023; Toronto, Ontario) with virtual populations of 5000 patients. Simulations were performed to predict PK exposures for TAM when switching to TV-46000 q1m and q2m 2–6 weeks after the last injection of R064766 at steady state.

Results: R064766 displayed a delayed-release profile that started around 3 weeks post injection, hence the need for 21 days of oral supplementation during initiation. TAM concentrations were then maintained at therapeutic levels for 4–6 weeks, after which (at week 7) they began to diminish. TV-46000 has a rapid initial release that results in therapeutic plasma levels within 6–24 hours of the first injection and eliminates the need for loading dose(s) and/or oral supplementation during initiation. This is followed by a slower secondary release that results in maximal plasma concentration (C_{max}) at 8–14 days, and then maintains therapeutic concentrations over 1–2 months, depending on dosing. Based on comparisons between a variety of simulated PK exposures, TV-46000 50 mg q1m/100 mg q2m (2 mg/day [d] oral risperidone equivalent), 75 mg q1m/150 mg q2m (3 mg/d oral risperidone equivalent), and 100 mg q1m/200 mg q2m (4 mg/d oral risperidone equivalent) correspond

most closely with R064766 25 mg, 37.5 mg, and 50 mg q2w, respectively. Once comparable doses were identified, suitable washout durations, defined by similar TAM plasma exposures during and after the switch, were determined. Initiating TV-46000 4–6 weeks after the last dose of R064766 resulted in similar trends for C_{max} and C_{min} ratios for all TV-46000 doses, durations (q1m, q2m), and sites of administration (abdomen, upper arm), compared with R064766 at steady state (albeit at different magnitudes depending on dose and washout duration). A 4-week gap resulted in a higher C_{max}, but a similar C_{min}, for TV-46000 versus R064766 at steady state. A 6-week gap provided a C_{max} that was similar to R064766 at steady state, but a lower C_{min}. A 5-week gap provided the most comparable C_{max} and C_{min} values overall. For all washout durations, C_{max} and C_{min} ratios began to approach 1.0 with subsequent injections.

Discussion: These PopPK simulations revealed switching to TV-46000 at 4–6 weeks after the last dose of R064766 provided generally comparable PK exposures by the second dose of TV-46000. Among the simulated scenarios, initiating TV-46000 at 5 weeks after the last dose of R064766 provided PK exposures that were closest to that achieved with R064766 at steady state. Clinician discretion will determine which switching strategy is best in context based on a variety of factors such as patient preference, scheduling convenience, and concerns about tolerability or symptom breakthrough.

T228. VISUAL PERCEPTUAL DISTURBANCES IN PSYCHOSIS IN REAL, AUGMENTED, AND VIRTUAL ENVIRONMENTS: A SYSTEMATIC REVIEW AND EXPERIMENTAL DATA

Léon Franzen^{*1}, Chaya Chromik¹, Fabian Müller², Marco Heide¹, Will Palmer³, Kristina Hedelt¹, Frederike Schröpfer¹, Sofia Eickhoff¹, Ben Alderson-Day⁴, Malte Wöstmann⁵, Stefan Borgwardt¹

¹University Hospital Schleswig-Holstein/University of Lübeck, ²University of Basel, ³Yale University, ⁴Durham University, ⁵University of Lübeck

Background: While much is known about the frequency and phenomenology of auditory hallucinations in psychotic disorders, distortions and hallucinations in the visual modality remain elusive. Investigation of these perceptual disturbances bears much potential for early detection and individualized interventions since 60% of people on the psychosis spectrum experience visual distortions. These are associated with conversion to full-blown psychosis. This substantial proportion demonstrates that visual disturbances occur frequently, but their role has been underestimated. Further, tracking visual perception in psychosis is important as free-viewing eye-tracking studies demonstrate limited visual exploration, scaling with risk and clinical status. These studies build the basis for tracking gaze behavior in virtual and augmented reality (VR and AR). We tap into these technologies' unique potential to present controlled, immersive, and ecologically valid simulations of visual disturbances. Combining both lines of research will allow insights into the nature of visual disturbances and open avenues for potential individualized interventions.

Methods: First, we conducted a systematic review on evidence for use cases of immersive technologies in the early detection and intervention of psychosis, with a specific focus on visual disturbances. This review screened 1130 studies and paves the way for the following empirical investigations. Second, we are empirically studying the relation between visual disturbances and psychosis using visual search and perceptual decision-making paradigms in real-world and VR environments. We will collect behavioral, eye-tracking, and cognitive data on altered perceptual processing that can originate from changes in perceptual sensitivity or

decision bias. Our approach gains strength by testing the same participants from across the psychosis continuum (i.e., general population, patients at risk, and with manifested psychosis) within each environment. We aim to collect data from 50 participants. We will use machine learning to identify patterns in these multimodal data and attempt to stratify participants accordingly – with results being compared to official clinical information.

Results: The systematic review identified 20 relevant studies across immersive technologies. Synthesis shows that these technologies offer significant advantages for understanding, assessing, and treating psychotic disorders, including VR simulations of psychotic perceptual experiences. VR is safe and well-tolerated by patients with psychosis. However, only few studies have used immersive technology to screen for visual disturbances. This may be partly explained by patients' difficulty with describing those experiences. More challenges include patients' worse spatial recognition performance in VR and accurately simulating visual disturbances that mirror psychotic experiences. Data collection is on-going. Our hypotheses include increasingly restricted free-viewing eye movement patterns with increasing schizotypy and clinical severity, consistent across real-world and VR environments.

Discussion: Paradigms screening for visual disturbances in truly immersive environments are in their infancy and interventions remain scarce. Our new, well-controlled VR environments, also allow for acquiring rich information on attention and cognition from eye movements within the same group of patients, which has rarely been considered together thus far. This approach could uncover mechanistic links associated with individual phenomenology and may lay the foundation for developing individualized interventions of positive visual symptoms of psychosis.

T229. INVESTIGATING THE EFFECTS OF ADJUNCTIVE TRANSCRANIAL DIRECT CURRENT STIMULATION ON TREATMENT ADHERENCE IN SCHIZOPHRENIA: STUDY PROGRESS

Jianmeng Song^{*1}, Julia Kim¹, Yasaman Kambari¹, Aron Amaev¹, Edgardo Torres Carmona², Ali Abdolizadeh³, Teruki Koizumi¹, Vincenzo De Luca¹, Daniel Blumberger¹, Gary Remington¹, Bruce Pollock¹, Ariel Graff-Guerrero¹, Philip Gerretsen¹

¹*Centre for Addiction and Mental Health, University of Toronto*, ²*Centre for Addiction and Mental Health and University of Toronto*, ³*Centre for Addiction and Mental Health (CAMH), Toronto, Ontario; Institute of Medical Science, University of Toronto, Toronto, Ontario*

Background: Medication adherence is critically important to the treatment of schizophrenia. Nonadherence occurs in up to 60% of patients with schizophrenia with more than 80% of nonadherent patients discontinuing their medication by 6 months. Nonadherence is not only associated with worse symptom severity, but also increased rates of relapse and hospitalization. Impaired insight into psychosis is one of the principal drivers of antipsychotic drug nonadherence. This study seeks to explore for the first time the effects transcranial direct current stimulation (tDCS) as an adjunctive treatment to improve antipsychotic medication adherence in patients with schizophrenia. The intervention will target brain regions implicated in insight into psychosis.

Methods: Participants with schizophrenia with stable medication treatment were randomized to receive either bilateral PPA active or sham 2mA tDCS for 20 sessions. Antipsychotic medication adherence will be assessed post-tDCS as follows: (1) pill count by pharmacy weekly; (2) plasma concentrations every 4 weeks; and (3) the clinician rated measure of adherence every 4 weeks during the 12-week follow-up period.

Results: 17 participants (9 active and 8 sham, 9 (53%) treated with clozapine) have completed the study intervention, with 1 dropped out during follow-up. The mean age is 43.5 (SD = 14.6). The male to female ratio is 15:2. The baseline mean illness severity PANSS score is 64.6 (SD = 13.7).

Discussion: The study is actively recruiting. Positive results will demonstrate that adjunctive tDCS has the potential to alter patients' attitudes toward their illness and treatment, in turn, improving antipsychotic medication adherence and clinical outcomes.

T230. BASELINE FUNCTIONAL CONNECTIVITY PREDICTS THE IMPACTS OF YOGA AND AEROBIC EXERCISE ON MEMORY AND ATTENTION IN EARLY PSYCHOSIS

Peilun Song¹, Xiujuan Geng², Sherry KW Chan³, Wing Chung Chang³, Edwin HM Lee³, Eric YH Chen⁴, Yaping Wang¹, Jessie JX LIN*⁴

¹Zhengzhou University, ²Chinese University of Hong Kong, ³The University of Hong Kong,

⁴The Hong Kong Polytechnic University

Background: Impairments of attention and memory are evident in early psychosis, and are associated with functional disability. Exercise intervention including yoga and aerobic exercise have been shown to improve cognitive functioning in psychosis. Yet, the underlying neural basis related to the impacts of these exercise interventions, particularly whether the functional connectivity at baseline predicts the cognitive outcomes after exercise interventions remains unknown.

Methods: A total of 140 female patients with early psychosis were recruited and 124 received the allocated intervention in a randomized controlled study of 12 weeks of yoga or aerobic exercise compared with a waitlist group. The primary outcomes were cognitive functions including memory and attention. Secondary outcome measures were the severity of psychotic and depressive symptoms, and structural and functional magnetic resonance imaging (MRI). This is a secondary analysis of the resting-state functional connectivity in 71 patients with completed MRI scans (27 in yoga, 24 in aerobic exercise, and 20 in the waitlist group). After the preprocessing, the Power-264 atlas was used to obtain mean time courses of 264 regions of interest (ROIs). The ROI-wise functional connectivity was obtained by computing the Pearson correlation coefficients between each pair of time courses of the ROIs. Thus, the functional connectivity within and between neural networks was measured to investigate the correlations between the network metrics at baseline and the pre-post changes of memory and attention in three groups. Age, duration of illness, and medication dosage were controlled as covariates.

Results: The correlation between one-versus-all-others functional connectivity of the Ventral Attention Network (VAN) at baseline and the changes of short-term memory, and the correlation between one-versus-all-others functional connectivity of the Memory Retrieval Network (MRN) at baseline and the changes of verbal memory were significantly different among the three groups.

Further post-hoc analyses showed that in yoga group, one-versus-all-others functional connectivity of MRN at baseline was negatively associated with the changes of verbal memory, within-network connectivity of the Fronto-Parietal Network (FPN) and pairwise network connectivity between the Default Mode Network (DMN) and the Dorsal Attention Network (DAN) were positively associated with the changes of psychomotor coordination and attention, respectively. In aerobic exercise group, only one-versus-all-others functional

connectivity of VAN at baseline was found to be negatively associated with the changes of short-term memory.

Discussion: Our findings suggested that VAN and MRN were significantly related to the effectiveness of exercise intervention on memory. Compared with aerobic exercise, yoga had impacts on more brain networks including FRN, DMN and DAN, which were significantly associated with psychomotor coordination and attention. Functional connectivity within and between these brain networks at baseline may predict different cognitive outcomes after different exercise interventions.

T231. REMOTE CARE IN A TIME OF CRISIS: REACT-NORV - A VIDEO-BASED FAMILY INTERVENTION FOR CAREGIVERS TO PEOPLE EXPERIENCING PSYCHOSIS

Erlend Mork*¹, Kristin Hatløy², Marit Holter³, Inger Stølan Hymer⁴, Kristine Kling⁵, Fiona Lobban⁶, Ingrid Melle⁷, Jenny Pedersen⁸, Hilde Kristin Aam Szabo⁸, Kristin Lie Romm⁹

¹*Oslo University Hospital, Division of Mental Health and Addiction, Early Intervention in Psychosis Advisory Unit for South East Norway*, ²*Stavanger University Hospital, TIPS - Centre for Clinical Research in Psychosis, Stavanger, Norway*, ³*Division of Mental Health and Addiction, Vestfold Hospital Trust, Toensberg, Norway*, ⁴*Early Intervention in Psychosis Advisory Unit for South East Norway*, ⁵*Early Intervention in Psychosis Advisory Unit for South East Norway, Clinic of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway*, ⁶*Lancaster University*, ⁷*Institute for Clinical Medicine, University of Oslo, Oslo, Norway*, ⁸*Sanderud Hospital, Psychiatric Health Services Division, Innlandet Hospital Trust, Norway*, ⁹*Oslo University Hospital, Division of Mental Health and Addiction, Norway*

Background: Psycho-educative family interventions have been shown to reduce caregiver burden and improve health outcomes in carers of family members with psychoses. However, during the COVID-19 pandemic, such interventions was difficult to access. The Relatives Education and Coping Toolkit (REACT) consists of a toolkit for caregivers, offering psychoeducation and tasks to enable the user to identify and work on solutions. The program has been tested in a small Norwegian pilot study previously, with phone support. During the pandemic, video support became possible. Due to a hasty need for new solutions during the pandemic, we were able to test the implementation of this program in a realistic clinical setting in combination with remotely delivered video-consultations. The aim was to investigate the feasibility of REACT-NORV delivered during, and in the aftermath of the Covid-19 pandemic and to explore potential characteristics that might influence the benefit of the intervention.

Methods: Carers of people with psychosis (n=62) were asked to participate when offered access to REACT-NORV within mental health in Norway during the Covid-19 pandemic. Consecutively recruited carers received up to weekly support for 16 weeks from trained family therapists. The main form of support was through video consultation, but the supporters could be flexible if needed. Data was collected at baseline and at 6 months and included questions regarding the influence of the pandemic on the family, user friendliness of the intervention (System usability scale), level of distress (Relatives stress Scale) and expressed emotions (the Family Questionnaire).

Results: Fifty nine percent of carers had 8 or more consultations (range 1-16). The majority (60%) reported received most of the support during video sessions. However, a substantial minority received mixed support, and reported to receive most of the support by phone (32%)

or face to face (8%). Having the first consultation face to face was important to many carers, but carers who received support primarily by video were less inclined to deem this. Caregivers experienced a significant reduction in distress and in expressed emotions post-intervention. Change in distress and expressed emotions were primarily observed among mothers/female carers, and not fathers/male carers. A majority of both male (60%) and female (51%) carers reported that the burden on their own health was reduced after the REACT-NORV intervention. Carers rated the intervention as user friendly (System usability scale mean score 82), but emphasized the importance of the human support by the family therapists. Changes attributed to the Covid-19 pandemic at baseline, such as worsening of symptoms or reduced access to treatment/services for the sick family members, did not seem to influence the benefit for the carers. The main barriers to attend to the program were challenges related to the situation in the household and lack of time.

Discussion: The intervention proved feasible to deliver in standard clinical care with support from trained family therapists. REACT-NORV was well received by the participating carers, but the observed gender differences should be further explored. REACT-NORV may contribute to increased access to support for carers of people with psychosis when options for delivering face to face interventions are limited. There is a need to explore further, who will benefit from guided online programs directed towards families, and who will need more extensive single and multiple family work to be able to reach a broader group with appropriate help.

T232. SHIFTING PERSPECTIVES: SUBSTANCE USE DISORDER'S ROLE IN PHYSICAL ACTIVITY AMONG INDIVIDUALS WITH SCHIZOPHRENIA AND PSYCHOSIS DISORDER

Florence Piché¹, Lucie Venet-Kelma¹, Chantal Plourde², Ahmed Jérôme Romain³

¹University of Montreal, ²Université du Québec à Trois-Rivières, ³University of Montreal Hospital Research Centre

Background: People with psychotic disorder, such as schizophrenia, tend to have a low physical activity level and a more sedentary lifestyle. This can be attributed to various obstacles such as side effects of antipsychotic medication, comorbidities, low mood, and lack of social support. While substance use disorder (SUD) is commonly viewed as a detrimental aspect of individuals with mental disorder, recent research challenges this notion. In our recent study, higher levels of physical activity were observed in people with SUD compared to other mental disorders (such as bipolar disorder, major depression, etc.) Our study aims to verify whether, when compared to a population with psychotic disorders and schizophrenia, this remains true. Objective: (1) Compare the level of physical activity between people with psychotic disorder as well as SUD with people with psychotic disorder only. (2) Compare the level of physical activity between people with schizophrenia with SUD with people with schizophrenia only.

Methods: Cross-sectional study using the database SIMPAQ (23 countries) including 1013 participants all evaluated by a psychiatrist. Mental disorder included schizophrenia spectrum disorders, bipolar disorder, depressive disorders, anxiety disorders, obsessive-compulsive disorders, substance-related and addictive disorders, neurocognitive disorders, and other disorders. We form groups using the severity of symptom for SUD and psychotic disorder. Individuals must reach the threshold (slight or greater) in the questionnaire DSM-5 self-rated level 1 cross-cutting symptoms measure to be considered in the SUD group or in the psychotic disorder group. For the schizophrenia group, we use the diagnosis made by the

psychiatrist. We formed four groups, G1: people with the psychotic disorder and SUD, G2: people with only psychotic disorder, G3: people with schizophrenia and SUD, G4: people with only schizophrenia. To evaluate physical activity, we used the simple physical activity questionnaire and to compare physical activity levels, we used a one-way ANOVA.

Results: Characteristic for groups 1 and 2 were similar for age (G1: 37.7 ± 12.1 years; vs. G2: 38.4 ± 13.6 years), but different for the proportion of women (G1: N = 44, 35.2% vs. G2: N = 72, 51.1%). Characteristic for groups 3 and 4 groups were also similar for age (G3: 36.1 ± 12.3 years vs. G4: 36.2 ± 12.4 years) and different for the proportion of women (G3: N = 28, 21.1% vs. G4: N = 67, 40.6%). For the objective 1, we found a significant difference in physical activity levels between people with SUD and psychotic disorder (2.44 ± 1.91 h of physical activity/week) compared with people with only psychotic disorder (1.97 ± 1.63 h of physical activity/week; $p=0.04$). For objective 2, we found that among people with schizophrenia, no difference was found regarding physical activity levels (G3: 2.15 ± 1.73 ; vs. G4: 1.80 ± 1.54 h of physical activity/week; $p=0.08$).

Discussion: People with SUD seem to have different lifestyles compared with people with psychotic disorder that in people with schizophrenia in terms of level of physical activity. This study has the potential to help reshape our perception of SUD beyond its negative connotation. The observation that individuals dealing with both psychotic disorder and substance use issues appear to be more physically active suggests an opportunity to create pathways for guiding them toward healthier lifestyle habits. Naturally, further research is essential to comprehensively understand the interplay between physical activity, SUD, and psychotic disorder, as well as to identify the most effective approaches for treating and using physical activity in this population.

T233. EVENT - A CLUSTER-RANDOMIZED CLINICAL TRIAL ON THE USE OF THE DECISION SUPPORT APP SDM-ASSISTANT TO SELECT THE MOST APPROPRIATE ANTIPSYCHOTIC IN HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA

Natalie L. Peter^{*1}, Spyridon Sifas², Katharina Müller³, Ivana Ivandic², Keelin Hyde², Natascha Wilde², Sophie Peter², Alessandro Rodolico², Alkomiet Hasan⁴, Peter Brieger³, Stephan Heres⁵, Johannes Hamann⁶, Stefan Leucht²

¹*Sektion Evidenzbasierte Medizin in der Psychiatrie und Psychotherapie, Klinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar, School of Medicine and Health, Technische Universität München,* ²*Sektion Evidenzbasierte Medizin in der Psychiatrie und Psychotherapie, Klinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar, School of Medicine and Health, Technische Universität München, Deutschland,* ³*kbo Isar Amper Klinikum München,* ⁴*Department of Psychiatry, Psychotherapy and Psychosomatics, University of Augsburg,* ⁵*kbo-Klinik für Psychiatrie und Psychotherapie Nord. Koelner Platz 1, Haus 7 80804 Muenchen, Germany,* ⁶*Klinikum Mainkofen*

Background: Selecting the most suitable antipsychotic based on the latest scientific evidence repeatedly presents doctors and patients with major challenges. By introducing our digital decision aid SDMA, we aim to provide the latest meta-analytic data in an easily accessible way and thus promote evidence-based shared decision-making.

Methods: A total of 18 wards at 4 centres in the cities of Munich and Augsburg were randomly assigned to either the control or intervention setting using a matched-pair design. Included patients (schizophrenia spectrum disorder, acutely ill, 18-65 years) were interviewed

at two time points during their inpatient stay and 3 months after discharge. At the same time, the treating physicians assessed the severity of illness, level of functioning and patient involvement in treatment decisions. After the first appointment (baseline), the patients and doctors in the intervention group were given access to the app, in which the patients were able to indicate treatment goals, previous experience and preferences with certain medications. Then, the doctors could indicate any previous illnesses or special patient characteristics. In the end, the app presented more detailed information on the antipsychotics in question, as well as a graphical overview of the effectiveness and the frequency of various side effects in comparison with other drugs. Our primary outcome was the patient version of the SDM-Q-9 (per protocol), which measures the perceived degree of involvement in treatment decisions. Secondary outcomes included patients' attitude towards treatment and medication, preferred extent of shared decision-making, and side effects of medication. Qualitative surveys accompanied the quantitative assessments.

Results: (at the time of submission still preliminary): Of the n=153 included patients, n=74 were recruited from intervention wards, and n=79 were recruited from control wards. The drop-out rate in the intervention and control group was 0.46 and 0.39, respectively. The difference between intervention and control was small and considered clinically insignificant (intervention mean (SD): 25.90 pts. (8.02); control 26.23 pts. (9.01); difference (linear mixed-effects model): -0.57 pts. (95%-CI -7.46 to 4.00)). The other outcomes are currently analysed.

Discussion: We successfully implemented the use of a shared decision-making app in an acute inpatient setting. The acuteness and extremely high workload of clinicians posed several challenges to the strict implementation of our protocol. While our primary outcome failed to exhibit considerable differences between intervention and control, the application was well received by both patients and providers, and facilitated discussions on the topics of treatment choice and side effects. We think the application could be of even more use in outpatient settings later in the course of treatment, when a certain stabilization has been reached and emerging or persisting side effects begin to play a bigger role for treatment choice and adherence. As a next step, we will make our decision-making aid SDMA available in other languages and extend it to different medication groups.

T234. LOST CONNECTIONS: NEGATIVE SOCIAL EXPERIENCES HEIGHTEN PSYCHOTIC SYMPTOMS IN A COMMUNITY SAMPLE

Elyssa Barrick¹, Grant Nelson¹, Sarah Hope Lincoln¹

¹Case Western Reserve University

Background: Several current theories suggest that social disconnection may underlie psychotic symptoms. The social defeat hypothesis (Selten et al., 2013) links exclusion from a majority group to increased risk of psychotic disorders, and the social deafferentation hypothesis (Hoffman, 2007) proposes that social withdrawal and isolation result in neural changes associated with psychotic symptoms. However, much of the supporting evidence for these hypotheses is correlational. Experimental validation of such hypotheses often entails assessing changes in outcome variables based on a predictor, a common approach in affective research using mood-induction paradigms. The field of psychosis research encounters unique challenges in this area due to the absence of established psychosis-induction paradigms for neurotypical individuals. Despite these challenges, this concept is not beyond the realm of feasibility. Even among individuals with psychotic disorders, there are observable daily and momentary fluctuations in symptoms. While psychotic symptoms are often measured in the

laboratory as traits, their real-world manifestation tends to be more transient in nature. This study aimed to 1) explore whether psychotic-like experiences (PLEs) could be temporarily induced in a non-psychiatric community sample, and 2) test whether simulating socially excluding experiences increased momentary PLEs.

Methods: Online participants (N = 862) recruited via Prolific completed the study using Qualtrics. Inclusion criteria included: US residency, no reported neurodiversity or ongoing/history of mental illness, and English as a primary language. We created the Momentary Assessment of Psychotic-like Experiences (MAPE), a 20-item measure, to assess in-the-moment positive and negative dimensions of PLEs. Higher MAPE scores indicate increased endorsement of PLEs. Following randomization into one of four conditions (inclusion, exclusion, sadness, neutral), participants completed the MAPE (pre score), engaged in a 5-minute writing session where they recounted an experience consistent with their condition, followed again by the MAPE (post score).

Results: Our main analysis tested the impact of writing conditions on PLEs. First, change scores (post-MAPE minus pre-MAPE) were computed within participants. Next, a Kruskal-Wallis test was conducted to examine group differences in change scores. Results revealed a statistically significant group difference $\chi^2(3) = 234.35$, $p < .001$, $\epsilon^2 = 0.26$. Pairwise comparisons using Dunn's test and Bonferroni showed significant increases in PLEs for exclusion (M = 2.71) compared to inclusion (M = -2.88) and neutral conditions (M = -1.71; all p s $< .001$). Additionally, there were significant increases for the sadness condition (M = 6.02) compared to inclusion, neutral and exclusion conditions (p s $< .001$). We then compared changes in specific symptoms between exclusion and sadness conditions. Using t-tests with Bonferroni corrections, we found that negative affect increased more following sadness (M = 3.84) than exclusion (M = 2.19), $t(407.27) = -4.57$, $p < .001$. Similarly, negative symptoms increased more for sadness (M = 1.70) than exclusion (M = 0.80), $t(420.32) = -3.14$, $p = .01$. However, paranoia increased more for exclusion (M = 0.97) than sadness (M = 0.25), $t(435.64) = 4.45$, $p < .001$.

Discussion: To our knowledge, this is the first study to provide evidence that PLEs can be temporarily induced in neurotypical individuals through a behavioral paradigm, a phenomenon induced by recalling socially negative and isolating events. Interestingly, the results show a unique dissociation: recalling sad experiences heightens affective and negative symptoms, whereas recalling exclusionary events increases paranoia.

T235. SOCIAL STIGMA AND PSYCHOSIS: EXAMINING HALLUCINATION VALENCE, DIAGNOSTIC CONTEXT, AND EXPOSURE TO INDIVIDUALS WITH MENTAL ILLNESS

Alicia Villanueva van den Hurk^{*1}, Julie Walsh-Messinger²

¹University of Detroit Mercy, ²University of Dayton

Background: Individuals with psychosis face profound social stigma, contributing to the perception that they are uniquely dangerous and aggressive. Previous research has shown that hallucination valence (positive vs negative) affects stigma, but neutrally valenced hallucinations have not been studied. Additionally, individuals with schizophrenia and other serious mental illness experience greater stigmatization than those diagnosed with other psychiatric disorders, but this stigmatization has not been compared to psychosis in the context of a non-psychiatric disorder. The present study examined the effects of clinical

diagnosis and auditory hallucination valence on stigmatization of fictional patients with psychosis. Additionally, because social contact is an effective strategy against all stigmas, the effect of exposure to individuals with mental illness (EMI) and its interaction with the aforementioned variables was also explored.

Methods: Undergraduate students (N=120) completed the Level of Contact Report online to measure EMI. The following week participants were presented with six fictional patient descriptions, three diagnosed with bipolar I disorder and three with a brain tumor. After each description five audio recordings were presented as examples of that patient's auditory hallucinations, which were pleasant, unpleasant, or neutral in valence based on ratings provided in a previous study. Participants then completed the Bogardus Social Distance Scale to assess the extent to which they would be willing to accept a social relationship with each of the fictional patients.

Results: There were no differences in stigmatization of bipolar I patients compared to those with a brain tumor, but there was a main effect for valence ($F=41.33$, $p < .001$, partial $\eta^2 = .259$). Stigmatization was higher for patients with negatively valenced auditory hallucinations compared to neutral ($p < .001$) and positive ($p < .001$). Similarly, participants were less accepting of a social relationship with patients experiencing neutral hallucinations than they were of patients with positive hallucinations ($p < .001$). Regarding EMI, participants with low exposure reported greater stigmatization compared to participants with high EMI ($F=5.05$, $p=.026$, partial $\eta^2 = .021$) and there was a significant interaction between hallucination valence and EMI ($F=5.04$, $p=.007$, partial $\eta^2 = .041$). Participants with high EMI reported greater stigmatization of patients with negatively valenced hallucinations compared to those with neutral ($p < .001$) and positive ($p < .001$); stigmatization for neutral hallucinations was higher compared to those with positive ($p < .001$). In the low EMI group, stigmatization was only higher for patients with negative hallucinations compared to positive ($p=.03$).

Discussion: These results suggest that hallucination valence has greater impact on psychosis stigmatization than diagnostic context, and that exposure to individuals with mental illness may reduce this stigmatization. These findings propose potential mechanisms that may underlie the stigmatization of psychosis, which can potentially inform future interventions aimed at reducing social stigma towards psychosis. This can be particularly beneficial given the negative effects of stigma on psychosis prognosis. Future studies should examine cross-cultural effects and explore whether diagnostic context only affects certain types of stigmatizations (i.e., physical proximity, friendship, romantic relationship).

T236. COMPARATIVE EFFICACY OF ORAL VS. LAI FORMULATIONS OF EIGHT SECOND-GENERATION ANTIPSYCHOTICS IN ACUTE SCHIZOPHRENIA TREATMENT: A NETWORK META-ANALYSIS AND SYSTEMATIC REVIEW

Dongfang Wang^{*1}, Johannes Schneider-Thoma², Spyridon Sifakis³, Yikang Zhu⁴, John M Davis⁵, Josef Priller⁶, Stefan Leucht⁷

¹Section Evidence Based Medicine in Psychiatry and Psychotherapy; Klinikum Rechts der Isar, Technical University of Munich, ²Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, ³Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, School of Medicine, Technische Universität München, ⁴Klinikum Rechts der Isar, Technical University of Munich; Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, ⁵University of Illinois, ⁶Technical University of

Munich, School of Medicine, ⁷Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technische Universität München

Background: There is a long-standing debate about whether long-acting injectable antipsychotics (LAIs) are better than oral formulations. Therefore, this study aimed to compare second-generation LAIs with their oral formulations for the acute treatment of schizophrenia by network meta-analysis (NMA).

Methods: We conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs). We focused on adult patients in the acute phase of schizophrenia. Interventions and control groups considered were risperidone, paliperidone, aripiprazole, olanzapine, and placebo, administered either orally or via injection. We synthesized data on overall symptoms, complemented by 17 other efficacy and tolerability outcomes. The synthesis was achieved through a frequency-based NMA. Confidence in the evidence was assessed using CINeMA (Confidence in Network Meta-Analysis).

Results: We analyzed 115 eligible RCTs, encompassing 25,550 participants. All drugs were significantly more efficacious than placebo with the sequence olanzapine LAI -0.66 [-1.00; -0.33], risperidone LAI -0.59[-0.73;-0.46], olanzapine oral -0.55[-0.62;-0.48], aripiprazole LAI -0.54[-0.71; -0.37], risperidone oral -0.48[-0.55;-0.41], paliperidone oral -0.47[-0.58;-0.37], paliperidone LAI -0.45[-0.57;-0.33], aripiprazole oral -0.40[-0.50; -0.31]. Further sensitivity analysis concerning overall symptoms yielded consistent findings. Confidence in the evidence was generally moderate to low according to our evaluation with CINeMA.

Discussion: In conclusion, during the acute treatment phase, the efficacy of LAIs does not surpass that of orals, while LAIs present some advantages over oral formulations in the realm of side effects. These findings equip clinicians with insights to weigh the risks and benefits between oral and injectable agents when managing patients in the acute phase.

T237. ENHANCING SCHIZOPHRENIA CLASSIFICATION THROUGH QUANTILE-BASED POLYGENIC RISK SCORE ANALYSIS

Gianluca Christos Kikidis^{*1}, Leonardo Sportelli², Alessandro Bertolino¹, Daniel Weinberger², Giulio Pergola²

¹University of Bari Aldo Moro, ²Lieber Institute for Brain Development

Background: In the latest Genome-Wide Association Study (GWAS) on schizophrenia (SCZ), common variants surviving correction for multiple comparisons were identified at 287 distinct genomic loci. Polygenic risk score (PRS) analysis explained a median variance of 0.073 in liability, specifically focusing on Single Nucleotide Polymorphisms (SNPs) with GWAS p-values below .05. It is commonly preferred to select the PRS containing variants with p LESS THAN .05 for best trade-off between number of variants included and proportion of liability explained. Notably, the rank of an individual within a group can change remarkably based on the classifier used, e.g., different PRSs computed at variable thresholds of SNP inclusions. We hypothesize that, given the inherent uncertainty in the multitude of classifiers, a centrality measure of an individual's position in a cohort may yield superior classification performance compared to the current optimal classifier, i.e., the standard PRS. Our proposed approach involves calculating the mean and standard deviation from all risk percentiles within each individual to capture the risk distribution and predict case/control status more accurately.

Methods: Our study involved 1686 genotypes of Caucasian adults (45% female) from the University of Bari (UNIBA) cohort, comprising 1098 neurotypical controls (NC) and 588

patients with SCZ, as well as 1280 postmortem genotypes of Caucasian adults (40.2% female) from the NIH SIB Study cohort, including 648 NC and 632 SCZ patients. Additionally, genotypes from the Psychiatric Genomics Consortium wave 2 sites, totaling 36,000 individuals with SCZ and over 113,000 NC in 39 sites, were included. After quality controls, we calculated the PRS based on the latest GWAS SCZ variants. Risk percentiles were then calculated for each commonly used p-value threshold. We introduced a novel approach, quantile-based Polygenic Risk Score (qPRS), utilizing the mean and standard deviation from all risk percentiles within each individual to determine the quantile risk of an individual. We predicted case/control status using a generalized linear regression model, comparing the classic PRS approach with our qPRS. Sensibility/sensitivity analyses were performed with the area under the receiving operating curve of different scores on diagnosis. Finally, we conducted a meta-analysis with a paired t-test between each different PGC site.

Results: Our findings revealed a superior performance of the qPRS compared to the standard PRS. In UNIBA, Nagelkerke's pseudo-R² for qPRS was 0.20, surpassing the classic PRS with a pseudo-R² of 0.15. Similarly, in the NIH SIB Study cohort, the qPRS demonstrated higher Nagelkerke's pseudo-R² (0.23) compared to the PRS (0.16). Moreover, enhanced accuracy and precision in classifying case/control status were observed with the qPRS (AUC 78% vs 75% with PRS). Meta-analysis across all PGC2 sites indicated that the qPRS explained an average of 22% of variance (95% CI [0.19, 0.25]), outperforming the classic PRS (17%, CI [0.15, 0.20]). Our approach consistently outperformed the classic approach in terms of variance explained across PGC sites ($t(38) = 8.37$, $p = 1.72 \times 10^{-10}$).

Discussion: Our analyses suggest that genetic classifiers without genome-wide significant SNPs contribute to SCZ heritability. The consideration of the entire PRS distribution, potentially representing diverse genetic pathways, enables a more accurate classification of patients and controls. Additionally, this method employs a population-based approach, using risk percentiles within a population, thus potentially increasing its potential applicability to diverse datasets.

T238. FEASIBILITY AND EFFECTIVENESS OF DIGITAL HEALTH INTERVENTIONS IN PEOPLE WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Urska Arnautovska¹, Kathryn Vitangcol², Mike Trott², Alyssa Milton³, Ellie Brown⁴, Namal Balasooriya⁵, Joseph Firth⁶, Dan Siskind⁷, Dan Siskind^{*8}

¹Faculty of Medicine, The University of Queensland, ²The University of Queensland, ³University of Sydney, ⁴University of Melbourne, ⁵Centre for Health Service Research, The University of Queensland, ⁶University of Manchester, ⁷School of Medicine, The University of Queensland, Brisbane, MIRT, Woolloongabba Community Health Centre, Addiction and Mental Health Services and MIRT, ⁸Metro South Addiction and Mental Health Service

Background: People living with schizophrenia are at increased risk of chronic diseases and can experience persisting psychosis symptoms which significantly impair their quality of life. The advancement in digital technology such as smartphones has the potential to improve health outcomes and social functioning in this at-risk group. This systematic review aimed to examine the effect of digital health interventions delivered among people with schizophrenia on a range of health-related outcomes, including psychosis symptoms, cognition, depression, medication adherence, self-management, and functioning.

Methods: A search of PubMed, CINAHL, EMBASE, Scopus and Cochrane databases was conducted to identify randomised controlled trials that reported outcomes of interventions delivered via a website, mobile phone, or other devices in people with schizophrenia (or related psychotic disorders). All potential studies were screened for eligibility by two reviewers.

Results: Our search produced 47,364 from which 35 eligible articles were identified. Primary and secondary outcomes of each study were grouped into psychosis symptoms (total, positive, and negative); quality of life; global functioning; social functioning; global cognition; medication adherence; and depression. The interventions examined in these trials were found to be feasible, with low recruitment but high retention rates. The effects of interventions on outcomes were variable (Hedge's g range -0.06-1.25) and showed potential for improving psychosis symptoms, depression, and cognition.

Discussion: This systematic review provides strong evidence on the feasibility of digital health interventions for people living with schizophrenia and supports the potential for clinical effectiveness of such treatment designs in improving mental health in this population.

T239. CAN RECOVERY-ORIENTED REHABILITATION LANGUAGE IN CLINICAL DOCUMENTATION ENHANCE RECOVERY-ORIENTED PRACTICE?

Veronica De Monte¹, Angus Veitch², Frances Dark¹, Carla Meurk³, Marianne Wyder¹, Maddison Wheeler¹, Kylie Carney¹, Stephen Parker³, Steve Kisely³, Dan Siskind^{*1}

¹*Metro South Addiction and Mental Health Service*, ²*Independent Researcher*, ³*University of Queensland Faculty of Medicine*

Background: In alignment with recovery-oriented practice principles, this study introduces a novel method for assessing the presence of recovery-oriented rehabilitation language in clinical documentation. It also evaluates the impact of a training intervention aimed at improving the use of such language within a community-based rehabilitation team.

Methods: Eleven case managers underwent training that provided instruction in recovery-oriented rehabilitation principles. The effectiveness of this training was quantified using automated textual analysis of clinical documentation, which utilised a specialised dictionary comprising rehabilitation-consistent, person-centred, and pejorative terms. This analysis was conducted on the KNIME platform. Pre-training and post-training documents, 50 and 77 respectively, were compared using inferential statistics to identify changes in language frequency.

Results: Post-intervention analysis revealed a significant increase, from 37% to 48%, in the average percentage of sentences containing recovery-oriented rehabilitation terms, marking a 28% relative rise ($P < 0.001$). Despite this improvement, there was no notable change in the use of person-centred or pejorative terms, which could be attributed to the already high baseline use of person-centred language (22%) and the minimal use of pejorative language (2.3%).

Discussion: The findings demonstrate that the computer-assisted text analysis method can successfully detect enhancements in the use of recovery-oriented rehabilitation language following brief training interventions. The study suggests that such training can influence the language of clinical documentation and that automated text-analysis offers a promising technique for rapidly assessing language use within mental health services.

T240. INFLAMMATORY AND COGNITIVE EFFECTS OF COVID-19 INFECTION IN SCHIZOPHRENIA

Stephanie Kulaga^{*1}, Matthew Glassman², Shawna Dougherty³, Sathyaikumar Korrapati³, Mallory Shriver⁴, Kristen Marx⁴, Fang Liu⁵, Sharon August⁵, Deanna L. Kelly⁶

¹MPRC, University of Maryland SOM, ²Maryland Psychiatric Research Center, University of Maryland School of Medicine, ³Maryland Psychiatric Research Center, ⁴University of Maryland, ⁵University of Maryland Baltimore, Maryland Psychiatric Center, ⁶University of Maryland Baltimore, Maryland Psychiatric Research Center

Background: The role of viral infections in the pathophysiology of schizophrenia-related disorders (SRD) has been well-characterized and appears to be primarily mediated through inflammatory effects. Individuals with SRD have been shown to have both elevated serum viral antibody titers and increased pro-inflammatory cytokine levels. Several such cytokines are involved in activation of the kynurenine pathway (KP), which breaks down tryptophan (TRP) and may be disturbed in SRD. Kynurenic acid (KYNA), a breakdown product of the KP, is thought to contribute to cognitive impairments observed in SRD. Coronaviruses have been shown to have increased antibody titers in individuals with SRD and it has been postulated that the COVID-19 pandemic could lead to increased SRD diagnoses in the future. COVID-19 has been associated with neuropsychiatric presentations, including psychosis, and notable cognitive effects sometimes following even mild to moderate infection. COVID-19 has also been associated with increases in pro-inflammatory cytokines and KP metabolites, both of which have been linked to both acute infection severity and long-COVID symptoms. Individuals with SRD have had higher morbidity and mortality from COVID-19 than other populations, which may be related in part to baseline immune disturbances. Literature on COVID-19 infection in those with SRD is limited and largely focused on severe infection requiring hospitalization. Little is currently known about the effects of mild to moderate COVID-19 infection on immune parameters, cognition and other clinical parameters in people with SRD.

Methods: We aimed to recruit 40 individuals with SRD diagnoses, half with history of COVID-19 infection 1 month to 1 year prior and half without. No participants were hospitalized for COVID-19. All participants completed a MATRICS cognitive testing battery, psychiatric symptom questionnaires, and a blood draw at a one-time study visit. Serum was analyzed for kynurenine, KYNA, TRP, inflammatory markers and SARS-CoV-2 anti-nucleocapsid and anti-spike antibodies. Complete blood counts (CBC), metabolic panels (CMP) and vital signs were also measured.

Results: 23 participants (57.5%) had a history of COVID-19 infection and 17 did not (42.5%). There were no significant differences between groups in kynurenine, KYNA, TRP, CBC, CMP, positive or negative psychotic symptom scores, overall MATRICS scores or cognitive subdomain scores. The COVID-19 group had significantly higher mean IL-8 than the non-infected group (14.48 vs 7.73, $p=0.01$), as well as higher IL-6 (8.75 vs 3.81, $p=0.069$) and TNF-alpha (24.97 vs 8.83, $p=0.057$), though these did not reach significance. Participants with history of COVID-19 infection reported a mean of 11.4 (SD=13.9) long-COVID symptoms. We will also report on the relationships of antibody levels, cytokines, and KP metabolites to cognitive and psychiatric outcomes, as well as to long-COVID symptoms.

Discussion: In our population of participants with SRD, those with a history COVID-19 infection had higher levels of several inflammatory cytokines. Most existing literature on COVID-19 in individuals with SRD focuses on those hospitalized with severe infection. To our knowledge, this is the first evidence that mild to moderate COVID-19 infection leads to

lasting inflammatory changes in individuals with SRD. Further analyses will examine the relationship of these inflammatory markers to outcome variables.

T241. PHYSICAL HEALTH AND TRANSITION TO PSYCHOSIS IN PEOPLE AT CLINICAL HIGH RISK

Andrea De Micheli^{*1}, Umberto Provenzano², Kamil Krakowski², Dominic Oliver³, Stefano Damiani⁴, Natascia Brondino⁵, Philip McGuire⁶, Paolo Fusar-Poli⁷

¹*Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Institute of Psychiatry, Psychology and Neuroscience, King's College London,* ²*Department of Brain and Behavioural Sciences, University of Pavia,* ³*Early Psychosis: Interventions and Clinical Detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London,* ⁴*University of Pavia, Department of Brain And Behavioral Sciences,* ⁵*Department of Brain and Behavioural Sciences, University of Pavia,* ⁶*Department of Psychiatry, University of Oxford,* ⁷*Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, OASIS Service, South London and Maudsley NHS Foundation Trust, Department of Brain and Behavioral Sciences, University of Pavia, National Institute for Health Research, Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust,*

Background: The clinical high risk for psychosis (CHR-P) construct represents an opportunity for prevention and early intervention in young adults, but the relationship between their psychosis risk and physical health is still unclear.

Methods: We conducted a RECORD-compliant clinical register-based cohort study, selecting the long-term cumulative risk of developing a persistent psychotic disorder as the primary outcome. We investigated associations between primary outcome and physical health data with Electronic Health Records at the South London and Maudsley (SLaM) NHS Trust, UK (January 2013–October 2020). We performed survival analyses, using Kaplan-Meier curves, long-rank tests, and Cox proportional hazard models.

Results: The database included 137 CHR-P subjects, 21 CHR-P developed psychosis during follow-up and the cumulative incidence of psychosis risk was 4.9% at 1 year and 56.3% at 7 years. Using log-rank tests, psychosis risk might change between different levels of nicotine and alcohol dependence. Kaplan-Meier curve indicates that non-hazardous drinkers may have a lower psychosis risk than non-drinkers. In the Cox proportional hazard model, nicotine dependence presented a hazard ratio of 1.34 (95%CI. 1.1 – 1.64) (p-value 0.01), indicating a 34% increase of psychosis risk for every additional point on the Fagerström Test for Nicotine Dependence (FTND).

Discussion: Our findings confirmed that a comprehensive assessment of tobacco and alcohol intake, diet, and physical activity in CHR-P subjects is key to understanding how physical health contributes to psychosis risk.

T242. MUVA PHYSICAL ACTIVITY INTERVENTION IMPROVES SOCIAL FUNCTIONING IN PEOPLE WITH A SEVERE MENTAL ILLNESS: A PRAGMATIC STEPPED WEDGE CLUSTER RANDOMIZED TRIAL

Lisanne Koomen*¹, Ilona van de Meent¹, Jeroen Deenik², Edwin van Dellen¹, Hugo Schnack³, Henri van Werkhoven¹, Wilma Swildens⁴, Prof. dr. Berno van Meijel⁵, Wouter Staal⁶, Frederike Jorg⁷, Floor Scheepers⁸, Wiepke Cahn¹

¹UMC Utrecht, ²GGz Centraal, Amersfoort, ³University Medical Center Utrecht, ⁴Altrecht Institute for Mental Health Care, ⁵Department of Psychiatry, Amsterdam UMC, ⁶Karakter, ⁷University of Groningen, ⁸Department of Psychiatry, University Medical Center Utrecht, Utrecht

Background: Severe mental illness (SMI), including psychosis, places a substantial burden on individuals, resulting in persistent symptoms, reduced social functioning, and compromised physical health. While physical activity (PA) interventions show promise in enhancing both mental and physical well-being, individuals with SMI encounter significant obstacles in engaging in PA. This study aimed to assess the impact of the Muva physical activity intervention on social functioning and secondary outcomes.

Methods: Employing a pragmatic stepped-wedge cluster randomized trial design, we evaluated Muva, which focused on addressing barriers to PA for individuals with SMI by actively involving mental health workers. Muva incorporates a serious game, provides additional lifestyle education, and optimizes medication regimens through medication reviews. The control group received standard care. We conducted mixed-effects linear regressions to measure changes in the primary outcome, social functioning, and secondary outcomes including quality of life, psychiatric symptoms, PA levels, BMI, waist circumference, and blood pressure.

Results: We enrolled 84 patients in three intervention clusters and 38 patients in the control cluster. In comparison to the control group, patients receiving Muva demonstrated clinically significant improvements in social functioning, in interpersonal communication (B=9.07, CI=4.05-14.09) and independence competence (B=5.03, CI=2.49-7.56).

Discussion: The Muva physical activity intervention improved social functioning among individuals with SMI. However, strategies for overcoming implementation barriers are essential to ensure better integration into everyday clinical practice.

We received funding from the Dutch Heart Association [2019T101] for the conduct of the study.

T243. LONG-TERM IMPACT OF ANTIPSYCHOTIC TREATMENT ON RENAL FUNCTION IN INDIVIDUALS WITH A FIRST EPISODE OF PSYCHOSIS: A 3-YEARS PROSPECTIVE STUDY

Claudia Ovejas Catalán¹, Paloma Fuentes Pérez¹, Carmen Flor Gómez¹, Javier Sastre Yáñez¹, Jorge Romay González¹, Rocio Perez-Iglesias¹, Maria Juncal Ruiz¹, Paula Suarez-Pinilla¹, Benedicto Crespo Facorro², Javier Vázquez-Bourgon*³

¹University Hospital Marques de Valdecilla -IDIVAL; University of Cantabria, ²Hospital Universitario Virgen del Rocío. CIBERSAM. Universidad de Sevilla, IBiS, Sevilla, ³University Hospital Marques de Valdecilla -IDIVAL; University of Cantabria; CIBERSAM

Background: Patients with schizophrenia display a wide variety of medical conditions. Chronic kidney diseases are highly prevalent in schizophrenia increasing its morbidity and early mortality. These kidney alterations may be present even from early stages of the psychosis, thus we recently reported that drug-naïve patients suffering a first episode of psychosis presented a poorer renal function when compared with a control group (García-

Rizo et al. 2022). Besides, it has been proposed a nephrotoxic effect of antipsychotic treatments. Our aim is to compare the long-term (3 years) progression of the glomerular filter rate between a cohort of individuals with a first episode of psychosis and a control group. We hypothesize that baseline differences in renal function between patients with psychosis and controls will increase throughout follow-up, possibly due to a nephrotoxic effect of antipsychotics.

Methods: The study was part of a larger prospective longitudinal study on first episode non-affective psychosis, the PAFIP program, in the Marqués de Valdecilla University Hospital (Santander, Spain). 440 drug-naïve first episode psychosis (FEP) patients and 81 controls were evaluated for renal function according to its glomerular filter rate (GFR). Confounders such as age, sex, body mass index, blood pressure and tobacco use were also considered. Estimated Glomerular Filter Rate (eGFR) was calculated with the CKD-EPI Creatinine Equation (version 2009) (Levey et al., 2009) as follows: $eGFR_{cr} = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]. Where: Scr = standardized serum creatinine in mg/dL; $\kappa = 0.7$ (females) or 0.9 (males); $\alpha = -0.329$ (female) or -0.411 (male); $\min(Scr/\kappa, 1)$ is the minimum of Scr/ κ or 1.0; $\max(Scr/\kappa, 1)$ is the maximum of Scr/ κ or 1.0; Age (years).

Analyses of covariance (ANCOVA) were performed to compare means between groups discarding the possible confounding effect of basal eGFR. In the model, change in glomerular filter rate overtime was included as the dependent variable, while age, sex, BMI, basal eGFR and tobacco use were included as co-variables. The Statistical Package for Social Science (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the 0.05 level.

Results: A significant reduction in GFR was found between FEP and healthy controls both at baseline (97.4 vs 108.4 ml/min/1.73 m², p LESS THAN 0.001) Indeed, when categorized the GFR following usual cut-points references (LESS THAN 90, and ≥ 90 ml/min/1.73 m²) significant differences were also displayed, with significantly more psychosis patients among the poorer kidney function group (LESS THAN 90 ml/min/1.73 m²) at baseline (39.1% vs 9.9%, p LESS THAN 0.001) and at 3-years follow-up (28.6% vs 2.5%, p LESS THAN 0.001). ANCOVA analysis covarying for potential confounders (i.e.: age, sex, BMI, tobacco use, and basal GFR) showed a significant differences between psychosis and control groups in GFR change; although both groups increased their GFR overtime, the increase was significantly smaller among psychosis patients (estimated marginal means: 2.7 vs 6.4 ml/min/1.73 m², $p=0.021$). ANCOVA analyses comparing the effect of 6 different antipsychotic treatments (i.e. aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone, and haloperidol) on GFR change over the 3-years follow-up showed significant differences between groups (p LESS THAN 0.001). Interestingly, those patients initially treated with olanzapine and haloperidol showed a reduction in mean GFR (-6.7 and -8.8 ml/min/1.73 m², respectively) while the other antipsychotics showed increments in mean GFR. Olanzapine and haloperidol showed significantly smaller changes in GFR than the rest of antipsychotic treatments. These results were also observed following a per protocol approach.

Discussion: Our results showed that the reduced renal function observed at early staged of psychosis is maintained at long-term. However, unexpectedly we did not observe a worsen in GFR overtime in the psychosis group. Interestingly, specific antipsychotic treatments (olanzapine and haloperidol) appeared to have a deleterious effect on GFR. These findings suggest some vulnerability associated with the diagnosis which might produce a greater

impact on kidney function depending on the type of antipsychotic to which the patient is exposed.

T244. PATIENT CHARACTERISTICS AND CARDIOVASCULAR HEALTH BEHAVIORS FOR COMMUNITY-DWELLING ADULTS WITH SCHIZOPHRENIA IN KOREA

Seon-Young Hwang¹, Yu-Mi Song², Pil-Hwa Heo³, Sra Kim¹, Katherine Cahir*⁴, Heeyoung Lee⁴

¹Hanyang University, ²Hanmaeum Independent Living House, ³Seongbuk Community Health Center, ⁴University of Pittsburgh School of Nursing

Background: Cardiovascular disease (CVD) is a leading cause of death and is prevalent among individuals with severe mental illness (SMI), such as schizophrenia. The incidence of metabolic syndrome, a cluster of CVD risk factors, is found to be two to three times higher in individuals with SMI compared to the general population, partly due to unhealthy lifestyle behaviors. Notably, the death rates of people with SMI aged 50–75 have a nearly two-fold increased risk of CVD. Given the significant health disparities and elevated CVD risk among people with SMI, the purpose of this study is to compare patient characteristics and cardiovascular health behaviors by age group (i.e., those under the age of 50 and those aged 50 or older) living in the community to inform the development of interventions tailored to the unique needs of individuals with schizophrenia.

Methods: A cross-sectional observational design was employed, and participants were recruited from 13 mental health service centers in Korea. Inclusion criteria comprised individuals: a) diagnosed with schizophrenia/schizoaffective disorder based on DSM-5 criteria; b) aged 30 years and older, capable of communication, and willing to participate; c) who signed the consent form; and d) for those residing in group homes, they had to have lived there for more than three months. Excluded from the study were individuals with cognitive decline, communication difficulties, or intellectual disabilities. Data were collected with a survey for demographic and clinical information and standardized instruments, including dietary habit attitude, the International Physical Activity Questionnaire (IPAQ), and cardiovascular health behaviors. Descriptive statistics, t-test, and one-way ANOVA were employed.

Results: A total of 237 participants completed the surveys. Of these, 133 (56.1%) were aged under 50, while 104 (43.9%) were aged 50 or older. There were 67 (50.4%) males and 66 (49.6%) females under the age of 50. In the 50 or older age group, there were 41 males (39.4%) and 63 (60.6%) females. One hundred sixteen participants lived in group homes. Both groups exhibited similar behavioral patterns of smoking, alcohol drinking, snack intake, and physical activity (ps GREATER THAN .05). Of those under age 50, 33% reported having medical conditions such as hypertension, diabetes, dyslipidemia, or angina, while 45.2% of those aged 50 or older had medical conditions (ps GREATER THAN .05). Participants aged 50 or older were taking medications for their medical conditions, while 27.8% of participants under 50 were taking medications for their medical conditions (p=.02). Among participants aged 50 or older, their engagement in cardiovascular health behaviors and dietary habits attitude were significantly higher compared to those under 50 (ps LESS THAN .05).

Discussion: More attention is warranted for individuals under the age of 50 with schizophrenia, as they do not engage in health-promoting behaviors. These findings highlight

the importance of implementing education and early behavioral interventions to promote a healthy lifestyle and encourage regular follow-ups with health care providers to effectively manage cardiovascular risks among people with schizophrenia.

T245. LONG TERM EVALUATION ABOUT THE MAINTAIN OF HIGH INTENSITY INTERVAL TRAINING EFFECTS ON PSYCHOTIC DISORDERS

Lucie Venet-Kelma*¹, Amal Abdel-Baki², Ahmed Jérôme Romain¹

¹*University of Montreal*, ²*Centre Hospitalier de l'Université de Montréal*

Background: Physical inactivity is one of the factors in the reduction of life expectancy in people with psychotic disorders. This physical inactivity occurs because of the psychotic disorders expression that leads to limitation in the daily life, poor lifestyle habits, and associated diseases. Physical inactivity is explained by barriers to physical activity (PA) and by the lack of commitment to long-term autonomous practice. PA improves overall physical and mental health, but approximately 30% of people with psychotic disorders drop out of the PA intervention in which they were engaged. The aims were to examine the long-term HIIT exercise effect among people with psychotic disorders six months after participation to an exercise intervention, and to determine which predictors could facilitate participation in PA and thus, reduce dropout.

Methods: A sample of 66 individuals included (37.9% of women, 30.73 ± 7.23 years old), with psychotic disorders were subjected to a 6-month interval training of running on a treadmill, twice 30 minutes per week, after which they had free access to the facilities used. Data from individuals who participated to the PA intervention ($n = 66$) with psychotic disorders were analyzed by a linear mixed model at three times: in baseline, after the 6-months intervention and follow-up period 6 months after the end of the intervention (12 months after baseline). The measures concern the evaluation of positive, negative, and general symptoms with the Positive And, Negative Syndrome Scale (PANSS), as well as overall functioning with the Global Assessment Functioning (GAF) and social functioning with the Social and Occupational Functioning Assessment Scale (SOFAS).

Results: After cessation of the intervention, the results showed a maintenance of benefits in negative ($p = 0.004$) and general ($p = 0.01$) symptoms. Otherwise, regarding the predictors of PA participation, results demonstrated that individuals who participated in less than 64% of the sessions were those with a lower level of global ($p=0.02$) and social ($p=0.00$) functioning and had more severe symptoms (PANSS) (negative: $p=0.02$; positive: $p=0.01$; general: $p=0.04$).

Discussion: The benefits observed were maintained in terms of negative and general psychopathology symptoms, which leads us to believe that the intervention needs to be improved in its modes of action to achieve greater maintenance of benefits. Otherwise, both global and social functioning, as symptoms severity were associated with PA participation. These elements should be considered to reduce dropout in future PA interventions, and encourage the reinvestment of good practices daily to maintain the benefits of PA.

T246. PREVENTION AND PREDICTION OF RELAPSE IN SCHIZOPHRENIC PATIENTS: RCT RESULTS ON INTEGRATIVE COGNITIVE REMEDIATION DURING 8-YEAR FOLLOW-UP

Daniel Mueller*¹, Rosa Mueller-Szer², Linda Grossenbacher¹

¹University Hospital of Psychiatry and Psychotherapy/University of Bern, ²Cantonal Hospital, Departement of Oncology and Cantonal Psychiatry Hospital (RFSM/FNPG), Fribourg

Background: Relapses are a major burden for schizophrenic patients, their relatives and caregivers. Preventing and predicting relapses is therefore a serious challenge for psychiatric treatment.

Methods: In the present RCT study, the relapse prevention potential after a psychotherapeutic intervention in addition to standard treatment was investigated over 8 years. The used psychotherapy approach was Integrated Neurocognitive Therapy (INT), a group approach with interventions in 11 neuro- and social-cognitive domains, which are partly PC-supported including therapy elements from psychoeducation, CBTp and emotion as well as stress regulation. 71 outpatients with schizophrenia (diagnosed according to ICD-10) were assigned to either an INT group (30 sessions over 15 weeks) or a standard treatment (TAU). Relapse rates were evaluated during follow-up periods of 1, 5 and 8 years. A test battery was collected before and after treatment and at the 1-year follow-up.

Results: The relapse rates for INT and TAU did not differ significantly in the first year. 5 and 8 years after the end of treatment, the relapse rates for INT (48%/52%) were significantly lower than for TAU (77.8%/82.8%). Rehospitalization days differed significantly too (8-year follow-up: INT=34.8 days; TAU=102.4 days). Predictors: During the 1-year follow-up, there was a significant correlation between higher relapse rates and lower social-cognitive performance levels (emotional processes, schemas). Relapse rates in the first year after completion of treatment predicted the course of relapses and rehospitalization days during the 5- and 8-year follow-up. At the 5- and 8-year follow-up, higher symptomatology, particularly positive symptoms, as well as higher levels of psychosocial functioning and verbal (working) memory were also found to be predictors of reduced rehospitalization days.

Discussion: There seems to be evidence that INT can significantly reduce relapses and thus the days of rehospitalization compared to TAU over a longer observation period of 8 years. Predictors for this appear to be relapse rates, positive symptoms, psychosocial functioning and working memory after a 1-year follow-up.

T247. DOES GENDER MATTERS IN THERAPEUTIC ALLIANCE? EXPLORING PATIENT-THERAPIST DYADS IN SCHIZOPHRENIA SPECTRUM DISORDER

Giovanni de Girolamo*¹, DIAPASON Consortium²

¹IRCCS St. John of God Clinical Research Centre, Brescia, ²IRCCS St. John of God Clinical Research Centre

Background: Despite the importance of therapeutic-alliance (TA), evidence regarding the impact of gender and gender correspondence in therapist-patient pairs on the alliance is limited and varied, especially for patients with severe mental disorders. This research aims to fill this gap by specifically analysing the influence of gender and gender correspondence on the levels and in TA, assessed using the Working Alliance Inventory (WAI) completed by both patients and therapists, within a sample of patients with schizophrenia spectrum disorder (SSD).

Methods: Besides a number of assessment tools covering psychopathology (BPRS and BNSS), psychosocial functioning (SLOF), time perception (ZTPI), each patient completed the Working Alliance Inventory short-form (WAI-SF) for patients (WAI-P) and was asked to

rate a specific staff member with he/she had a "one-to-one" therapeutic relationship defined as "case manager" by care setting. Similarly, each staff member completed the WAI short form for staff (WAI-T) for up to 3 different patients they were caring for. The WAI-SF includes 12 items that can be rated on a 7-point Likert scale, from 1 ("never") to 7 ("always"), with a total score ranging 12 to 84, with higher scores indicating a greater WA: three subscales measuring the three domains of WA can be computed: (a) agreement between patient and therapist about treatment goals (Goals); (b) agreement between patient and therapist on tasks to achieve these goals (Task); and (c) quality of the bond between patient and therapist (Bond). The discrepancy between therapist and patient assessments of the working alliance was computed by subtracting the therapist ratings from the patient ratings on the WAI. WAI-P and WAI-T scores, both total scores and subscales, were stratified by gender dyad groups: male patients with male therapists, male patients with female therapists, female patients with male therapists, and female patients with female therapists. We tested the differences between dyads using Anova and paired t-tests. To further understand the association of gender and gender correspondence with patient-reported scores (WAI-P) and therapist-reported scores (WAI-T), we constructed linear regression models.

Results: The WAI total score, as well as the subscale scores did not significantly differ between gender-based dyads, neither at the therapists nor at the patients' evaluations. Gender correspondence had a significant positive effect on the WAI-P task ($p = 0.030$), with a coefficient of 1.312, while no other significant associations were identified. In the complex model, the gender of patients and therapists interacted with a significant positive effect when both are male ($p = 0.013$), resulting in a coefficient of 3.893. There were no significant differences between patient and staff ratings across dyads; however, male patients had higher Goal ratings compared to both, their paired female ($M=20.4$; $SD=5.0$, vs. $M=19.5$; $SD=3.6$; $p = .022$) and male therapists ($M=21.1$, $SD=4.5$, vs. $M=19.5$; $SD=3.8$; $p = .034$). In linear regression analyses testing the effect of gender and gender correspondence on WAI scores, neither the patient nor the therapist gender was associated with the WAI-P or with the WAI-T total scores, nor with the majority of the WAI subscale scores in patients or staff evaluations after adjustment for levels of psychopathology. The only exception was the significant association between gender correspondence within the dyad and a higher WAI-P task score ($\beta=1.31$; $p=0.03$), and in particular in the case of male patient/male therapist dyad ($\beta=3.89$; $p=.013$) (Table 3).

Discussion: This study examined the relationships between gender and gender correspondence within a therapeutic dyad, and the working alliance in patients with SSD and their treating therapists. The main findings are those of no effects of gender on the levels of working alliance as assessed with the WAI by patients or therapists. Additionally, we found that gender correspondence within the dyad had limited effects on WAI ratings, with the only exception of higher scores on the Task dimension of the WAI-Patient in case of a male dyad. Similarly, gender and gender correspondence had only marginal influence on agreement in alliance between patients and therapists, with male patients scoring their alliance, and in particular their Goal levels relatively higher than their therapists. The best agreement between patients' and therapists' scores was found especially in case of female patients, and in particular in the female-female dyad, while the poorest levels of agreements appeared in case of male patients. This study is among the first to examine the role of gender and gender matching in shaping WA among patients with a diagnosis of SSD and living in a residential facility. Gender and gender correspondence seem to have only marginal effects on the task dimension of the working alliance as perceived by the patients. Although the female patient - female therapist dyad appeared to show the best agreement in alliance, male patients seemed to perceive their WA stronger than their therapists. The dimensions mostly affected by gender/gender correspondence were those of goals and tasks, suggesting that a clear

agreement on therapeutic goals and tasks is recommended, especially when working with SSD patients.

T248. WORKING ALLIANCE IN TREATING STAFF AND PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDER LIVING IN RESIDENTIAL FACILITIES

Giovanni de Girolamo*¹, DIAPASON Consortium²

¹*IRCCS St. John of God Clinical Research Centre, Brescia*, ²*IRCCS ST. John of God Clinical Research Centre*

Background: Working Alliance (WA) is an important aspect of treatment for patients with Schizophrenia Spectrum Disorders (SSD). Establishing a therapeutic alliance in care settings with patients with SSD can be challenging due to their difficulties in building positive interpersonal relationships. A recent systematic review highlighted the role played by specific characteristics of patients with SSD in the therapeutic alliance assessments of both patients and therapists. Specifically, negative symptoms, younger age, and poor pharmacological treatment adherence seem to impact therapeutic alliance ratings. Positive symptoms, particularly paranoia, may also limit the establishment of a collaborative approach. Understanding the factors associated with better therapeutic alliance is crucial for implementing therapeutic programs and improving clinical outcomes, as well as reducing drug prescriptions and hospitalization risk. In the multicentre project on "Daily time use, Physical Activity, quality of care and interpersonal relationships in patients with SSD" (DiAPASon) data on WA were collected in people with SSD and staff members in their daily care. The present study aimed to (a) analyze the correlation between patient and staff WAI ratings; (b) identify socio-demographic and clinical variables associated with WA in patients and staff; and (c) examine factors associated with profiles of high vs. low WAI-rating discrepancy in the patient-therapist dyads.

Methods: Besides a number of assessment tools covering psychopathology (BPRS and BNSS), psychosocial functioning (SLOF), time perception (ZTPI), each patient completed the Working Alliance Inventory short-form (WAI-SF) for patients (WAI-P) and was asked to rate a specific staff member with he/she had a "one-to-one" therapeutic relationship defined as "case manager" by care setting. Similarly, each staff member completed the WAI short form for staff (WAI-T) for up to 3 different patients they were caring for. The WAI-SF includes 12 items that can be rated on a 7-point Likert scale, from 1 ("never") to 7 ("always"), with a total score ranging 12 to 84, with higher scores indicating a greater WA: three subscales measuring the three domains of WA can be computed: (a) agreement between patient and therapist about treatment goals (Goals); (b) agreement between patient and therapist on tasks to achieve these goals (Task); and (c) quality of the bond between patient and therapist (Bond). The discrepancy between therapist and patient assessments of the working alliance was computed by subtracting the therapist ratings from the patient ratings on the WAI.

Results: The final sample assessed with the WAI includes 303 patients and 165 health workers. Pearson's correlation showed a statistically significant positive correlation ($p=.314$; p LESS THAN .001) between WAI-P and WAI-T total ratings. WAI-P total ratings also correlated significantly with all WAI-T subscales [Task ($p=.332$; p LESS THAN .001); Goals ($p=.295$; p LESS THAN .001); Bond ($p=.209$; p LESS THAN .001)]. Also, WAI-T ratings were significantly and positively correlated with WAI-P subscales [Task ($p=.301$; p LESS THAN .001); Goals ($p=.249$; p LESS THAN .001); Bond ($p=.277$; p LESS THAN .001)].

Similarly, all WAI-P subscales were significantly and positively correlated with WAI-T subscales even after Bonferroni correction, except for the correlation between WAI-T Bond subscale and WAI-P Goals subscale ($p=.145$; $p=.014$). Linear regression showed that patients with higher educational levels reported significantly lower ratings at WAI-T ($\beta=-0.50$, $p=.044$): for each education year, WAI-P rating decreased by 0.5 points. As for patients' socio-demographic factors associated with WAI-T, linear regression analysis revealed that being in a not working or studying condition was associated with significant lower total WAI-T ratings ($\beta=-4.17$, $p=.015$). The severity of psychopathology, as assessed with BPRS and BNSS, was negatively associated with both WAI-T ($\beta=-0.10$, $p=.002$) and WAI-P total ratings ($\beta=-0.19$, p LESS THAN .001). The level of functioning, measured using SLOF, was positively associated with both WAI-P ($\beta=0.12$, p LESS THAN .001) and WAI-T total ratings ($\beta=0.14$, p LESS THAN 0.001).

Discussion: First, patients with higher levels of education reported significantly lower scores on the WAI-P, suggesting a possible link between the patient's level of education and successful WA. Secondly, patients who were not involved in work or study had significantly lower scores on the staff WAI (WAI-T): this may suggest that if the patient is involved in productive activities, this may facilitate a good therapeutic alliance from the therapist's perspective. Furthermore, patients with shorter hospitalizations (LESS THAN 1 year) reported higher WAI-P scores than those with longer hospitalizations (GREATER THAN 5 years), suggesting that prolonged hospitalization may be associated with a negative effect on goal sharing through tasks and the development of a valuable therapeutic alliance. Furthermore, while the severity of psychopathology was inversely correlated with both WAI-P and WAI-T scores, the level of psychosocial functioning showed a positive correlation with both scores. This highlights the contrasting roles of clinical severity and psychosocial factors in assessing the therapeutic alliance between patients and staff.

T249. PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS FOR TREATMENT-RESISTANT SCHIZOPHRENIA: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Nurul Salahuddin^{*1}, Alexandra Schütz², Gabi Pitschel-Walz¹, Susanna Mayer¹, Anna Chaimani³, Josef Priller¹, Stefan Leucht¹, Irene Bighelli¹

¹Technische Universität München, ²Ludwig-Maximilians-Universität München, ³Paris Descartes University

Background: Many patients with schizophrenia do not respond satisfactorily to pharmacological treatments. Additional treatment options, such as psychological and psychosocial interventions, could be useful as add-on treatments. However, their role and comparative efficacy in this population are not known. We, therefore, investigated the efficacy, acceptability, and tolerability of psychological and psychosocial interventions for individuals with treatment-resistant schizophrenia (TRS).

Methods: We included randomized controlled trials (RCTs) comparing psychological or psychosocial interventions in adults with TRS. The main outcome was overall symptoms measured with validated and published rating scales. To investigate the eligible studies from the inclusion criteria, we searched for all RCTs by performing a systematic database search on BIOSIS, CINAHL, Cochrane CENTRAL, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PsycINFO, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform up to 31.01.2020, the Study registry of Cochrane Schizophrenia Group up to 31.03.2022 and PubMed and CENTRAL up to 31.07.2023. Random effects pairwise meta-

analyses and network meta-analyses have been performed to calculate standardized mean differences (SMDs) or risk ratios (RRs) with 95% confidence intervals (CIs). The study protocol was registered in PROSPERO with the number CRD42022358696.

Results: We included 60 RCTs that were eligible for qualitative synthesis after excluding 24526 records by title and abstract screening and 5540 records at full-text screening. Of these, 52 RCTs with 5812 participants comparing 20 psychological and psychosocial interventions provided data for network meta-analysis. When compared to treatment as usual with 95% CIs, we found that music therapy, integrated intervention, occupational therapy, virtual reality intervention, and cognitive behavioral therapy (CBT) were more efficacious in reducing overall symptoms. The confidence in the estimates ranged from moderate to very low. We found no indication of publication bias.

Discussion: CBT is a promising intervention to reduce the overall symptoms of TRS patients. Other psychological and psychosocial interventions could also be considered and recommendable for further investigation.

T250. COMPARING THE EFFECTS OF COGNITIVE RESTRUCTURING, COGNITIVE DEFUSION, AND THOUGHT MONITORING ON VOICE-HEARING DISTRESS IN PSYCHOSIS

Talia Leibovitz*¹, Michael Best¹

¹*University of Toronto Scarborough*

Background: Cognitive Behavioural Therapy for psychosis (CBTp) is effective to reduce symptoms of psychosis but effects are typically only moderate. To improve the efficacy of CBTp, it is critical to determine the mechanisms of change. Cognitive restructuring is a commonly used approach in CBTp and is hypothesized to generate therapeutic change. Cognitive defusion is a technique used to change the relationship an individual has with their thoughts or beliefs whereas cognitive restructuring targets the content of one's beliefs. Neither cognitive restructuring or cognitive defusion have been examined as a mechanism of CBTp, therefore it is unclear what approach to working with cognitions is most effective in psychosis. The current study evaluated the effectiveness of cognitive restructuring (CR), cognitive defusion (CD), and thought monitoring (TM) in reducing the distress of auditory verbal hallucinations (AVH).

Methods: Participants were randomly assigned to a therapeutic exercise condition: CR, CD, or TM. A graduate clinical psychology student guided participants through their assigned therapeutic exercise with an equivalent worksheet modified across conditions. The Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ) and Global Rating of distress were used to measure AVH-related distress. The Brief Mood Introspection Scale (BMIS; Mayer and Gaschke, 1988) was used to measure mood, the CHoice of Outcome In Cbt for psychosEs measure – Short Form (CHOICESF) to measure CR ability, and Cognitive Fusion Questionnaire (CFQ) to measure cognitive fusion. Following the therapeutic exercises, each participant was asked to provide feedback about the exercise to gather qualitative data.

Results: Twenty-six participants (CR = 8, CD = 9, TM = 9) with a psychotic disorder and distressing AVHs completed the study. There were no significant time by group interactions on HPSVQ distress ($F(2,23) = 0.85$, $p = .442$, $\eta^2p = .07$), global distress ($F(2, 23) = 1.18$, $p = .327$, $\eta^2p = .09$), CR ability ($F(2, 23) = 0.15$, $p = .863$, $\eta^2p = .01$), or cognitive fusion ($F(2, 23) = 1.41$, $p = .265$, $\eta^2p = .11$). There were no significant main effects of condition or time on HPSVQ distress, global distress, cognitive fusion, or cognitive restructuring ability. Exploratory paired t-tests demonstrated a significant difference between pre and post-

intervention HPSVQ distress for the CR group ($M_{diff} = 2.13$, 95% CI [1.08, 3.17], $t(7) = 4.82$, $p = .002$), however, not for the global distress ratings ($M_{diff} = 10.47$, 95% CI [-5.51, 26.45], $t(7) = 1.55$, $p = .165$). Differences between pre- and post-intervention HPSVQ and global distress scores were not significant for the CD and TM groups. Cognitive fusion pre-intervention was significantly correlated with mood ($r = -.64$, $p < .001$) and global distress ($r = .49$, $p = .012$) at baseline. CR ability (CHOICE-SF) was significantly correlated with mood (BMIS; $r = .57$, $p = .002$), however, not with HPSVQ ($r = -.10$, $p = .633$) or global distress measures ($r = -.25$, $p = .224$) at baseline. Qualitative feedback was available for 22 of the 26 (TM = 8, CD = 8, CR = 6). Positive feedback was provided by seven participants in the TM group, five participants in the CD group, and all participants in the CR group. Negative feedback was provided by one participant in the TM condition, three participants in the CD condition, and no participants in the CR condition.

Discussion: The exploratory and qualitative results suggested that CR may be effective at reducing voice-related distress; however, further examination is required. Qualitative feedback suggested that the CD milk exercise may actually increase distress for some individuals. Further research may be warranted to examine the differential effects of CBTp techniques to reduce voice-related distress.

T251. REWARD LEARNING AS A POTENTIAL MECHANISM FOR IMPROVEMENT FOLLOWING COGNITIVE REMEDIATION: A PILOT STUDY OF SCHIZOPHRENIA AND HEALTHY CONTROLS

Frances Dark^{*1}, Gabrielle Ritchie², Graham Galloway³, Matteo Cella⁴, Veronica De Monte⁵, Victoria Gore-Jones⁵, Marcus Gray³

¹*Metro South Addiction and Mental Health Services*, ²*Metro South addiction and Mental Health Service*, ³*Translational Research Institute, Brisbane, Australia*, ⁴*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁵*Metro South Addiction and Mental Health Services*,

Background: Cognitive remediation (CR) therapy is routinely used as a treatment for cognitive impairments and functional difficulties in people with schizophrenia. However, little is known about the mechanism of action. It is proposed that a potential mechanism of effect of CR is the engagement of the reward learning pathways with associated enhanced behavioural motivation and improved functioning.

Methods: This is a pre-post pilot study examining the impact of CR on reward learning and neurocognition. Ten participants aged between 18 to 35 years ($M = 26.1$ years, $SD = 5.30$), diagnosed with a schizophrenia spectrum disorder, completed a reward learning task with two conditions (social reward vs. non-social reward) during functional magnetic resonance imaging (fMRI) before and after 12 weeks of CR. To validate this task, reward learning was also assessed in 10 healthy controls, matched to patients for age, sex, and premorbid function. Neural differences reflecting modality (social v non-social learning) valence (reward vs loss feedback) and group (control, patients pre-CR, patients post-CR) were examined [see figure 1A]. All neural findings are corrected for inflated type 1 error reflecting multiple comparisons.

Results: Paired samples t-tests analysed the neurocognitive measures pre and post CRT intervention. The Benjamini-Hochberg correction to adjust for multiple comparisons was applied and maintain the false-discovery rate at .25. Participants improved significantly on tasks of verbal memory (adjusted $p = .014$) and executive function (adjusted $p = .028$) after

CR. Neural function clearly differentiated modality (social versus non-social learning) particularly within visual and face processing regions. Likewise neural responses clearly differed by valence (reward vs loss feedback within the default mode network and group (increased right temporal cortex responses within patients. Finally we observed a significant 3-way interaction (group x valence x mode) within the anterior cingulate and basal ganglia, with patients showing reduced responses to negative social feedback.

Discussion: Our pilot results demonstrate positive effects in people with schizophrenia spectrum disorder following Cognitive Remediation therapy, with initial results suggesting improvements in executive function and verbal working memory. Our reward learning task clearly demonstrates neural systems reflecting sensitivity to positive versus negative feedback, social versus non-social learning context, and differential cortical responses within schizophrenia spectrum disorder relative to control participants. Moreover, these neural systems appear to interact, reflecting reduced sensitivity to negative social feedback in people with schizophrenia spectrum disorder. Recruitment of participants, and further analysis of the impact of CR on patterns of neural response is ongoing.

T252. STIGMATIZATION OF PEER SUPPORT WORKERS AND ASSOCIATED FACTORS: A PARTICIPATIVE STUDY

Adrien Seguela*¹, Antoinette Prouteau²

¹*University of Bordeaux 2*, ²*University of Bordeaux, Human Sciences College and Department of Adult Psychiatry, Jonzac Hospital*

Background: Mental health practices are shifting towards a recovery-focused model, emphasizing the values and needs of individuals facing mental health challenges and employing a collaborative approach. Peer support is increasingly recognized as a valuable tool to implementing person-centered, rights-based and recovery approaches (OMS, 2021). Notably, the benefits of peer-support are mainly related to personal recovery variables such as hope, empowerment and self-efficacy (Thomas et al., 2018; Burke et al. 2019). However, qualitative data (Adams, 2020; Lynn Ng and Barlas, 2023; Wall et al., 2022) and literature addressing the barriers to peer support work (Ibrahim et al., 2020; Mutschler et al., 2022) showed that peer workers can be the targets of stigmatization in their workplace. However, this study did not describe the specific situations of stigmatization experienced by peer support worker and do not provide data on the associated lived experiences. This study aims to i) identify stigmatizing situations experienced by peer workers on their workplace ii) describe the frequency and the intensity (i.e. the level of stigma experienced) of these situations as reported by peer workers, iii) identify factors associated with these occurrences.

Methods: Initially, a focus group-like methodology was conducted with nine peer workers in order to collaboratively identify the most relevant situations of stigmatization experienced. Subsequently, based on these identified situations, an online survey will be disseminated among mental health professionals (e.g. peer workers, psychiatrists...) to quantify the frequency and the intensity of the stigmatization experienced by peer workers and explore associated factors. We hypothesize that peer workers will experience the stigmatizing situations i) more frequently and ii) with a higher degree of stigmatization than the other mental health professionals.

Results: The focus group allowed the identification of 34 situations experienced as stigmatizing by the peer workers. A collaborative work was done in order to reformulate and select the most relevant of them. Peer workers reported experiencing stigmatization at several levels such as structural (i.g. lack of access to tools, resources, and support needed to

accomplish the job), interpersonal (i.g rejection for collaboration, infantilization, skills disqualification) or internal (i.g. anticipation and self-stigma during job interview, setback during team meetings). The online survey will be disseminated among mental health professionals and results will be presented at the Schizophrenia International Research Society in 2024.

Discussion: This study will allow to identify the stigmatizing situations (and associated factors) experienced by peer workers in the mental health workplace. This contribution would highlight that stigmatization in the mental health workplace extends to peer support. This evidence could be exploited to facilitate and support the implementation of peer support workers. Finally, the identification of associated factors will provide relevant leverage to reduce the stigmatization of peer support workers.

T253. WISH LIST TO CLINICIANS AND RESEARCHERS FROM PEOPLE WITH LIVED EXPERIENCE OF BIPOLAR DISORDER

Cecilie Busch*¹, Isabel Kreis², Margrethe Collier Høegh³, Torill Ueland³, Carmen Simonsen⁴, Sofie R Aminoff⁴, Elizabeth Ann Barrett⁴, Thomas Bjella³, Ingrid Melle², Trine Vik Lagerberg³

¹Norwegian Centre for Mental Disorders Research (NORMENT), Psychosis Research Section, Oslo University Hospital, ²Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, ³Norwegian Centre for Mental Disorders Research (NORMENT), Psychosis Research Section, Oslo University Hospital, ⁴Early Intervention in Psychosis Advisory Unit for South East Norway, Clinic of Mental Health and Addiction, Oslo University Hospital,

Background: Despite national guidelines for the treatment of bipolar disorder and a substantial amount of research conducted in the field, we know less about what people with bipolar disorder actually want. People with lived experience can contribute to research through providing valuable input on what areas to focus on, and through increasing awareness of what is actually helpful treatment. With this in mind, we conducted an online survey asking people with lived experience of bipolar disorder what help they want from clinicians and what research questions they find important.

Methods: An online survey entitled “Wish list to clinicians and researchers from people with bipolar disorder” was distributed through posts on NORMENT’s and the Norwegian Bipolar Association’s Facebook profiles. The survey was open from the International Bipolar day 30.03.23 to 16.04.23. For the wish list to clinicians the participants were asked: “As of today: what do you wish a clinician could help you with?”. Survey alternatives included 16 pre-defined response options regarding treatment and two possibilities of not needing/wanting treatment. Each participant could tick off 1 to 3 topics. For the wish list to researchers the participants were asked: “What do you wish there was more research on?” The survey alternatives included 20 pre-defined research topics, and participants were asked to rate them on a scale from 1 (unimportant to me) to 5 (very important to me). In addition, participants were given the opportunity to provide personal comments about which topic was most important to them in both sections.

Results: There was a total of 416 responders, 80% women and 17% men, 3 % non-binary. Three of four respondents were between 26 and 55 years old. For the wish list to clinicians the following five alternatives were rated highest: a) Stabilization of depression, mania, psychosis or suicidal thoughts (27,2 %) b) Teach me to cope with, and stabilize, my emotions

(24,5 %), c) Help me to process trauma (24,5 %), d) Teach me to cope with stress (23,8 %), e) Increase my awareness of triggers and warning signs (23,3 %). For the wish list to researchers three topics were rated particularly high relative to other items: a) The association between BD and cognitive functions (M=4.58, 68.5 % of the respondents rated this item 5), b) More effective medication with less side effects (M=4.56, 73.1 % rated this item 5), c) What has been helpful to those who have recovered (M=4.54, 67.1 % rated this item 5). The remaining items were ranked M=4.21 and below. Examples of comments were: “A lot of side effects. And they reduce the quality of life”, “Knowing that I am slow because of my disorder, and not stupid, would prevent me from ruminating and becoming depressed”, “Gives me Hope!” and “The more research, the more informed we get”.

Discussion: Participants’ wishes to clinicians appear to align well with the Norwegian treatment guidelines for bipolar disorder, although the survey indicates that not everyone receives such treatment. Interestingly the participants’ top four wishes for clinical help, can be viewed as expressions of emotional suffering. With regard to research, the three most highly rated topics can be viewed as the responders need for knowledge both for themselves and for the clinicians. The wish for more effective medication with fewer side effects is well known, underlining the urgency of precision medicine. For cognition, there were many comments related to its detrimental effect on functioning and quality of life, highlighting the need for increased focus on cognition in the clinic. The fact that people with bipolar disorder want to learn from others that have recovered, can be viewed as a need for hope and inspiration in a lifetime disorder.

T254. ‘MUSIC MATTERS’ – A QUALITATIVE EVALUATION OF A NURSE-LED STRUCTURED, GROUP-BASED MUSIC PROGRAM COMPLEMENTARY TO EARLY INTERVENTION IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS

Signe Marie Abild¹, Sofie Schuster¹, Julie Midtgaard*¹

¹*University of Copenhagen*

Background: Schizophrenia is a severe mental illness that exerts lasting effects on functional levels, social withdrawal, and quality of life. While music therapy has demonstrated promise in improving these areas, there is a dearth of research exploring the impact of music programs led by mental health care professionals without formal music therapy training in the context of early intervention in psychosis. This study aimed to conduct a qualitative evaluation of a once-weekly, 12-week, nurse-led music group, forming a band, offered as an adjunct to early intervention for young people experiencing first-episode psychosis. The specific objectives were to explore social interaction and the experiences of participants and instructors in relation to the music group and to provide focal points for implementation in clinical practice.

Methods: We applied an Interpretive Description methodology approach including a combination of data collection methods and sources. We combined key informant interview (n=1), group and email-based interviews (n=6), and participant observation (6 sessions x 1.5 hrs; 9 hrs in total), to ensure a comprehensive understanding reflecting the complexity of the program. The data were transcribed, thematized, and analyzed inductively using NVivo12 to facilitate deeper insight and an understanding of the music group in a clinical practice setting. Data was generated between June 2022 and February 2023.

Results: A total of ten participants, comprising eight service users and two employees, were included. The analysis resulted in three main themes: Practicalities of the music program, Restored identity, and Music as medicine, reflecting the potential of the music group to contribute to a sense of non-patient identity, decrease symptoms related to mental illness, and

create a sense of belonging to a musical community. Specifically, participants recounted enrolling in the music program to revive their musical interest and reconnect with their past. Being in a band provided them with roles like guitarist, pianist, or singer, offering a contrasting identity to their illness. Additionally, some noted that the music sessions boosted their well-being and mood regulation including provided room for a feeling of connection to their inner emotions. For some, engaging with an instrument's rhythm and beat acted as a calming distraction from anxiety.

Discussion: This study investigated the impact and delivery of an ongoing, nurse-led music group in the context of treatment of first-episode psychosis. The findings suggest that such groups could provide a structured way for patients to connect socially through a shared, non-clinical activity. Specifically, our study suggests that supervised music sessions among peers, guided by skilled mental health staff, hold promise in helping participants manage their thoughts and alleviate anxiety-related symptoms. Hence, participation in music groups can potentially promote recovery. In this regard, it is imperative that the music-setting should be promoted as a non-therapeutic, non-clinical setting, offering the participants an identity as musicians rather than patients. Moreover, to create a reliable environment, each session must be built around the same recognizable structure to decrease anxiety, but with the possibility of adapting the content of the sessions to accommodate the individual needs of the participants. However, it should be emphasized that while the current study offers suggestions on how to organize music as a complementary intervention in the treatment of early psychosis, it does not provide definitive answers related to effectiveness.

T255. CHARACTERIZATION, HEALTH CARE RESOURCE UTILIZATION (HCRU), AND COST OF US MEDICAID PATIENTS WITH NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Claudia Hastedt*¹, Theresa Cassidy², Ling Zhang²

¹Boehringer Ingelheim International GmbH, ²Boehringer Ingelheim Pharmaceuticals, Inc.

Background: Persistent negative symptoms (NS) of schizophrenia (SZ) place a significant burden on patients. Often underdiagnosed, NS have a huge impact on functioning and quality of life for people living with schizophrenia. This retrospective real-world evidence study in the US investigated if patients diagnosed with NS utilize more health care services and incur higher treatment costs compared to SZ patients without a NS diagnosis.

Methods: SZ and the NS patients were identified using administrative claims data from the Merative™ MarketScan® Multi-State Medicaid Database based on schizophrenia diagnoses (ICD10 F20, ICD9 295) and diagnoses of residual schizophrenia with negative symptoms (ICD10 F20.5, ICD9 295.60). The study included adult patients (≥18 years) with at least one year of SZ history during 2017 to 2020. The index date was determined as the first SZ diagnosis date or NS diagnosis occurring after one year of SZ history. A non-NS cohort was created that included SZ patients without any NS diagnosis during the 4-year study period to calculate more accurate cost differences between diagnosed NS patients and the overall SZ patient cohort. Propensity score matching (PSM) with a 1:1 ratio at 0.2 caliper without replacement method was used to balance the NS versus non-NS cohort based on age, sex and history of disease. Cost in USD in the year after index date was reported. After PSM, a generalized linear model with gamma distribution log link function was applied to estimate the cost difference between cohorts.

Results: The study included 81,681 SZ patients and 2,181 (2.7%) with a NS diagnosis. Among the SZ patients, 77,906 had no NS diagnosis (non-NS). The mean (standard deviation

[SD]) age of the patients in the overall SZ patient cohort was 48.8 (15.1), with mean age of 52.1 (14.9) and 48.7 (15.1) in the in NS and non-NS cohorts, respectively. Male patients accounted for 59.1% of all SZ patients, 61.5% of NS patients, and 58.9% in the non-NS cohort. After controlling for demographic differences, the mean total cost in USD (sum of medical and medication cost) during the first year of follow-up after index date, was higher in NS patients: 45,344 (60,491) compared to matched non-NS patients 40,268 (55,282). Medical costs were the main cost driver for both NS 40,109 (58,444) and non-NS patients 36,031 (53,945). Medication costs were 5,235 (12,101) and 4,237 (9,848) in NS and non-NS patients, respectively. Cost analysis from a log gamma model showed a significant difference ($p < 0.001$) in the mean total cost between NS compared to non-NS patients with adjusted risk factors. Patients diagnosed with NS generated approximately 11% higher medical cost and 24% higher medication cost compared to patients without diagnosed NS. Mean outpatient (OP) medical cost observed in NS patients were higher than in matched non-NS patients: 32,718 (55,298) versus 31,457 (52,330). The largest cost driver of OP cost was from skilled nursing facility, accounting for 54% and 46% of the total OP cost in NS patients versus non-NS patients. This corresponded to mean costs of 17,583 (51,264) in NS patients compared to 14,615 (45,344) in non-NS patients. Inpatient (IP) cost and emergency room (ER) cost were also higher in NS patients compared to non-NS patients: 5,723 (18,987) versus 3,615 (15,025) for IP costs, and 1,667 (6,573), versus 960 (3,529) for ER costs.

Discussion: Medication and medical cost in SZ patients with NS were higher compared to patients without a NS diagnosis. These results confirm the high burden of NS on patients and the economic burden on the care system, highlighting the need for innovative care approaches for these patients.

T256. LONG-TERM POOR OUTCOME IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS WITH META-REGRESSION OF 20-YEAR FOLLOW-UP STUDIES

Ida-Marie Mølstrøm^{*1}, Julie Nordgaard², Annick Parnas³, Rasmus Handest³, Jonas Berge⁴, Mads Gram Henriksen⁵

¹Mental Health Center Amager, ²Mental Health Centre Amager, Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, ³Psychiatric Center Amager, ⁴Department of Clinical Sciences, Division of Psychiatry, Lund University, ⁵Mental Health Center Amager, Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen

Background: Schizophrenia affects individuals in different ways. Some may experience more severe symptoms than others, resulting in significant problems with both their mental and social well-being. These impairments can lead to social isolation and, in extreme cases, homelessness. How do we best support and prevent individuals with severe schizophrenia from slipping through the cracks?

Methods: We conducted a systematic review and meta-analysis on long-term follow-up studies of schizophrenia until April 21, 2021. We included only prospective studies with at least 20 years of follow-up on patients diagnosed with schizophrenia, and the studies had to include face-to-face clinical evaluation. We analyzed the outcome in three groups: 'recovery,' 'good or better' (including 'recovery'), and 'moderate or better' (including 'recovery' and 'good

or better'). We used random-effects meta-analysis and meta-regression to examine the mean estimates and possible moderators.

Results: We included 14 studies (1,991 individuals) published between 1978 and 2020. These studies used different scales and definitions to measure the outcomes, and some used the same definition to describe different outcomes. To ensure a fair comparison of outcomes across studies, we created a unified template for outcome definitions and cutoffs based on earlier recommendations from other studies. We found that 40% of people with schizophrenia live with continuous poor outcome, including poor social function. 60% had good to moderate outcome, including 22.4% in recovery. Furthermore, the outcomes were unchanged over time.

Discussion: Despite extensive treatment and research, there is a significant portion of people with schizophrenia who continue to be severely affected by the disorder. Recovery and good outcome are certainly possible; schizophrenia remains a severe and complex mental illness. Despite a century of research and efforts to improve treatment, the prognosis shows limited change.

T257. DELUSIONAL DIMENSION AND COGNITIVE FLEXIBILITY: INTEREST OF ASSOCIATED SUBJECTIVE MEASURES WITH NEUROPSYCHOLOGICAL MEASURES TO STRENGTHEN THE RECOVERY PROCESS IN A PSYCHOSOCIAL REHABILITATION PATHWAY

Marie-Cécile Bralet*¹, Alexandre Durand², Alexandre Carpentier³, Marion Feron², CRISALID-HDF Team², Claire Rascle⁴

¹Service CRISALID-HDF CHI Clermont de l'Oise, ²Service CRISALID CHI Clermont de l'Oise, ³Service SPR CHI Clermont de l'Oise/UPJV, ⁴CSN2R -(MGEC-CHU)-Université Lille

Background: Psychosocial interventions are supported by substantial evidence of efficacy in many outcome measures. Rehabilitation interventions should be considered as an evidence-based practice and need to be a part of the standard treatment of schizophrenia. To improve functional recovery an integrated and multifaceted assessment approach could be proposed using clinical, neuropsychological and self-reporting tools during rehabilitation pathway. Self-reporting can enhance a patient's feeling of involvement in the recovery process, improving metacognition, self-esteem. The objective of this presentation is: firstly to describe the motivational and metacognitive approach used at the beginning of the psychosocial rehabilitation pathway in order to allow the patient to self-determine and engage in personalized psychosocial rehabilitation care; secondly, to illustrate this approach through the dimensional exploration of delusional conviction by studying the correlation between a self-reporting tool, PDI 21 and a neuropsychological measure of cognitive flexibility, TMT B, within a rehabilitation cohort

Methods: Description of the psychosocial rehabilitation pathway at the CRISALID-HDF Rehabilitation Dsychiatric Department (Clermont de l'Oise Psychiatric Hospital, Hauts de France area, France) in a cohort of 40 patients suffering from schizophrenia (DSM 5 criteria) describing the different steps with clinical and neuropsychological tools, using quantitative/semi-structured and patient centered assessments. Correlation analysis between PDI 21 inventory delusions, sub-score conviction and cognitive flexibility measured by TMT B (level of significance p LESS THAN 0, 05)

Results: We found a significant correlation between PDI 21 sub-score conviction and TMT B : 0, 37 (p= 0, 017).

Discussion: Using self-report/subjective measures combining to neuropsychological and clinical semi-structured assessments could improve motivation and metacognitive dimensions among people with schizophrenia engaged in recovery-oriented rehabilitation program. This multifaceted assessment approach must be evaluated regarding recovery criteria outcomes. Qualitative/subjective clinical tools may be more relevant to the evaluation of rehabilitative care.

T258. THERAPISTS AS KEY FACILITATORS IN EFFECTIVE COGNITIVE REMEDIATION: A BAYESIAN NETWORK META-ANALYSIS

Anika Poppe¹, Tim Brands², Tim van Brouwershaven³, Michael Thomas⁴, Antonio Vita⁵, Elizabeth Twamley⁶, Marieke (Gerdina) Pijnenborg⁷, Lisette Van der Meer^{*7}

¹Lentis Psychiatric Institute, ²LVR-clinic Viersen, ³Lentis Psychiatric Institute, ⁴Colorado State University, ⁵University of Brescia, ⁶Department of Psychiatry, UC San Diego and Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, ⁷University of Groningen

Background: Cognitive remediation (CR) is an intervention designed to target cognitive functioning such as attention, memory, executive functions, social cognition, and metacognition, with the intention of lasting benefits and transfer to everyday life. According to a recent consensus among experts, there are four core elements necessary for CR programs to be successful: (1) targeted cognitive exercises, (2) guidance by a specially trained therapist, (3) teaching of cognitive strategies, and (4) generalization procedures to extend training gains to real-world settings. This meta-analysis aimed to identify the most effective combination of these elements in improving the everyday functioning of individuals with schizophrenia.

Methods: We conducted a systematic search in the databases PubMed, Cochrane Library, and PsycINFO, and ClinicalTrials.gov for randomized controlled trials that included participants diagnosed with schizophrenia, implemented CR, and included a functional outcome measure. We performed two Bayesian random-effects network meta-analyses to compare the effects of CR with different combinations of the four core elements on functional outcome measures and cognitive outcome measures.

Results: The network meta-analyses included 86 studies (5982 participants) and revealed that three combinations of the core elements resulted in significant improvements in everyday functioning compared to treatment as usual: cognitive exercises plus therapist ($g = 0.25$, 95% CrI [0.01, 0.49]), cognitive exercises plus therapist and generalization procedures ($g = 0.38$, 95% CrI [0.09, 0.66]), and cognitive exercises plus therapist, generalization procedures, and problem solving strategies ($g = 0.31$, 95% CrI [0.15, 0.47]). All other combinations of the four core elements did not result in significantly larger benefits in everyday functioning compared to treatment as usual. The combination of cognitive exercises, a therapist, and generalization procedures was 85.4% most likely to be the most effective treatment combination. For cognitive outcomes, the same combinations of core elements resulted in significant improvements compared to treatment as usual ($g = 0.23$ - 0.38). These results were not significantly influenced by study quality ($b = 0.08$, 95% CrI [-0.18, 0.34]).

Discussion: This meta-analysis emphasizes the crucial role of therapists in administering cognitive remediation training. When the other three core elements are combined without a therapist's involvement, the outcomes do not significantly surpass those of control interventions in enhancing cognitive and everyday functioning. The findings collectively

indicate that the most effective approach of cognitive remediation involves the combination of cognitive exercises and generalization procedures facilitated by a therapist, aiming to improve everyday functioning.

T259. INVESTIGATING THE LONG-TERM PREDICTIVE VALUE OF IMMUNE MARKERS IN PSYCHOSIS AND THE MODERATING ROLE OF CANNABIS USE

Isabel Kreis^{*1}, Kristin Fjelnseth Wold¹, Mashhood A. Sheikh², Maren Caroline Frogner Werner¹, Eivind Bakken², Nils Eiel Steen¹, Ingrid Melle¹

¹NORMENT, Institute of Clinical Medicine, University of Oslo, ²Oslo University Hospital

Background: The immune system appears to be implicated in psychotic disorders. Several cross-sectional studies have explored if markers of inflammatory and immune response could serve as biomarkers of diagnosis, symptom severity, and treatment resistance. However, very few studies have investigated them as potential predictors of psychosis outcomes and symptom development, and there are no prospective long-term studies in this area. Furthermore, inconsistencies in findings from cross-sectional and short-term prediction studies suggest the presence of moderating factors, but this has not been investigated in depth. A relevant candidate is cannabis use, which is known to impact both the immune system and psychotic relapse risk. We aim to address these research gaps by investigating to what extent immune marker levels at baseline can predict the risk of psychiatric readmission per year over a 10-year follow-up, and the role of cannabis use as a potential moderator.

Methods: 159 individuals (46% female) with first-episode psychosis (schizophrenia spectrum = 46%, bipolar spectrum = 29%, other psychosis = 25%) were included from the Norwegian Thematically Organized Psychosis (TOP) study. Data collected at the study baseline, including demographic, clinical, and cannabis use information, were linked with national health registry data prospectively, spanning a 10-year time frame. Contacts with specialized health services (inpatient care, outpatient contacts, or day treatment) due to schizophrenia spectrum diagnoses or bipolar disorder during each of the 10 follow-up years were extracted to reflect psychiatric readmission. Plasma levels of immune markers previously linked to psychotic symptoms and treatment response (CRP, IL-1Ra, sIL-2R, gp130, sTNFR-1) were measured at baseline, log- and z-transformed, and used to calculate a composite score (CSI). A logistic mixed effects model was used to assess the effect of CSI, cannabis use, follow-up year, and their interactions on readmission risk.

Results: Adjusted for covariates (age, gender, nicotine use, antipsychotic medication), preliminary results revealed a main effect of year, with readmission risk decreasing over time (OR = 0.69, p LESS THAN .001, 95% CI [0.65, 0.74]). There were no main effects of CSI or cannabis use on readmission risk. However, a two-way interaction between year and cannabis use (OR = 1.20, p LESS THAN .01, CI [1.05, 1.38]) indicated a stronger negative effect of year on readmission risk in non-users. Furthermore, a two-way interaction between CSI and cannabis use (OR = 0.53, p LESS THAN .01, CI [0.33, 0.86]) revealed a strong negative association between CSI and readmission risk in cannabis users only. Finally, as suggested by a significant three-way interaction (year*ICS*cannabis: OR = 1.09, p LESS THAN .01, CI [1.03, 1.15]), the association between year and readmission risk was moderated by CSI in cannabis users only. Specifically, among users there was a strong negative effect of year at medium-to-low CSI levels, while this effect was absent at high CSI levels. In contrast, the association between year and readmission risk was the same across all levels of CSI in non-users.

Discussion: These findings suggest that the relationship between immune markers and the course of psychosis is nuanced and influenced by cannabis use. This emphasizes the importance of considering cannabis use as a moderator of the link between immune markers and psychosis outcomes in future studies. The mechanisms underlying the complex interplay between inflammatory and immune processes, cannabis use, and the long-term course of psychosis remain to be unraveled.

T260. LEVEL OF FUNCTION ASSESSED BY CASE MANAGERS AND RELATIVES AND ITS ASSOCIATION WITH SYMPTOMATIC REMISSION SUSTAINABILITY IN SCHIZOPHRENIA

Madeleine Johansson¹, Iris van Dijk-Härd², Lars Helldin³, Lars Helldin*⁴

¹*Department of Psychiatry, NU Health Care Hospital, Department of Psychology, Karlstad University,* ²*Department of Psychiatry, NU-Hospital Groups,* ³*Department of Psychiatry, NU Health Care Hospital,* *Department of Psychology, Karlstad University,* ⁴*NU-Hospital Group, Karlstad University*

Background: General level of functioning is impaired in schizophrenia. The impairment covers several domains such as activity of daily living, social adaptation, and work ability. Patients' cognitive performance is central for their functional capacity and level of function within the society. Negative symptoms are also important for long-term functional outcome. This study addresses the influence of remission status on patients' functional performance.

Methods: Case managers and relatives rated patients' function with the Specific Level of Functioning Scale (SLOF). 147 patients were rated by case managers and of those 47 were also rated by a close relative. Patients were then followed during a period of three years with annual symptomatic remission assessments. Based on their remission status over time they were divided into three groups: Always in Remission (AwR), Altering in Remission (AnR), and Never in Remission (NiR). The six different domains in SLOF were then analyzed with a One-way ANOVA and a Tukey Post-Hoc test regarding their association to the different patterns of long-term remission status.

Results: The One-way ANOVA showed significant findings for Physical functioning, Personal care skills, Interpersonal relations, Activities, and Work skills with p-values between LESS THAN 0.001 and 0.041 for the case manager ratings. Only Social acceptability was not significant. Post-Hoc test found significant differences between all groups of remission patterns. When relatives' ratings were analyzed, the One-way ANOVA were significant for Interpersonal relations and Work skills and the Post-Hoc test revealed that the difference was between AwR and NiR.

Discussion: The study indicates that not only cognition and negative symptoms are associated with functional performance. There are also differences between different patterns of long-term remission status, in some of the domains between all groups and in others just between AwR and NiR. The differences between the ratings of case managers and relatives, may be partly due to the different sample sizes (147 vs 47). A possible conclusion is that to achieve best conditions for functioning it is necessary to reach a situation of sustainable symptomatic remission.

T261. EXERCISE INTENSITY AND EMOTIONAL AND PSYCHOPHYSIOLOGICAL FACTORS IN GYM-BASED HIGH-INTENSITY

FUNCTIONAL TRAINING COMMUNITIES FOR YOUNG ADULTS WITH SEVERE MENTAL ILLNESS – PRELIMINARY DATA FROM THE VEGA TRIAL

Victor Sørensen^{*1}, Martin F. Andersen², Bolette S. Rafn³, Bjørn H. Ebdrup⁴, Julie Midtgaard⁵

¹*Centre for Applied Research in Mental Health Care (CARMEN) and Center for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Center Glostrup, University of Copenhagen,* ²*Centre for Applied Research in Mental Health Care (CARMEN), Mental Health Center Glostrup, University of Copenhagen, Department of Physiotherapy, University College of Northern Denmark,* ³*Centre for Applied Research in Mental Health Care (CARMEN), Mental Health Center Glostrup, University of Copenhagen, Danish Cancer Society National Cancer Survivorship and Late Effects Research Center (CASTLE), Department of Oncology, Copenhagen University Hospital Rigshospitalet,* ⁴*Center for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Centre Glostrup, University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen,* ⁵*Centre for Applied Research in Mental Health Care (CARMEN), Mental Health Center Glostrup, University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen*

Background: Exercise is a beneficial and cost-effective adjunctive treatment in people with severe mental illness (SMI), with potential for improving multiple outcomes. Furthermore, exercise may induce acute and short-term improvements of emotional and psychophysiological factors, such as mood and physical well-being. High-intensity functional training (HIFT), utilizing constantly varied functional exercises and various activity durations that does not necessarily include rest intervals, has become increasingly popular as community-based exercise. HIFT holds the potential to facilitate personal recovery through its pronounced emphasis on skill acquisition, and when delivered in communities, it may also support other recovery aspects of the connectedness, hope, and optimism about the future, identity, meaning in life, and empowerment (CHIME) framework. To our knowledge, we here provide the first preliminary data on the acute effects of HIFT on emotional and psychophysiological factors in people with SMI.

Methods: This analysis is derived from the ongoing Vega trial investigating the value of gym-based group exercise versus usual care for young adults (18-35 years) with SMI (ClinicalTrials.gov ID: NCT05461885). Training sessions were supervised by certified Vega instructors at three commercial HIFT-gyms across Denmark. Each session lasted one hour and was divided into warm up, part A (resistance training), part B (workout of the day), and cooldown. Heart rate (HR) was monitored on chest straps at random sequential occasions where participants were blinded to the HR output during the sessions. Rate of perceived exertion (RPE) of each session part was collected with the Borg scale, ranging from 6-20, at the end of each session part. Physical well-being, mood, and mental energy was collected before and after each training session on 10cm VAS-scales, and differences was analysed with paired t-tests.

Results: Data was collected during 16 sessions with a mean attendance per session of 3.0 ± 0.8 (mean $\pm$ SD) with a total of 46 measurements (18 unique participants) from May to November 2023 across the three sites. Each part of the exercise sessions lasted 8.2 ± 2.7 , 14.8 ± 4.7 , 17.8 ± 4.2 , and 6.2 ± 1.8 minutes for warm up, part A, part B, and cooldown, respectively. Average %HR relative to age-predicted maximal HR (%HR_{max}) was 67.3 ± 7.9 (12.3 ± 1.9 RPE), 71.2 ± 7.8 (14.4 ± 2.2), 81.3 ± 5.7 (17.2 ± 1.5), and 68.3 ± 6.0 (9.7 ± 2.4) for warm up, part A, part B, and cooldown, respectively. Further, the average and maximally achieved

%HRmax was 74 ± 5.8 and $93.9 \pm 6.3\%$ across the entire training session, respectively. Acute changes were not observed for physical well-being ($P=0.190$), however, average mood increased with 1.5cm (0.8, 2.1 0.95CI; $P < 0.001$), corresponding to a relative change of 46.2% (28.3, 64.0 0.95CI), and average mental energy increased with 1.6cm (0.9, 2.3 0.95CI; $P < 0.001$), corresponding to a relative change of 62.4% (32.5, 92.2 0.95CI). Changes in mood and mental energy was not correlated with training intensity.

Discussion: The present preliminary analysis shows that the exercise communities in the Vega trial induce acute improvements in mood and mental energy. Additionally, the intensity of the HIFT training sessions results in elevations in HR and RPE corresponding to high-intensity exercise. Thus, the intended exercise intensity of HIFT is achievable and tolerable for people with severe mental illness. Future research in exercise communities should consider exploring predictive markers for acute changes in emotional and psychophysiological factors to identify meaningful values for persons with SMI to improve physical activity offers and engagement.

T262. CULTURAL AGREEMENTS ABOUT ETIOLOGY OF SCHIZOPHRENIA AND EXPRESSED EMOTION IN MEXICAN FAMILIES

Ricardo Audiffred-Jaramillo*¹

¹*Universidad de Guadalajara*

Background: Schizophrenia is a severe and persistent mental disorder that affects around 21 million people worldwide. The etiology of schizophrenia is currently understood as heterogeneous and multifactorial. Genetic and environmental factors are the most common explanations to the onset of schizophrenia, but along with these, hybridized cultural ideas coexist between medical, superstitious, or religious paradigms. Objective: To identify the relation between cultural beliefs about schizophrenia, etiology and Expressed Emotion. Method: The present study used a mixed-method design, with an analytical approach for ethnographic research. The sample was confirmed by 40 people, relatives of patients diagnosed with schizophrenia, selected with a simple random probabilistic sampling. Results A valid cultural consensus was found with statistical significance ($p \leq 0.05$). Emotional trauma in childhood was identified as the leading cause of schizophrenia, followed by hereditary factors, emotional problems, head trauma, mistreatment, and divine will. Best-informed relatives showed less Emotion Expressed than those with less cultural competence Conclusion: Mexican families in this study were closer to scientific knowledge about etiology of schizophrenia, but religious ideas and compassionate explanations were part of this hybridized model.

Methods: This research used the tools of cognitive anthropology to analyze through semantic structures, the cultural consensus of relatives of individuals with schizophrenia on the etiology of schizophrenia, and its relation with the EE. This study has a mixed design with an analytical method used in ethnographic research.

Results: The sample consisted of 40 relatives of individuals with schizophrenia from 18 different families in the Area Metropolitana de Guadalajara. Emotional trauma in childhood was identified as the first cause of schizophrenia described by family members (16%). The next factor was heredity with 15% and was followed by emotional problems (12%), head trauma (7%), mistreatment (5%), and divine will (5%), among others. It should be noted that variables related to neural problems and brain substances (4%) occupied the last places on the list but were still part of the valid cultural consensus. A single valid cultural consensus was

found, with a variability ratio of 39,130 and a statistical significance lower than ($p \leq 0.05$), which included 95.4% of all possible variations of the model items, with a multidimensional diagram with stress of 0.01.

Therefore, it resulted that 55% of the sample in this study had a low EE and the remaining 45% had a high EE. Based on the single-factor ANOVA, there was no significant difference between gender ($p = .898$), marital status ($p = .839$), religion ($p = .473$), schooling ($p = .382$), occupation ($p = .479$), or family relationship ($p = .170$) with the expressed emotion. Participants with adequate cultural competence (good informants) who provided answers attached to the valid cultural consensus on etiology of schizophrenia and people with inadequate cultural competence (bad informants) were categorized in order to analyze a possible association with high EE. Subjects with inadequate cultural competence showed a high EE ($p = \leq .05$) ($t = -9.15$; 95% CI [64.50-40.66]).

Discussion: This research studied the cultural consensus about etiology of schizophrenia and its possible relation with high EE. The hypothesis of this study sustained that there is a link between the cultural beliefs about schizophrenia etiology and high EE. And, as it has been shown, the comprehension about etiology has an impact on family expression of EE. Best-informed relatives express less EE. Being directly involved with a person with a mental disorder allows people to understand the reality of this illness in a deeper way. However, relationship or closeness does not exempt any individual from having a deficient understanding of this mental condition. The lack of knowledge resulting from the absence of information or misinformation about schizophrenia, usually generates negative attitudes or social rejection against people who live with it. The attitude of rejection or acceptance towards people with a mental disorder will depend on how people understand their condition. As for the EE, 45% of relatives with the role of caregivers of the person with schizophrenia presented a high EE and it was precisely this percentage of people who provided an understanding of the etiology that did not match the cultural consensus of this study. The percentage of relatives identified with high EE, matches with the data found in another research in Mexico, (19) where 42% of the people showed high EE. The fact that a significant association has been found between EE and those who live with the person with schizophrenia, confirms the theory of EE, which states that this phenomenon falls on those who spend more time with the patient and have bigger responsibilities in his or her caregiving. This study also corroborates the statement of Barrowclough and cols; and Cozolino and cols., which argues that relatives with high EE seem less informed about schizophrenia.

T263. ECOLOGICAL VALIDATION OF ATTACHMENT STATES AS MEDIATORS OF THE RELATIONSHIP BETWEEN CHILDHOOD ADVERSITY AND SUBCLINICAL PSYCHOTIC AND AFFECTIVE PHENOMENA IN DAILY LIFE

Pilar Torrecilla^{*1}, Tamara Sheinbaum², Thomas R. Kwapił³, Neus Barrantes-Vidal⁴

¹Universitat Autònoma de Barcelona, ²Instituto Nacional de Psiquiatria "Ramón de la Fuente Muñiz", ³University of Illinois at Urbana-Champaign, , ⁴Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona

Background: It is well established that childhood adversity is associated with psychotic phenomena at both clinical and nonclinical levels. In the last few years, increased attention has been given to the psychological mechanisms that may underlie this association. In particular, insecure attachment styles have been shown to mediate the associations between childhood adversity and psychosis expression. However, only a few studies have examined attachment in naturalistic daily-life conditions, that is attachment states, in relation to psychosis. More so, most of these studies do not distinguish between the dismissing and fearful styles. The present study aimed at testing the ecological validity of four attachment states (secure, preoccupied, dismissing, fearful) assessed in daily life using Experience Sampling Methodology (ESM) by examining their association to trait-like attachment styles. Secondly, and following previous studies supporting the role of insecure attachment trait-like styles as an explanatory mechanism of the pathway from childhood adversity to psychosis, we examined whether insecure attachment states mediated the effects of childhood adversity on subclinical psychotic phenomena in the flow of daily life.

Methods: The study comprised a total of 159 nonclinical college students (mean age=28, sd=2.3) with a wide distribution of schizotypy traits belonging to the Barcelona Longitudinal Schizotypy Study (BLISS). Participants were assessed with a self-report measure of childhood adversity and trait-like attachment and completed Experience Sampling Methodology (ESM) over 7 days. First, multilevel structural equation models were used to examine whether state attachment styles were predicted by trait-like attachment styles, and whether attachment states predicted subclinical psychotic-like experiences (PLE), paranoia, negative and positive affect. Second, multilevel mediation models were conducted to examine the indirect effect of childhood adversity on subclinical experiences via insecure attachment states (preoccupied, dismissing and fearful) in daily life.

Results: Secure attachment state was positively associated with secure trait-like attachment, and negatively associated with dismissing, fearful and disorganized attachment styles. Preoccupied attachment state was positively associated with preoccupied trait-like style, dismissing state with dismissing trait-like and the fearful state with the fearful trait-like attachment style. Individuals with higher secure attachment state reported decreased paranoia, PLE, and negative affect, and increased positive affect, whereas the fearful attachment state showed the opposite pattern of associations. Multilevel mediation analyses revealed a significant indirect pathway of childhood adversity to paranoia, positive PLE and negative affect through preoccupied and fearful attachment states, but not through dismissing state. The fearful attachment state also mediated the association of adversity and decreased positive affect.

Discussion: The present study i) ecologically validated four attachment states suggesting that stable trait-like attachment styles may translate to daily life fluctuations, and ii) showed that childhood adversity impacts the expression of psychosis-like and affective subclinical symptoms through increased levels of insecure attachment states in the flow of daily life. The findings are consistent with previous studies and support psychological models of psychosis expression, which may inform ecological momentary interventions based on attachment-informed approaches.

T264. DIVERGENT TRAJECTORIES OF INTRACORTICAL MYELIN CONTENT DURING THE EARLY PHASE OF SCHIZOPHRENIA SPECTRUM DISORDERS

Filip Spaniel¹, Tereza Nekovářová¹, Jana Kopřivová¹, Lea Jakob*¹, Antonín Škoch¹, Marián Kolenič¹, Petra Fürstová¹, Markéta Fialová¹, Kristina Hakenová¹, Václav Čapek¹

¹*National Institute of Mental Health, Czech Republic*

Background: The distinctive phylogenetic characteristics of the human brain is marked by abundant myelin and an extended period of developmental myelination. Maladaptive myelination is implicated in various neurodegenerative and neuropsychiatric disorders, including schizophrenia. This study specifically examines intracortical myelin content (ICM) in schizophrenia, delving into its deviant ontogenetic trajectories.

Methods: Using T1w/T2w MRI, we compare the longitudinal development of ICM in patients at the early stage of schizophrenia (n=265) to a healthy ontogenetic database.

Results: Preliminary findings reveal deviations in ICM trajectories within four years post-onset, leading to the identification of two distinct clusters: a hypermyelination cluster (comprising 75% of all cases) and a hypomyelination cluster (25% of cases).

Discussion: Notably, persistent negative symptoms, as assessed by PANSS, are observed in the hypomyelination cluster, remaining stable since the first visit and persisting across all four years of follow-up.

T265. HELPING AND IMPEDING FACTORS IN ACHIEVING PERSONAL RECOVERY 2 YEARS AFTER THE FIRST EPISODE OF PSYCHOSIS: A QUALITATIVE STUDY

Inge Heijden-Hobus^{*1}, Bram-Sieben Rosema², Manna Alma², Iris Sommer³, Nynke Boonstra⁴

¹*Janssen Cilag, Johnson and Johnson SIO*, ²*UMCG*, ³*University Medical Center Groningen, Department of Neuroscience and Department of Psychiatry*, ⁴*NHL Stenden University of Applied Science, Leeuwarden, the Netherlands/ University of Utrecht*

Background: Experiencing a first episode of psychosis (FEP) can be a distressing and life-altering event for individuals and their families. It is still widely assumed that schizophrenia is a chronic disease for which recovery is not possible.. However, the concept of recovery can be explained in different ways. A traditional focus in research and clinical care is clinical recovery (Wilken et al., 2006)., while people with lived experience usually focus on the concept of personal recovery. Other used concepts entail functional, occupational, and social recovery. Personal recovery in the context of first psychosis refers to the process through which individuals regain a sense of control, purpose, and meaning in their lives despite the challenges posed by their condition. It goes beyond symptom reduction and encompasses various aspects of an individual's well-being, including psychological, social, and emotional dimensions. Personal recovery emphasizes the importance of hope, self-determination, and empowerment for individuals to live fulfilling lives beyond the confines of their illness (van Eck et al., 2018). To date, little is known about the most important helping and/or hindering factors in a personal trajectory of recovery after a first episode of psychosis.

Methods: The current qualitative study used a descriptive, interpretative phenomenological approach to gain insight into the factors that helped or hindered individuals in their trajectory toward personal recovery. Interviews with participants who were 24 months in remission of a FEP were conducted by a female and a male researcher, the latter being an expert with lived experience.

Results: Thirty-one FEP patients who were in remission for 24 months were interviewed (mean age: [sd]; 16 male, 15 female). Of all participants, 19 had a paid job when 24 months in remission after their first psychosis. Working hours varied between 5 and 40 hours a week. Six main themes could be distinguished from the analyses of the transcripts of

interviews: balance, self-understanding, existential and fundamental conditions, support, prospect, and remaining symptoms. Sub-themes emerged within each theme. Having meaningful daily activities helped individuals to find their balance. These activities also acted as a fundament for existential conditions or the pursuit of prospect. Support came from significant others and professionals, the latter not always perceived as helping. Stigma or self-perceived stigma was a hindering factor in achieving personal recovery.

Discussion: The current study found six themes emerging out of qualitative interviews with individuals who were in 24 months after recovery of their first episode of psychosis. Participants were able to indicate which factors either helped or hindered them during their trajectory towards achieving personal recovery. Having meaningful activities emerged throughout all themes, which may be one of the main goals to act upon in clinical practice when helping individuals recover from their first episode of psychosis. More insight and research are needed to address the leverage points for addressing the right trajectory toward personal recovery. In rebuilding their lives again, personalized paths must be drawn.

T266. THE RELATION OF FORMAL THOUGHT DISORDER WITH SOCIAL COGNITION AND THEIR EFFECTS ON SOCIAL FUNCTIONING IN SCHIZOPHRENIA PATIENTS AND FIRST DEGREE RELATIVES

Özge Türkoğlu^{*1}, Hanife Avcı², A. Elif Anil Yagcioglu³

¹*Hacettepe University Faculty of Medicine*, ²*Hacettepe University*, ³*Hacettepe University Faculty of Medicine*

Background: Formal thought disorder (FTD) is considered to be one of the core symptoms of schizophrenia and a possible risk indicator as they are seen in milder forms in first-degree relatives of patients. Social cognition deficits in schizophrenia have been shown in many studies and its relation with other symptoms such as FTD is an important area of research. This study aims to determine FTD and social cognition deficits including theory of mind (ToM), emotion recognition and social knowledge in schizophrenia patients and their first degree relatives (siblings), to examine the relation between FTD and social cognition domains, to examine the effects of FTD and social cognition skills on social functioning and quality of life in patients.

Methods: Participants consisted of N=100 patients diagnosed with schizophrenia according to DSM-5, N=41 siblings of schizophrenia patients without psychiatric disorders, and N=60 healthy controls. The sociodemographic characteristics of all participants were noted in detail, as well as the clinical information of schizophrenia patients. All participants were administered the Turkish version of Thought and Language Disorder Scale (TALD), the Reading the Mind in the Eyes Test, the Hinting Task, the Facial Emotion Identification Test, the Facial Emotion Discrimination Test and the Situational Features Recognition Test-2 as social cognition tests, the Digit Span Test, the Verbal Fluency Test and the Auditory Consonant Trigram Test (ACT) for neurocognitive assessment, and the Personal and Social Performance Scale (PSP) to assess social functioning. Additionally, in schizophrenia patients, the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI) were administered to determine the severity of illness, and the Quality of Life Scale was administered to assess quality of life.

Results: The results of the study revealed that schizophrenia patients had higher scores in all domains of TALD (p LESS THAN 0.05) and significant impairments in all social cognition tests compared to controls (p LESS THAN 0.05), while siblings' group had only more positive FTD than controls (p LESS THAN 0.05), and did not differ from controls in terms of

social cognition skills. In schizophrenia patients, negative FTD was negatively correlated with ToM ($r(100) = -0.471$, $p < 0.001$) and emotion recognition ($r(100) = -0.329$, $p = 0.001$) among social cognition domains, whereas in healthy controls, the presence of symptoms related to negative FTD was negatively correlated with ToM ($r(60) = -0.368$, $p = 0.004$) and social knowledge performance which are SFRT-2 hit action recognition ($r(60) = -0.452$, $p < 0.001$) and SFRT-2 hit goal recognition scores ($r(60) = -0.437$, $p < 0.001$). In schizophrenia patients, negative FTD was found to be associated with lower social functioning ($r(100) = -0.447$, $p < 0.001$) and deterioration in quality of life ($r(100) = -0.513$, $p < 0.001$), whereas ToM skills were found to be associated with an increase in quality of life ($r(100) = 0.296$, $p = 0.003$). In schizophrenia patients, social functioning and quality of life were best predicted by negative FTD and social knowledge performance, whereas in healthy controls, social functioning was best predicted by symptoms related to negative FTD and ToM skills.

Discussion: The results of this study suggest that among FTD in schizophrenia patients, mainly negative FTD is associated with social cognition deficits, and negative FTD and social knowledge performance have substantial effects on social functioning and quality of life of schizophrenia patients. It is important to better understand negative FTD and negative symptoms in general and social cognition deficits in schizophrenia patients and to prioritize the development of treatment approaches targeting these areas in order to improve the social functioning and quality of life of patients.

T267. NEUROIMAGING BIOMARKERS OF ANTIPSYCHOTIC TREATMENT RESPONSE – A REVIEW OF THE LITERATURE, AND PRELIMINARY FINDINGS SURROUNDING THE UTILITY OF EEG ASSESSMENTS FOR TREATMENT STRATIFICATION

Magdalene de Rozario^{*1}, Emily Painter², Tahnee Bridson³, Sarah Herniman³, Andrew Thompson³, Ilvana Dzafic³, Stephen Wood³

¹University of Melbourne, ²Orygen, ³Orygen and Centre for Youth Mental Health, University of Melbourne

Background: Up to a third of patients with schizophrenia do not experience sufficient improvement of symptoms and functioning on their first two trials of antipsychotic medications. This is concerning as ineffective antipsychotic treatment early in psychotic illness can lead to exacerbations of psychotic symptoms that impair daily functioning – leading to worse long-term outcomes. Given the considerable burdens associated with psychosis, there is a clear need to identify successful treatments, earlier in the course of illness. Numerous efforts have been made to identify different biomarkers for predicting antipsychotic treatment responses for patients with psychotic disorders. However, there are no known published systematic reviews pulling available evidence on this topic together. This systematic review is currently in preparation, and aims to identify any previously studied neuroimaging biomarkers proposed to be potential predictors of antipsychotic treatment response in individuals presenting with First Episode Psychosis (FEP) or a psychotic disorder.

Methods: The study is being conducted in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of three electronic databases (MEDLINE, PsycINFO, and EMBASE) was conducted in May 2022. Data synthesis is currently in progress.

Results: Relevant data from selected studies has been extracted, and the narrative synthesis is currently underway to consolidate all available research on neuroimaging biomarkers that have potential to predict antipsychotic treatment response in individuals presenting with FEP or a psychotic disorder. The clinical utility of the different neuroimaging biomarkers in the prediction of antipsychotic treatment response will be discussed.

Discussion: Through identifying the most efficacious treatments as early into a patient's treatment as possible, clinicians can avoid the prescription of ineffective drugs and enable more rapid treatment responses. This can enhance patient welfare, while also bringing a considerable economy to the healthcare system.

T268. THETA-BURST RTMS IN SCHIZOPHRENIA TO AMELIORATE NEGATIVE AND COGNITIVE SYMPTOMS: A DOUBLE-BLIND, SHAM-CONTROLLED, RANDOMIZED CLINICAL TRIAL

Boglarka Orbán-Szigeti^{*1}, Karolin Suri², Kinga Farkas², János Réthelyi², Gábor Csukly²

¹*Semmelweis University*, ²*Semmelweis University*

Background: Schizophrenia, a prevalent mental disorder affecting around 1% of the global population, is characterized by significant challenges in social cognition and the presence of negative symptoms, such as blunted affect and emotional withdrawal. These factors substantially contribute to the psychosocial functioning deficits and long-term disability associated with schizophrenia. Both the state-like and trait-like aspects of social cognition are compromised in individuals with this condition. Traditional approaches to treatment, including antipsychotic medications and psychosocial interventions, have shown limited effectiveness in alleviating negative and cognitive symptoms in schizophrenia. While there is emerging clinical evidence suggesting that new therapeutic protocols based on theta-burst stimulation can significantly enhance the efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression, the available data on similar augmented therapies for schizophrenia remain scarce. The variability in network impairments among individuals may explain why some patients respond positively to specific stimulation sites while others do not.

Methods: In light of this, we propose an augmented theta-burst stimulation protocol for individuals with schizophrenia, targeting two regions associated with negative symptoms: the vermis of the cerebellum and the left Dorsolateral Prefrontal Cortex (DLPFC). We plan to randomize ninety participants with schizophrenia who exhibit negative symptoms, aged between 18 and 50 years, into two groups in a 1:1 ratio—active stimulation and sham stimulation. The TBS parameters we will employ adhere to standard TBS protocols, featuring 3-pulse bursts at 50 Hz, administered every 200 ms (at 5 Hz), with an intensity set at 100% of the active motor threshold. Over a four-week period, we intend to administer 1800 stimuli to the vermis and 1800 stimuli to the left DLPFC daily, split into two 9.5-minute sessions.

Results: The primary outcome measure will be the change in the severity of negative symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS). Secondary efficacy endpoints will encompass changes in cognitive flexibility, evaluated through the Wisconsin Card Sorting Test, as well as improvements in social cognition, measured by the 'Reading the Mind in the Eyes' test, facial emotion recognition, and the 'Faux pas' test. The safety assessment will focus on monitoring the occurrence of serious adverse events.

Discussion: In summary, the objective of our study is to establish the safety and effectiveness of theta-burst stimulation as a treatment modality for alleviating negative symptoms in schizophrenia.

T269. TRANSDIAGNOSTIC CHARACTERISTICS OF ANTICIPATORY AND CONSUMMATORY AFFECTIVE RESPONSES IN SCHIZOPHRENIA AND DEPRESSION SPECTRUM DISORDERS

Lei Shen^{*1}, Chi Xie¹, Yi Wang², Chao Yan³

¹East China Normal University, ²Institute of Psychology Chinese Academy of Sciences, ³Key Laboratory of Brain Functional Genomics (MOE and STCSM), Shanghai Changning-ECNU Mental Health Center, School of Psychology and Cognitive Science, East China Normal University

Background: Anhedonia is a multidimensional construct encompassing anticipatory and consummatory pleasure, and it manifests across a range of psychiatric disorders. However, the common and unique mechanisms that underlie these affective difficulties between schizophrenia and depression spectrum disorders remain unclear. This study aimed to apply the network approach to explore the characteristics and interplay between anticipatory and consummatory affective responses among individuals within the schizophrenia and depression spectrums.

Methods: A total of 762 participants were recruited, including a healthy control group (HC, $n = 394$), clinical patients comprising schizophrenia (SCZ, $n = 115$) and major depressive disorder (MDD, $n = 60$), as well as a subclinical group comprising individuals with schizotypal traits (ST, $n = 83$) and subclinical depression (SD, $n = 110$). All participants completed the Monetary Incentive Delay (MID) task, designed to investigate momentary affect during the anticipation and consumption of rewards. Partial correlation networks were constructed using anticipatory and consummatory affective responses, calculated by averaging the valence subjective rating scores as nodes. Separate network comparisons were conducted to examine differences in network structure, global strength, and edge weights within the schizophrenia and depression spectrum.

Results: The linear mixed-effects model on the valence ratings during the anticipatory and consummatory phases revealed that a consistent pattern of diminished affective responses in clinical patients (vs. HC), encompassing individuals with SCZ and MDD, in relation to both the anticipation and consumption of reward gain and loss. However, the subclinical individuals including SD and ST showed similar affective response characteristics to HC, but their negative affect significantly increased under reward loss conditions ($p = .007$). Network analysis indicated that the global strength of the network for anticipatory and consummatory affective responses in the subclinical group was significantly lower than that of clinical patients ($S = 1.509$, $p = .049$; $GS_{clinical} = 4.838$, $GS_{subclinical} = 3.329$) and HC ($S = 1.561$, $p = .013$; $GSHC = 4.890$, $GS_{subclinical} = 3.329$), suggesting a less consistent and more fluctuating pattern of response in the subclinical group. Within-spectrum comparisons further highlighted that the commonly impaired affective pattern was predominantly concentrated on a noticeable attenuation in pleasure to reward anticipation and outcome among the clinical SCZ and MDD. Moreover, the individuals within the depression spectrum displayed higher levels of negative affect in response to reward loss compared to those within the schizophrenia spectrum. Importantly, there were significant differences in the network structure of affective responses between the schizophrenia and depression spectrum ($M = 0.551$, $p = .0005$). In contrast to the depression spectrum, the schizophrenia spectrum demonstrated stronger connections in pleasurable affective responses during both reward anticipation and consumption (i.e., Anticipatory_Gain--Consummatory_Gain; $t = 0.304$, $p = .032$; edge weights: the schizophrenia spectrum = 0.658, the depression spectrum = 0.354).

Discussion: The present study unveiled common abnormal affective patterns in patients with schizophrenia and depression. Our findings suggested that the diminished interplay of affective response functions in subclinical individuals might serve as a risk factor for progressing to clinical levels of anhedonia. The inter-relationship between anticipatory and consummatory pleasure may elucidate distinct mechanisms underlying anhedonia in the schizophrenia and depression spectrum.

T270. ESTABLISHMENT OF A DIGITAL THERAPEUTIC ALLIANCE IN PATIENTS LIVING WITH NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Abhishek Pratap^{*1}, Cornelia Dorner-Ciossek², Cassandra Snipes³, Brendan D. Hare⁴, Olya Besedina³, Thomas Mick³, Eehwa Ung⁵, Alankar Gupta⁶, Shaheen E. Lakhan³

¹*Boehringer Ingelheim Pharmaceuticals, Inc.; King's College London; University of Washington*, ²*Boehringer Ingelheim International GmbH*, ³*Click Therapeutics, Inc.*, ⁴*Boehringer Ingelheim Pharmaceuticals, Inc.; Click Therapeutics, Inc. (at time of study)*, ⁵*University of California, San Francisco (UCSF); Click Therapeutics, Inc. (at time of study)*, ⁶*Click Therapeutics, Inc. (at time of study)*

Background: There are no approved pharmacotherapies for treating experiential negative symptoms (ENS) of schizophrenia. While treatment guidelines recommend psychosocial interventions for this population, access to these treatments is limited. Prescription digital therapeutics (PDTs), which are evidence-based digital therapeutics that receive regulatory authorisation and require a prescription for utilisation, may be able to deliver psychosocial interventions to people with schizophrenia. One of the critical success factors of face-to-face therapy is the effective establishment of a therapeutic alliance between the patient and healthcare professional. A similar bond established between a patient and PDT, which could be referred to as a digital working alliance (DWA), may also help to improve treatment outcomes. Two studies determined whether patients with moderate–severe ENS of schizophrenia could form and maintain an effective DWA with beta versions of CT-155. CT-155 is a PDT in development for the treatment of ENS of schizophrenia. Additionally, it was determined if the strength of the DWA varied by patient demographics or ENS symptom severity.

Methods: Two exploratory, single-arm, multi-centre studies lasting 3 (Study 1) or 7 (Study 2; NCT05486312) weeks included adults with schizophrenia and self-reported ENS. Patients were receiving stable antipsychotic medication for ≥ 12 weeks and had on-demand access to beta versions of CT-155. Patient demographics were captured at screening, and negative symptoms were evaluated using the Motivation and Pleasure Scale-Self-Report (MAP-SR) at screening and the clinician-administered Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP) at baseline. The overall strength of the DWA at Weeks 1 and 3 in Study 1 and at Week 3 in Study 2 was assessed using the mobile Agnew Relationship Measure (mARM); a score ≥ 5 represented a positive alliance. A post hoc analysis assessed correlations between the strength of the DWA (mARM scores) and patient age and ENS severity (MAP-SR and CAINS-MAP scores) using Spearman's correlation coefficients. mARM scores were compared across Race (Black or African American versus Other) using an F test.

Results: In Studies 1 (N=49) and 2 (N=50), patients had a median (range) age of 46 (18–64) and 53.5 (23–64) years and 71% and 80% of patients were male, respectively. The mean (standard deviation; SD) overall MAP-SR score at screening was 22.6 (6.8) in Study 1 and

14.9 (8.9) in Study 2. ENS were moderate–severe at baseline as determined by a mean (SD) overall CAINS-MAP score of 2.37 (0.76) in Study 1 and 2.28 (0.92) in Study 2. A positive DWA was established and maintained between patients and the PDT in Study 1 (mean [SD] mARM: 5.15 [0.74] at Week 1 and 5.16 [0.77] at Week 3). In Study 2, a positive DWA was observed at Week 3 (mean [SD] mARM: 5.36 [1.06]). In the post hoc analysis (Study 1: n=40, Study 2: n=45), there was no statistically significant correlation between mARM scores and either age (Study 1: $r=0.31$, $p=0.054$; Study 2: $r=0.15$, $p=0.32$), MAP-SR scores at screening (Study 2: $r=0.11$, $p=0.48$) or baseline CAINS-MAP scores (Study 1: $r=-0.16$, $p=0.36$; Study 2: $r=-0.13$, $p=0.41$). mARM scores were not significantly affected by Race (Study 1: F-test=1.193, $p=0.719$; Study 2: F-test=1.162, $p=0.747$).

Discussion: Establishing a positive DWA may be critical for the successful treatment of patients using a PDT. These early findings demonstrate that patients with moderate–severe ENS of schizophrenia were able to consistently establish a positive DWA with beta versions of CT-155, which overall, was not affected by age, race or negative symptom severity.

Funding: Boehringer Ingelheim and Click Therapeutics.

T271. CASE REPORT OF TREATMENT OF NEUROLEPTIC MALIGNANT SYNDROME IN CHILD AND ADOLESCENT

Moon Doo Kim^{*1}, Won-Myong Bahk², Bo-Hyun Yoon³, Kwanghun Lee⁴, Sang-Yeol Lee⁵, Young Jun Kwon⁶

¹*School of Medicine, Jeju National University*, ²*Yeouido St. Mary's Hospital, The Catholic University of Korea*, ³*Naju National Hospital*, ⁴*Dongguk University Hospital*, ⁵*Wonkwang University School of Medicine and Hospital*, ⁶*Soonchunhyang University*

Background: Neuroleptic Malignant Syndrome (NMS) is a rare clinical syndrome occurring due to idiosyncratic reaction after use of neuroleptics. Recently, the use of antipsychotics has been increasing in psychosis, mood disorder, and destructive behavior disorder in the field of child and adolescent psychiatry. We report a case of neuroleptic malignant syndrome in a patient with acute schizophrenia after treatment with antipsychotics.

Methods: Case Report.

Results: A 14-year-old male patient, diagnosed with schizophrenia in May of 2021, was admitted to the psychiatric closed ward due to worsening of psychotic symptoms on October of 2020. Pineal cystoma and pituitary microadenoma were detected incidentally on MRI conducted after hospitalization, and consultation with the department of pediatrics recommended close observation. Because 7 mg of risperidone monotherapy, initiated after hospitalization, caused akathisia, it was reduced to 6 mg. Even though akathisia subsided slightly, risperidone was combined alternatively with aripiprazole, ziprasidone, and quetiapine due to residual symptoms. Treatment effects were closely evaluated for more than 4 weeks while slowly increasing dosages. After treatment with 6mg of risperidone in combination with 300 mg of quetiapine, 80 mg of propranolol for prevention of akathisia, and 1.5 mg of benzodiazepine, psychotic symptoms and difficulties in communication improved enough to be discharged. However, while preparing for the discharge, the patient showed worsening of psychotic symptoms including auditory hallucination. Quetiapine was increased to 600 mg, and symptoms, when severe, were controlled with IM injection of 2.5 mg of haloperidol and 2 mg of lorazepam. Since March 25th of 2021, due to manifestation of

paralytic ileus from worsening of underlying constipation, all the oral medications were stopped along with NPO for treatment; in addition, IM injection of haloperidol was only allowed for the symptom control. Mental symptoms were worsened within 3 days after termination of oral medications while using IM injections of 10 mg of haloperidol and 8 mg of lorazepam per day. The day before the onset of neuroleptic malignant syndrome, IM injection of 15 mg of haloperidol and 10 mg of lorazepam resulted in vomiting, headache, fever of 39°C, systemic tremor and stiffness, confusion in consciousness, tachycardia and sweating. On April 1st of 2021, with suspicion of neuroleptic malignant syndrome, the patient was transferred to ICU at our institution. Blood work-up performed on day of admission at ICU indicated CPK 2836 IU/L and myoglobin 337.2 ng/ml, and CPK, after peaking at 4493 IU/L, continuously decreased and was normalized by the 18th day at ICU. Diazepam (IV), dantrolene, domperidone, L-Dopa/benserazide and cold blanket were applied because the patient continuously screamed due to fever, stiffness, tremor, and psychotic symptoms. Even though confusion improved after 3 days, nausea and vomiting persisted for 8 days. Tremor, stiffness, and fever were stabilized after 3 days, but aspiration pneumonia occurred on the 8th day and recovered on the 15th day at ICU. Tachycardia improved after 17 days. Recovery of hematologic abnormalities such as increased CPK and myoglobin and leukocytosis were followed by stabilization of tremor, stiffness, and high fever on the 18th day.

Discussion: Known risk factors of NMS are 1) male, 2) combination of more than two antipsychotic, 3) history of previous EPS symptoms or NMS, 4) psychiatric disorders such as severe agitation, mood disorder, or delirium, 5) recent initiation or increasing dose of antipsychotics, 6) IM injection of antipsychotics, 7) poor physical conditions like dehydration, infection, malnutrition, brain tumor, encephalitis, or AIDS, 8) use of zuclopenthixol acetate (clopixol acuphase), and 9) substance abuse. In this case, because the patient had 6 of the risk factors described above, which are biological vulnerabilities due to pineal cystoma and pituitary micro adenoma, dehydration and malnutrition caused by paralytic ileus, and sudden change in IM antipsychotics and dosage, it was critical to consider more carefully in medication injection and changes in dosage. Although the patient showed both fever and muscular stiffness, it is common not to present with both fever and muscular stiffness as required by diagnostic criteria of DSM-IV in child and adolescent NMS while using atypical antipsychotics. In addition, it is difficult to diagnose because atypical antipsychotics takes twice longer incubation time until the disease manifestation than typical antipsychotics. However, the increase in CPK, as shown in all cases of child and adolescent NMS, provides diagnostic specificity. Once diagnosed with NMS, immediate hydration and efforts to lower body temperature are critical to prevent complications like acute renal failure, and use of dantrolene, bromocriptine, and benzodiazepine is helpful in shortening the treatment period. In cases of NMS in patients who cannot terminate use of neuroleptics due to underlying mental disorders, ECT is an effective method to treat both NMS and mental disorders. Safety and efficacy of ECT have been already proven, and it is highly recommended when needed.

T272. SCHIZOMICS: A CIBER MULTIDISPLINARY DESIGN TO OPTIMIZE SCHIZOPHRENIA TREATMENT BASED ON MULTI-OMICS DATA AND SYSTEMS BIOLOGY ANALYSIS

Alba Toll^{*1}, Bianca Sanchez², Jordi Alonso³, Angel Carracedo⁴, Joaquin Dopazo Blazquez⁵, Juan Manuel Falcon Perez⁶, David Fraguas Herráez⁷, Maria Paz Garcia Portilla⁸, Clemente García Rizo⁹, Antonio Gil¹⁰, Eva Maria Grassa Bello¹¹, Ángela Ibáñez Cuadrado¹², Anna Mané¹³, Itziar Montalvo Aguirrezabala¹⁴, Jose Manuel Olivares Diez¹⁵, Josep Ribalta Vives¹⁶, Elena Rodriguez Cano¹⁷, Gemma Rojo Martínez¹⁸, Vanessa Sanchez Gistau¹⁹, Iñaki Zorrilla²⁰, Benedicto Crespo Facorro², Javier Labad²¹

¹*Institut de Neuropsiquiatria i Addiccions (INAD), Hospital del Mar*, ²*Hospital Virgen del Rocío*, ³*Institut Mar d'Investigacions Mèdiques*, ⁴*Universitat de Santiago de Compostela*, ⁵*Fundacion Progreso y Salud*, ⁶*CIC bioGUNE - Centro de Investigación Cooperativa en Biociencias*, ⁷*Hospital 12 de Octubre*, ⁸*Universidad de Oviedo*, ⁹*Hospital Clínic de Barcelona*, ¹⁰*Instituto de Biomedicina de Sevilla*, ¹¹*Hospital de la Santa Creu i Sant Pau*, ¹²*Hospital Ramón y Cajal*, ¹³*Institut de Neuropsiquiatria i Addiccions (INAD), Hospital del Mar, Barcelona*, ¹⁴*Parc Sanitari Parc Taulí*, ¹⁵*Hospital Álvaro Cunqueiro, Vigo*, ¹⁶*Universitat Rovira i Virgili, Tarragona*, ¹⁷*FIDMAG Germanes Hospitalàries Research Foundation*, ¹⁸*Instituto de Biomedicina de Málaga (IBIMA)*, ¹⁹*Hospital Universitario Institut Pere Mata*, ²⁰*Hospital Universitario Araba*, ²¹*Consorci Sanitari del Maresme*

Background: Schizophrenia is a severe and chronic mental disorder which onset typically occurs in late adolescence to young adulthood. The keystone of schizophrenia treatment is antipsychotic medications. Newer or second-generation antipsychotics (SGAs) widely used to treat psychosis may improve positive symptoms and are quite often associated to weight gain, metabolic changes and increased risk of cardiovascular diseases. Individual response and side effects profiles associated to these drugs are highly variable, and identifying the optimal treatment for any patient is often a trial and errors process that can span many years and even then, response is often poor. In this regard, the use of combined multi-omics approaches might constitute a diagnostic tool for personalizing the treatment since the first psychotic episode. To enable the implementation of mainstream precision medicine to improve the sightlessness traditional symptom-driven practice in schizophrenia treatment, allowing treatment selection or approach using predictive biomarkers of clinical response and toxicity to tailoring better-personalized treatments. We propose a multidisciplinary prospective study to deciphering the heterogeneity in clinical response and hepatic-metabolic side effects in schizophrenia. We rely on: (1) a carefully designed multicenter (11 CIBERSAM centers) prospective randomized clinical trial on first episode schizophrenia-spectrum individuals; and (2) a wide implementation of high-throughput technologies (omics) and systems biology approaches to elucidating biological mechanisms related to clinical response and appearance of metabolic side effects.

Methods: This project will be formed by five work packages (WP):

WP1: To set up a randomized open-label clinical trial to compare effectiveness and security of aripiprazole and paliperidone.

WP2: To collect and identify multiomics profiles in schizophrenia to characterize new mechanisms related to treatment response and thus, clustering a priori individuals with higher or lower like hood of respond to specific antipsychotics.

WP3: To phenotyping the effect of antipsychotics on blood glycemic, lipidic and hepatic outcomes at 1 year to characterize molecular mechanisms related to clinical and side effects outcomes at medium term.

WP4: Using bioinformatic and computational techniques for delivering highly relevant models of personalized treatment response and side effects.

WP5: Project Management and Organization.

Results: Understanding patient's biological heterogeneity at baseline in conjunction with thorough prospective clinical data will significantly lead to determining predisposition and predictive biomarkers and pathways eventually providing optimal and personalized care for schizophrenia individuals. We hypothesize that multi-omics data and systems biology analysis will permit clustering schizophrenia individuals and tailoring the most beneficial therapeutic option for each person at the right time.

Discussion: SchizOMICS assembles a team with a breadth of interdisciplinary excellence in the clinical milieu of schizophrenia and hepatic, glycemic and lipidic diseases, as well as in high-throughput omic approaches to analyze biological samples and integrating these multi-dimensional omics data into biologically meaningful context challenging.

The application of data-driven systems biology and machine learning approaches could provide a predictive understanding of schizophrenia treatment response, and pave the way to the development of novel biomarkers and rational design of schizophrenia therapeutics.

T273. A LONGITUDINAL ASSESSMENT OF GYRIFICATION PATTERNS AND SULCAL MORPHOLOGY IN ADOLESCENTS AT FAMILIAL RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Simon Poortman^{*1}, Louise ten Harmsen van der Beek¹, Jakub Jamárik², Nikita Setiaman¹, Manon Hillegers¹, Neeltje Van Haren¹

¹Erasmus MC, ²Erasmus MC, Masaryk University

Background: Early diagnosis and intervention are essential for managing and improving long-term outcomes of severe mental illness, highlighting the need for reliable early biomarkers. This longitudinal study explores cortical folding development in offspring of parents with schizophrenia or bipolar disorder (SZo and BDo, respectively). Cortical gyrification, the remodeling of brain surface morphology to create sulci and gyri and thereby expanding the cortical surface area, has emerged as a promising endophenotypic marker for psychosis and risk of SZ and BD. The gyrification index (GI), which is the ratio of the pial and outer hull perimeters from structural T1-weighted magnetic resonance imaging (MRI) images, can be used to quantify this marker and has been shown to be a more stable marker of neurodevelopment than gray matter volume-based measures. Other measures that are of interest are sulcal length, depth, and width which have not yet been investigated in offspring at familial high-risk for schizophrenia or bipolar disorder.

Methods: We obtained 286 T1-weighted MRI scans of 184 offspring (aged 8–18 years at baseline) of at least one parent diagnosed with bipolar disorder (n=78) or schizophrenia (n=52) and offspring of parents without severe mental illness (n=54); 102 offspring underwent a follow-up scan (on average 3.9 years between scans). Local Gyrification Index (LGI; FreeSurfer) and sulcal morphological measures (i.e., sulcal depth, length, and width; BrainVisa) were computed and analyzed using linear mixed-effects models. To correct for multiple comparisons, we applied a Benjamini-Hochberg false discovery rate (FDR) correction (q=0.05).

Results: At baseline, no significant differences in LGI and sulcal depth, length, and width were found. A significant effect of age on both LGI and sulcal measurements was found, with decreasing LGI, sulcal depth and length and increasing sulcal width. The effect of age on LGI and sulcal trajectories was not significantly different in SZo and BDo as compared to control offspring, nor between SZo and BDo.

Discussion: This research emphasizes that cortical folding is not static but rather evolves over time. The decrease in IGI potentially reflects synaptic pruning during adolescence, where unnecessary neural connections are eliminated. We found no indication for aberrant age-related brain developmental changes in cortical folding that could precede the onset of schizophrenia or bipolar disorder.

T274. ASSOCIATIONS BETWEEN SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (SUPAR) CONCENTRATION AND PSYCHIATRIC DISORDERS – A SYSTEMATIC REVIEW AND META-ANALYSIS

Jennifer Murphy^{*1}, Anna Zierotin², David Mongan³, Colm Healy², Subash Raj Susai¹, Brian O'Donoghue², Mary Clarke², Karen O'Connor⁴, Mary Cannon¹, David Cotter¹

¹Royal College of Surgeons in Ireland, ²University College Dublin, Ireland, ³Queen's University Belfast, United Kingdom, ⁴University College Cork, Ireland

Background: There is some evidence that suggests that inflammation is associated with the pathogenesis of psychiatric disorders. Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker of chronic inflammation, which is thought to provide a more stable index of systemic inflammation than more widely used biomarkers. This review aims to synthesise studies that measured suPAR concentrations in individuals with a psychiatric disorder, to determine if these concentrations are altered in comparison to healthy participants.

Methods: Comprehensive literature searches from inception to June 2023 were conducted of five relevant databases (PubMed, Web of Science, Embase, Scopus and APA PsychInfo). Random-effects meta-analyses were performed to compare the standardised mean difference of suPAR levels for individuals with any psychiatric disorder relative to controls. Separate meta-analyses of suPAR levels were conducted for individuals with schizophrenia or other psychotic disorder and depressive disorder. Risk of bias was assessed using the Newcastle Ottawa Scale. Post-hoc sensitivity analyses included excluding studies at high risk of bias, and analyses of studies that measured suPAR concentrations in serum or plasma separately.

Results: The literature search identified 115 records. Eleven full-text studies were screened for eligibility and 9 studies were included for review. No significant difference was observed in suPAR levels between individuals with any psychiatric disorder compared to controls (SMD = 0.42, 95% CI [-0.20, 1.04]). However, those with depressive disorder had elevated suPAR levels relative to controls (SMD = 0.61, 95% CI [0.34, 0.87]). Similarly, there was no evidence of a significant difference in suPAR levels in individuals with any psychiatric disorder when studies at high risk of bias were excluded, but elevated suPAR concentrations for those with schizophrenia or other psychotic disorder were found (SMD = 0.98, 95% CI [0.39, 1.58]). Furthermore, studies that analysed plasma suPAR concentrations found elevated plasma suPAR levels in individuals with any psychiatric disorder relative to controls (SMD = 0.84, 95% CI [0.38, 1.29]), while studies measuring serum suPAR levels in any psychiatric disorder did not find a difference (SMD = -0.61, 95% CI [-1.27, 0.04]). For plasma, elevated suPAR concentrations were also identified for those with schizophrenia or other psychotic disorder (SMD = 0.98, 95% CI [0.39, 1.58]).

Discussion: When studies measuring either serum or plasma suPAR were considered, no significant difference in suPAR levels were observed between psychiatric disorder groups, although significantly elevated suPAR levels were detected in those with moderate to severe depressive disorder. However, plasma suPAR levels were significantly elevated in those with any psychiatric disorder relative to controls, while no difference in serum samples was found.

A similar finding was reported for schizophrenia or other psychotic disorder. The findings suggest that suPAR could represent a plasma transdiagnostic marker for these disorders and support the hypothesis that chronic inflammatory dysregulation contributes to the pathology of schizophrenia and depressive disorder. Future longitudinal studies are required to fully elucidate the role of this marker in the psychopathology of these disorders.

T275. FIRST EPISODE PSYCHOSES IN OVER-35 YEARS OLD: UNCOVERING POTENTIAL ACTIONABLE TARGETS FOR EARLY INTERVENTION SERVICES

Maria Ferrara*¹, Ilaria Domenicano¹, Aurora Marchi¹, Lorenzo Benini², Cristina Sorio², Elisabetta Gentili³, Martino Belvederi Murri¹, Spyridon Zotos², Franca Emanuelli², Luigi Grassi¹

¹*Institute of Psychiatry, University of Ferrara*, ²*Integrated Department of Mental Health and Pathological Addictions*, ³*Department of Engineering, University of Ferrara*,

Background: Early Intervention in Psychosis programs (EIS) have been historically designed around the care needs of young individuals. Since 2012, Ferrara (Italy) has successfully implemented an EIS dedicated to FEP and individuals at risk for psychosis, between the age of 15 and 35 years old. However, it has been shown that a significant group of individuals, especially women, have their onset later in life, but are excluded from EIS based on their age. The aim of this study is to compare the sociodemographic and clinical characteristics of patients who had their FEP treatment earlier than 35 years old with those of individuals who had theirs later, in order to uncover actionable clinical targets for a potentially vulnerable group of FEP individuals.

Methods: In this retrospective study individuals, aged 18-65, with a primary diagnosis of affective and non-affective, non-organic FEP, were identified in the FEPSY dataset, which includes data on who had access to community psychiatric services in Ferrara province since 1991, selecting only those who were admitted between 2012 and 2021. Patients were compared for sociodemographic, clinical, and pathway-to-care characteristics based on their age of access (under-35 and over-35) with bivariate analysis. Chi-squared tests and t-tests were performed to compare categorical variables and normally distributed variables, respectively. Mann-Whitney tests were used to analyze skewed continuous variables.

Results: A total of 854 individuals were identified, most of whom were over 35 years old (61.8%). Compared to the under-35 group, the over-35s were significantly more represented by women (55.7% vs 32.5%, $p < 0.01$), married (27.8% vs 6.1%, $p < 0.01$), living with their own family (28.8% vs 10.4%, $p < 0.01$), more frequently diagnosed with affective psychoses (21.6% vs 13.5%, $p < 0.01$) and delusion disorders (22.2% vs 19.0%, $p < 0.01$). Compared to the under-35 group, a lower proportion of those over-35 were hospitalized (47.2% vs 63.5%, $p < 0.01$). Antipsychotics were the psychotropic category most frequently prescribed in both groups, while the long-acting formulation (LAI) was less frequently prescribed in the over-35s (6.3% vs 9.0%, $p=0.36$). Antidepressants were more prescribed in the over-35s (15.3% vs 8.0%, $p < 0.01$). In the under-35s, affective psychosis was twice as frequent in women compared to men (22.6% vs 9.1%, $p < 0.01$). In both age groups, women were less frequently prescribed LAI compared to men (1.7% vs 12.3% in under-35s, $p=0.04$; 3.7% vs 10.0% in over-35s, $p=0.07$).

Discussion: This study confirmed that there is indeed a significant segment of the older population suffering from FEP and this vulnerable group mainly includes women. These

findings support the need to expand the age criteria for extant EIS, to reorient the clinical service offered to accommodate older people's care needs, and more specifically to tailor such services for women with FEP.

T276. THE ASSOCIATION BETWEEN EXECUTIVE FUNCTIONING AND SOCIETAL RECOVERY IN PEOPLE WITH A PSYCHOTIC DISORDER

Ruth Rietveld^{*1}, Bernice van Aken¹, Andre Wierdsma¹, Yolande (Y) Voskes², Marieke Pijnenborg³, Jaap van Weeghel⁴, Niels Mulder⁵

¹Erasmus MC, ²Amsterdam UMC/GGz Breburg, ³University Groningen, ⁴Phrenos/Tilburg University, ⁵Erasmus MC/Parnassia Groep

Background: Societal recovery (SR) is one of the most valued forms of recovery in people with psychotic disorders. Often, people with psychotic disorders report wanting to go back to work, study, or wanting to participate in society differently, like being a friend, brother or sister. However, very few clients succeed in taking on the roles they value. It is known that these clients often experience severe cognitive impairments, especially in the executive functions. These functions are important for how we interact with the world. Therefore, it is thought that these executive functions - might play a key role in SR.

Methods: This study is cross-sectional, and part of a cohort of 323 people with a psychotic disorder (the UP'S study). SR was measured using the World Health Organization - Disability Assessment Schedule 2.0 (WHO-DAS). This was divided into two subscales: the Daily Functioning (DF) scale and the Social Functioning (SF) scale. FR was measured using the Behavior Rating Inventory of Executive Functioning Adult version (BRIEF-A) and the Tower of London (TOL). Employment status was divided in 'Not active', 'Otherwise active' (e.g. volunteer work) and 'Active'. Model selection was based on the Wald-test.

Results: 323 participants with a mean age of 41,5 years are part of the UP'S cohort study. The mean disability score on DF was 30.3, whereas the mean SF disability score was 43.2. The BRIEF-A showed to have an effect on both the DF (= 5.1) and SF (= 5.1), whereas the TOL only had an effect on the DF (= -1.8). Furthermore, for employment status only being 'Otherwise active' had an influence on DF (= -4.5). There was no influence of employment status on SF.

Discussion: There is an important difference between self-reported and performance-based measured executive functioning in relation to Daily and Social Functioning. Furthermore, being 'Otherwise active', i.e., being a volunteer or looking for a job, has a positive influence on perceived disabilities in Daily Functioning.

T277. UNVEILING THE NRN1 GENE EPIGENETIC-EXPRESSION BRAIN CORRELATES IN SCHIZOPHRENIA

Carmen Almodóvar-Payá^{*1}, Marcos Moreno², Mariona Latorre-Guardia³, Edith Pomarol-Clotet³, Luis F. Callado⁴, Carme Gallego², Mar Fatjó-Vilas⁵

¹FIDMAG Research Foundation, Barcelona; CIBERSAM (Biomedical Research Network in Mental Health); Faculty of Biology, University of Barcelona (UB), ²Molecular Biology Institute of Barcelona (IBMB-CSIC), ³FIDMAG Research Foundation, CIBERSAM (Biomedical Research Network in Mental Health), ⁴Department of Pharmacology, University

of the Basque Country (UPV/EHU), CIBERSAM (Biomedical Research Network in Mental Health), ⁵FIDMAG Research Foundation, CIBERSAM (Biomedical Research Network in Mental Health), Department of Evolutionary Biology, Ecology and Environmental Sciences (BEECA), Faculty of Biology, University of Barcelona (UB),

Background: Schizophrenia (SZ) is characterised by neuroanatomical and synaptic plasticity alterations (Berdens et al., 2020; Keshavan et al., 2020). The *Neuritin1* gene (*NRN1*) has emerged as a pivotal gene central to these processes. Firstly, *NRN1* is associated with SZ susceptibility and cognitive performance (Fatjó-Vilas et al. 2016; Chandler et al. 2010). Secondly, *NRN1* ranks among the most differentially methylated genes in the prefrontal cortex when comparing patients and controls (Pidsley et al. 2014). Lastly, its expression exhibits sensitivity to neurotherapeutic agents (Dyrving et al. 2014; Alme et al. 2007). Our goal was to provide a comprehensive understanding of the interplay between methylation and gene expression within the *NRN1* locus. In post-mortem brain samples, we aimed to compare the methylation and mRNA levels between patients diagnosed with SZ and healthy controls and to analyse the correlation between *NRN1* methylation and expression patterns.

Methods: We used post-mortem brain tissue samples, both from the prefrontal cortex and the hippocampus. The samples came from 30 healthy subjects (HS) and 20 subjects with schizophrenia (SZ). Patients were classified based on the presence of clozapine (SZ-Clz) or the absence of antipsychotic drugs (SZ-Free) in their bloodstream at the time of death. The obtained molecular data included i) *NRN1* mRNA expression using qRT-PCR, and ii) methylation levels across the three previously identified differentially methylated islands between HS and SZ using EpiTYPER™ methodology. The statistical analyses comprised i) assessing expression level differences between groups using ANOVA, ii) examining methylation differences through Partial Least Square Discriminant Analysis (PLS-DA; R package “mixOmics”), and iii) exploring the correlation between expression and methylation components. All analyses were adjusted by sex, age, post-mortem delay, and samples' ph.

Results: *NRN1* expression was altered in patients with SZ, specifically those treated with clozapine, with a significant decrease in mRNA levels in both the prefrontal cortex and hippocampus. The PLS-DA analyses revealed that *NRN1* methylation, whether in the prefrontal or hippocampal regions, did not distinguish between HS and SZ-Free. Nevertheless, the hippocampal *NRN1* methylation effectively stratified between HS and SZ-Clz and correlated with hippocampal *NRN1* mRNA levels.

Discussion: These findings provide evidence that both *NRN1* expression and epigenetic changes are associated with SZ, especially in patients treated with clozapine. In addition, the observed correlation between epigenetic and mRNA profiles in the hippocampus suggests *NRN1*'s potential role as a molecular effector of this antipsychotic drug, deepening our understanding of the underlying mechanisms. Our results add to existing animal models detailing *NRN1* expression and epigenetic modifications post-antipsychotic treatment (Dyrvig et al. 2014; Park et al. 2014), emphasizing its pivotal role in the response to such pharmacological intervention.

Acknowledgements: i) Fundació Alicia Koplowitz; ii) Acadèmia de les Ciències Mèdiques i de la Salut de Catalunya i de Balears (predoctoral contract to CA-P); iii) Instituto de Salud Carlos III through the contract to M Fatjó-Vilas (CP20/00072), co-funded by European Regional Development Fund (ERDF)/European Social Fund "Investing in your future"; iv) AGAUR- 2021SGR1475.

T278. GLUTAMATE AND GABA-RELATED ANTERIOR CINGULATE CONNECTIVITY IN SCHIZOPHRENIA: ASSOCIATION WITH SYMPTOM DOMAINS

Jonas Persson*¹, Simon Cervenka², Linda Steinholtz², Jan Weis³, Robert Bodén²

¹*Uppsala University*, ²*Department of Medical Sciences, Psychiatry, Uppsala University*,

³*Department of Surgical Sciences, Radiology, Uppsala University*

Background: Both glutamate and gamma-aminobutyric acid (GABA) are implicated in the pathophysiology of schizophrenia. Previous studies have shown associations between altered levels of these neurotransmitters and prefrontal functional connectivity patterns in patients with schizophrenia, but less is known of how these effects relate to major symptom domains of the disorder.

Methods: Patients with longterm schizophrenia (n=27) and healthy controls (n=34) underwent resting-state functional magnetic resonance imaging (fMRI) and 1H Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) to measure glutamate and GABA levels within the anterior cingulate cortex (ACC). Positive, negative, and affective symptoms were measured with the Brief Psychiatric Rating Scale (BPRS). Seed-based connectivity was used to assess group differences in voxel-wise whole-brain ACC-connectivity and its relationship to GABA and glutamate. Summary measures from these analyses were in turn correlated to the three symptom domains.

Results: Glutamate, but not GABA, was reduced in patients compared to controls. A voxel-wise group comparison revealed reduced connectivity in patients compared to controls encompassing the ACC and bilateral insula. Overall, ACC glutamate levels were positively associated with ACC-connectivity to left insula, thalamus, midbrain, and left cerebellum. When correlating the average connectivity within this glutamate-related network to symptoms in patients, a significant relationship was found with negative symptoms only ($r=.45$, $p=.018$).

Discussion: The results are consistent with reduced prefrontal glutamate levels leading to reduced connectivity among salience processing regions, in turn contributing to negative symptoms in patients with schizophrenia. These findings add to our mechanistic understanding of this debilitating set of symptoms.

T279. THE DEVELOPMENT AND VALIDATION OF A MEDICINES OPTIMISATION TOOL TO PROTECT THE PHYSICAL HEALTH OF PEOPLE WITH SEVERE MENTAL ILLNESS (OPTIMISE)

Aoife Carolan*¹, Dolores Keating¹, Stephen McWilliams¹, Caroline Hynes¹, Mary O'Neill², Fiona Boland³, Sharon Holland⁴, Judith Strawbridge³, Cristin Ryan⁵

¹*Saint John of God Hospital Ltd.*, ²*Tallaght University Hospital*, ³*Royal College of Surgeons in Ireland*, ⁴*Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne*,

⁵*Trinity College Dublin*

Background: The life expectancy of people with Severe Mental Illness (SMI) is shorter than those without SMI, with multimorbidity and poorer physical health contributing to health inequality. Screening tools could potentially assist the optimisation of medicines to protect the physical health of people with SMI. The aim of our research was to design and validate a

medicines optimisation tool (OPTIMISE) to help clinicians to improve physical health in people with SMI.

Methods: A review of existing published guidelines, PubMed and Medline was carried out. Literature was examined for medicines optimisation recommendations and also for reference to the management of physical illness in people with mental illness. Potential indicators were grouped according to physiological system. A multidisciplinary team with expertise in mental health and the development of screening tools agreed that 83 indicators should be included in the first draft of OPTIMISE. The Delphi consensus technique was used to develop and validate the contents. A 17-member multidisciplinary panel of experts from the UK and Ireland completed 2 rounds of Delphi consensus, rating their level of agreement to 83 prescribing indicators using a 5-point Likert scale. Indicators were accepted for inclusion in the OPTIMISE tool after achieving median score of 1 or 2, where 1 indicated strongly agree and 2 indicated agree, and 75th centile value of ≤ 2 . Interrater reliability was assessed among 4 clinicians across 20 datasets and the chance corrected level of agreement (kappa) was calculated. The kappa statistic was interpreted as poor if 0.2 or less, fair if 0.21-0.4, moderate if 0.41-0.6, substantial if 0.61-0.8, and good if 0.81-1.0.

Results: Consensus was achieved after 2 rounds of Delphi for 62 prescribing indicators where 53 indicators were accepted after round 1 and a further 9 indicators were accepted after round 2. Interrater reliability (IRR) of OPTIMISE between physicians and pharmacists indicated a substantial level of agreement with a kappa statistic (κ) of 0.75.

Discussion: OPTIMISE is a 62 indicator medicines optimisation tool, developed using Delphi consensus methodology, to assist decision making in those treating adults with SMI. IRR of OPTIMISE is substantial with an overall level of agreement (κ) of 0.75. This means that when physicians and pharmacists have access to the same medical information relating to people with SMI, they reliably achieve a substantial level of agreement when applying the various indicators within the tool. Validation of other medicines optimisation demonstrated similar levels of agreement in IRR studies. A high level of IRR improves the utilisation and reliability of OPTIMISE among different healthcare professionals in clinical settings. OPTIMISE has the potential to improve medicines optimisation by ensuring preventative medicines are considered when clinically indicated. Further research including wider validation and implementation of OPTIMISE is required to demonstrate its true benefit.

T280. SAFETY DATA OF ICLEPERTIN (BI 425809) FROM PHASE 1 HEALTHY VOLUNTEERS AND PHASE 2 PATIENTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

Fredrik Gruenenfelder¹, Peter Nagy*¹, Yury Shatillo², Michael Desch², Eric Fu³, Corey Reuteman-Fowler³

¹Boehringer Ingelheim International GmbH, ²Boehringer Ingelheim Pharma GmbH and Co. KG, ³Boehringer Ingelheim Pharmaceuticals, Inc.

Background: Iclepertin (BI 425809) is a potent and selective inhibitor of GlyT1 in Phase 3 clinical development for cognitive impairment associated with schizophrenia (CIAS). The Phase 1 development so far includes 330 healthy volunteers (HV, 278 on iclepertin; 52 on placebo). In Phase 2, 709 patients with CIAS were treated (438 on iclepertin; 271 placebo).

Methods: This is a descriptive abstract and no methodology was used/required.

Results: In Phase 1, 162 HV on iclepertin (58.3%) and 17 on placebo (32.7%) participants reported any adverse events (AEs) across all the dosing, 2 (0.7%) were severe in intensity and

14 (26.9%) were defined drug-related by the investigator. 5 (1.9%) AEs lead to treatment discontinuation, and 5 (1.9%) AEs were significant according to ICH E3. No AE of special interest (AESI) and serious AE (SAE) were reported. The most common Preferred terms in HVs compared to placebo were headache (50 [18%] vs 5 [9.6%]), Dizziness (28 [10.1%] vs 3 [5.8%]), Nasopharyngitis (15 [5.4%] vs 3 [5.8%]), Back Pain (15 [5.4%] vs 2 [3.8%]), Nausea [23 (8.3%) vs 1 [1.9%]]; Fatigue [18 (6.5%) vs 3 [5.8%]], Vomiting [15 (5.4%) vs 1 [1.9%]]. No Suicidal ideation or behavior was reported. No notable decrease in hemoglobin or hematocrit compared to placebo treatment was observed.

In Phase II, 204 (46.6%) patients with CIAS on iclepertin versus 131 (48.3%) on placebo reported any AEs. 10 (2.3%) treated participants versus 3 (1.1%) placebo-controlled patients had AEs of severe intensity and 76 (17.4 %) versus 50 (18.5%) were defined drug-related by the investigator. 14 (3.2%) versus 8 (3.0%) patients discontinued treatment due to an AE, and 11 (2.5%) versus 7 (2.6%) AEs were significant according to ICH E3. One (0.2%) AESI occurred on iclepertin versus 0 on placebo. 13 (3.0%) vs 6 (2.2%) SAEs have been reported. The most common Preferred terms were Headache [40 (9.1%) vs 20 (7.4%)], Somnolence [17 (3.9%) vs 7 (2.6%)], Dizziness [17 (3.9%) vs 6 (2.2%)] and Nasopharyngitis [29 (6.6%) vs 14 (5.2%)]. The SAE Schizophrenia was reported in 2 (0.5%) patients on iclepertin and 1 (0.4%) patient on placebo. Suicidal ideation was reported in 1 (0.2%) patient on iclepertin and 3 (1.1%) patients in the placebo group.

Discussion: Iclepertin was well tolerated by both HVs and CIAS patients. No dose-dependent trends were observed for the overall number of AEs. The well-known class effect, hemoglobin decrease, showed dose-dependency in one of the phase II trials in CIAS patients, however none of the changes were considered to be clinically relevant. No meaningful changes were observed in the analyzed ocular safety parameters compared to placebo treatment.

T281. MOTIVATIONAL INTERVIEWING FOR ACUTE PSYCHOSIS: A FEASIBILITY STUDY

Rahel Horisberger*¹, Janani Panchalingam¹, Claudio Corda¹, Nicolas Kleisner¹, Achim Burrer¹, Tobias Spiller¹, Erich Seifritz¹, Philipp Homan¹

¹*University Hospital of Psychiatry/University of Zurich*

Background: While guidelines recommend combining pharmacological therapy with psychotherapeutic methods already during the acute phase of schizophrenia spectrum disorders, few therapeutic interventions are available. In addition, low therapeutic adherence and resistance to treatment altogether are common obstacles during the acute phase. Motivational interviewing, a directive, client-centered counseling style for eliciting behavior change, is well suited to address these challenges. Here, we conducted a pilot study in acutely ill individuals with schizophrenia spectrum disorders to test the feasibility and effectiveness of Motivational Interviewing. We hypothesized that Motivational Interviewing is a feasible intervention in acutely ill individuals with schizophrenia spectrum disorders.

Methods: The primary objective was to investigate the impact of a brief intervention with Motivational Interviewing in an acute psychiatric inpatient setting on factors that impact treatment outcome including therapeutic alliance, changes in symptom severity, adherence to treatment, motivation for further psychotherapy and others. Inpatients with a diagnosis of

psychosis, aged between 18 and 65 years, were randomized to receive four sessions of Motivational interviewing (treatment condition) or four sessions of supportive counseling (control condition) in a single-blinded, within-therapist, parallel-group design. Speech was recorded during the sessions.

Results: Within a year, thirty-four participants were included of which 23 completed the whole study (11 in the treatment group, 12 in the control group), clearly demonstrating the feasibility of the study. While we did not formally test for statistical significance due to the pilot design, the raw data showed that therapists rated therapeutic adherence as improved in both conditions. Similarly, we saw a reduction in positive symptoms in both conditions.

Discussion: This study demonstrated the feasibility of Motivational Interviewing for acutely ill individuals with schizophrenia spectrum disorders. The study also showed that therapeutic alliance as well as psychotic symptoms improved but this awaits formal testing in a prospective clinical trial.

T282. THE PROCESSING OF FACIAL EXPRESSIONS USING MOVEMENT KINEMATICS IN SCHIZOPHRENIA PATIENTS – AN FMRI STUDY

Anastasia Pavlidou^{*1}, Evin Demir², Sofie von Känel², Sophie Sowden³, Jennifer Cook³, Sebastian Walther²

¹University of Bern, University Hospital of Psychiatry and Psychotherapy, Translation Research Centre, ²University of Bern, University Hospital of Psychiatry and Psychotherapy, Translation Research Centre, Bern, Switzerland, ³Centre for Human Brain Health, School of Psychology, University of Birmingham

Background: Understanding and recognizing facial expressions is crucial for successful social interactions. While schizophrenia patients often exhibit deficits during the recognition of different facial expressions, most stimuli used are either pictures or videos of different faces that lack ecological validity, and require the processing of multiple cues at once. In recent years, movement kinematics which refers to the detailed analysis of the speed, coordination and timing of the facial muscles involved in conveying emotions, have become an integral part in understanding the complexities of how facial muscles contribute to the recognition of various facial expressions. To this end, the current study utilized movement kinematics of facial expressions together with functional Magnetic Resonance Imaging to compare the neural correlates involved during the recognition of these facial expressions between schizophrenia patients and healthy controls.

Methods: We included 11 schizophrenia patients and 13 healthy controls matched for age and gender and measured their BOLD responses during the visual processing of the movement kinematics of four different facial expressions (angry, happy, sad and neutral) across multiple trials. Each trial started with a fixation cross (3-6 seconds), followed by a facial expression stimulus (~5 seconds), after which participants were asked to rate how 'angry/happy/sad' each stimulus was using a 1 (not angry/happy/sad) – 5 (very angry/happy/sad) Likert scale. Thus, each stimulus was rated three times; once for how angry the participants thought the stimulus appeared, once for how happy, and once for how sad. Group effects for the facial expression vs rest contrast were tested using between sample t-tests separately for each emotion (angry, happy, sad and neutral) and the results were corrected for multiple comparisons (pFDR LESS THAN 0.05). Brain images were acquired using a 3T Siemens Prisma scanner.

Results: Between group analyses revealed higher BOLD activation in schizophrenia patients' vs healthy controls during the processing of angry, happy and sad facial expressions in bilateral anterior cingulate gyrus, superior frontal gyrus, precuneus, as well as right angular gyrus. In contrast, healthy controls exhibited higher BOLD activation during the processing of happy and sad facial expressions in bilateral inferior/middle frontal gyrus, as well as, right anterior insula, supramarginal gyrus and supplementary motor area. We observed no group differences for the neutral facial expressions.

Discussion: Our results suggest that schizophrenia patients and healthy controls recruit different neural areas during the processing of the movement kinematics of different facial expressions. These differences might be crucial in unraveling the complexities of emotional processing impairments in schizophrenia patients and can help in developing novel targeted interventions that can improve their emotional processing. We expect greater differences as more participants are included in the study.

T283. IMMUNOMODULATORY EFFECTS OF PSYCHOTROPIC AGENTS: BETA DEFENSIN 2 LEVEL ASSOCIATED WITH ANTIPSYCHOTICS USE

Monica B. E. G. Ormerod^{*1}, Mashhood A. Sheikh², Thor Ueland³, Gabriela Hjell⁴, Linn Sofie Sæther³, Synve Hoffart Lunding³, Ingrid Torp Johansen³, Linn Rødevand³, Torill Ueland³, Trine V. Lagerberg³, Ingrid Melle³, Srdjan Djurovic⁵, Ole A. Andreassen³, Nils Eiel Steen⁶

¹Section for Precision Psychiatry, Oslo University Hospital, ²NORMENT, Centre, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway, ³Oslo University Hospital, University of Oslo, ⁴Oslo University Hospital, University of Oslo, Østfold Hospital, ⁵Oslo University Hospital, University of Oslo, University of Bergen, ⁶Oslo University Hospital, University of Oslo and Diakonhjemmet Hospital

Background: Immunomodulatory effects of psychotropic agents used to treat severe mental disorders (SMDs) have been suggested. This includes effects of antipsychotics (AP) on pro- and anti-inflammatory cytokines and markers of immune activation, as well as immunomodulatory effects of antidepressants (AD) and mood stabilizers (MS). However, findings are inconsistent and there is a need for well-adjusted studies. In the current cross-sectional study, we investigated the immunomodulatory effects of psychotropic agent use and dosage in a large sample of individuals with SMDs, applying comprehensive adjustments for potential confounders.

Methods: Participants with SMDs [N = 852, including schizophrenia spectrum (N = 588), and bipolar disorders (N = 264)] were included from the major hospitals in Oslo, Norway. We also recruited a healthy control group (HC, N=645) from the same catchment area for comparison of immune marker levels. We analyzed a panel of forty-four immune markers with use and dosage of AP, AD and MS using linear regressions with adjustments for age, sex, body-mass index (BMI), C-reactive protein (CRP), diagnosis and the Positive and Negative Syndrome Scale (PANSS) score. P-values LESS THAN 0.001 were considered significant. Participants with CRP GREATER THAN 10.0 were excluded to prevent impact from acute infections on immune marker levels.

Results: Plasma levels of human beta defensin 2 (BD-2) was positively associated ($\beta = 0.19$, p LESS THAN 0.001) with AP use in the fully adjusted model, while a similar positive trend was observed for soluble tumor necrosis factor receptor 1A (sTNF-R1) ($\beta = 0.07$, $p = 0.004$), and between MS use and sIL-2R ($\beta = 0.11$, $p = 0.004$). There were no other significant

associations between immune marker levels and psychotropic agent use, and no significant associations with psychotropic agent dose.

Discussion: The study revealed that antipsychotic agent use was associated with increased levels of BD-2. Beta defensins have broad innate immune functions including antimicrobial effects but may be immunomodulating and act as a chemoattractant for TNF activated neutrophils which could enhance disruption of blood-brain barrier function. The current results suggest that studying the effects of antipsychotics on release of beta-defensins from relevant cells and effects on neutrophils could be relevant in SMD. Lack of significant dose-dependent associations and the cross-sectional design are limitations to our findings. Identifying effects on specific immune factors might potentially help improve antipsychotic treatment strategies in SMDs.

T284. SUBSTANCE USE AND PSYCHOTIC-LIKE EXPERIENCES IN ADOLESCENCE DURING THE COVID PANDEMIC: A POPULATION BASED CROSS-SECTIONAL STUDY OF ADOLESCENTS IN IRELAND

Ronan Fleury^{*1}, Lorna Staines², Jessica Ohland³, Emmet Power³, Colm Healy⁴, Mary Cannon⁵

¹Royal College of Surgeons in Ireland, ²Royal College of Surgeons in Ireland, Department of Health Psychology, ³Royal College of Surgeons in Ireland, Department of Psychiatry, ⁴University College Dublin, School of Medicine, ⁵Royal College of Surgeons in Ireland, Department of Psychiatry,

Background: Evidence has shown adolescence as a developmentally sensitive period, characterised by biopsychosocial changes. Given this sensitivity, adolescence can be vulnerable to maladaptive behaviours, including substance use, with the potential to cause mental health concerns e.g., psychotic like experiences (PLE). This study aimed to investigate the association between substance use and PLE in Irish youth during this time period. We secondarily examined gender differences in the association.

Methods: This cross-sectional study is based on the 2021 Irish Planet Youth Programme. This school-based survey incorporated North Dublin, Cavan, and Monaghan, and included 40 schools, targeting 15–16-year-olds. The outcome of interest is PLEs, measured using the Adolescent Psychotic Symptom Screener (APSS). This self-reported seven-item tool assesses several PLEs e.g., hallucinations, grandiosity, and delusions. For the purposes of this analysis we used both a continuous score and a binary measure whereby PLE was defined as APSS score GREATER THAN 2. Primary exposure variables included cannabis use, alcohol use, and smoking within the past 30 days. Covariates included gender, rural vs urban living and ethnicity. Analysis using STATA included descriptives, mean differences and binary logistic regressions (BLR).

Results: The sample size was 4,404, with males accounting for 51%, females 44% and gender-diverse 4.5%. 7.5% (n=302) reported using cannabis, 35.4% (n=1433) reported drinking alcohol, and 12.3% (n=514) reported smoking tobacco. We found a significant mean difference in APSS scores between cannabis (N=282) and non-cannabis users (N=3,536), ($\chi^2(1) = 16.2$, $p = 0.0001$); between alcohol (N=1,330) and non-alcohol users (N=2,435), ($\chi^2(1) = 16.2$, $p = 0.0001$) and between smokers (N=470) vs non-smokers (N=3,421) ($\chi^2(1) = 58.01$, $p = 0.0001$). We found an increased risk of PLE as a categorical variable (i.e., score of GREATER THAN 2 on APSS) among cannabis users vs non users of cannabis (OR=2.36, 95% CI [1.85,3.02] and this effects remained significant following adjustment for covariates

(aOR=2.31, 95% CI [1.80,2.96]). Male users had an increased adjusted odds of PLE compared to male controls (aOR=2.15, 95% CI [1.51,3.05]). Likewise, female cannabis users had an increased adjusted odds compared to controls (aOR=2.58 95% CI [1.76,3.78]). Gender-diverse individuals using cannabis had an increased adjusted odds (aOR=2.8 95% CI [0.76,10.31]) compared to non-cannabis using controls. We found a significant association between PLE and alcohol use (OR=2.33, 95% CI [1.15,3.54]) which remained significant following adjustment (aOR=1.57, 95% CI [1.35,1.82]). Male alcohol users had an increased adjusted odds of PLE compared to non-alcohol using control males (aOR=1.43, 95% CI [1.14,1.8]). Female alcohol users had an increased adjusted odds compared to female controls (aOR=1.63 95% CI [1.31,2.03]). Gender-diverse individuals had an increased adjusted odds compared to controls (aOR=1.74 95% CI [0.84-3.61]). There was a significant association between PLE and smoking (OR=1.95, 95%CI [1.56,2.32]) which remained significant following adjustment (aOR=1.57, 95%CI[1.35,1.82]). Male users had an increased adjusted odds of PLE compared to male controls (aOR=2, 95% CI [1.46,2.76]). Female smokers had an increased adjusted odds compared to female controls (aOR= 1.9 95% CI [1.43,2.5]). Gender-diverse had an increased adjusted odds compared to controls (aOR=2.89 95% CI [0.99,8.45]). The interaction between all three substances reported an increased adjusted odds ratio of PLE (aOR=3.7, 95% CI[2.6,5.2], relative to those to who use none of the substances.

Discussion: These results highlight a significant association between all three substances explored and PLE. Cannabis is associated with the largest increased odds of PLE in comparison to alcohol and smoking. This effect did not markedly differ by gender. This survey was carried out during the pandemic. Covid-19 posed a series of new challenges to young people, such as increased isolation and lack of social services. In Ireland, schools were closed for 6-months, with two additional lockdowns for 8-months restricting access to sports, clubs, and after school activities. Within this context, the rates of substance use increased substantially within this age group in Ireland. These results have highlighted the need for further monitoring of mental health effects of the pandemic on youth. It would also be important to monitor the persistence of PLE in these young people and the associations with other mental health problems. This research was funded by the Health Research Board (Ireland).

T285. DO NEGATIVE SYMPTOMS CAUSE COGNITIVE IMPAIRMENTS, OR DO COGNITIVE IMPAIRMENTS CAUSE NEGATIVE SYMPTOMS: CAUSAL INFERENCE OF THE RELATIONSHIP BETWEEN NEGATIVE SYMPTOMS AND COGNITION OVER TIME

Christy Au-Yeung^{*1}, Keita Christophe¹, Martin Lepage²

¹*McGill University*, ²*McGill University, Douglas Mental Health University Institute*

Background: Both negative symptoms (NS) and cognitive impairments, notably verbal memory, are key predictors of functioning and remain a crucial therapeutic need. They appear during illness prodrome, highlighting their relevance to the etiology. In addition, cross-sectional and longitudinal links between NS and cognition have been firmly established, suggesting a common underlying foundation. Given their clinical significance, there have been separate advances in their treatment, including psychological treatments like cognitive remediation and pharmacotherapies for NS. However, enhancing treatment planning and development necessitates elucidating the directionality and potential causal links in their relationship, which are currently understudied and inconclusive.

Conflicting evidence for the directionality of the relationship has been demonstrated, with some suggesting poorer cognition leads to more severe NS, while others suggest that more severe deficits in NS lead to cognitive impairments. These studies primarily rely on mediation models which have been criticized for their inability to detect robust causal mediators, instead being contingent on assumed causal models. The current study seeks to overcome past methodological limits to understand which symptom predicts and potentially causes the other, within the first two years of psychosis onset, using a cross-lagged panel model design.

Methods: The Recovery After an Initial Schizophrenia Episode Early Treatment Program Data collected between 2010-2017, held in the NIMH Data Archive was used. In the study, those experiencing their first episode of psychosis received one of two early treatment interventions. The current analysis focuses on a subset of the population aged 20+, as there exist reliable cognitive norm scores in this age group (N=338). Participants had a mean age at baseline of 24.6 (SD= 4.9) and were 73% males to females. Assessments of cognition (BACS, Verbal Memory) and NS (PANSS) were conducted at baseline, 12 and 24 months. A nested random-intercept autoregressive cross-lagged panel design was used to examine whether NS predict future cognitive abilities, and/or whether cognitive abilities predict future NS levels. The model with the best fit was selected using chi-square differences test.

Results: In the best fitting model, it was observed that all paths from baseline to 12 months and from 12 months to 24 months were equal ($\chi^2(df) = 22.638(9)$, CFI = 0.96, RMSEA= 0.067). Cognition, assessed by verbal memory, significantly predicted future NS ($\beta = -0.77$, $p = 0.000$). Specifically, decreases in cognitive abilities predicted greater NS severity. On the other hand, the relationship that NS had in predicting future NS was non-significant ($\beta = -0.02$, $p = 0.78$). Cognition significantly predicted future cognition ($\beta = 0.63$, $p = 0.000$), such that better cognition at baseline predicts improved cognition at future timepoints. NS did not significantly predict cognition ($\beta = -0.018$, $p = 0.071$).

Discussion: This study employs a novel method enabling causal inference, revealing that cognition predicts future NS within two years of psychosis onset. These findings support the neurocognitive model of schizophrenia, which posits that cognitive deficits primarily contribute to the development of the disorder. In addition, these findings have implications on treatment development, for instance in the development of NS treatments that leverage cognitive approaches. Findings that NS do not predict future NS severity add to the literature highlighting the lack of stability in NS during early stages of psychosis. In summary, these findings further our understanding of these core dimensions of schizophrenia and in better understanding of symptoms in early stages of psychosis.

T286. THE EFFECT OF ADVERSE CHILDHOOD EXPERIENCES AND DIFFERENT TYPES OF BULLYING ON ATTENUATED PSYCHOTIC SYMPTOMS IN YOUNG ADULTS

Donncha Hanna^{*1}, Callum Urquhart², Ciaran Shannon³

¹Queens University Belfast, ²Queens University, ³IMPACT Research Centre, Northern Health and Social Care Trust

Background: Associations have been found between Adverse Childhood Experiences (ACEs) and attenuated psychotic symptoms (APS). However there is a lack of consensus on the potential relationships between traditional bullying (indirect, physical and verbal) or

cyber bullying and APS. This study explored the relationship between traditional forms of bullying and cyberbullying on APS when controlling ACEs.

Methods: 1528 adults (18-35) completed a range of measures including the Adverse Childhood Experience Questionnaire, Retrospective Bullying Questionnaire and Prodromal Questionnaire (PQ16) through Amazon's online crowdsourcing service Mechanical Turk (MTurk). Hierarchical multiple regression models explored the effects of demographics, ACEs, traditional bullying and cyberbullying on APS as measured by the PQ16.

Results: Responses on the PQ16 indicated that 84.1% of the sample experienced at least one APS, while 28.4% experienced 6 or more items which may be suggestive of at At Risk Mental State (ARMS). Participants reported experiencing high levels of verbal bullying, especially in Middle/High School (75.5%), and lower levels of cyber bullying (2.2-16.5%). The final regression model, which included ACEs and all forms of bullying explained 15% of variance in relation to the number of items endorsed on the PQ16. Traditional forms of bullying made a unique contribution of 4.6% to the regression model which increased by 0.6% when cyberbullying was included.

Discussion: The presence of bullying during childhood significantly contributes to the prediction of the presence of APS, even when other adverse childhood experiences are controlled for; in addition, cyberbullying has been shown to make a very small but significant contribution to APS, over and above more traditional forms of bullying.

T287. THE ASSOCIATION OF STIGMA AND RESILIENCE WITH TREATMENT DELAY IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA

Nataliia Maronchuk^{*1}, Kie Takahashi², Yuya Mizuno³, Jean Paul⁴, Fabienne Post⁴, Timo Schurr⁴, Ellen Rubinstein⁵, Hiroyuki Uchida², Alex Hofer⁴

¹Medical University Innsbruck, Department of Psychiatry and Psychotherapy, ²Keio University School of Medicine, ³Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁴Medical University of Innsbruck, ⁵North Dakota State University

Background: Schizophrenia affects approximately 0.7% of the world population and is associated with considerable morbidity as well as a 3- to 4-fold increased risk of death in contrast to the general population. A promising strategy for mitigating the negative consequences of this disorder is to encourage early help-seeking and the use of medical resources. Knowledge of the factors contributing to treatment delay among individuals diagnosed with schizophrenia is currently limited. By identifying treatment barriers, such as internalized stigma or a low degree of resilience, measures can be taken to reduce the burden of untreated illness and improve treatment outcomes. This can be achieved through shortening the duration of untreated illness (DUI).

Methods: In this ongoing study, stigma and resilience are assessed by means of the Social Impact Scale (SIS) and the Resilience Scale for Adults (RSA), respectively. In addition, various demographic and clinical data are collected.

Results: So far, 20 individuals have been included into the study. Preliminary findings indicate that there is no significant association between DUI and stigma ($r=0.187$, $p=0.443$). Additionally, the degree of resilience failed to demonstrate a significant correlation with DUI ($r=-0.080$, $p=0.744$). Accordingly, we did not find any evidence for an association between stigma, resilience, and DUI in individuals living with schizophrenia. However, a significant negative correlation was observed between resilience and stigma ($r=-0.504$, $p=.028$),

indicating that higher levels of resilience are associated with a lower perception of stigmatization.

Discussion: These preliminary results have to be seen with caution as a larger sample size is clearly needed to get insight into patients' outlooks and encounters in seeking help for mental health issues. Further research into the relationship between DUI, stigmatization, resilience, perceived quality of life, religiosity, and social engagement may be crucial for public health interventions aiming to mitigate the impact of mental disorders and reduce the global burden of schizophrenia.

T288. BEHAVIORAL ASSESSMENT OF COGNITIVE MODELS OF SCHIZOPHRENIA USING NOVEL MOUSE CANTAB-LIKE TEST BATTERY

Konstantin Andrianov*¹, Jenan Azaizah¹, Inna Gaisler-Salomon¹

¹*University of Haifa*

Background: Cognition is among the first domains to be affected in schizophrenia, and can predict the onset of psychosis. Measuring cognitive changes in schizophrenia is a complex process, which often involves a battery of multiple tests, where individual performance is compared to the average performance of the healthy population. Animal models are often used to probe into mechanisms of cognitive dysfunction. However, animal models of cognitive dysfunction in schizophrenia and other disorders usually focus on a single cognitive domain using a limited number of cognitive assays. In addition, behavioral analysis is performed at the group level without reference to individual variability.

Methods: In the present study, we designed a battery of cognitive tests equivalent to the schizophrenia relevant human CANTAB battery. This battery included multiple relevant assays per animal such as learning, memory, social behavior tests, problem solving and extra dimensional set shifting. To assess the relevance of the battery to schizophrenia research, we tested glutamate dehydrogenase (Glud1)-deficient mice, previously shown to mimic schizophrenia-like phenotypes (Lander et al. 2019). The performance of each animal in each assay was compared to the average performance of a control group, and the classification of animals into levels of cognitive vulnerability was based on abnormal performance in several assays. Animals were categorized into three groups: High-, Average- or Low-cognitive performers.

Results: We found an unequal distribution of cognitive performance in the different genotypes tested.

Discussion: This indicates that the novel mouse CANTAB-like battery may be a useful tool for the assessment of cognitive abnormalities in schizophrenia.

T289. IMPORTANCE OF CHILDHOOD TRAUMA IN SUICIDAL BEHAVIOR IN FIRST-EPISODE PSYCHOSIS

Regina Vila-Badia*¹, Alicia Colomer-Salvans¹, Clara Serra-Arumí¹, Anna Butjosa², Núria Del Cacho¹, Helena Escobedo-Pareras¹, Judith Usall¹

¹*Parc Sanitari Sant Joan de Déu*, ²*Hospital Sant Joan de Déu*

Background: Suicidal behavior and childhood trauma are two relevant variables in individuals experiencing a first-episode psychosis (FEP) and should be considered during

treatment. However, the majority of studies have examined these variables separately. Therefore, our goals were to investigate the prevalence of suicidal behaviors and childhood trauma, as well as to examine the impact of childhood trauma on suicidal risk controlling for covariates of interest.

Methods: This research was part of a longitudinal observational study called 'PROFEP Group' in Catalonia. The patients belong to Mental Health Parc Sanitari Sant Joan de Déu and Hospital Germans Trias i Pujol (for adults) and Hospital Sant Joan de Déu (for children and adolescents) health care sector. 129 participants with FEP (39♀; 90♂) were included. The Childhood Traumatic Questionnaire (CTQ), which is divided into emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect subscales, was used to evaluate childhood trauma and the Plutchik suicide risk scale was used to assess suicide ideation, suicide attempts and suicide risk. The statistical analysis was conducted using frequencies, the Mann-Whitney U test, and linear regression models controlling for the following variables: THC consumption, perceived stress, and psychotic and depressive symptoms.

Results: Patients with FEP reported 51.2% experiencing suicidal ideation, 17.8% having made suicide attempts, and 45.7% being at suicidal risk. Regarding childhood trauma, 53.5% reported some form of CT; specifically, 16.3% reported sexual abuse, 30.2% emotional abuse, 11.6% physical abuse, 17.1% emotional neglect, and 20.2% physical neglect. Finally, after controlling for covariates, greater levels of emotional abuse, increased perceived stress, more symptoms of depression, and higher THC consumption were predictive variables for elevated scores of suicide risk.

Discussion: There was a higher prevalence of suicidal behavior and childhood trauma in FEP patients, and the relationship between these two variables, especially with emotional abuse, was evident. For this reason, it is important to consider both variables in the evaluation and treatment to improve the prognosis, quality of life, and well-being of these patients.

T290. BIO-COMPARABILITY OF LONG-ACTING ORAL WEEKLY RISPERIDONE LYN-005 TO DAILY RISPERIDONE (STARLYNG-1 STUDY)

Nayana Nagaraj¹, Anna Legedza², Elan Cohen³, David P. Walling⁴, Richard Scranton^{*2}
¹Lyndra Therapeutics Inc., ²Lyndra Therapeutics, ³CenExel Hassman Research Institute, ⁴CNS Network, LLC

Background: LYN-005 is a long acting, once weekly formulation of risperidone that aims to reduce the pill burden and improve treatment adherence in individuals with schizophrenia and schizoaffective disorders. The LYN-005 capsule consists of 6 polymeric arms that are connected to a flexible core and encapsulated as a folded star shaped formulation. The coated drug arms ensure a sustained release of the drug over the course of the week. In the pivotal STARLYNG-1 study, the pharmacokinetics of the 15 and 45mg doses were compared to the 2mg and 6mg once daily Risperdal.

Methods: In this open label, parallel group study, clinically stable participants with schizophrenia or schizoaffective disorder on a stable dose of antipsychotic drug were eligible to participate in the study. Participants received a total daily 2mg or 6mg (as 1mg twice daily / 2mg once daily or 3mg twice daily / 6mg once daily doses) Risperdal based on the participants' current antipsychotic dose. Following a run-in with daily Risperdal for 7 days, participants received 5 doses of once weekly (OW) LYN-005. In addition to LYN-005, participants also received half dose of the IR run-in as supplemental in week 1. Primary

endpoints included comparison of C_{min}, C_{max} and C_{avg} of LYN-005 at week 5 to that of Risperdal on the last day of run-in (Day -1). Secondary endpoints included change in PANSS from baseline to week 5 and treatment emergent adverse events (TEAEs) from week 1 to week 5. A total of 90 completers were planned for the study, with an interim analysis (IA) after 46 subjects completed the final PK visit. The IA allowed for the study to be either stopped for success or continued with sample size re-estimation. Pharmacokinetic parameters were calculated using non-compartment analysis.

Results: Approximately 83 subjects were enrolled in the study with 47 subjects completing the study. Dropout rate in Risperdal (n=16 over 1 week) and LYN-005 (n=18 over 5 weeks) periods were similar. Following LYN-005 administration, sustained release of risperidone was noted across all 5 doses. At the IA, GMR (90% CI) of C_{min} [1.02 (0.86, 1.22)], C_{max} [0.84 (0.77, 0.92)], and C_{avg} [1.03 (0.94, 1.15)] met the prespecified primary endpoint criteria of C_{min} (90% CI >0.8), C_{max} (90% CI <1.25), and C_{avg} (90% CI between 0.8-1.4). No notable change was observed in the positive and negative symptom scale (PANSS) scores from baseline to week 5.

LYN-005 was generally safe and well tolerated. Most common TEAEs were in the gastrointestinal (GI) system organ class, majority of which were mild (75%) and transient. GI AEs longer than 3 days included dyspepsia, GERD, and constipation. The incidence of GI AEs on LYN-005 decreased week over week. Two serious AEs (esophagitis and worsening of psychosis) were reported in the study with participants having recovered fully shortly thereafter.

Discussion: The study demonstrated bio-comparability of LYN-005 at 2 dose levels (15mg and 45mg) to Risperdal (2mg and 6mg respectively) with drug concentrations maintained above the therapeutic threshold across the dosing period and well below the peak concentrations of immediate release Risperdal. Both high and low doses were well tolerated. The new oral weekly risperidone LYN-005 formulation has the potential to reduce pill burden, as well as improve medication compliance and quality of life in individuals with schizophrenia or schizoaffective disorder.

T291. Brilaroxazine Phase 3 Recover Trial in Acute Schizophrenia Supports Efficacy, Safety, and Effects on Neuroinflammation

Laxminarayan Bhat^{*1}, Seema Bhat², Arulprakash Ramakrishnan², Wasim Khan², Amardeep Neburi², Simeen Khan²

¹Reviva Pharmaceuticals Holdings Inc, ²Reviva Pharmaceuticals Holdings Inc.

Background: Brilaroxazine, a serotonin-dopamine signaling modulator, displays partial agonist activity at D₂/3/4 and 5-HT_{1A}/2A receptors and antagonist activity at 5-HT_{2B}/7 receptors with binding affinity for 5-HT_{2B} > D₂. It also reduces proinflammatory cytokines, an underlying disease driver. Phase 1 studies in healthy volunteers and stable schizophrenia patients have established its safety and pharmacokinetic profile. Phase 2 investigation has confirmed efficacy and safety in acute schizophrenia or schizoaffective disorders. This experience set the foundation for the pivotal Phase 3 RECOVER trial to investigate brilaroxazine's safety and efficacy and explore its effects on neuroinflammation and sexual dysfunction.

Methods: This study involved a randomized, double-blind, placebo-controlled, multicenter design. It evaluated brilaroxazine (15 mg or 50 mg daily) in acute schizophrenia patients (N=411) for 28 days. Brilaroxazine 15 mg and 50 mg and placebo administered were in 140, 134, and 137 patients, respectively. PANSS total score vs. placebo, baseline to Day 28, was

the primary endpoint. Positive and negative symptoms, PANSS social cognition, excitement/agitation, personal and social performance (PSP), and clinical global impression severity (CGI-S) were secondary endpoints. Changes in Sexual Function Questionnaire (CSFQ) examined the effect on disease-related dysfunction. Analysis of neurotrophin BDNF and inflammatory cytokines (IL-6, IL-8, MCP-1, MIP-1beta) explored brilaroxazine's effects in mediating neuroinflammation.

Results: Brilaroxazine 50 mg produced a 10.1-point greater reduction vs. placebo (-23.9 vs. -13.8, $p < 0.001$) for the primary study endpoint, PANSS total score. It also resulted in significant and clinically meaningful Positive ($p < 0.001$), Negative ($p = 0.003$), and Negative Marder Symptoms ($p = 0.002$); PANSS Social Cognition ($p < 0.001$) and Excitement/Agitation ($p < 0.001$); PSP ($p < 0.001$); and CGI-S ($p < 0.001$), compared with placebo. The 15 mg dose was numerically superior for all endpoints and significant for social cognition ($p = 0.024$) and PSP ($p = 0.022$) vs. placebo. Treatment-emergent adverse events (TEAEs) rates for brilaroxazine 15 mg, 50 mg, and placebo were 34.5%, 35.5%, and 30%, and discontinuation rates were 19%, 16%, and 22%, respectively. The most frequent TEAEs included headache $< 6\%$ and somnolence $< 7.5\%$. Adverse events of special interests (AESIs) included weight gain $< 5.9\%$ and 2.1% with 50 and 15 mg doses, and akathisia and extrapyramidal symptoms $< 1\%$ with the 50 mg dose. Prolactin levels decreased in both doses, and thyroid hormone changes mirrored placebo. Brilaroxazine improved BDNF levels, decreased proinflammatory cytokines IL-6, IL-8, MCP-1, and MIP-1beta, and enhanced sexual function ($P < 0.05$) in females versus placebo.

Discussion: Brilaroxazine achieved significant efficacy at 50 mg and activity at 15 mg vs. placebo for multiple symptom domains in acute schizophrenia. Both doses were well tolerated. Improvement in inflammatory cytokine biomarker levels vs. placebo offers insight into this agent's effect on mitigating neuroinflammation, a contributing pathology to schizophrenia. Enhancement of sexual function (e.g., desirability) represents another significant finding that may relate to negative symptom improvement. These findings highlight that brilaroxazine appears to be a novel addition to the treatment armamentarium for schizophrenia and suggests potential application to other schizoaffective disorders.

T292. RL-007, A NOVEL ORAL NEUROMODULATOR BEING DEVELOPED TO TREAT COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA – A NON-CLINICAL AND CLINICAL OVERVIEW

Sarah McEwen^{*1}, Matt Pando¹, Gary Walker¹, Srinivas Rao², John Donello¹
¹*Recogify Life Sciences*, ²*atai Life Sciences*

Background: Schizophrenia is a severe mental illness and considered a complex polygenic and multifactorial disorder, involving abnormalities in neurotransmission, including the GABAergic and cholinergic synaptic pathways. Cognitive impairment associated with schizophrenia (CIAS), arising from aberrant neuromodulation, is observed in approximately 80% of schizophrenia patients and viewed as having the strongest influence on everyday functioning. These cognitive deficits are a critical target for new treatment development, as there are currently no approved therapies for CIAS. This will be the first presentation of the novel oral neuromodulator, RL-007, to provide the scientific and clinical evidence of RL-007 to potentially become a first in class therapy to improve cognition in schizophrenia patients.

Methods: Data will be summarized from preclinical studies of RL-007 that have explored the role GABAergic and cholinergic neuromodulation play in the compound's unique pharmacology. Data will be presented from a translational model of cognitive

impairment (scopolamine challenge) that was used to test the pro-cognitive effects in a series of animal and human studies. Safety and tolerability data will be summarized from over 500 participants from 10 clinical trials who have been administered RL-007. Lastly, we will present data from clinical trials that measured cognitive performance, including a Phase 2 pilot study conducted in CIAS.

Results: RL-007 enhances GABAergic signaling and hippocampal synaptic plasticity (long-term potentiation, LTP), via GABAB receptor dependent neuromodulation. RL-007 also acts synergistically with acetylcholine to enhance cholinergic signaling. RL-007 was found to be safe and well-tolerated, including in a CIAS population, and without typically observed GABAergic or cholinergic side effects. RL-007 reverses scopolamine-induced learning and memory deficits across species. Clinical studies of RL-007 found improved cognitive performance, specifically for verbal learning and memory and processing speed. Additionally, a correlation between cognitive performance and functional outcome was observed.

Discussion: RL-007 has shown a unique pharmacological profile that could assist in restoring neurotransmission abnormalities in CIAS, including GABAB modulating properties and enhanced cholinergic pathway activity through excitatory signaling. RL-007 is a safe and well-tolerated compound in humans and does not produce sedating or parasympathetic side effects. Furthermore, we have found consistent evidence for improving cognition in non-clinical and clinical studies, specifically learning and memory abilities, making RL-007 a promising compound to potentially treat CIAS. A Phase 2, placebo-controlled clinical trial in CIAS is currently underway to explore the cognitive and functional benefits of RL-007.

T293. Glutamate Modulation by Evenamide as an Add-On to TRS Patients Not Responding to Their Current Antipsychotics is Associated With Clinically Important Improvement Across Outcome Measures: Results From 1-Year, Open-Label Trial

Ravi Anand*¹, Alessio Turolla², Giovanni Chinellato³, Francesca Sansi², Arjun Roy⁴, Richard Hartman⁵

¹Anand Pharma Consulting, ²Newron Pharmaceuticals SpA, ³Newron pharmaceuticals, ⁴CliniRx, ⁵NeurWrite LLC

Background: The management of schizophrenia with 1st/2nd generation antipsychotics has led to >30% of the patients becoming treatment resistant schizophrenics (TRS). Preclinical, neurometabolic and mechanistic studies suggest that TRS is associated with excess glutamatergic [Moghaddam et al 2012], but normal dopaminergic transmission: this may explain why 5HT2/D2 blockers are ineffective in TRS. Studies in rodents, primates, and humans have demonstrated that the use of glutamate antagonists is suggestive of benefit in patients with schizophrenia. [Demjaha et al 2014]

In vivo microdialysis studies in rats demonstrated that evenamide was devoid of any effect on basal glutamate levels but attenuated the excessive glutamate release. Evenamide, a NCE, structurally unrelated to any existing/in development AP is highly selective for sodium channels, not interacting with any other CNS receptors, neurotransmitters, enzymes, or transporter. Animal studies indicated the efficacy of evenamide in ameliorating behavioral disturbances induced by dopamine/cholinergic/glutamatergic antagonists. [Bortolato et al 2018]

A pilot, placebo controlled study in patients with schizophrenia inadequately responding to aripiprazole/risperidone provided a statistically significant signal of efficacy on PANSS positive and CGI-C further supporting its benefits in TRS patients. [Anand et al 2018]

Methods: The tolerability and the long term benefits of glutamate modulation by evenamide was assessed in study 014/015, a phase 2, multinational, randomized trial with an initial 6 week, followed by 46 week extension phase with evenamide administered at 3 fixed doses (7.5, 15, 30 mg bid) as an add on treatment in patients with TRS not responding to their current AP.

Patients on a stable dose of an AP, who met criteria for TRS [Howes et al 2017], with PANSS total ≥ 70 and predominant positive symptoms (score of 4 or more on ≥ 2 core symptoms and a PANSS positive total score ≥ 20), a CGI-S rating from 4 to 6 (moderately to severely ill) were enrolled.

Efficacy, assessed by a trained psychiatrist blinded to treatment, was based on PANSS, CGI-S/C, and functioning (LOF) ratings. Changes from baseline and categorical analyses within each dose group were analyzed for the PANSS and CGI S/C using a paired t-test.

Results: 161 patients with TRS (males= 69%; mean age= 37.7 year; mean duration of illness= 6.8 year; baseline PANSS= 79.4; CGI-S= 4.5) were randomized, of whom 153 completed 6 weeks of treatment, and 144 of these patients continued into 46 week extension with 85% of them completing 1 year of treatment. [Anand et al 2023]

At week 6, the PANSS mean change from baseline was -11.9% improving to -20% at 1 year. The proportion of patients with a clinically meaningful improvement in symptoms (PANSS $\geq 20\%$ [Meltzer et al 2008; Rosenheck et al 1997]) doubled from 6 week (15.4%) to 6 month (34.0%) and increased further at 1 year (41.8%) with the vast majority (~90%) of the patients who met this level of improvement preserving their response at 1 year. In addition, ~30% of patients improved by at least 2 categories in disease severity (CGI-S), and 45% were rated at least 'much improved' (CGI-C).

The high completion rate, the low number of patients with treatment related adverse events (9.4%), discontinuation for adverse events (1.9%), and the absence of psychotic relapses, confirmed the good tolerability of evenamide.

Discussion: These results indicate a unique pattern of gradual, but sustained efficacy across all efficacy measures up to 1 year at all doses, supporting the role of glutamate release inhibition in the therapy of TRS. These encouraging results support the hypothesis that patients with TRS may have excess glutamatergic transmission that would respond to glutamate but not 5HT₂/D₂ modulation.

T294. CLINICAL DEVELOPMENT OF EMRACLIDINE FOR PSYCHOSIS IN SCHIZOPHRENIA AND ALZHEIMER'S DISEASE

Erica Koenig^{*1}, Matthew Leoni¹, Ih Chang¹, Koji Takahashi¹, Zheng Ren¹, Meera Tugnait¹,
Lillian Frohlich¹, Raymond Sanchez¹

¹Cerevel Therapeutics, LLC

Background: Emraclidine is a novel, highly selective, positive allosteric modulator of M4 muscarinic acetylcholine receptors (mAChRs), the activation of which may reduce psychotic symptoms by reducing excess dopamine signaling in the striatum. Recent data confirm target engagement of emraclidine in healthy adults (~60% M4 receptor occupancy across plasma concentrations of 350-900 ng/mL [Duvvuri et al., ACNP Meeting, 2023]). Emraclidine is currently under investigation for the treatment of schizophrenia and Alzheimer's disease psychosis (ADP). Here, we summarize emraclidine clinical data and ongoing clinical trials.

Methods: Part B of a two-part phase 1b trial (NCT04136873; Krystal et al., Lancet. 2022;17;400:2210-2220) was a 6-week, randomized, double-blind, placebo-controlled trial in adults with schizophrenia experiencing acute exacerbation of symptoms that evaluated the

safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (change from baseline in Positive and Negative Syndrome Scale [PANSS] and Clinical Global Impression-Severity [CGI-S] score) of emraclidine doses identified in Part A (ie, 30 mg once daily [QD], 20 mg twice daily [BID]). A subsequent 8-week, phase 1 trial (NCT05245539) evaluated change from baseline in ambulatory blood pressure in participants with stable schizophrenia receiving emraclidine 10 mg or 30 mg QD.

EMPOWER-1 (NCT05227690) and EMPOWER-2 (NCT05227703) are ongoing phase 2, 6-week randomized trials evaluating fixed doses of emraclidine in adults with schizophrenia experiencing an acute exacerbation of psychosis (CGI-S ≥ 4 , PANSS total score 85-120). Participants are randomized 1:1:1 to placebo or 1 of 2 doses of emraclidine (30 mg or 10 mg QD [EMPOWER-1]; 30 mg or 15 mg QD [EMPOWER-2]). The primary endpoint is change from baseline to Week 6 in the PANSS total score; secondary endpoints include the CGI-S, PANSS responders, extrapyramidal symptoms, suicidality, metabolic parameters, and safety. EMPOWER-1/EMPOWER-2 participants (and de novo participants) may be eligible for EMPOWER-3 (NCT05443724), a 52-week, open-label extension trial evaluating safety and tolerability of emraclidine 30 mg QD in adults with schizophrenia. An ongoing phase 1, multiple-ascending-dose trial (NCT05644977) is evaluating the safety, tolerability, and PK of emraclidine in healthy elderly adults.

Results: In Part B of the phase 1b trial (N=81), the most common adverse events were similar across placebo, emraclidine 30-mg QD, and 20-mg BID cohorts (headache: 26%, 30%, 26%, respectively; nausea: 4%, 7%, 7%, respectively). Modest increases in supine blood pressure and heart rate observed with emraclidine treatment initiation decreased over time and were not clinically meaningful vs placebo by treatment end. At Week 6, emraclidine 30 mg QD and 20 mg BID were associated with 19.5-point (difference vs placebo -12.7, nominal P=0.023) and 17.9-point (difference vs placebo -11.1, nominal P=0.047) reductions from baseline in the PANSS total score, respectively, with associated reductions across PANSS subscales. In the ambulatory blood pressure monitoring trial, the least squares mean change from baseline at Week 8 for systolic blood pressure was -2.7 mm Hg and -0.4 mm Hg for the emraclidine 10-mg and 30-mg QD groups, respectively.

Discussion: Current data support further investigation of emraclidine as a once-daily treatment for schizophrenia without the need for titration, leading to initiation of the phase 2 EMPOWER program and the phase 1 trial evaluating the safety, tolerability, and PK of emraclidine in elderly adults to support clinical development for treatment of ADP. The emraclidine program aims to establish selective targeting of M4 mAChRs as a novel treatment approach for schizophrenia and ADP.

T295. A RANDOMIZED, DOUBLE-BLIND, ACTIVE COMPARATOR-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ULOTARONT IN PATIENTS WITH SCHIZOPHRENIA

Leslie Citrome¹, Heather Dworak², Kenneth S. Koblan³, Robert Goldman³, Hailong Cheng³, Alison Fitzgerald³, Antony Loebel³, Armin Szegedi³, Nicholas DeMartinis^{*4}

¹New York Medical College, Valhalla, NY, ²Sumitomo Pharma America, Inc., ³Sumitomo Pharma America, Marlborough, MA, ⁴Sumitomo Pharma America

Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity that lacks direct D2 and 5-HT2A receptor antagonism. Ulotaront is in clinical development for the treatment of schizophrenia. The pharmacological, safety and

tolerability profile of ulotaront appears to be distinct from atypical antipsychotics based on preclinical [Dedic et al., Int J Mol Sci 2021; Dedic et al., Mol Metab 2024] and clinical [Koblan et al., N Engl J Med 2020; Correll et al., NPJ Schizophr 2021; Kane et al., Neuropsychopharmacology 2023] data demonstrating minimal to no association with extrapyramidal symptoms (EPS), no prolactin effects, and a potentially favorable metabolic profile. The current study was designed to evaluate the long-term safety and tolerability of ulotaront, for ulotaront as a novel treatment for schizophrenia. Exploratory analyses were included to compare ulotaront to an atypical antipsychotic (quetiapine XR).

Methods: This was a multicenter, randomized (in a 2:1 ratio), double-blind, parallel-group, 52-week, flexible-dose study evaluating the safety and tolerability of ulotaront (50-100 mg/d) versus quetiapine XR (QXR; 400-800 mg/d), in adult patients with a DSM-5 diagnosis of schizophrenia who were clinically stable for ≥ 8 weeks prior to screening and had a PANSS total score ≤ 80 at study entry. Patients who were treatment resistant to antipsychotic medication or who had a history of inadequate response or intolerability to quetiapine or quetiapine XR were excluded from study entry. The primary study outcomes were safety related, including incidence of overall adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, change from Baseline in body mass index (BMI) and waist circumference, clinical laboratory tests, and ECG parameters.

Results: In the safety population treated with ulotaront (N=201) and QXR (N=102), total discontinuations were 47.8% vs. 44.1%, respectively, and AEs leading to study discontinuation were 22% vs. 21%. The most common AEs for ulotaront vs. QXR ($\geq 10\%$ in either group) were somnolence (6.0% vs. 20.6%), insomnia (14.9% vs. 10.8%), schizophrenia (14.4% vs. 5.9%), anxiety (13.9% vs. 9.8%), constipation (3.5% vs. 11.8%), and weight increase (4.0% vs. 10.8%). Mean changes from Baseline to Week 52 in weight-associated parameters for ulotaront vs. QXR were as follows: weight (-1.2 vs. +1.4 kg; p LESS THAN 0.001), BMI (-0.4 vs. +0.5 kg/m²; p LESS THAN 0.001), and waist circumference (-1.4 vs. +1.4 cm; p LESS THAN 0.05). There was no clinically-significant Baseline to Week 52 changes in either treatment group in laboratory (including glycemic indices, lipids, prolactin) or vital sign parameters. In secondary effectiveness measures (PANSS total and subscale scores), there were no significant differences in change from Baseline to Week 52, or to any intermediate time-point, between ulotaront and QXR.

Discussion: The results of this study extend the findings from a previously-reported 6-month Phase 2 study to 52 weeks [Correll et al. 2021], demonstrating that long-term treatment with ulotaront is safe and well-tolerated with no unexpected adverse effects for this novel TAAR1 agonist class drug. The notable lack of adverse effects of ulotaront on lipids and glycemic indices, and the significant reduction in weight and waist circumference, are consistent with preclinical research suggesting that ulotaront improves glycemic control and reduces body weight in rodent models of diabetes, obesity, and iatrogenic weight gain [Dedic et al., 2024].

T296. TRAJECTORIES OF PSYCHOTIC-LIKE EXPERIENCES AND AUTISTIC TRAITS ACROSS EARLY ADOLESCENCE AND THEIR ASSOCIATION WITH BASELINE WHITE MATTER ALTERATIONS

Grace Jacobs*¹, Suheyra Cetin-Karayumak², Nora Penzel³, Johanna Seitz-Holland⁴, Hajer Nakua⁵, Lindsay Oliver⁶, Nikos Makris², Steve Pieper², Fan Zhang², Lauren J. O'Donnell², Yogesh Rathi⁴, Stephanie Ameis⁵

¹Brigham and Women's Hospital, Harvard Medical School, ²Brigham and Women's Hospital, Harvard Medical School, ³Massachusetts General Hospital, Harvard Medical School,

⁴Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, ⁵Centre for Addiction and Mental Health, University of Toronto, ⁶Centre for Addiction and Mental Health

Background: During childhood, psychotic-like experiences (PLEs) and autistic traits may co-occur, with the presence of one increasing the risk of the other. At the individual level, both PLEs and autistic traits show variable trajectories with persistent symptoms associated with poor cognition, brain alterations, and elevated risk for developing psychiatric disorders. However, co-occurring PLEs and autistic trait trajectories are poorly understood, and potential underlying structural brain features remain unknown. Childhood and adolescence are an important period of maturation for brain white matter, and alterations during this time may be related to or predictive of emerging symptoms. We investigated whether childhood white matter features are associated with trajectories related to persistent or increasing PLEs and/or autistic traits in a pediatric population-based sample.

Methods: The Prodromal Questionnaire Brief and a subset of 15 items from the Child Behavior Checklist were used to measure PLEs and autistic traits, respectively, at baseline (ages 9-10), year 1, year 2, and year 3 in 9965 (48% female) children from the Adolescent Brain Cognitive Development (ABCD) Study. Latent Class Growth Analysis (LCGA) was used to identify trajectory groups separately for PLEs and autistic traits. Goodness of fit measures AIC, BIC, log likelihood and entropy, as well as posterior probabilities of class membership were used to determine optimal models. Harmonized diffusion imaging white matter tractography measures of fractional anisotropy (FA) in 57 white matter tracts were examined in a subset of 7892 participants. ANCOVAs assessed baseline FA differences between trajectory groups (covarying for age, sex, and head motion).

Results: The LCGA models identified three trajectory groups for PLEs: 1) persistent low (89.5% of the sample), 2) increasing (3.7% of the sample), and 3) decreasing (6.8% of the sample); and three trajectory groups for autistic traits: 1) persistent low (87.3% of the sample), 2) increasing (6.8% of the sample), and 3) decreasing (5.9% of the sample). Among the trajectory groups, a greater number of females had increasing PLEs (60.3%), while a greater number of males had decreasing PLEs over time (60%, $X^2=29.7$, $df=2$, $p < 0.001$). A greater number of males also had decreasing autistic traits over time (62%, $X^2=26.8$, $df=2$, $p < 0.001$). Compared to children with both persistent low or no PLEs and autistic traits ($n=7721$): i) children with increasing PLEs only ($n=261$) featured lower baseline FA in 19 tracts, with the largest effects in the left inferior longitudinal fasciculus (ILF, $F=10.7$, $df=1$, $p=0.001$), left thalamo-parietal ($F=10.6$, $df=1$, $p=0.001$), and middle longitudinal fasciculus ($F=9.1$, $df=1$, $p=0.002$); ii) children with increasing autistic traits only ($n=527$) featured lower baseline FA in 8 tracts, with the largest effects in the right posterior limb of the internal capsule ($F=12.8$, $df=1$, $p < 0.001$), right striato-frontal ($F=6.9$, $df=1$, $p=0.008$), and left thalamo-parietal ($F=6.5$, $df=1$, $p=0.01$); iii) children with both initially high or increasing PLEs and autistic traits ($n=247$) featured lower baseline FA in 7 tracts with the largest effects in the left corona-radiata-frontal ($F=13.3$, $df=1$, $p < 0.001$) and left ILF ($F=10.1$, $df=1$, $p < 0.001$).

Discussion: PLEs and autistic trait trajectories across adolescence were associated with lower baseline white matter FA. Different tracts were associated with the presence of co-occurring persistent/increasing PLEs and autistic traits, versus only PLEs or autistic traits. Examining changes in both PLEs and autistic traits over time can help improve our understanding of this critical developmental period and important variables that may alter risk for worsening trajectories.

T297. THE TIMING AND SEVERITY OF CLOZAPINE-ASSOCIATED NEUTROPENIA: IS THE RISK OVERSTATED?

Allison Brandt^{*1}, Frederick Nucifora¹, Peter Zandi¹, Russell Margolis¹

¹*Johns Hopkins University School of Medicine*

Background: Treatment-resistant schizophrenia (TRS), defined by lack of response to two or more antipsychotic trials, is highly disabling. Clozapine has been shown to be superior to all other antipsychotics for TRS. However, the agent remains underutilized in the United States, in part due to concerns about potentially dangerous clozapine-associated neutropenia and the need for long-term hematologic monitoring and registry requirements. This study investigates patient demographics, rates of neutropenia, and the timing of neutropenia in those who started clozapine at a large academic medical system.

Methods: Data was collected from Johns Hopkins Medicine (JHM) electronic medical record between 2013 and 2023, accessed using the Schizoaffective Disorders Precision Medicine Center of Excellence registry on the Precision Medicine Analytics Platform. The registry includes demographic characteristics, medical history, medications, and lab results. Those whose first prescription for clozapine in the system was for 50mg or less were considered to be starting clozapine. Absolute neutrophil counts (ANC) prior to starting clozapine were reviewed, and patients with two ANC counts LESS THAN 2000 cells/ μ L, more than 30 days apart, without other explanation, were presumed to have Duffy-null Associated Neutrophil Count (DANC). Based on ANC counts during clozapine use and presumed DANC status, patients were divided into groups who experienced no neutropenia (ANC $\geq$ 1500 cells/ μ L or $\geq$ 1000 cells/ μ L if DANC), mild (1000 – 1499 cells/ μ L), moderate (500 – 999 cells/ μ L), and severe neutropenia (LESS THAN 500 cells/ μ L). Neutropenia for those with DANC was defined as ANC LESS THAN 1000 cells/ μ L and severe if ANC LESS THAN 500 cells/ μ L. Demographics were compared between groups and timing of first neutropenia was explored.

Results: Out of 308 patients started on clozapine, ANC data were available for 287 patients, of whom 38% were female, 62% male, 5% were Asian, 45% white, and 46% Black, 2% were Hispanic. The mean age was 39.2 years. The mean ANC before starting clozapine was 4640 cells/ μ L and the mean ANC while taking clozapine was 4600 cells/ μ L. Nineteen patients met clinical criteria for presumed DANC, and none developed neutropenia while taking clozapine. Fourteen patients (4.9%) developed neutropenia, 12 (4.2%) had mild neutropenia and two (0.7%) had moderate neutropenia. No patients developed severe neutropenia. Out of the 14 patients who developed neutropenia, 10 did so within eight months of starting clozapine, and one of the remaining four developed neutropenia only during COVID infection. Both patients who developed moderate neutropenia did so in the first 35 days of clozapine use. There were no significant differences in age, gender, race, or ethnicity among neutropenia groups, except that all patients with presumed DANC identified as Black. Three patients stopped receiving clozapine at JHM after developing neutropenia. The rest were continued on clozapine after neutropenia and neutropenia resolved.

Discussion: While ANC monitoring is required indefinitely in the US for patients taking clozapine, these results suggest that the risk of neutropenia after eight months is low and the risk of severe neutropenia during clozapine use is minimal. These findings suggest a need for careful reconsideration of current ANC monitoring requirements. Excessive and indefinite ANC monitoring may limit the most effective use of clozapine.

T298. DYNAMIC BRAIN ALPHA CONNECTIVITY IN RESTING-STATE EEG: QUANTIFYING BRAIN NETWORK STATE EVOLUTION IN INDIVIDUALS WITH PSYCHOSIS

Romain Aubonnet^{*1}, Mahmoud Hassan², Paolo Gargiulo³, Stefano Seri⁴, Giorgio Di Lorenzo¹

¹Laboratory of Psychophysiology and Cognitive Neuroscience, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy, ²School of Engineering, University of Reykjavik, Reykjavik, Iceland, ³Institute of Biomedical and Neural Engineering, Reykjavik University, Reykjavik, Iceland, ⁴College of Health and Life, Wellcome Laboratory for MEG Studies, Aston Brain Centre, Aston University, Birmingham, West Midlands, United Kingdom

Background: Schizophrenia is a multifaceted disorder that presents a complex challenge, demanding a nuanced understanding of its neurophysiological underpinnings for effective treatment. Traditional static connectivity analyses fall short in capturing the dynamic intricacies of the brain, prompting the exploration of innovative methodologies. Our project addresses this gap by delving into dynamic connectivity analysis using electroencephalography (EEG) signals. Our aim is to unveil the nuanced dynamics of brain connectivity states in individuals with schizophrenia, shedding light on the intricate interplay of neural networks.

Methods: We conducted a study involving 78 individuals with psychosis and 60 control subjects from the OpenNeuro database. Participants underwent 5-minute resting-state EEG recordings with eyes open, utilizing a 60-channel setup. Source reconstruction was executed using eLORETA, defining 68 regions of interest (ROIs) based on the Desikan-Killiany atlas. A power spectral density (PSD) analysis was performed in the alpha band (7-13Hz). Then, functional connectivity in the alpha band was estimated using the weighted phase lag index (wPLI). Adapting methods from the classical EEG microstate approach, we performed clustering with modified k-means to identify distinct brain network states (BNS). Backfitting and smoothing were applied to each subject's data, and BNS metrics (coverage, duration, occurrence, and transition matrices) were extracted. Additionally, the dominant function of each BNS was evaluated using graph theory metrics. Statistical analyses were performed on these metrics to discern differences between control and psychosis subjects. A correlation analysis was conducted between these metrics and the scores of the cognitive domains of MCCB, as well as psychopathological scales (SANS, SAPS, GAFAS).

Results: The PSD analysis revealed significant differences in almost every ROI, with a lower power in individuals with psychosis. Correlation analysis demonstrated a Pearson coefficient between 0.2 and 0.3 (p-value LESS THAN 0.02) between speed of processing and working memory scales and PSD values, as well as a correlation of -0.3 (p-value LESS THAN 0.01), with PSD and SANS scales. The clustering analysis identified seven distinct BNS. Statistical analyses revealed significant differences (p LESS THAN 0.01, effect size GREATER THAN 0.3), in transitions between BNS, underlining the dynamic nature of neural interactions. These transitions, mostly in regions associated with visual and default mode network (DMN) cortices, emerged as main points of divergence when comparing BNS in psychosis and control subjects. Correlation analysis showed a Pearson coefficient of 0.3 (p-value LESS THAN 0.002) between transition probabilities and reasoning and problem-solving scales for patients with schizophrenia, and a Pearson coefficient around 0.2 (p-value LESS THAN 0.02) between speed of processing, visual learning, and verbal learning scales and the transition probabilities for all Control and Psychosis subjects.

Discussion: The observed disparities in BNS, particularly during transitions, suggest an intricate interplay of neural dynamics in individuals with psychosis. The prominence of

visual and DMN cortices in these differences implicates specific brain regions in the pathology of schizophrenia, which is also confirmed by the correlation between those results and cognitive scales.

Our findings pave the way for a deeper understanding of dynamic brain connectivity alterations in psychosis, providing potential avenues for targeted therapeutic interventions. Further exploration of these dynamic network states holds promise for refining diagnostic approaches and tailoring treatment strategies for individuals with schizophrenia.

T299. LATENT CLASSES BASED ON CLINICAL SYMPTOMS OF MILITARY RECRUITS WITH MENTAL HEALTH ISSUES AND THEIR CLINICAL RESPONSES TO TREATMENT

Jeongwon Eo*¹, Duk-In Jon¹, Eun Hee Park¹, Hyun Ju Hong¹

¹*Hallym University Sacred Heart Hospital*

Background: In South Korea, all men at the age of 18 or older are required to serve at military for a certain period as an obligation. These recruits should be able to withstand psychological stress and pressures of rapid adaptation of the unique and new environment in military. The number of military recruits facing adaptation issues has been on the rise, necessitating an evaluation for active service. In our previous study (Park et al., 2023), we classified the military recruits with mental issues according to latent profile analysis (LPA) and examined the treatment response during six months. In this study, we further examined clinical characteristics over the next six months.

Methods: Ninety-two participants were analyzed with LPA using MMPI-2 clinical profiles in the previous study. The three classes were identified: mild maladjustment (Class 1, n=14), neurotic depression and anxiety (Class 2, n=36), high vulnerability and hypervigilance (Class 3, n=42). At 12 months, Clinical Global Impression-Severity and Global Assessment of Functioning were assessed to test their long-term changes.

Results: While Class 1 and 2 significantly improved over 6 months, Class 3 showed little or no improvement even with more medications in our previous study. During the 6-month follow-up period, 50% of Class 1, 38.9% of Class 2, and 41.5% of Class 3 were dropped. It was during this period that their level of military service was decided. Class 1 and 2 which showed marked improvement up to initial 6 months, did not demonstrate substantial further improvement during follow-up period with a considerable portion stopped visiting hospital. Subjects in Class 3, who showed little or no improvement during initial 6 months, demonstrated continued improvement in this study, although their symptoms still appeared relatively severe.

Discussion: This study suggests clinical implications for treatment plan and intervention of each subgroup classified based on MMPI-2 clinical profiles of military recruits who might show maladjustment to serve. The long-term continuous treatment for Class 3 patients will be needed, even after exemption from active duty.

T300. THE EFFECTS OF DISTINCT ENVIRONMENTAL ENRICHMENT PROTOCOLS ON MEMORY AND/OR LEARNING IN SCHIZOPHRENIA RODENT MODELS: A SYSTEMATIC REVIEW

Sinem Güneri*¹, Emine Ilgın Hoşgelen², Köksal Alptekin³

¹Dokuz Eylül University, Graduate School of Health Sciences, ²Dokuz Eylül University, Graduate School of Health Sciences, Department of Neuroscience, ³Dokuz Eylül University, Faculty of Medicine, Department of Psychiatry

Background: Memory and learning deficits are prominent cognitive markers for schizophrenia, which may be evaluated in schizophrenia animal models through several behavioral tasks. Environmental enrichment (EE) protocols are thought to have a positive impact on memory and learning deficits, encompassing a range of interventions designed to enhance sensory, cognitive, and social stimulation in laboratory animals (Vaquero-Rodríguez et al., 2023). As EE interventions are multimodal and multifactorial, there is no evaluation determining which components of EE protocols are essential for the positive impact on cognitive domains in schizophrenia animal models. This review, therefore, focuses on the effects of different EE protocols' components on memory and learning deficits in schizophrenia rodent models.

Methods: In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, a search was conducted in two academic databases, Web of Science (WoS) and PubMed, by two independent researchers (SG and EIH) in January 2024. Articles meeting the following eligibility criteria were included: (1) studies solely involving rodents, (2) studies presenting a schizophrenia model, (3) environmental enrichment (EE) as an only intervention, (4) studies utilizing standard housing as a comparator, (5) studies assessing changes in memory and/or learning through relevant parameters (e.g., discrimination index), and (6) studies published in English. Exclusions were applied for (1) studies with a different protocol of EE and/or a different rearing condition as comparators, (2) studies lacking a clear specification of their research approach as a schizophrenia model, and (3) studies categorized as letters, reviews, comments, editorials, or duplicates. The SYRCLE's strategy was used for quality assessment of the involved studies.

The parameters extracted encompassed various factors such as the type of species, strain, gender, age, number of animals at the commencement of housing, the start of the behavioural experiment, the enrichment category (whether social, cognitive, or physical), the average behavioural outcome parameter, and the specific behavioural test utilized.

Results: The systematic search identified 169 records of articles, of which 60 duplicates were excluded. Afterwards, 109 articles were screened and subjected to the eligibility criteria, leading to the exclusion of 86 articles via abstract reading. After full-text reading of 23 studies, 7 of these were excluded. Therefore, 16 studies were included in this systematic review. Among these studies, the types of schizophrenia model were as follows: 8 pharmacological, 3 neurodevelopmental, and 5 genetic. While 11 studies used rats, the rest of the studies used mice. The time intervals and onsets of EE protocols are quite diversified. 5 of the studies enhanced social interaction, but all studies adopted physical activity and cognitive stimulation. Among behavioral tasks, Morris Water Maze (n=6) and Novel Object recognition tests (n=3) were most used to evaluate these deficits. EE protocols failed to ameliorate the memory and/or learning deficits in 7 out of 16 studies. 3 out of 4 studies presented no reversal of these symptoms with EE in females, while this ratio is 4 out of 12 studies in males.

Discussion: There are some contradictions regarding to which components of EE are more effective in treatment. In rodents, the onset, duration, and time intervals of EE protocols may be the reason of failure in improving some types of memory and/or learning deficits. Due to limited number of studies and divergence in EE protocols, affecting components and gender differences are elusive. Therefore, it is obvious that additional research is needed in both genders for considerable interpretation and comparison. To ensure the credibility and

widespread acceptance of EE's positive impact, it is imperative to implement a valid standardization process.

T301. MONOCYTE/LYMPHOCYTE RATIO (MLR) AS A PROXY FOR INFLAMMATION IN A SAMPLE OF CHILD AND ADOLESCENT PSYCHIATRIC INPATIENTS

Maria Gariup^{*1}, Guillermo Muñoz Sánchez², Azucena González², Carles Serra-Pagés³, Astrid Morer⁴

¹OPUS YOUNG Study, Child and Adolescent Psychiatric Center Glostrup, ²Immunology Service, Hospital Clínic, ³Immunology Service - Hospital Clínic, Barcelona University, ⁴Child and Adolescent Psychiatry Dept., Hospital Clínic and Barcelona University

Background: Research shows increased inflammatory state in subgroups of psychiatric patients through the diagnostic spectrum. Most data regard CRP and certain proinflammatory cytokines (CK), as interleukin-6 (IL-6), IL-1beta, TNF-alfa and the chemokine MCP-1 (Monocyte chemoattractant protein-1). Cytokines have shown complex actions both in the peripheral system and in the central nervous system (CNS), but their measurement is not part of the standard laboratory tests.

In search of more inexpensive and reproducible inflammation markers, recent psychiatry research has focused on monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR), predictors of cardiovascular, autoimmune and other systemic diseases. These markers have been found elevated among adult patients with psychotic and mood disorders versus healthy controls (HC), especially in acute phases of diseases (Cheng et al., 2022; M.G. Mazza et al., 2019; Mario Gennaro Mazza et al., 2018), and in preliminary studies in children and adolescents (C and A) with depression, psychosis and ADHD (Gędek et al., 2023; Henry Taylor et al., 2023; Özyurt and Binici, 2018). Our group has described higher cytokines (IL-1beta, IL-6, IL-8, MCP-1 and IP-10) and monocyte count in a transdiagnostic group of C and A acute inpatients, vs. a control group in the same age range (8-17) (Gariup et al., 2015). Here we compare MLR, NLR and PLR between the two groups and analyze their correlation with cytokines and clinical scales.

Methods: 77 consecutive Child and Adolescent inpatients and 34 Healthy Controls (HC) were recruited. Mean age (SD) were 15.1 (2.4) and 15.7 (2.7), male ratio 52% and 41% respectively (p GREATER THAN 0.05 for both). MLR, NLR and PLR were compared between the two groups, and between HC and 5 diagnostic clusters of inpatients (U- Mann Whitney). Spearman correlations between MLR, NLR and PLR with cytokines, CRP, age, BMI, and stressful-life events (SLE), anxiety (SCARED), global assessment of functioning (GAF), Autism Spectrum Screening Questionnaire (ASSQ) and Conners Parent Rating Scales Revised (CPRS) were assessed for the whole sample.

Results: MLR was higher in the whole patient group (p=0.049) and in the subgroup of anxiety and OCD disorders (p=0.015) vs HC. We found no significant differences in NLR and PLR distribution between patient group/subgroups and HC.

CONTROLS	(n=34)	PATIENTS	(n=77)	ADJUSTMENT
(n=5)	ANXIETY and OCD (n=17)	DEPRESSION	(n=19)	BAD
MANIA or MIXED (n=14)	PSYCHOSIS and SAD (n=22)			

MLR mean (SD)	0.17 (0.07)	0.20 (0.08)	0.20 (0.07)	0.21 (0.05)	0.19 (0.09)
	0.18 (0.06)	0.21 (0.12)			
	p=0.049*	p=0.223	p=0.015*	p=0.584	p=0.370
	p=0.140				

MLR, NLR and PLR correlated significantly with each other and with CRP. Moreover, MLR correlated with IL-1beta, IL-2, IL-8, IP-10, and ASSQ, with a trend for IL-6, IFN-gamma and GAF; NLR with IL-2, IL-6, with a trend for BMI and IL-4; PLR with IP-10.

Spearman's Rho

	MLR	NLR	PLR	CRP	BMI	IFNg	IL1b	IL2	IL4	IL6	IL8	IP10
ASSQ												
MLR		.584**	.585**	.389**		0.159	.221*	.199*		0.164	.193*	
	.196*	.343*	-0.163									
		0,000	LESS THAN	.001	0.001		0.096	0.02	0.036			
	0.086	0.042	0.047	0.01	0.088							
NLR	**		.606**	.510**	0.174		.256**	0.181	.190*			
			LESS THAN	.001	LESS THAN	.001	0.093					
	0.007	0.057	0.045									
PLR	**	**		.326**								
	.237*											
				.008								.016

Discussion: Results show higher MLR in a cohort of acute C and A psychiatric inpatients with described higher inflammatory cytokines vs HC. Of the three parameters, MLR showed the most correlations with cytokines.

Despite mutual correlations between the three markers, and with CRP, no difference was found for NLR and PLR between patients and controls, in contrast with adult literature and with some previous studies on C and A population. This may be due to sample size, young age and/or heterogeneity of diagnosis.

Results support a possible role of MLR as an inexpensive biomarker of the inflammatory profile in C and A psychiatric population.

To our knowledge this is the first work in psychiatric population relating MLR, NLR and PLR to cytokine levels.

T302. PSYCHOLOGICAL DISTRESS OF SCHIZOPHRENIA AND AT-RISK PSYCHOSIS UPON PANDEMIC ASSOCIATED WITH HIPPOCAMPUS ALTERATIONS: A LONGITUDINALLY MIXED-METHOD STUDY

Qian Guo^{*1}, Lihe Chen¹, Hao Hu¹, Dan Zhang¹, Zexin Zhao², Yao Hu¹, Xiaohua Liu¹, Guanjun Li¹, Jijun Wang¹

¹Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine,
²Zhongshan Hospital, Fudan University

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic in 2019 and induced extensively negative effects on long-term outcomes of mental health worldwide. It is widely accepted that impact might be more overwhelming on vulnerable population with severe mental disorders such as schizophrenia (SCZ). Hippocampus, one of core subcortical nuclei to modulate stress response, plays a unique role in psychopathological mechanism in SCZ. So far, there is no study investigating neuroimaging alterations of SCZ or at-risk psychosis in response to the stress of pandemic. In present research, we aimed to investigate the longitudinal impact of the COVID-19 pandemic on psychological distress and hippocampus features in individuals with first-episode schizophrenia (FES) and clinical high risk for psychosis (CHR).

Methods: Current study was based on existing cohorts of FES and CHR in Shanghai Mental Health Center. A total of 49 FES, 92 CHR, and 73 HC were recruited during the period of the pandemic (from August 2020 to March 2022). At baseline, participants underwent assessments including scales of PHQ-9, GAD-7, PSS-10, PCL-5, Coronavirus Impact Scale (CIS) and T1-weighted imaging on a 3.0 T S Verio MRI scanner. Nine patients were volunteered to participate semi-interview. During the large-scale outbreak of the epidemic in Shanghai (from April to May 2022), 20 FES, 42 CHR, and 43 HC were followed up with above scales and additional scales related to coping strategy (perceived social support scale, simplified coping style questionnaire, and Rosenberg self-esteem scale). Characteristics of hippocampal subfields was preprocessed by FreeSurfer (v6.0). Variance analysis, principal component analysis, and multiple linear regression analysis were applied to compare differences among three groups. Content analysis was used to encode qualitative data of semi-interviews.

Results: Demographic data among three groups showed no differences in age and gender, while HC showed higher level of education. Results of variance analysis demonstrated that levels of psychological distress were significantly elevated in FES and CHR. And the total scores of CIS was significantly higher in FES when compared to the CHR ($P=0.019$) and HC ($P=0.003$). Differences were observed in volume of bilateral hippocampal fissure ($F=4.46$, $P=0.013$; $FL=3.56$, $P=0.031$), right parasubiculum ($F=3.64$, $P=0.029$) and right hippocampus-amygdala transition area (HATA) ($F=3.30$, $P=0.040$) among three groups. Of note, psychological distress at baseline positively correlated to right parasubiculum volume in FES ($r=0.37$, $P=0.036$). Semi-interviews demonstrated that the negative coping strategies of FES patients were prominent.

At follow-up, the inter-group differences disappeared among three groups. The degree of psychological distress decreased in FES after large-scale outbreak of the epidemic, while the degree of COVID-19 impact was significantly increased in CHR ($P=0.018$) and HC ($P<0.001$). Additionally, differences in the total scores of PSSS ($F=3.81$, $P=0.026$) and SCSQ-Active ($F=3.73$, $P=0.028$) were observed across groups, with decreased PSSS scores in CHR ($P=0.033$) and lower scores of SCSQ-Active in FES ($P=0.029$). Multiple linear regression showed that passive coping strategy was related to elevated psychological distress at follow-up for FES, while positive factor was associated with lower psychological distress at follow-up for CHR and HC. Finally, volume of left hippocampal fissure at baseline was negatively correlated with the change of PSS scores ($R=-0.65$, $P=0.012$) and CIS scores ($R=-0.59$, $P=0.033$) in FES.

Discussion: The outbreak of COVID-19 pandemic has prominent effects on individuals with FES and CHR. Negative coping strategy is a risk factor for psychological distress of FES,

while positive factors such as social support, positive coping strategies, and self-esteem are protective factors for CHR and HC. Notably, alterations in hippocampal subfields of FES patients are highly correlated to their psychological distress and can predict long-term stress symptoms.

T303. PREVALENCE OF PSYCHOTIC SPECTRUM ILLNESS IDENTIFIED BY SYSTEMATIC SCREENING IN GENERAL PSYCHIATRIC SETTINGS: A META-ANALYSIS

Cheryl Y. S. Foo*¹, Jacqueline A. Clauss¹, Catherine J. Leonard¹, Katherine Dokholyan¹, Corinne Cather¹, Daphne Holt¹

¹*Massachusetts General Hospital*

Background: The absence of systematic detection strategies within general psychiatric services contributes to substantial treatment delays for individuals with psychosis. We conducted a meta-analysis to estimate rates of psychotic symptoms and likely psychotic disorders identified by screening treatment-seeking samples to inform the implementation of routine psychosis screening in outpatient psychiatric settings.

Methods: PubMed and Web of Science databases were searched to identify empirical studies that contained information on the point prevalence of psychotic symptoms, psychotic disorders, or clinical high-risk for psychosis syndrome (CHRS) identified by screening in outpatient samples aged 12-64 receiving general (i.e., not specialized) psychiatric care. Included studies were published between 2006 and 2023. Psychotic symptoms were identified by validated self-reported questionnaires (e.g., Prodromal Questionnaire), and psychotic disorders and CHRS by gold-standard structured interview assessments (e.g., Structured Interview for Psychosis-Risk Syndrome, Comprehensive Assessment of At Risk Mental States). A meta-analysis of each outcome was conducted using the DerSimonian and Laird method of estimating effect sizes in a random effects model, which accounts for between-sample heterogeneity by weighting each sample by sample size and variance.

Results: 36 independent samples from 13 countries involving n=24,979 outpatients were included in the meta-analysis. Among a general outpatient psychiatric population, the prevalence rate for screening for supra-threshold psychotic symptoms was 42.2% (95% CI: 30.1-52.7%; 25 samples, n=22,114). The prevalence rate for psychotic disorders was 8.7% (95% CI: 6.5-10.8%; 25 samples, n=15,903). The prevalence rate of CHRS was 24.3% (95% CI: 20.4-28.2%; 23 samples, n=15,991).

Discussion: High rates of psychotic spectrum illness in general psychiatric settings underscore the need for psychosis screening. These base rates in clinical settings can be used to estimate positive screen rates and resources required to conduct assessments to accurately identify and triage individuals with psychotic disorders and CHRS.

T304. A LONGITUDINAL STUDY OF BIDIRECTIONAL CAUSAL RELATIONSHIPS BETWEEN PSYCHOTIC EXPERIENCES AND PSYCHOLOGICAL DISTRESS: MODERATING EFFECT OF GENDER

Feten Fekih-Romdhane*¹, Lilia Houissa¹, Ahmad Abu-Akel², Alexandre Andrade Loch³, Majda Cheour¹, Souheil Hallit⁴

¹Tunis El Manar University, Faculty of Medicine of Tunis, ²University of Haifa, ³Universidade de Sao Paulo, ⁴Holy Spirit University of Kaslik

Background: Although the co-occurrence of psychotic experiences (PEs) and psychological distress symptoms is growingly recognized in several major previous studies, there is still a lack of literature which clearly outlines how these two psychopathological entities affect each other over time. This study is intended to add to the literature by examining: (a) the longitudinal, bidirectional associations between PEs and psychological distress in a sample of Tunisian adolescents, and (b) whether these associations are moderated by sex.

Methods: A total of 510 Tunisian adolescent students (mean age of 16.05 ± 1.01 years, 61.2% females) took part in a prospective longitudinal study. PEs and psychological distress were measured at three occasions over a one-year period. The cross-lagged panel modeling approach was adopted.

Results: The current results showed that the experience of PEs at baseline triggered later psychological distress (at 6 months), which had in turn led to further exacerbation of psychological distress at 12 months of follow-up. Temporally primary psychological distress symptoms were not a significant predictor for the development of later psychotic symptoms in the whole sample. However, temporal patterns between adolescent distress and psychotic symptoms differed for girls and boys. Adolescent girls who initially presented with PEs had an elevated risk of developing later psychological distress, and adolescent boys who firstly endorsed psychological distress were at higher risk of experiencing new onset psychotic symptoms over time.

Discussion: Findings suggest that patterns of associations between PEs and distress differ across sex in adolescent populations. Depending on sex, one factor can be an early marker for the other, and routine screening for one outcome is warranted when the other is present. This also implies that prevention and intervention strategies for adolescents who present with PEs or psychological distress need to be tailored to sex in order to reach maximum effectiveness. In particular, psychological distress could potentially serve as a primary target for decreasing and mitigating PEs in boys, and vice versa for girls. As for research perspectives, long-term follow-up studies (e.g., birth cohorts) still need to study the different possible pathways by which the two constructs could influence each other over longer periods of time. It is also crucial to investigate and better understand factors other than sex, such as a wider age range (adolescence versus early adulthood), that may moderate the relationships between psychosis and distress. Finally, the field may benefit from future experimental research testing whether targeting one of the two conditions (i.e., PEs and psychological distress) could reduce the incidence of the other in adolescents.

T305. PSYCHOTIC AND DISSOCIATIVE SYMPTOMS IN THE GENERAL POPULATION: A LATENT PROFILE ANALYSIS

Ho-wang Bryan Yu*¹, Chui-de Chiu¹, Suzanne Ho-wai So¹

¹The Chinese University of Hong Kong

Background: Psychiatric patients presenting with co-occurring positive psychotic symptoms and dissociative symptoms, compared to those with only either spectrum of symptoms, exhibit more severe symptomatology and poorer functioning. While existing literature has also corroborated the interrelatedness between psychotic and dissociative symptoms in non-clinical samples, further understanding of the frequency and pattern of their co-occurrence among the general population is limited. By using a large community sample, the current

study aimed to identify the distinct profiles of individuals demonstrating varying levels of psychotic and dissociative symptoms, using multidimensional measures that reflect their heterogeneity. The identified profiles were then compared on various outcomes (depression, anxiety, and daily functioning).

Methods: Samples were recruited through mass mail advert in local universities, snowball sampling, social media platform, and distribution of pamphlets in local communities. Participants completed a cross-sectional online survey battery encompassing the Community Assessment of Psychic Experiences-Positive scale (CAPE-P), Dissociative Experiences Measure Oxford (DEMO), basic demographics, and outcome measures (i.e., Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 Scale, and WHO Disability Assessment Schedule 2.0-Short Form). To identify the profiles characterised by the heterogeneous spectra of psychotic and dissociative symptoms, subscores of CAPE-P (Persecutory Ideations, Bizarre Experiences, Perceptual Anomalies) and DEMO (Unreality, Numbness/Disconnect, Memory Blanks, Zone-Out, Vivid Internal World) were entered as indicator variables in Latent Profile Analysis (LPA). The identified profiles were compared on levels of symptoms and outcomes using Multivariate analysis of variance (MANOVA) and post-hoc analyses.

Results: The current sample consisted of 2,852 adults (mean age = 34.76; 72.3% female). Four distinct profiles were identified. Amongst the four profiles, Profile 1 (81.1%) reported the lowest mean levels across all CAPE-P and DEMO subscores (ps LESS THAN .001). Profiles 2 (9.8%) and 3 (6.6%) had moderate subscores on CAPE-P and DEMO. Profile 2 scored higher than Profile 3 on unreality and numbness/disconnect (ps LESS THAN .001), whereas Profile 3 scored higher than Profile 2 on persecutory ideations, bizarre experiences, and perceptual anomalies (ps LESS THAN .001). Profile 4 (2.5%) reported the highest levels of all CAPE-P subscores and most of the DEMO subscores (ps LESS THAN .001; except unreality and numbness/disconnect when compared to Profile 2). In terms of outcome measures, levels of depression, anxiety, and disturbance to functioning were the highest in Profile 4, followed by Profiles 2 and 3 (which did not differ from each other, ps GREATER THAN .050), and then Profile 1 (ps LESS THAN .001).

Discussion: This is the first study to use a large community sample and multidimensional measures to address the knowledge gap of identifying latent subgroups with distinct profiles of co-occurring psychotic and dissociative symptoms. While the vast majority of the sample (81.1%) reported low levels of psychotic and dissociative symptoms on average, 18.9% of individuals experienced psychotic and dissociative symptoms that co-occurred to various extents. The use of multidimensional measures delineated two moderate-severity profiles that showed contrasting observations, revealing one profile characterised by heightened overall psychotic symptoms, and another profile heightened dissociative symptoms (unreality and numbness/disconnect). The findings also revealed a subgroup, although smallest in proportion, within the general population who had high severity of psychotic and dissociative symptoms at the same time. Comparison between profiles demonstrated that individuals with the highest level of both psychotic and dissociative symptoms also suffered from the poorest emotional and functioning outcomes. Future investigations may look into putative factors or mechanisms that potentially predict the variation in class membership.

T306. CLINICAL STATUS AND FUNCTIONING OF ADULTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS IN THE UNITED STATES: FINDINGS FROM THE MENTAL AND SUBSTANCE USE DISORDERS PREVALENCE STUDY

Natalie Bareis*¹, Mark Edlund², Heidi Guyer², Lisa Dixon¹, Mark Olfson³, Thomas Smith¹, Lydia Chwastiak⁴, Maria Monroe-DeVita⁴, Marvin Swartz⁵, Jeffrey Swanson⁵, Elizabeth Sinclair Hancq⁶, T. Scott Stroup¹

¹*Columbia University Department of Psychiatry*, ²*RTI International*, ³*Columbia University Mailman School of Public Health*, ⁴*University of Washington*, ⁵*Duke University School of Medicine*, ⁶*Treatment Advocacy Center*

Background: Life circumstances and characteristics of individuals living with schizophrenia spectrum disorders (schizophrenia) in US households are inadequately understood. Prior epidemiologic studies identifying prevalence of schizophrenia have been limited by use of screening questionnaires that reduce the accuracy of diagnostic determinations due to the complexity of schizophrenia. Clinical studies have been limited to individuals receiving treatment.

Methods: The US Mental and Substance Use Disorders Prevalence Study, conducted from October 2020-October 2022, is the first US national epidemiologic study of schizophrenia and other behavioral disorders since 2003. Unique to this epidemiological study, clinically trained interviewers administered the Structured Clinical Interview for the DSM-5 to make diagnoses among adults aged 18-65 years and collected their sociodemographic information. Using sampling weights, we compared adults with and without schizophrenia with respect to their sociodemographic characteristics and functioning; among adults with schizophrenia, we examined clinical characteristics.

Results: Among the household sample, people who identified as Black were 3.3 times as likely to have schizophrenia as those who identified as White (28.6% vs. 13.4%; Adjusted Odds Ratio 3.3, 95% confidence interval 1.3-8.1). These individuals were more likely to have completed no more than a high school or a GED degree (63.9% vs 36.3%, AOR 3.5, 1.6-7.7), less likely to be employed (16.9% vs. 61.0%; AOR 0.12, 0.1-0.3) and more likely to have annual family income LESS THAN \$20,000 (36.9% vs. 17.0%; AOR 3.6, 1.3-10.5) than those without schizophrenia. They were also less likely to be married or in a relationship than those without schizophrenia (25.3% vs 49.8%, AOR 0.3, 0.2-0.7; 29.7% vs 69.7%, AOR 0.4, 0.2-0.9 respectively). Alcohol and cannabis were the most common substances used by individuals with schizophrenia, with cannabis use 3 times as likely among those with than without schizophrenia (AOR 3.2, 1.7-6.0). Cigarette use was 4 times as likely among individuals with than without schizophrenia (51.1% vs 21.2%, AOR 4.2, 2.1-8.3). Mean Global Assessment of Functioning scores were poor and lower among people with than without schizophrenia (44.8 [standard error 2.0] vs. 77.2 [0.5], p LESS THAN 0.01). Among people with schizophrenia, 51.7% (95% CI 34.0-69.4) had a major depressive episode and 17.3% (4.7-30.0) met criteria for post-traumatic stress disorder in the past year. In the past year 56.4% (37.7-75.0) received mental health outpatient treatment and 25.5% (12.7-38.3) received minimally adequate treatment (≥ 1 antipsychotic and ≥ 4 outpatient visits).

Discussion: This innovative national epidemiological study found that people with schizophrenia in US households experience pervasive social and economic disadvantages. While prior long-term longitudinal cohort studies have found that many people with schizophrenia have achieved life milestones and may recover, in this cross-sectional study most were unemployed, many lived in poverty, and a majority had serious functional impairment. Few received adequate treatment despite the development of multiple effective psychosocial and antipsychotic treatments. In addition, the increased prevalence of schizophrenia among individuals who identify as Black, even when diagnoses were obtained using a semi-structured diagnostic interview, should be considered in relation to systemic factors such as poverty, trauma exposure and discrimination that are risk factors for psychosis

and may contribute to these higher rates. Policies, interventions, and further research are needed to mitigate these problems.

T307. REDUCED PITCH RANGE IN SCHIZOPHRENIA: TOWARDS QUANTIFICATION OF FLAT AFFECT THROUGH PROSODY AND SEMANTIC ANALYSIS OF SPEECH SAMPLE

Yunlai Gui^{*1}, Mingyuan Li¹, Mikisha Lyn Doop¹, Manaan Kar Ray², Lena Palaniyappan³, Timothy J. Crow⁴, Sohee Park¹

¹*Vanderbilt University*, ²*The Metro South Addiction and Mental Health Services*, ³*McGill University*, ⁴*University of Oxford*

Background: Past research indicates that prosody processing is impaired in schizophrenia. Monotonous speech in individuals with schizophrenia (SZ) is associated with negative symptoms such as flat affect (Parola et al., 2020; de Boer et al., 2023). But due to the variability of speech production, it has been difficult to quantify prosody from acoustic features of speech samples in clinical contexts. The current study examined both acoustic and semantic features of speech produced by SZ and healthy controls (CO) in structured clinical interviews from the UK and USA. In addition, we also recruited a small group of individuals with affective disorders (AF) to explore acoustic variations between schizophrenia and other psychiatric disorders.

Methods: There were two studies (acoustic and semantic). Speech samples were recorded by asking 4 open-ended neutral (home, hobbies) and emotional (sex, god) interview questions. Demographic information and symptom ratings were collected. Study 1 focused on the acoustic properties of the speech from 35 SZ, 15 AF, and 37 CO in Oxford, UK. We extracted the minimum and maximum fundamental pitch using Praat (praat.org) for the 4 topics. Study 2 focused on the semantics using the same interviews, which were transcribed verbatim. Transcripts from a total of 22 SZ and 13 CO participants from the UK and USA were available for analysis. We used the Linguistic Inquiry and Word Count (LIWC-22) software to extract content summary variables including word count, emotional tone, words per sentence, and linguistic variables that summarize parts of speech including pronouns, prepositions, verbs, and adjectives.

Results: In study 1, SZ had the most compressed pitch range while CO had the largest pitch range ($F(2,79)=4.89$, $P < 0.01$). We found a significant interaction between the themes (neutral vs. emotional) and diagnosis, such that SZ had a decreased pitch range when talking about emotional themes; AF remained constant, while CO had an increased pitch range ($F(2,79)=3.49$, $P=0.035$). In addition, for the God topic, reduced pitch range was correlated with negative symptoms ($r(45)=-0.34$, $P=0.019$), and higher maximum pitch was correlated with lower depressive scores ($r(45)=-0.33$, $P=0.027$). Higher maximum pitch was also correlated with lower depressive scores for the home topic ($r(42)=-0.33$, $P=0.031$). Overall, SZ spent less time talking during the emotional questions than CO ($F(2,79)=3.37$, $P=0.039$). In study 2, SZ used fewer emotional words than CO only when discussing home ($F(1,32)=5.45$, $P=0.026$), with no other group differences in content emotionality. The severity of negative symptoms was related to reduced use of affective words when talking about home ($r(22)=0.49$, $P=0.022$) and sex ($r(22)=0.65$, $P < 0.01$). Overall, SZ used more personal pronouns than CO ($F(1,33)=5.62$, $P=0.024$), while CO used more

prepositions ($F(1,33)=6.09$, $P=0.019$), adjectives ($F(1,33)=4.62$, $P=0.039$) and have more words per sentence than SZ ($F(1,33)=8.75$, $P < 0.01$).

Discussion: While CO increased the pitch range in emotional speech, the pitch range was reduced in SZ. Semantic analysis showed that SZ overall was not different from CO in their use of affective words. Given the symptom correlation, reduced pitch range could be a possible measure to estimate negative symptoms, regardless of emotional valences in speech samples. In addition, the semantic analysis showed that SZ talked about topics in a more specific way by using more personal pronouns such as “I”, while the speech content for CO was richer and more abstract with more adjectives and words per sentence. A larger and more age-matched sample would provide a better picture as subject recruitment is still ongoing.

T308. CORRELATION ANALYSIS BETWEEN COMPUTATIONAL MEASURES OF VOICE AND SPEECH AND PANSS SCORES FROM PATIENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS IN REMISSION

Hugo Corona Hernández^{*1}, Janna de Boer¹, Silvia Ciampelli¹, Mara Fennema¹, Alban Voppel¹, Sanne Koops¹, Iris Sommer¹

¹*University Medical Center Groningen, University of Groningen*

Background: Clinical research capitalizing on methods of spoken language processing (SLP) (i.e., voice-related and acoustic measures) to assess psychotic symptoms has sought to find evidence that this quantitative approach can qualify as reliable, valid, and objective. A criterion to examine this consist in testing whether SLP measures correlate to the gold standard used in research and clinical practice to assess the severity of psychotic symptoms in individuals with schizophrenia-spectrum disorders (SSD), i.e., the Positive and Negative Syndrome Scale (PANSS). A recent meta-analysis (Parola et al., 2020) pulled evidence that pitch variability, proportion of spoken time, and pause duration correlate to negative symptoms as measured by PANSS scores. Yet, it also emphasized that replicating these findings having a large sample size and using a standardized set of acoustic features is warranted, which we decided to set as the aim of this study.

Methods: Data from 111 patients with SSD in remission was collected. Severity of psychotic symptoms was assessed using the PANSS. Three scores were used for this study: the PANSS scale total, and the totals of the negative and positive subscales. Patients’ speech was elicited using a semi-structured interview comprising open-ended questions designed to prevent excessive emotional arousal. Individual audio recordings of each patient's speech were the basis to computationally derive the 88 acoustic features of the extended Geneva Minimalistic Acoustic Parameter Set (eGeMAPS). Correlational analyses between each of the three total PANSS scores and the acoustic features were done separately. A two-steps visual inspection of scatter plots first without and then with regression line was used to identify pairs of variables seemingly showing a linear correlation, allowing to select the variables for statistical tests. Normal distribution of residuals was assessed through Shapiro–Wilk tests to determine whether (non)-parametric correlations were appropriate. Adjusted p-values $< .05$ were considered significant, correcting for multiple comparisons using the Bonferroni method.

Results: Shapiro-wilk tests confirmed that non-parametric (spearman) correlations were needed. The PANSS scale total score seemed to linearly relate to 28 eGeMAPS features, 14 out of which correlated to PANSS scale total with absolute ρ between .30 and .36 (all adj-p $< .05$). Most of these were measures of loudness ($n = 5$). The PANSS

negative total score seemed to linearly relate to 39 eGeMAPS features, 17 out of which correlated to PANSS negative total score with absolute ρ between .30 and .48 (all adj-p LESS THAN .05). Most of these were measures of loudness ($n = 7$). The PANSS positive total score seemed to linearly relate to 30 eGeMAPS features, with measures related to fundamental frequency ($n = 9$), loudness ($n = 8$), timbral information ($n = 5$), sound intensity ($n = 5$), and pronunciation of vowels ($n = 3$). There were no significant correlations between the PANSS positive total score and these 30 features.

Discussion: Our results suggest that SLP measures can capture information related to both negative psychotic symptoms and total psychopathology, unlike that of positive symptoms. Future research should disentangle whether loudness differently accounts for negative psychotic symptoms and total psychopathology.

T309. CONDITIONED HALLUCINATIONS ARE ASSOCIATED WITH INCREASED TOP-DOWN CONNECTIVITY: AN INTRACRANIAL EEG STUDY

Yufei Cai¹, Julia Rodriguez-Sanchez*², Yanyan Li¹, Chao Zhang³, Rick Adams², Daniel J. Hauke², Kai Zhang³, Albert Powers⁴, Liang Wang¹

¹CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, ²University College London, ³Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, ⁴Yale University School of Medicine, New Haven, CT

Background: Auditory hallucinations are a major feature of psychosis spectrum disorders. Growing evidence suggests that they are caused by an overreliance on prior beliefs, which dominate inference above incoming sensory evidence. Conditioned hallucinations (CH) can be induced in healthy individuals by pairing stimuli across two modalities (Powers et al., 2017, Science), allowing to investigate the role of perceptual priors and sensory evidence, as well as the underlying neural mechanisms.

Methods: Intracranial electroencephalography data was collected from 19 patients with medically-refractory epilepsy during the CH task. Briefly, participants were instructed to detect a 1000-Hz auditory target embedded in white noise which co-occurred with a visual stimulus. In a subset of 7 patients, we used dynamic causal modelling to analyse effective connectivity between the posterior superior temporal sulcus (STS) and the inferior frontal gyrus (IFG), previously shown to mediate CH.

Results: Replicating past results, participants reported perceiving a tone on trials when no target was present (CH trials), with higher CH rates in those with high hallucination proneness. During CH trials, there was increased alpha/beta (8-30 Hz) activity in the IFG and increased gamma (30-150 Hz) activity in the STS, compared with trials where participants correctly reported the absence of a target. The STS also showed delayed gamma activity in CH relative to correct hit trials. Both effects were best explained by a task-modulated increase in connectivity from the IFG to the STS (posterior probability GREATER THAN .95).

Discussion: We show that task-induced hallucinations are caused by an increase in top-down connectivity. Our results support the hypothesis that hallucinations arise from an overreliance on prior beliefs.

T310. SELF-ESTEEM IN CHILDREN WITH FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER AND CONTROLS ASSESSED LONGITUDINALLY IN A POPULATION-BASED COHORT STUDY

Mette Krantz^{*1}, Ditte Ellersgaard², Nicoline Hemager³, Maja Gregersen⁴, Anne Søndergaard³, Aja Greve⁵, Julie Marie Brandt⁶, Lotte Vedum⁷, Melanie Ritter¹, Christina Bruun Knudsen⁷, Anna Krogh Andreasen⁸, Carsten Hjorthøj⁹, Ole Mors¹⁰, Anne Thorup¹¹, Merete Nordentoft¹²

¹Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR, ²Mental Health Services in Capital Region of Denmark, Mental Health Centre Copenhagen, ³CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, ⁴CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR, ⁵Psychosis Research Unit, Aarhus University Hospital Psychiatry, ⁶CORE-Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, ⁷The Psychosis Research Unit, Aarhus University Hospital Psychiatry, ⁸Psychosis Research Unit, Aarhus University Hospital - Psychiatry, ⁹Copenhagen Research Center for Mental Health-CORE; Mental Health Center Copenhagen, Copenhagen University Hospital, Denmark, ¹⁰Psychosis Research Unit, Aarhus University Hospital, ¹¹Mental Health Services in Capital Region of Denmark, Child and Adolescent Mental Health Centre, ¹²Copenhagen Research Centre for Mental Health (CORE), Mental Health Centre Copenhagen, Copenhagen University Hospital

Background: Self-perception is of immediate importance for well-being and quality of life and low self-esteem is a risk factor for mental illness. Children of parents with schizophrenia or bipolar disorder are at increased risk of experiencing a range of difficulties related to developmental, parental and social factors which might influence self-esteem negatively, and further, their risk of developing mental illness is increased, compared to the background population. Therefore, assessing self-perception and identifying predictors of low self-perception in this group can aid to obtain knowledge on how to support a positive development and possibly prevent mental illness.

Methods: In a nationwide cohort of children of parents with schizophrenia or bipolar disorder, we assessed self-esteem at ages 7, 9, 11 and 14 with the questionnaire "I Think I am", age-appropriate versions, consisting of the subscales "Physical appearance", "Skills and talents", "Psychological well-being", "Relationships with family" and "Relationships with others". Background information concerning family characteristics and interviews concerning psychopathology, level of parental functioning, levels of stimulation and support provided at home, and bullying was assessed for both children and caregivers.

Results: A total of 519 children participated with data from at least one time point (N=514 at age 7, N=466 at age 9, N=439 at age 11, and N=415 at age 14). Across all time points of assessment, children of parents with schizophrenia had lower total scores compared with controls ($p \leq 0.001$), and at age 11, this was also the case for children of parents with bipolar disorder ($p = 0.002$). Across all ages except for age 9, overall differences were found between groups in proportions with low, medium, and high self-esteem. For children of parents with schizophrenia, subscale differences both concerning skills, appearance, well-being and relationships were present at all assessments while no subscale differences were present between children of parents with bipolar disorder and controls at age 7. However, subscales resembling those with differences between the schizophrenia risk group and controls began

likewise to differ for the bipolar risk group from age 9. Experience of bullying, and low levels of stimulation and support provided at home at age 7 predicted low age 14 self-esteem, and low self-esteem at age 7 predicted presence of a mental disorder at age 11.

Discussion: This study demonstrates that particularly children of parents with schizophrenia, but also bipolar disorder, perceive themselves more negatively than children of parents with none of these disorders. It highlights the need for awareness of low self-esteem among children at familial high risk of severe mental disorder, and suggests that awareness of risk factors for self-esteem, including experience of bullying and living in an inadequate home environment, is needed. Further, our results suggests that self-esteem may be a relevant predictor of later psychopathology and thus relevant to assess for prevention and early intervention among children at familial risk of schizophrenia or bipolar disorder.

T311. PREVALENCE OF PSYCHOTIC DISORDERS IN PROBLEM GAMBLERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Olivier Corbeil*¹, Laurent Béchard², Elizabeth Anderson³, Charles Desmeules⁴, Maxime Huot-Lavoie⁴, Lauryann Bachand³, Sébastien Brodeur⁴, Pierre-Hugues Carmichael⁵, Christian Jacques³, Marco Solmi⁶, Isabelle Giroux³, Michel Dorval², Marc-André Roy⁴, Marie-France Demers²

¹Laval University, ²Faculty of Pharmacy, Laval University, ³School of Psychology, Laval University, ⁴Faculty of Medicine, Laval University, ⁵Center of Excellence on Aging in Quebec, ⁶Department of Psychiatry, University of Ottawa

Background: High rates of psychiatric comorbidities have been found in people with problem gambling (PBG), including substance use, anxiety, and mood disorders. Psychotic disorders have received less attention, although this comorbidity is expected to have a significant impact on the course, consequences, and treatment of PBG. This review aimed to estimate the prevalence of psychotic disorders in problem gamblers.

Methods: Medline (Ovid), EMBASE, PsycINFO (Ovid), CINAHL, CENTRAL, Web of science, and ProQuest were searched on November 1, 2023, without language restrictions. Studies involving people with PBG and reporting the prevalence of psychotic disorders were included. Risk of bias was assessed using the Joanna Briggs Institute critical appraisal for systematic reviews of prevalence data. The pooled prevalence of psychotic disorders was calculated using a random effects generalized linear mixed model.

Results: Of 1271 records screened, 22 studies (n = 19,131) were included. The overall prevalence of psychotic disorders was 4.9% (95% CI, 3.6 – 6.5%, I² = 88%). Among the different types of psychotic disorders, there were no significant differences between the prevalence of schizophrenia, non-affective psychotic disorders, and any psychotic disorders, including affective psychoses. No differences were found for factors such as type of population (treatment-seekers vs non-treatment-seekers) and treatment setting (inpatient vs outpatient). The majority of included studies had a moderate risk of bias.

Discussion: There is a need to better understand the comorbidity of psychotic disorders in problem gamblers, as this knowledge is key to promoting appropriate prevention and treatment strategies for the non-negligible proportion of individuals affected.

T312. HOMOCYSTEINE, RENAL FUNCTION AND NEUROLOGICAL SOFT SIGNS IN INDIVIDUALS WITH SCHIZOPHRENIA

Michael Treiber*¹, Sofia Athanasiou², Kostas Chovardas², Theocharis Kyziridis², Olympia Letsiou², Eva-Maria Tsapakis², Konstantinos Fountoulakis²

¹Medical University of Vienna, ²Aristotle University of Thessaloniki

Background: Schizophrenia is associated with several markers of inflammation and aberrant neurodevelopment. Homocysteine (Hcy) is suggested to have a pathogenic impact on neurodevelopment, the cardiovascular system and renal function, through induction of oxidative stress and excitotoxicity. Neurological soft signs (NSS) refer to a group of subtle sensory and motor deficits, linked to symptom severity in schizophrenia. In this study we aim to evaluate associations between psychopathology, NSS, Hcy, and blood-based parameters of renal function in individuals with schizophrenia.

Methods: Patients were recruited at the 3rd Department of Psychiatry of Aristotle University of Thessaloniki (Ethics Committee approval no. 74/2023, 17/12/2023). We recruited (a) in-patients with schizophrenia following acute symptom resolution and stabilization, and (b) stable out-patients with schizophrenia provided they were on maintenance treatment for a minimum of six months. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). We evaluated NSS using the Greek version of the Neurological Evaluation Scale (NES). Blood samples were drawn after an overnight fasting and tobacco abstinence for over twelve hours. We used the Pearson correlation with Bonferroni post-hoc corrections for multiple comparison to test for correlations between PANSS scores, NSS, Hcy, Folate, and biochemical indices of renal function, namely urea and creatinine.

Results: A total of 26 patients (10 female and 14 in-patients) with schizophrenia were included in this preliminary analysis of an ongoing observational study. Mean age of participants was 41.3 (SD 11.2) years. We observed hyperhomocysteinaemia (Hcy levels GREATER THAN 10 $\mu\text{mol/L}$) in 87% of our sample. The correlation between Hcy and NSS was not significant. In an explorative analysis, however, NSS were significantly correlated with PANSS scores ($r=.390$, $p=.05$). The “sensory integration” subgroup of the NES correlated significantly with the PANSS positive scale scoring ($r=.522$, $p=.009$). After Bonferroni correction, Pearson’s correlations revealed a significant association between Hcy and folate ($r=-.594$, $p=.014$), urea ($r=.559$, $p=.030$), but the correlation between Hcy and creatinine did not survive Bonferroni correction.

Discussion: Our preliminary data showed that Hcy levels are positively associated with renal function parameters such as urea and creatinine, although the correlation with creatinine did not remain significant after correction for multiple comparisons. Imbalance in the Hcy metabolism, thus oxidative stress and excitotoxicity, have been associated with renal dysfunction [Yang et al. 2020]. High Hcy levels, associated with increased creatinine and blood urea levels, were reported in hypertension, a main cause of renal dysfunction and a comorbidity often found in individuals with schizophrenia. On the other hand, Hcy levels were negatively associated with folate levels. Moreover, the positive correlations between the “sensory integration” subgroup of the NES and the PANSS positive scale scoring seem to contribute to reported findings on the impairment of sensory integration in psychotic disorders. Hcy did not correlate with symptom severity or NSS. These are preliminary results, however, and recruitment is currently ongoing to increase the validity of our conclusions. Nevertheless, it should be kept in mind that antipsychotics per se may be associated with renal function decline, thus further research investigating strategies that are lowering Hcy levels, such as folic acid and cyanocobalamin (Vitamin B12) substitution might provide deeper insight.

T313. PSYCHOTIC EXPERIENCES AND ITS CLINICAL CORRELATES IN ADOLESCENTS WITH PTSD SECONDARY TO A RECENT SEXUAL ASSAULT

Olga Puig-Navarro^{*1}, Judit Nova², Laura Blanco³, Radua Joaquim⁴, Lydia Fortea⁵, Anna Fabregas⁶, Fortea Adriana⁷

¹Program for the Prevention and Treatment of Psychological Consequences in Women Victims of Sexual Assault (SA Program). Hospital Clinic of Barcelona, 2017SGR881, FCRB/IDIBAPS. CIBERSAM, ²Fundació Clinic per la la Recerca Biomèdica (FCRB/IDIBAPS)., ³SA Program. Department of Psychiatry, Hospital Clinic of Barcelona., ⁴IMARD Research group. Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB/IDIBAPS). University of Barcelona. CIBERSAM., ⁵IMARD Research group. Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB/IDIBAPS)., ⁶EMMA group. Pediatric Service. Hospital Universitario Vall Hebron. UAB., ⁷SA Program. Department of Psychiatry, Hospital Clinic of Barcelona / Fundació Clinic per la la Recerca Biomèdica (FCRB). CIBERSAM.

Background: Adolescence is the developmental period with the highest risk of suffering a sexual assault (SA) as well as a critical period for developing psychotic symptoms. Sexual trauma is a significant risk factor for developing psychosis (Lowey, 2019; Varese, 2012). Posttraumatic Stress Disorder (PTSD) symptoms partly mediate the association between trauma and psychotic experiences (PEs) (Strelchuk et al., 2022). AIM: To examine PEs and its clinical correlates in a sample of adolescent women survivors of a recent SA.

Methods: Ongoing prospective longitudinal study including help-seeking adolescent women who meet criteria for PTSD attended in the two reference clinical programs for sexual violence in Barcelona (Hospital Clínic, Hospital Vall d'Hebrón). Sample: 24 SA-PTSD adolescents (17.2±1.6 years, 82% Caucasian, age at SA 16.5±1.8) and 22 community control adolescents (CC, 17.4±1.1 years, 91% Caucasian). Inclusion/exclusion criteria: 12-18 years, meeting criteria for PTSD secondary to SA suffered in the previous year, IQ GREATER THAN 70, not having neurological conditions. Additional exclusion criteria for CC sample were having a history of sexual violence or PTSD. Instruments: Clinician-Administered PTSD scale for DSM-5-Child/Adolescent version (CAPS-CA-5), Community Assessment of Psychic Experiences-42, Spanish version (CAPE-42), Adolescent Dissociative Experiences Scale (A-DES), Global Functioning: Role and Social scales.

Results: SA-PTSD and CC adolescents did not significantly differ in age ($t=0.49$, $p=0.626$), race ($\chi^2=2.91$, $p=0.234$) nor familial socioeconomic status (mostly medium, $t=0.51$, $p=0.612$). CA-CAPS-5 symptoms severity in SA-PTSD group was high (total symptoms: 40.14±9.42). SA-PTSD adolescents had higher PEs than CC (CAPE-42 total symptoms: 91.38±21.14 VS 67.18±11.93, $t=4.83$, p LESS THAN 0.001; positive dimension: 1.9±0.48 VS 1.5±0.31, $t=3.82$, p LESS THAN 0.001; negative: 2.3±0.60 VS 1.8±0.40, $t=3.86$, p LESS THAN 0.001; depressive: 2.6±0.69 VS 1.7±0.25, $t=5.85$, p LESS THAN 0.001) and higher distress levels (positive dimension: 2.3±0.51 VS 1.73±0.50, $t=4.01$, p LESS THAN 0.001; negative: 2.45±0.68 VS 2.03±0.46, $t=3.86$, p LESS THAN 0.001; depressive PEs: 2.76±0.60 VS 2.2±0.64, $t=3.11$, $p=0.003$).

Total CAPE-42 symptoms in SA-PTSD adolescents were correlated with PTSD intrusion symptoms (0.631, $p=0.002$), mood/cognitive alterations (0.513, $p=0.015$), hiperarousal (0.445, $p=0.038$) and total PTSD symptoms (0.654, $p=0.001$), and with dissociative symptoms (0.756, p LESS THAN 0.001). They were negatively correlated with social functioning (-0.545, $p=0.009$). Positive PEs were correlated with PTSD total severity symptoms (0.596, $p=0.003$), intrusion symptoms (0.504, $p=0.017$), hiperarousal (0.555,

p=0.007) and dissociative symptoms (0.731, p LESS THAN 0.000). Negative PEs were correlated with PTSD total severity symptoms (0.524, p=0.012), intrusive (0.496, p=0.019) and mood/cognitive PTSD alterations (0.478, p=0.025), and with dissociative symptoms (0.647, p=0.001). They were negatively correlated with lower social functioning (-0.580, p=0.005). Depressive PEs were correlated with PTSD total severity symptoms (0.666, p=0.001), intrusive (0.788, p LESS THAN 0.001), and mood/cognitive PTSD symptoms (0.536, p=0.010) and dissociative symptoms (0.638, p=0.001), and with lower social (-0.689, p LESS THAN 0.001) and role (-0.523, p=0.012) functioning.

Discussion: Adolescents with SA-PTSD showed higher PEs than CC and experienced them as more distressing. PEs were correlated with PTSD symptoms severity, dissociative symptoms and poorer functioning. Positive, negative and depressive PEs appeared to be specifically correlated with different dimensions of PTSD whereas dissociative symptoms appeared to be correlated with all them. ACKNOWLEDGMENTS: Fund Alicia Koplowitz.

T314. GENE EXPRESSION IMPUTATION PROVIDES CLINICAL AND BIOLOGICAL INSIGHTS INTO TREATMENT-RESISTANT SCHIZOPHRENIA POLYGENIC RISK

Lucía Prohens Coll*¹, Natalia Rodriguez², Alex Gonzalez-Segura², Albert Martínez-Pinteño³, David Olivares Berjaga⁴, Irene Martínez Serrano⁵, Aitor González⁶, Gisela Mezquida⁷, Mara Parellada⁸, Manuel J. Cuesta⁹, Miquel Bernardo¹⁰, Patricia Gassó¹¹, Sergi Mas¹²

¹Universitat de Barcelona, ²University of Barcelona, ³Department of Basic Clinical Practice, Unit of Pharmacology, University of Barcelona, ⁴Department of Basic Clinical Practice, University of Barcelona, ⁵University of Barcelona, Hospital Clinic, ⁶Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), ⁷Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, Hospital Clinic of Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); University of Barcelona, ⁸CIBERSAM, Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, ⁹Department of Psychiatry, Complejo Hospitalario de Navarra. IdiSNA, Navarra Institute for Health Research, Pamplona, ¹⁰Hospital Clinic Barcelona. Universitat Barcelona. IDIBAPS. CIBERSAM, ¹¹University of Barcelona-IDIBAPS-CIBERSAM, ¹²Department of Basic Clinical Practice, University of Barcelona, IDIBAPS, CIBERSAM

Background: Treatment-resistant schizophrenia (TRS) is defined as a less than 20% reduction of positive symptoms after at least two trials of non-clozapine antipsychotics, each at an adequate dose and duration of treatment, and potential comorbid factors such as addiction (Potkin et al., 2020) and poorly treated due to the underutilization of clozapine, the gold standard and only evidence-based antipsychotic prescribed for this condition (Rubio and Kane, 2020). As longer delays in clozapine initiation are associated with poorer treatment outcomes (Shah et al., 2018) the identification of predictors and biomarkers for the early detection and treatment of TRS is an essential step. In this study, we investigated

the biological and clinical aspects of TRS within a polygenic framework. With a gene expression imputation LESS THAN on from the largest genome-wide association LESS THAN on study GWAS of TRS (Pardiñas et al., 2022) we could translate it to regulatory mechanisms that can be associated with clinical features of TRS in a cohort with first episode psychosis (FEP).

Methods: We performed transcriptome imputation LESS THAN on using S-PrediXcan in the largest GWAS of TRS to find gene LESS THAN cally regulated gene expression (GReX). To test if the GReX was associated with TRS, we performed a TWAS using predic LESS THAN on models (MASHR-based models) trained on nine brain LESS THAN ssues based on GTEx v8 release data: putamen (PUT), substantia nigra, (SN) prefrontal cortex (FL), hypothalamus (HTH), hippocampus (HIP), cerebellum (CB), caudate (CAU), anterior cingulate cortex (CNG) and amygdala (AMY). Next, for each LESS THAN ssue, we constructed a GReX risk score (GReX-PS) of the iden LESS THAN fied genes in a sample of genotyped FEP pa LESS THAN ents to test the associa LESS THAN on of the GReX-PS with clinical phenotypes, including clinical symptomatology, global func LESS THAN oning and cogni LESS THAN ve performance.

Results: GReX-RSs constructed with the SN, HIP and AMY at a p-value = 0.5 were significantly (p LESS THAN 0.001 according to Holm-Bonferroni sequen LESS THAN al correc LESS THAN on method) associated (SN: $R^2=0.061$, $F(3197)=4.25$, p LESS THAN 0.001; HIP: $R^2=0.088$, $F(3197)=6.33$, p LESS THAN 0.001; AMY: $R^2=0.098$, $F(3197)=7.14$, p LESS THAN 0.001) and significantly predicted (SN: $\beta=0.15$, 95 % CI= p GREATER THAN 0.001) and was significantly associated with more cogni LESS THAN ve impairments in sustained agen LESS THAN on ($\beta=-0.13$, 95 % CI=[-0.20;- 0.05], p LESS THAN 0.001). The p-value of 0.5 was selected because it explained the largest propor LESS THAN on of variability in all cases. In comparison with random sets of proteins of similar size from the genome, the PPI networks built with the lists of genes included in the GReX-RS, (using pvalues= 0.5) which were significantly associated with clinical data (SN 814 genes, HIP 887 genes, AMY 1155 genes and FL 1112 genes), showed significantly more connec LESS THAN ons than expected ($p=1.9\times10^{-5}$; 1.9×10^{-3} ; 1.8×10^{-6} ; 1.0×10^{-16} ; respec LESS THAN vely). A cluster analysis iden LESS THAN fied two func LESS THAN onal clusters in the SN network, cluster 1 enriched with biological processes related to the immune system and the major histocompa LESS THAN bility complex II, and cluster 2 enriched with mitochondrial gene expression and transla LESS THAN on and RNA metabolic processes. The HIP network included three clusters: cluster 1 enriched with cellular metabolic processes (including nitrogen compounds, RNA, DNA and proteins) and response to stress, cluster 2 enriched with transport and immune system processes, and cluster 3 enriched with acid metabolic processes. Two clusters were iden LESS THAN fied in the network constructed with AMY genes: cluster 1 enriched in nucleic acid processes and cluster 2 enriched in cellular localiza LESS THAN on processes. Finally, three clusters were defined in the FL network: cluster 1 enriched in nucleic acid processes, cluster 2 enriched in acid and lipid metabolic processes and cluster 3 enriched in mitochondrial gene expression.

Discussion: Our analysis provides evidence that the polygenic basis of TRS includes gene LESS THAN c variants influencing gene expression in key brain areas like the substantia nigra, hippocampus, amygdala and prefrontal cortex, which are closely related to the suggested clinical predictors of TRS (persistence of nega LESS THAN ve symptomatology and cogni LESS THAN ve altera LESS THAN ons in sustained agen LESS THAN on) in FEP pa LESS THAN ents. This gives more insight into the biological mechanisms and clinical explana LESS THAN on

underlying TRS, support the idea of TRS as a distinct subtype of schizophrenia with neurobiological differences from treatment-responsive schizophrenia, offering insights into improving prevention and treatment from the earliest stages of the illness.

T315. EFFECTS OF DELUSIONAL AND DISTRESSING MEMORIES ON NEGATIVE PRIMING PERFORMANCE AMONG INDIVIDUALS WITH DELUSIONS

Suzanne So¹, Chen Zhu^{*2}, Chui-de Chiu¹, Gloria HY Wong³, Ryan Balzan⁴, Sandra Saurman Chan¹

¹The Chinese University of Hong Kong, ²Shenzhen University, ³The University of Hong Kong, ⁴Flinders University

Background: It has been suggested that patients with schizophrenia have impaired inhibitory control (IC), manifested as problems in ignoring irrelevant information during information processing. Research has shown that IC is correlated with the overall severity of psychotic symptoms and that improvement in IC is associated with symptom reduction. It is of interest to examine the relationship between IC and delusions in particular, because it has been argued that delusions may be maintained by the failure to inhibit irrelevant information from entering the appraisal. It has been suggested that cognitive control may be further disrupted by aberrant salience, a tendency to attribute significance to irrelevant stimuli, which is heightened when an individual is experiencing psychotic symptoms actively. Therefore, adopting a single-symptom approach and a more sensitive negative priming (NP) paradigm, this study aimed to (i) examine the association between NP performance and delusions, and (ii) compare NP performance between a delusional memory condition and two control conditions (distressing memory and neutral).

Methods: Adults with schizophrenia and delusions (PANSS P1 score GREATER THAN 3) were tested with the negative priming (NP) paradigm, as well as clinical ratings and demographic measures. During the baseline interview, autobiographic memories of a delusional experience and a distressing experience were elicited using the MADS interview (Wessely et al., 1993) and the autobiographical memory test (AMT, Williams and Broadbent, 1986) respectively. For the AMT, participants were individually presented with negative emotion words (e.g. sad, regretful, angry, fearful, worried, frustrated). For both types of memories, participants were encouraged to provide detailed information about the experience and confirmed their ability to vividly recall it.

In the 96-trial numerical NP task, participants were instructed to respond to the count of integers while ignoring the identity of the integer. Reaction times (RT) and accuracy of the button-press responses were recorded. In the 48 NP trials, the target of the probe is the same as the distractor of the prime (e.g. '111' □ '2'), whereas in the 48 non-NP trials, the probe trial is unrelated to the prime (e.g. '44' □ '3'). An NP score is calculated as the RT difference between correct NP and non-NP trials. All participants completed the neutral condition first, followed by the two memory conditions in a counterbalanced order.

Results: The sample consisted of 68 patients (41.54±12.63 years of age, 34 females) with a non-affective schizophrenia spectrum disorder and active delusions. Forty-one were on medication (CPZ 481.07±500.09). The average number of years in psychiatric service was 8.5±8.79. The average IQ was 92.25±10.86. GAD-7 was 7.13±5.95. PHQ-9 was 8.76±6.54.

PANSS scores were 17.24 ± 4.57 (Positive), 13.79 ± 4.39 (Negative), and 29.46 ± 7.8 (General psychopathology). PANSS delusions (P1) score was 4.68 ± 0.97 . PSYRATS scores were 9.63 ± 11.93 (Hallucinations) and 13.82 ± 4.45 (Delusions). Across experimental conditions, the NP effect was relatively small (2.55 ± 30.33). One-way repeated ANOVA test found no significant effect of conditions ($F(2,132) = 0.54$, $p = 0.584$). None of the NP effects in any conditions was significantly correlated with PANSS delusions (P1), PSYRATS total scores, or PSYRATS dimensions scores (all p s GREATER THAN .050). The NP effects were not significantly correlated with IQ, PHQ-9, GAD-7 or antipsychotics (p s GREATER THAN .050).

Discussion: The negative priming effect was reduced in patients with delusions. This was not correlated with delusionality. Activation of memories did not significantly influence inhibition control.

T316. USING ACOUSTIC SPEECH ANALYSIS TO DIFFERENTIATE BETWEEN SCHIZOPHRENIA SPECTRUM DISORDERS AND BIPOLAR DISORDER

Sanne Koops^{*1}, Hugo Corona-Hernández¹, Mara Fennema¹, Janna de Boer¹, Silvia Ciampelli¹, Alban Voppel¹, Iris Sommer¹

¹*Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, the Netherlands.*

Background: Schizophrenia spectrum disorder (SSD) and bipolar disorder (BD) lay on a continuum and cannot always be distinguished. Yet, one or the other diagnosis has implications for treatment and prognosis. To complicate things further, diagnosis may change over time and in some patients diagnosis and treatment need to be re-assessed.

Given the importance of speech patterns during the diagnostic process in current clinical practice, there has been extensive research exploring the potential of automatic speech analysis to enhance the diagnostic process. To date, most of this research has focused on classifying diagnosed patients from healthy controls, or classifying between subtypes of similar diagnoses. However, it would be of large clinical value if a speech-based tool could aid in differentiating between psychiatric conditions. Here, we explored the value of using automatically extracted acoustic features of spontaneous speech in distinguishing patients diagnosed with SSD from patients diagnosed with BD.

Methods: Spontaneous speech was obtained during a short semi-structured interview of 64 participants diagnosed with SSD and 64 participants diagnosed with BD. Using OpenSMILE, the extended Geneva Acoustic Minimalistic Parameter Set (eGeMAPS) was used to extract 88 acoustic features. These features include 6 temporal parameters (e.g. speech rate), 24 frequency parameters, 43 spectral parameters (e.g. Mel-frequency cepstral coefficients) and 14 parameters related to energy or amplitude (e.g. intensity). These features were fed into a random forest algorithm with 10-fold crossvalidation to assess their ability in accurately classifying the two conditions. Gini-importance scores were calculated to estimate the importance of specific predictors in the model.

Results: The model reached an accuracy of 0.73 in classifying participants with SSD and BD on the basis of acoustic parameters of speech. The model showed an AUC of 0.79, precision of 0.69 and recall of 0.82. We found that voiced segments per seconds obtained the highest importance score in the final model, with on average more segments in people diagnosed as

BD ($M = 2.34$, $SD = 0.63$) than in those diagnosed with SSD ($M = 1.79$, $SD = 0.63$), indicating shorter speech segments in patients with BD.

Discussion: These initial results show that a machine learning classifier on the basis of automatically extracted acoustic speech parameters can distinguish between patients with SSD and BD. Voiced segments per seconds proved to be the most important predictor in this model. Shorter speech segments in BD may be attributed to symptoms related to (hypo)mania, such as more energetic or pressured speech, or jumping from topic to topic. Previous research demonstrated a higher rate of voiced segments in SSD compared to healthy controls. This may be more due to symptoms of disorganized speech in patients with SSD, resulting in more segmentation compared to healthy controls but with a less pronounced segmentation compared to BD.

Besides existing evidence of the potential of speech technology to differentiate a diagnosis from no diagnosis, these results now show that the technology also shows promise for differentiating between diagnostic categories in the field of psychiatry.

T317. EVALUATION OF DIFFERENT INTERVIEW PROTOCOLS WITH MACHINE LEARNING ALGORITHMS FOR AT-RISK MENTAL STATES (ARMS) CONVERSION SCREENING

João Medrado Gondim^{*1}, Alexandre Loch², Felipe Argolo³, Ana Caroline Lopes-Rocha⁴, Julio Cesar Andrade⁴, Martinus Theodorus van de Bilt⁴, Leonardo Peroni⁴, Natalia Mansur Haddad⁴, Guillermo Cecchi⁵, Natalia Mota⁶, Wagner Farid Gattaz⁴, Cheryl Corcoran⁷, Anderson Ara⁸

¹Campinas State University, ²University of Sao Paulo, ³Universidade de São Paulo (USP), ⁴Institute of Psychiatry, Laboratory of Neuroscience (LIM 27), University of Sao Paulo, Brazil, ⁵IBM TJ Watson Research Center, ⁶Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, ⁷Icahn School of Medicine At Mount Sinai, ⁸Department of Statistics, Federal University of Paraná, Curitiba-PR, Brazil

Background: At Risk Mental State (ARMS) is a preclinical stage indicating possible conversion of a patient into neurosis or psychosis. However, this preclinical stage is not deterministic for conversion alone, posing a problem when screening these patients. This work applies machine learning algorithms to investigate the use of two interview protocols with facial and head movement features, extracted from brief video-recordings, to assess whether ARMS participants will convert or not to psychosis.

Methods: 21 non-converters and 31 converters were interviewed with a memory reports protocol (MR) and the Structured Interview for Prodromal Syndromes subject overview (SO) while being recorded. We then extract facial landmarks frame-by-frame, employed to create facial and head movement features, either by simply summarizing each points' values (with median absolute deviation and interquartile range) or using them to create new features (head angles, distance or angle between points), also summarized later. 649 features were generated for both interviews from each participant, originating 1298 final features that were tested with Wilcoxon's Ranksum to select 87 that better separate the two groups, 4 from SO videos and 83 from RM videos.

These features were employed in the training of machine learning algorithms in different scenarios: first only the 4 SO features, secondly only the 83 RM features and then the 87 features from both videos used all together and separately with a Voting Classifier. Also, the

selected features were tested, comparing their correlation with 16 prodromal symptoms diagnosed values with Spearman's correlation test and their distribution with the absence (diagnosis ≤ 1) or presence (diagnosis ≥ 2) with Wilcoxon's Ranksum test.

Results: After 1000 rounds of leave-group-out training, each classifier achieved 72%, 79%, 79% and 81% F1 Score, using, respectively, SO, MR, both sets of features all together and separately. Considering the Sensibility (true positive rate), metrics were, respectively: 69%, 75%, 77% and 80%. Moreover, selected features from SO and MR videos showed significant p-values considering the absence or presence of differing prodromal symptoms, highlighting: the interquartile range of the angle between the tip of the nose and the midpoint between eyes, on the MR videos, and "Experience of Emotions and Self" (p-value: 0.0019) and the Spearman's correlation coefficient between the left corner of the mouth and the midpoint of the left eyebrow on the X axis, on the SO videos, and "Dysphoric Mood" (p-value: 0.0066). Also, 12 different MR features had a relevant (GREATER THAN 0.3) Spearman's correlation coefficient, emphasizing: the Spearman's correlation coefficient between two eyelids points in the Y axis and "Disorganized Communication" ($\rho=0.4251$).

Discussion: Our study shows how different protocols generate distinct information that, employed in combination, can provide diagnosticians with more precise information when assessing for conversion of ARMS participants. Selected features from SO and MR protocols showed significant correlations with different prodromal symptoms, leading to diverse usages of facial landmarks on the screening of ARMS patients.

T318. THE CLINICAL HIGH RISK STATE FOR SCHIZOPHRENIA SHARES NEURAL MECHANISMS OF SOCIAL COGNITIVE DEFICITS WITH CHRONIC SCHIZOPHRENIA

Jessica Lee^{*1}, Aida Murati¹, Nahian Chowdhury¹, Daniel Ruiz-Betancourt¹, Fabiola Plaza¹, Juan Sanchez-Peña¹, Gaurav Patel¹

¹*Columbia University and New York State Psychiatric Institute*

Background: Evidence suggests that social cognition disruptions are present in individuals at clinical high risk (CHR) of developing schizophrenia. However, whether the neural mechanisms underlying these disruptions are similar to participants with schizophrenia (SzP) remains unclear. Here we study whether CHRs share the same eye-tracking deficits and disruptions of the underlying temporoparietal junction and superior temporal sulcus (TPJ-STs) that we have previously found in SzP.

Methods: We collected eye-tracking data in 41 healthy controls (HC), 26 CHR and 43 SzP while they performed The Awareness of Social Inference Test (TASIT). We quantified eye-tracking deviation as the z-transformed distance from the mean of the HCs on each video frame. We further examined whether saccadic eye-movements towards moving facial expressions differed between groups as a function of both the face motion velocity and the amplitude of the saccade. To examine the functional integrity of the TPJ-STs, we used BOLD-fMRI data collected from a subset of 22 HC, 17 CHR and 23 SzP watching a 15-minute silent movie clip to quantify association of the inter-subject correlation (ISC) of each TPJ-STs area to TASIT performance. To examine the structural integrity of the TPJ-STs, we compared the functional connectivity from 22 minutes of resting state fMRI data collected from an overlapping sample of 41 HC, 30 CHRs and 42 SzPs.

Results: TASIT sarcasm performance in both HC and CHR was higher than SzP ($F(2,59)=13.67$, $p < 0.001$). However, CHR eye-tracking was divergent from HC

in the same intervals as SzP ($t(25)=3.75$, p LESS THAN .001). Additionally, CHRs made less large-amplitude saccades ($5-10^\circ$) to the same velocities of face-motion as SzP (37% reduction, p LESS THAN .01). In the movie-fMRI experiment, the ISC of the TPJm hub area in CHRs did not differ from HC as it did in SzP. However, only in CHRs, increased ISC of the TPJp high-level theory-of-mind area correlated with better TASIT sarcasm performance ($r(15)=-.66$, $p=.004$). In the resting-state fMRI experiment, we observed significantly decreased connectivity between the STS language and early visual areas ($F(2,111)=4.36$, p LESS THAN 0.05) in CHRs that was similar to SzPs. We also observed that the connectivity strength of the STS language to both late visual ($F(2,111)=4.11$, p LESS THAN 0.05) and auditory areas ($F(2,111)=5.02$, p LESS THAN 0.01) in CHRs was between HC and SzP.

Discussion: Together, the results suggest that CHR share some mechanisms of social cognition impairments with SzP. They also point to potential top-down mechanisms that mitigate the resulting impact of these impairments on social functioning. Identification of shared and distinct neural mechanisms of social perception in CHR and SzP will aid in better understanding of the pathophysiological mechanism underlying social deficits in schizophrenia.

T319. ASSESSING CONTROL OVER VISUAL AND VERBAL HALLUCINATIONS USING BISTABLE PERCEPTUAL TASKS

Gabriela Hernández-Busot*¹, Catalina Mourgues-Cordern², Adrianisse Vega-Reyes², Dayanna Seguí-Moró², Albert Powers III²

¹Yale, ²Yale University School of Medicine Department of Psychiatry

Background: Perceptual experiences, such as visual and auditory verbal hallucinations occur both in the general population and in those with psychosis. The degree to which individuals can voluntarily control such experiences significantly impacts their likelihood of seeking help. To determine whether control over perceptual events overall is higher in those with higher degrees of control over their hallucinations, we employed bi-stable auditory and visual tasks to a large sample of international voice-hearers.

Methods: The study analyzed data from 359 participants from the Yale Control Over Perceptual Experiences (COPE) study, who reported at least monthly auditory hallucinations over the last six months. We conducted our study using two bi-stable tasks: the auditory "Yanny or Laurel" task, where participants could hear either "Yanny" or "Laurel," and a visual task featuring dots perceived as moving either horizontally or vertically. The study was structured into six blocks, each designed to explore different facets of perceptual switching: The initial block established the 50% threshold for perceptual switches; the second block measured the natural rate of these switches, highlighting participants' inherent perceptual variability; the third and fourth blocks aimed to control perceptual changes, with the third block instructing participants to minimize perceptual switches and the fourth encouraging them to increase switches to evaluate perceptual flexibility; the fifth block measured the average time it took for participants to alter their percept along with low-level sensory biasing; and the final (sixth) block assessed how long participants could maintain a single perceptual viewpoint against low-level biasing in the opposite direction. This approach allowed for a nuanced understanding of how individuals perceive and modulate their sensory experiences in response to bi-stable stimuli. Subsequently, participants were subdivided based on their self-reported control over hallucinations into low (scores ≤ 2) and high (scores ≥ 3) control groups, utilizing the degree of control subscale from the COPE questionnaire.

Clinical measures such as the White Bear Suppression Inventory (WBSI), Launay-Slade Hallucination Scale (LSHS), Auditory Hallucinations Rating Scale (AHRs), COPE, and Peters et al. Delusions Inventory (PDI) were assessed.

Results: Preliminary findings show that individuals with lower control who exhibited higher tendencies towards thought suppression (as indicated by WBSI total, distraction, and intrusion scores of $r = -0.1055$, $r = -0.2009$, and $r = -0.1412$, respectively) were able to switch their visual perceptions more swiftly; this pattern was not observed in the high control group.

Discussion: These results suggest a potential mechanistic link between the propensity for thought suppression and the capacity to alter perceptions of ambiguous visual stimuli. In contrast, the lack of significant correlations within the high control group suggests that those with greater control over their hallucinations might employ different coping mechanisms or demonstrate a unique kind of perceptual adaptability. Future research will aim to refine these observations by employing a computational model to derive estimates of the precision of perceptual priors and examine how these estimates correlate with symptom severity. We also plan to evaluate performance metrics that are closely related to clinical outcomes.

T320. IMMUNOGLOBULIN LEVELS IN SCHIZOPHRENIA/OCD DURING RITUXIMAB TREATMENT: ASSOCIATIONS WITH CLINICAL RESPONSE

Mats Humble*¹, Sofia Sigra Stein¹, Daniel Eklund¹, Susanne Bejerot²

¹Örebro Universitet, School of Medical Sciences, ²University Health Care Research Center, Faculty of Medicine and Health, and School of Medical Sciences, Örebro University,

Background: It has been hypothesised both for schizophrenia (SCZ) and obsessive-compulsive disorder (OCD), that immunological/inflammatory factors are involved in the pathophysiology, at least in subgroups of patients. However, despite major research efforts within immunopsychiatry, we still lack a coherent view of detailed immune mechanisms and possible pathogens involved. Our aim was to scrutinise the clinical effects in SCZ and OCD of a potent immunomodulatory treatment that is proven useful in clearly autoimmune disorders (such as rheumatoid arthritis or multiple sclerosis) and relate these to immunochemical findings.

Methods: We conducted a small pilot study of treatment-resistant, severely ill psychiatric patients, 9 with SCZ and 10 with OCD. They were treated with rituximab, an anti-B-cell agent directed at CD20-carrying lymphocytes. One single infusion of 1000 mg rituximab (Mabthera®) was given at baseline and the patients were followed for one year. Symptoms were rated with Positive and negative syndrome scale (PANSS), Yale-Brown obsessive-compulsive scale (Y-BOCS) and Clinical global impression (CGI), and global functioning with Personal and social performance scale (PSP). Before the treatment and 5 months post-treatment, serum levels of the immunoglobulin classes IgA, IgG and IgM were measured. These were then related to therapeutic results and other clinical variables.

Results: A significant symptomatic and functional improvement was seen in 7/9 patients with SCZ and in 4/10 patients with OCD. Before treatment, IgA-values were bimodally distributed (.63 – 2.0 and 2.6 – 3.7 g/L, respectively, population reference .88 – 4.5). Two non-responder patients (one SCZ, one OCD) were IgA-deficient. The SCZ patients in the higher mode responded significantly better than those in the lower ($\chi^2 = 5.1$, df 1, $p = .023$). All five individuals with comorbid autism belonged to the low mode ($\chi^2 = 6.1$, df 1, $p = .013$). Baseline IgG ranged between 7.5 and 16.5 (reference 6.7 – 14.5 g/L) and IgM between .35 and 2.9 (.27 – 2.1 g/L). Two OCD patients had supranormal levels of IgM, one of them (a rituximab responder) also of IgG.

Discussion: We have shown an association between symptomatic improvement and immunoglobulin levels in SCZ, but not in OCD. Higher IgA at baseline was related to clinical response in SCZ but not in OCD. Since most serum IgA has its origin in the gut-associated lymphoid tissues (GALT), our findings suggest that interactions between the GALT and the enteric microbiome may be involved in SCZ. The study was explorative and due to the small sample size, all results should be viewed with utmost caution. Another limitation is that no subclass or isotype analyses were performed.

T321. NAVIGATING THE NEXUS: CHILDHOOD TRAUMA, CANNABIS USE, EMOTION REGULATION IN THE MULTI-HIT FRAMEWORK OF PSYCHOSIS

Kareem Hamada¹, Efim Oykhman¹, Lola Nedic¹, Nora Sun¹, Sahil Sood¹, Peter Levin¹, Nicole Rychagov¹, Matcheri Keshavan¹, Elisabetta C. del Re^{*2}

¹Harvard Medical School, ²Harvard Medical School, Veterans Affairs Boston Healthcare System, Beth Israel Deaconess Medical Center

Background: Over the past 20 years, the interplay between childhood trauma (CT), cannabis use (CA), emotion regulation (ER), and the development of psychosis spectrum disorders has garnered significant attention. The psychosis spectrum encompasses several disorders, such as Schizophrenia (SZ), Bipolar 1 with psychosis (BP), and Schizoaffective Disorder (SAD). The present review distills current knowledge on the relationship between CT, CA, and ER by examining literature published within the last five years. The objective is to present a concise yet comprehensive overview and propose a novel multi-hit framework for understanding the onset of psychosis.

Methods: To identify studies relating CT, CA and ER within psychosis, a search was conducted on December 10, 2023, in PubMed and Google Scholar. Studies were identified for fit using inclusion and exclusion criteria. Inclusion criteria were: 1) Relevance 2) Peer-reviewed papers 3) Within last 5 years, 4) English language 5) Quantitative or qualitative study design, 6) Populations: SZ, BP, SAD 7) Outcomes related to CT, CA, ER, and psychosis. Exclusion: 1) Irrelevant 2) Non-peer-reviewed 3) Pre-print 4) Not English, 5) Other diagnoses, 6) Animal studies, 7) Insufficient data or unclear methods 8) duplications.

Results: 54 studies were included in this review. As expected, psychosis patients have significantly higher prevalence of CT and CA. In the presence of both risk factors, CT and CA mediate each other's effect on psychosis risk, with contribution by risk genetic background. Poor emotion regulation was positively associated with both CT and CA and related to risk of developing psychosis. However, the influence of CT, CA, and emotion regulation varied across SZ, BP, and SAD.

Discussion: Our findings support a novel multi-hit framework for psychosis onset, wherein a combination of interacting environmental and genetic risk factors impact risk of psychosis. Emotion regulation impairment here is key, both as a risk and as an outcome of psychosis. Future studies should integrate emotion regulation assessments alongside CA, CT, and genetic risk factors to clarify interactions.

T322. OPEN BOARD

T323. SELF-ESTEEM AND SELF-STIGMA AMONG PERSONS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: A CROSS-SECTIONAL STUDY

Ana Silva Pinto*¹, Marta Almada², Alexandra Sousa³, Isabel Fonseca⁴, Paula Freitas², Alice Lopes²

¹*Unidade de Psiquiatria Comunitária, Serviço de Psiquiatria e Saúde Mental, Centro Hospitalar Universitário de Santo António,* ²*ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto,* ³*Unidade Corino de Andrade, Centro Hospitalar Universitário do Porto,* ⁴*EPIUnit and Instituto de Saúde Pública da Universidade do Porto (ISPUP),*

Background: The relationship between self-stigma and self-esteem in patients with severe Mental illness (SMI) has garnered increased attention in recent years. Few studies have been carried out in Portugal on this subject, for that reason this study aimed to explore the relationship between self-stigma and self-esteem among adults with a diagnosis of schizophrenia spectrum disorders (SSD). For this goal, we assess the prevalence of self-stigma of psychiatric patients with diagnosis of mental illness; and investigate the correlates of elevated self-stigma with self-esteem.

Methods: A total of fifty-one outpatients with severe mental illness diagnosis, participated in this cross-sectional study. They were recruited from a community psychiatry unit from Porto, Portugal. The attending psychiatrist assessed each by face-to-face interview technique. After voluntary informed consent, evaluations included sociodemographic data, illness characteristics, and self-reported standardized scales.

Self-stigma (ISMI) and Rosenberg self-esteem scale (RSES) were assessed. Data analyses were performed using the SPSS version 28.0 (IBM Corp., Armonk, NY). p-values LESS THAN 0.05 were considered significant.

Results: From the study sample, 66.7% were male, with mean age of 44.8 ± 11.0 and 56.9% were single. 33.3% reported living with their parents while 31.4% were living with a partner/spouse. Most participants had a diagnosis of schizophrenia (60.8%). Concerning the level of education, 58.8% completed basic education, and 23.5% achieved upper secondary education. Nevertheless, most patients were retired due to illness (62.7%) and 19.6% were employed. In this study, moderate to high self-stigma levels was found in 31.4 % participants. No significant correlations were found with age, level of education, age at diagnosis, duration of illness, and number of hospitalizations. In the correlation analysis between the study variables, a negative correlation between self-stigma and self-esteem ($\rho = -0.745$; P LESS THAN 0.001) was reported.

Discussion: Conclusion: This study investigates, the prevalence and the correlates of self-stigma and Self-esteem among outpatients within a community psychiatric unit from Porto, Portugal. Our findings suggest a high prevalence of elevated levels of self-stigma among these persons in the SSD. Moreover, our results support previous evidence that internalized stigma is strongly associated with diminished self-esteem. Therefore, targeting internalized stigma and self-esteem among persons with SMI will likely improve their clinical and functional outcomes.

T324. SUBCLINICAL PSYCHOTIC EXPERIENCES NOT ASSOCIATED TO OXIDATIVE STRESS AS INDICATED BY SKIN ADVANCED GLYCATION END PRODUCTS

Julia Hagen^{*1}, Amber Cornelissen¹, Rada Veeneman¹, Sanne van der Heijden¹, Arjen Sutterland¹, Jentien Vermeulen¹, Lieuwe de Haan¹

¹*Amsterdam UMC (AMC), University of Amsterdam*

Background: The pathophysiological role of redox dysregulation and oxidative stress in the development of schizophrenia is becoming increasingly evident. Advanced glycation end products (AGEs) are produced in a state of oxidative stress. Skin autofluorescence measures indicating AGEs (SAF-AGEs) serve as marker for cumulative oxidative stress.

Increased SAF-AGEs have been demonstrated in recent onset psychosis and chronic schizophrenia. Investigation of the association between SAF-AGEs and subclinical psychotic experiences in the general population can help further elucidate the relation between redox dysregulation and psychotic symptoms.

Methods: Data was provided by the Lifelines cohort study. Subclinical psychotic experiences were measured with the Psychosis Screening Questionnaire (PSQ). SAF-AGEs measurements were performed. In a linear mixed model, adjusting for family ties and sex, the association between age-adjusted Z-scores of SAF-AGEs and PSQ was assessed. Additionally, polygenic risk score for schizophrenia, sociodemographic factors, cardiometabolic parameters and presence of chronic illnesses were hierarchically added to the model.

Results: Of 30,862 included participants, 4.3% reported (subclinical) psychotic experiences (PSQ GREATER THAN = 1). Age-adjusted Z-scores of SAF-AGEs was not associated with PSQ ($B = .003$ [95% CI -4.98e-05 - 5.81e-03], $p = 0.054$) in a linear mixed model adjusting for sex and family ties. Adjustment for additional confounders and a sensitivity analysis in participants aged 25-50 years showed similar results. Post-hoc, earlier findings of an association between SAF-AGEs and a (self-reported) diagnosis of schizophrenia were replicated ($B = 0.65$ [95% CI 0.40 - 0.89], p LESS THAN 0.001).

Discussion: No association was found between SAF-AGEs and subclinical psychotic experiences in the general population. Results imply that subclinical psychotic experiences are unrelated to systemic oxidative stress.

T325. INVESTIGATION INTO THE EFFECTS OF LB-102 AND ITS ENANTIOMERS, LB-103 AND LB-104, ON COGNITIVE AND NEGATIVE DEFICITS IN THE SUB-CHRONIC PHENCYCLIDINE RODENT MODEL FOR SCHIZOPHRENIA SYMPTOMATOLOGY

Ben Grayson^{*1}, A R Vaino², Z Prensky², A Eramo², V T Grattan², C Clarke¹, J Fletcher¹, I Mitsadali¹, M Harte¹

¹*b-neuro, University of Manchester*, ²*LB Pharmaceuticals Inc*

Background: Sub-chronic treatment with the N-methyl-D-aspartate receptor (NMDAR) antagonist phencyclidine (scPCP) in adult rats produces behavioural and neurobiological changes of relevance to the symptomatology and pathophysiology of schizophrenia. We have demonstrated that this approach produces robust deficits in several behavioural paradigms, including novel object recognition (NOR) for cognition and social interaction (SI) for negative symptomology (Cadinu et al., 2018 *Neuropharmacol* 142: 41-62). As such NMDAR antagonist animal models are widely used for evaluating novel therapeutic candidates for these unmet clinical needs.

LB-102 is a novel analogue of amisulpride currently in development as a treatment for schizophrenia. Receptor occupancy studies, both in humans and in rodents, have shown that LB-102 binds to dopamine receptors in the brain at substantially lower doses than amisulpride while maintaining an equally benign safety profile (Abbas et al., 2009 *Psychopharmacology* 205: 119-128). LB-102, a racemic mixture ($K_i(5HT7/D2) = 38$), displays polypharmacology. LB-103 (S enantiomer) strongly binds to dopamine D2/3 receptors ($K_i(5HT7/D2)$ GREATER THAN 2500), while LB-104 (R enantiomer) preferentially binds to 5HT7 receptors ($K_i(5HT7/D2) = 1$) (Grattan et al., 2019, *ACS Omega* 4: 14151-14154).

Aim: We investigated the effects of LB-102, LB-103 and LB-104 to reverse cognitive and social behaviour deficits in the clinically relevant and well-validated scPCP model to understand the contributions of D2/3 and 5HT7 activity on behavioural outcomes.

Methods: Female Lister Hooded rats received vehicle (saline) or PCP (2 mg/kg, i.p. bidaily for 7 days, followed by a minimum 7-day washout period). Prior to the behavioural experiments rats were administered LB-102, LB-103 or LB-104 at 5, 15, or 45mg/kg (p.o., 180 minutes before testing). Animals were then tested in the NOR and SI tests to assess effects on cognitive and negative symptoms associated with schizophrenia.

Results: NOR - We found deficits in the discrimination index (DI, measure of novelty preference in the NOR task) in scPCP-treated animals, when compared to vehicle treated animals. Further analysis of the DI was carried out to compare the efficacy of LB-102, LB-103 and LB-104 at equivalent doses. A one-way ANOVA followed by planned post-hoc analysis found that: LB-102, LB-103 and LB-104 at 5 mg/kg had a significant reduction in DI when compared to vehicle treated animals. LB-102 and LB-104 at both 15 and 45 mg/kg had a significant improvement in DI when compared to scPCP treated animals, an effect not seen with LB-103.

SI - We report a significant reduction in sniffing duration induced by scPCP compared to vehicle. These deficits were reversed following acute treatment with LB-102 and LB-104 but not LB-103.

Discussion: In conclusion, LB-102 and LB-104, but not LB-103, were effective in overcoming scPCP-induced deficits in cognitive and social behaviour testing, which reflect specific schizophrenia symptom domains. These results suggest that the increased affinity of LB-104 for 5-HT7 manifests in behavioural assays but that the magnitude is subtle enough that 2X greater K_i is not noticeable. The relative decrease in dopamine binding with LB-104 may improve tolerability, though interrogating safety in animal studies can be challenging.

Lunch and Poster Session II

F1. DIFFERENCES IN CORTICAL NEUROIMAGING IN OFFSPRING OF PATIENTS WITH BIPOLAR DISORDER: INSIGHTS FROM INTELLIGENCE QUOTIENT STRATIFIED ANALYSES

Patricia Camprodon-Boadas^{*1}, María Ortuño², Inmaculada Baeza³, Elena De la Serna⁴, Josefina Castro-Fornieles⁴, Gisela Sugranyes⁵

¹Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), ²Fundació Clínic Recerca Biomèdica - Institut d'Investigacions Biomèdiques August Pi i Sunyer, Clinical and Experimental Neuroscience, ³Hospital Clínic de Barcelona, ⁴Hospital Clínic of Barcelona, 2014SGR489, CIBERSAM., ⁵Institute of Neuroscience, Hospital Clínic of Barcelona, 2014SGR489, CIBERSAM, CERCA-IDIBAPS

Background: Previous studies have failed to identify global differences in cortical neuroimaging measures between offspring of patients diagnosed with bipolar disorder (BpO) and controls (Sugranyes et al., 2015; 2017). However, BpO exhibit overall increased rates of psychiatric disorders and impairment in certain cognitive domains during youth, and some BpO have been found to belong to a poorer functioning cognitive cluster, in association with smaller lobar structural measures (Valli et al., 2022). The current study aimed to analyze cortical gray matter volume and surface area measures in an extended sample of these BpO, subdivided into three groups based on their intelligence quotient (IQ; high, medium, or low), in order to help further understand potential heterogeneity within these individuals based on a standardised measure.

Methods: The study involved a total of 404 data acquisitions, which included longitudinal assessments from 10 BpO with a low IQ, defined as a score less than 90 (BpO-L), 75 BpO with a medium IQ (BpO-M) with scores ranging between 90 and 110, 55 BpO with a high IQ (BpO-H), with a score exceeding 110, and 85 CcO, assessed at different time points. Participants were matched for age and sex. All participants completed an IQ assessment using the Wechsler Intelligence Scale for Children or Adults depending on age and underwent a structural magnetic resonance imaging scan on a 3Tesla scanner. Cortical surface reconstruction was applied to measure gray matter volume and surface area for each cortical lobe. Multilevel mixed-effects linear regression models were conducted, with cortical structural measures as dependent variable, including group, age, sex, and total intracranial volume as fixed factors. Additionally, random effects were incorporated for family relatedness (considering subjects who were siblings) and the subject code (accounting for different number of assessments).

Results: No significant differences were observed in age or sex between groups. Values of IQ (means, standard deviation) were 83.3 ± 2.9 for the BpO-L group, 102.5 ± 1.0 for the BpO-M group, 120.1 ± 1.1 for the BpO-H group and 108.9 ± 0.7 for the CcO group ($F = 72.176$; $p < 0.001$). Significant differences between groups were found in cortical gray matter volume in the left frontal lobe ($F = 2.742$; $p = 0.043$), though pairwise comparisons did not reveal significant differences between specific groups. Differences were also identified for cortical gray matter volume in the left temporal lobe ($F = 3.781$; $p = 0.011$), where CcO exhibited higher levels than BpO-L ($p = 0.050$). There were also significant group effects in surface area of the left frontal lobe ($F = 3.779$; $p = 0.011$), with the BpO-M group showing lower levels than both BpO-H ($p = 0.031$) and CcO ($p = 0.041$), and in the right temporal lobe ($F = 3.543$; $p = 0.015$), with the BpO-M group exhibiting lower levels than CcO ($p = 0.046$).

Discussion: Our study uncovered regions of diverging cortical structural metrics when stratifying BpO according to IQ. Incorporating additional variables such as functioning, or the presence of psychopathology will help to fully understand heterogeneity within this population. Further investigations into these factors will contribute to a more nuanced understanding of brain-based heterogeneity within the BpO group.

F2. BEYOND PSYCHOSIS RISK: VALIDATING TRANSDIAGNOSTIC, HETEROTYPIC HIGH-RISK CRITERIA

Rochelle Ye^{*1}, Cassandra Wannan², Stephen Wood², Joseph Kambeitz³, Lana Kambeitz-Ilankovic³, Stefan Borgwardt⁴, Paolo Brambilla⁵, Rebekka Lencer⁴, Eva Meisenzahl⁶, Raimo Salokangas⁷, Christos Pantelis⁸, Alessandro Bertolino⁹, Rachel Upthegrove¹⁰, Nikolaos Koutsouleris¹¹, Barnaby Nelson², Dominic Dwyer²

¹University of Melbourne, ²Orygen, ³University of Cologne, ⁴University of Lübeck, ⁵University of Milan, ⁶Ludwig Maximilians University, ⁷University of Turku, ⁸The University of Melbourne, ⁹University of Bari, ¹⁰University of Birmingham, ¹¹Ludwig-Maximilian-University

Background: The ultra-high risk for psychosis (UHR) criteria facilitated the development of an early identification and prevention paradigm in psychiatry. However, recent evidence shows that 76% of UHR individuals do not transition to psychosis and 68% develop other severe mental illnesses. Additionally, further research has demonstrated the presence of earlier illness stages preceding UHR. This evidence indicates a need to expand UHR to capture the transdiagnostic presentations of risk, heterotypic outcomes, and earlier stages of illness. The Clinical High At-Risk Mental State (CHARMS) criteria were developed to achieve these goals by operationalising four stages of illness: asymptomatic (Stage 0), mild impairment (Stage 1a), high-risk (Stage 1b), and severe illness (Stage 2). CHARMS has been validated in pilot studies with inconclusive results. We aimed to validate the CHARMS criteria in a large international sample of help-seeking individuals and to determine if the stages are associated with genetic risk for mental illness. We hypothesised that CHARMS Stage 1b would identify increased risk for serious mental illness and later stages of illness would be associated with increased genetic risk.

Methods: 749 help-seeking individuals from a longitudinal, multisite cohort study investigating prediction tools for psychosis-related outcomes (PRONIA) were stratified into four stages using CHARMS. Participants were assessed on positive, negative, and depression symptoms, social occupational functioning, and quality of life. DNA was extracted from 619 participants; schizophrenia and depression polygenic risk scores (PRS) were calculated using the Psychiatric Genomic Consortium reference sample, generated over a range of 10 P-values. Group differences were determined using ANOVAs and significant differences were explored using post-hoc t-tests. 2-sided P values were assessed at a significance level of false discovery rate corrected P LESS THAN .05. Linear mixed effects models were used to investigate longitudinal trajectories.

Results: Participants were stratified into Stage 0, Stage 1a, Stage 1b, and Stage 2. Significant group level differences between stages were found for all clinical and functioning measures, with higher stage associated with higher symptomatology and lower functioning. There were significant stage differences between positive, ($F_{3,719} = 212.30$, P LESS THAN .001, $\eta^2 = 0.47$), negative, ($F_{3,716} = 252.27$, P LESS THAN .001, $\eta^2 = 0.51$), and depressive symptoms, ($F_{3,668} = 287.29$, P LESS THAN .001, $\eta^2 = 0.56$). Significant increase in functioning impairment in both social ($F_{3,722} = 578.48$, P LESS THAN .001, $\eta^2 = 0.71$) and disability

domains, ($F_{3,722} = 432.81$, $P < .001$, $\eta^2 = 0.64$), across stages. Significant stage differences on quality of life ($F_{3,630} = 149.31$, $P < .001$, $\eta^2 = 0.42$), except between Stage 1b and Stage 2. These differences were largely maintained over time. Significant stage differences were found for schizophrenia PRS across four thresholds ($\eta^2 = 0.03$) and for depression PRS across five thresholds ($\eta^2 = 0.03$). Post hoc exploration showed linear increases in schizophrenia PRS score across stages. 14.3% of participants in Stage 1b transitioned to Stage 2 within 18 months.

Discussion: The findings validate CHARMS for identifying people at high risk of developing serious mental illness, and show that higher stage is associated with increased symptomatology, greater genetic risk, poorer functioning, and lower quality of life. Additionally, we demonstrate the utility of CHARMS in capturing early stages of illness preceding high-risk. There was no significant difference between Stage 1b and Stage 2 in quality of life. Overall, this highlights the need for early intervention and prevention beyond psychosis.

F3. ASSOCIATIONS BETWEEN CHILDHOOD MALTREATMENT SUBTYPES AND SYMPTOMS OF PSYCHOSIS, DEPRESSION, ANXIETY, AND POSTTRAUMATIC STRESS IN A MEXICAN GENERAL POPULATION SAMPLE

Tamara Sheinbaum^{*1}, Tecelli Domínguez², Fernando Salvador-Cabañas³, Lourdes Nieto², Rebeca Robles², Neus Barrantes-Vidal⁴, César Celada², Mauricio Rosel², Ricardo Saracco²

¹*Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"*, ²*Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"*, ³*Benemérita Universidad Autónoma de Puebla*, ⁴*Universitat Autònoma de Barcelona*

Background: Ample research demonstrates that childhood maltreatment confers risk for multiple forms of psychopathology across clinical and subclinical levels of expression, including depression, anxiety, posttraumatic stress, and psychosis phenotypes. However, studies on this topic in Latin American countries, such as Mexico, remain relatively scarce, especially those using a dimensional approach to assessing maltreatment and psychopathology. The present study aimed to examine (i) the prevalence of childhood maltreatment subtypes (emotional, physical, and sexual abuse and emotional and physical neglect) and (ii) associations between maltreatment subtype scores and dimensional assessments of depression, anxiety, posttraumatic stress, and positive psychotic experiences and related distress in a Mexican general population sample.

Methods: The sample comprised 1,550 participants (79.2% female; mean age=29.5 years) from the Mexican general population who completed a battery of self-report questionnaires via an online survey. The study measures included the Childhood Trauma Questionnaire, the Prodromal Questionnaire-Brief, the Posttraumatic Stress Disorder Checklist for DSM-5, and screening measures for anxious and depressive symptoms based on the World Health Organization's most recent classification of mental disorders for primary care settings.

Results: Using the established CTQ cut-off scores for "low to moderate severity," the prevalence of maltreatment in the sample was 63.1% for emotional abuse, 61.5% for emotional neglect, 47% for sexual abuse, 41.2% for physical abuse, and 37.8% for physical neglect. All the maltreatment subtypes had significant bivariate associations with positive psychotic experiences and distress as well as with the symptoms of depression, anxiety, and posttraumatic stress. The regression analyses examining the maltreatment subtypes as simultaneous predictors indicated that emotional abuse had a unique association with all the outcome

measures. Additionally, emotional neglect had a unique association with symptoms of depression, and sexual abuse had a unique association with symptoms of posttraumatic stress.

Discussion: The high prevalence of maltreatment in the sample is consistent with epidemiological research indicating that adverse and traumatic experiences are common in the Mexican population. In addition, the finding that emotional abuse was uniquely associated with all the outcome measures aligns with emerging research highlighting the critical relevance of emotional abuse as a risk factor for different forms of psychopathology, over and above other maltreatment subtypes. Furthermore, the specific associations found between emotional neglect and depression and between sexual abuse and posttraumatic stress are notable and parallel findings from the international literature. Overall, the results support previous calls for increased research and policy attention to the more “silent” types of maltreatment and underscore the need for longitudinal investigations to inform prevention and intervention efforts in the Mexican population.

F4. IMPLICATIONS OF MHC-CLASS II PEPTIDES ON B CELL LINES IN THE PATHOGENESIS OF SCHIZOPHRENIA

Nicole Brace*¹, Antonia Pritchard¹

¹*University of the Highlands and Islands*

Background: One of the leading hypotheses to the cause of schizophrenia is the two-hit theory. This proposes that an initial hit, caused by a genetic vulnerability to developmental disturbances, is followed by a second hit of an environmental trigger during a critical period of brain maturation, such as prenatal infection, stress, or drug abuse. This second hit activates the consequences of the first, leading to neurodevelopmental changes, brain dysfunction and schizophrenia. This study focuses on an immune disturbance as the second hit. Altered profiles of immune cells and mediators in the circulation and brain, and the presence of brain-reactive antibodies emphasize the role of immunity. A family history of autoimmune conditions increases the risk of schizophrenia, along with infection and inflammation. The major histocompatibility complex (MHC) cluster locus on chromosome 6 is a schizophrenia genome wide association study (GWAS) peak and experimental evidence suggests that MHC-class II peptide presentation is altered in schizophrenia patients. Mechanisms suggested include changes to the development and function of immune cells and neurons, and synaptic pruning; all of which could alter brain function. Anormal MHC II could promote survival of auto-reactive B cells contributing to a failure in immune tolerance. Together, these data suggest an association between B cell function and schizophrenia. Although many associations have been identified, the mechanism of involvement is still poorly understood.

Methods: Four B cell lines (two derived from healthy controls and two from schizophrenia patients) were selected. These cell lines were genotyped to determine their MHC class II allele types and MHC II peptide complexes were enriched for using an anti-human HLA-DR antibody, L243. Peptides were subsequently eluted from MHC complexes and, following liquid chromatography separation, analysed via high resolution mass spectrometry. The profile of identified peptides was analysed using Proteome Discoverer and the profile of peptides bound to specific MHC II genotypes was assessed using the IEDB prediction tools. Similarities and differences between the cell lines were investigated, including features of the proteins from which the peptides originated and of the peptides themselves in binding to the MHC II molecule.

Results: We found that the cell lines each contained a distinct repertoire of MHC II peptides, whilst there were some overlaps there were also many which were unique to each cell line and

unique to each condition. Global differences to the peptide properties, including the number of peptides and characteristic such as length and source, also appeared to be unique to the cell lines. We also observed that some of the peptides were derived from proteins and genes that have been implicated in schizophrenia.

Discussion: The heterogeneity of the immune response in humans, as well as in the disease and pathogenesis of schizophrenia is reflected in the MHC II genotypes of the cells and the MHC II peptide repertoire identified. Increasing the number of samples may identify peptide targets which may act as a biomarker for the disease.

In summary, this study provides novel insights into the molecular mechanisms of MHC-class II peptide presentation and its relevance to schizophrenia. Our results in conjunction with findings previously reported in the literature, suggest that MHC-class II peptides may play a role in the pathogenesis of schizophrenia by triggering autoimmune or cross-reactive responses against brain antigens. Understanding the nature of the MHC II peptides displayed by B cells adds a new dimension to the exploration of schizophrenia's causes, offering potential insights for early identification and improved patient outcomes.

F5. COMBINING THE RISK: A POLY-ENVIRONMENTAL RISK SCORE AND PSYCHOTIC EXPERIENCES IN ADOLESCENTS

Diandra Bouter¹, Nina Grootendorst*¹

¹*Erasmus University Medical Center*

Background: Psychotic experiences are common in adolescents and predictive of both psychotic and non-psychotic disorders. Many risk factors have been shown to be associated with psychotic experiences, yet investigating single risk factors does not account for the combined or even additive effect of risk factors. The poly-environmental risk score (PERS) combines well-researched environmental risk factors in a clinical model to calculate the risk for psychotic experiences.

Methods: The current study is embedded in a cohort of adolescents (n=966) at risk of psychopathology based in the Rotterdam area, the Netherlands. We used 16 binarized risk factors for psychosis obtained from meta-analyses to calculate the PERS. Adolescent risk factors were: winter or spring birth, obstetric complications, ethnic minority status, urbanicity, cannabis use and experiences of bullying, adverse life events, physical abuse, sexual abuse, and neglect. Six parental factors were used: higher paternal age, low socioeconomic status, psychopathology, substance abuse, divorce, and death.

Results: A higher PERS was positively associated with more psychotic experiences. Furthermore, the PERS was a clear indicator of adolescents reporting psychotic experiences above the cut-off for clinically relevant psychotic experiences.

Discussion: A combined score of multiple risk factors in the association with psychotic experiences in adolescents has a relatively small effect size as compared to the effect of the individual risk factors. Future research should take the combined effect of risk factors into account when examining the determinants of psychopathology.

F6. MESENCEPHALIC ASTROCYTE-DERIVED NEUROTROPHIC FACTOR (MANF) PREDICTS EMOTION PROCESSING IMPROVEMENT BY COGNITIVE REMEDIATION THERAPY IN RECENT-ONSET PSYCHOSIS

Francesc Estrada*¹, Josep Maria Crosas², Maribel Ahuir², Raquel Aguayo², Juan David Barbero², Meritxell Tost², Itziar Montalvo², Diego Palao², Javier Labad³

¹*Parc Taulí Sabadell (Spain)*, ²*Department of Mental Health, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona*,

³*Consorci Sanitari del Maresme, Mataró, Spain*

Background: Patients with schizophrenia show deficits in social cognition and particularly in the theory of mind (the ability to attribute mental states to oneself and others), which contribute to impairments in functional performance (1). Cognitive remediation therapy (CRT) might improve social cognitive deficits in people with schizophrenia (2), although there is an important variability in the response between patients. We aimed to explore whether proteomic biomarkers related to neurology processes could predict the response to CRT in emotion processing tasks in patients with recent-onset psychosis (ROP).

Methods: 28 stable outpatients (9 women) with ROP (psychotic disorders with LESS THAN 3 years of illness) aged between 18 and 35 years old were included in a randomized clinical trial (NCT04418570). Patients were randomized to receive a computerized CRT facilitated by a therapist for three months (2 sessions/week) (n=14) or treatment as usual (TAU) (n=14). The Emotion Recognition Task (ERT) from the CANTAB was used to assess emotion processing at baseline and after 3 months. Fasting blood samples were obtained at baseline and after 3 months. A Proximity Extension Assay (PEA) was conducted with Olink® Technology and the Olink Target 96 Neurology® panel was used to determine the protein expression of 92 neurology-related proteins in plasma. Statistical analyses were conducted in R. The glmnet package was used for performing a Lasso Regression (LR) in order to identify potential biomarkers associated with cognitive changes in ERT variables (reaction time and total hits), considering a coefficient GREATER THAN 0.1 in the LR. Significant biomarkers associated with longitudinal changes in ERT were included in a mixed linear regression testing the effects of time, group (CRT vs TAU), biomarker, and the interactions between time, group and biomarker.

Results: Of all 92 proteins explored in the Olink Neurology panel, one protein was associated in longitudinal changes in ERT reaction time: mesencephalic astrocyte derived neurotrophic factor (MANF), which had a coefficient of -0.146. When including MANF in the mixed linear regression analysis, a significant time x group x MANF interaction was found ($\eta^2=0.70$, $p=1.275e-06$). Patients with higher MANF expression at baseline visit reported improvements in ERT reaction time when compared to those with lower MANF.

Discussion: Our exploratory study suggests that MANF expression might predict the response in social cognition to CRT in people with early psychosis. Interestingly, MANF offers cellular protection in neurodegenerative disorders and promotes the survival of cultured midbrain dopamine neurons (3). If our results are replicated in further studies, MANF could be a biomarker that could help to identify early psychosis patients who would benefit from receiving CRT to improve emotion processing. Moreover, since MANF is also a potential therapeutic target in neurodegenerative diseases, it could be a potential target for future cognitive enhancement treatments in schizophrenia and related psychotic disorders.

F7. PREDICTORS OF BETTER ACADEMIC PERFORMANCE IN INDIVIDUALS WITH UHR FOR PSYCHOSIS

Alp Uçok*¹, Ezgi İnce Guliyev¹, Cem Horasan¹, Çağla Ceren Türkoğlu¹, Mesut Keskin¹, Melis Ceylan¹

Background: Lower levels of education have been associated with the development of psychosis. Investigating educational achievement in individuals with UHR for psychosis may shed light on the origins of the alterations and on the variability of outcomes in this group. The aim of this study is to search the predictors of better academic performance during the follow-up in individuals with UHR for psychosis.

Methods: Totally there are 150 individuals with UHR for psychosis in Early Psychosis Program in Istanbul Faculty of Medicine sample. All of them had completed a cognitive battery and we collected clinical data by using BPRS, CAARMS, SANS, SAPS, Calgary DSS, PAS, childhood trauma questionnaire and GAF at baseline. Twenty-nine of them were already university students or graduated from university. We obtained information by contacting them by telephone or e-mail if they dropped-out from follow-up. During the follow-up 30 of the individuals with UHR passed the university entrance examination and started university. We regarded these 30 individuals as with better academic performance, and compared their baseline clinical and cognitive parameters with the rest of the sample (n=72) by excluding those who have already attended university before first admission.

Results: Mean age of the sample is 20.4±4.4 and 71.3% of them are male. Mean duration of follow-up after first admission is 24.9±44.3 months. Baseline SANS score (34.9 vs 42.2, p=0.034) and alogia subscale score were lower in those with better academic performance. However, there was no difference both in SAPS and CAARMS scores at baseline. School performance between 12-15 years was related to academic performance later, but statistical significance was in trend level (p=0.07). Childhood physical trauma (5.3 vs 7.1, p= 0.004), emotional neglect score (11.2 vs 16.4, p=0.002) and CTQ total score (35.7 vs 44.9, p=0.01) were significantly lower in those with better academic performance. Composite scores of the attention, and executive function domains, and global cognitive performance were better (p LESS THAN 0.001 for all) in better academic performance group. Difference in composite score for learning-memory domain was in trend level (0.06). Although rate of middle-income families was relatively similar in both groups (63.5% vs 75.1%), frequency of low-income families was higher in worse academic performance group (28.8% vs 3.6%, p=0.009.) Family history of psychosis, alcohol/substance use, baseline level of depression, past suicide attempts and global functioning were not found related to later academic performance.

Discussion: Our findings suggest that baseline cognitive performance is strongly related to academic performance during the follow-up. However, some environmental variables like childhood trauma and economic level of their family have also an impact on academic performance. Besides these, lower level of negative but not positive symptoms was found related to better academic performance later.

F8. AN AUDIT OF THE CLINICAL MONITORING OF EXTRA-PYRAMIDAL SYMPTOMS (EPS) IN AN IRISH MENTAL HEALTH SERVICE (MHS)

Rebekah Aubry^{*1}, Thomas Hastings², Micheal Morgan³, Kevin Kilbride⁴

¹*Lucena Clinic, St John of God*, ²*Dr. Thomas Hastings M.P.C.*, ³*1HSE South Louth CAMHS, St. Mary's Hospital Campus*, ⁴*Program for the Homeless MHS, Usher's Island Day Hospital*

Background: Published studies demonstrate very low rates of EPS monitoring in patients prescribed antipsychotics. [1-2] EPS adversely quality of life, function and treatment adherence. [3-4] The 'HSE National Clinical Programme for Early Intervention in Psychosis' recommends that

medications should be reviewed regularly for side effects, and that the physical complications of medications should be monitored regularly and collaboratively [5] . ‘NICE Guidelines’ recommend assessment for movement disorders before starting antipsychotic medication, and to monitor and record side effects of treatment and their impact on functioning, and the emergence of movement disorders, regularly and systematically throughout treatment [6] . References:

1. Cortese L, et al. Assessing and monitoring antipsychotic-induced movement disorders in hospitalized patients: a cautionary study. *The Canadian Journal of Psychiatry*. 2004 Jan;49(1):31-6.
2. Butler MI, Chandrakanth J. Monitoring of extrapyramidal side effects in patients on antipsychotic treatment: a completed audit cycle. *Irish journal of psychological medicine*. 2016 Sep;33(3):165-9.
3. Schouten HJ, et al. Quality of life of elderly patients with antipsychotic-induced parkinsonism: a cross-sectional study. *Journal of the American Medical Directors Association*. 2012 Jan 1;13(1):82-e1.
4. Fleischhacker WW, Meise U, Günther V, Kurz M. Compliance with Antipsychotic Drug Treatment: Influence of Side Effects. *Acta Psychiatr Scand Suppl*. 1994;382:11-15.
5. HSE National Clinical Programme for Early Intervention in Psychosis; Model of Care Executive Summary. (Section 3.2 Pharmacotherapy). May 2019.
6. NICE Clinical Guideline; Psychosis and schizophrenia in adults, Treatment and management (Sections 1.3.6.1 and 1.3.6.4). 2014.

Methods: An Audit Tool and review of clinical notes in the prior 6 months evaluated: the rate of any EPS monitoring, subjective and objective EPS symptom monitoring rates, and any use of a structured assessment tool. The novel EPS Scale (EPSS) [7] was introduced following a 1h training session and video. EPS monitoring rates were re-audited 8 month post-intervention. In addition, NCHD’s completed anonymous pre/post intervention surveys rating their comfort

monitoring and documenting EPS, their current monitoring practices and the perceived quality and usefulness of the training. References:

7. Hastings T, Tibbo P, Williams R. Extrapyramidal Symptom Scale (EPSS). Canadian Consortium for Early Intervention in Psychosis. 2022.

Results: Pre-intervention Audit (t1, n=232) – Sep 2021, Only 14.8% of psychiatric inpatients’ records had any documentation of EPS monitoring (of those, 9.2% noted subjective symptoms and 14.8% noted objective symptoms). For community patients in the other two settings, there was no record at all. Post-intervention Audit (t2, n=214) – June 2022 The EPSS had been completed within the previous 6 months for 75% for the inpatients, 79.6% for the community rehabilitation patients, and 18% for the community/assertive outreach (specialist homeless) patients. Pre-intervention Survey (n = 12): The majority of respondents reported poor confidence levels in their ability to assess and document EPS and indicated that they never or only rarely used a structured tool. Post-intervention Survey (n=12): All respondents found the training session very helpful or helpful (4-5/5 on Likert-like scale), indicated that they believed the EPSS training session would result in an improvement in their ability to screen for and document EPS as part of their ongoing clinical practice.

Discussion: - We confirmed that EPS are not as frequently monitored as recommended, across multiple practice sites within a Dublin North City MHS. Monitoring rates improved across all participating practice following adoption of the EPSS. Successful adoption was possible at no cost. We intend to continue to use the EPSS and to audit performance in our MHS, to ensure ongoing high rates of adherence to practice standards for monitoring EPS.

F9. UNDERSTANDING AND PREVENTING VIOLENT CRIME IN INDIVIDUALS WITH SEVERE MENTAL DISORDERS – A MIXED-METHODS APPROACH (PREVIO): A STUDY PROTOCOL

Laoura Ziaka*¹, Martin Tesli², Unn Haukvik³, Jaroslav Rokicki¹, Christine Friestad¹

¹*Oslo University Hospital*, ²*Norwegian Institute of Public Health*, ³*University of Oslo*

Background: Epidemiological studies have estimated that individuals with severe mental illness commit approximately 5% of registered violent crime. For this patient group, management and prevention of violence risk is a shared responsibility between the criminal justice system and health services. As such, public and professional warnings are raised about system coordination and cooperation shortcomings which may hinder optimal treatment and increase suffering for this group. We present a three level cross disciplinary mixed-method study approach (PreVio) which in close collaboration with the practice field (police, correctional, and mental health services) seeks to enhance our understanding of violent crime in severe mental disorders. Our aim is fourfold: 1) examine changes in violent crime over time and the possible impact of legal reforms, 2) identify subgroups and developmental trajectories of crime and mental illness across the life course, 3) investigate sociodemographic and psychological risk and protective factors, 4) employ visual Methods: to study single cases and identify the link between events at the individual level.

Methods: The PreVio project (funded by Research Council Norway) combines large registry based epidemiological analyses (level 1) with clinical characterization/ studies on a quantitative small scale (level 2), and case based qualitative analyses (level 3). The quantitative data stem from two datasets: a population-wide registry linkage (ForenPsych, N $\approx$ 8 mill) with information on severe mental illness, violent crime, and sociodemographic factors, and a clinical dataset (sTOP, N $\approx$ 200 participants) including data on psychological characteristics and individual risk and protective factors for four groups (i.e., psychosis patients with and without a history of severe violence, non-psychotic violent offenders, healthy controls). Different statistical Methods: (e.g., logistic and Cox regression, difference-in-differences estimation, etc.) will be used. Qualitative explorations from visual criminology utilizing Life History Plots (LHP) of single cases will identify crucial time points for future interventions.

Results: The project is in its initial stages. The ForenPsych dataset has obtained approval from relevant ethical and legal authorities. Data from the National Population Register, The Norwegian Patient Registry, Penal Sanctions and sociodemographic variables from Statistics Norway are underway and include a wealth of variables not previously investigated. For the sTOP dataset, data collection has been completed and involves groups matched on age, sex, diagnosis, and clinical variables. Qualitative data will be derived from the sTOP study's available case material. LHP will be developed for a selected subsample. The selection of items for visualization will be informed based on the knowledge stemming from the project's quantitative part (i.e., ForenPsych and sTOP Results:). This dynamic approach ensures that qualitative analysis aligns with emerging quantitative findings.

Discussion: The PreVio project introduces an innovative, cross-disciplinary three level mixed-Methods: approach to the investigation of the relationship between severe mental disorders and

violent crime. Combining quantitative data for societal and clinical insights into violence prevalence and characteristics, the study also incorporates a qualitative component using the LHP visual method. Through multidisciplinary research involving experts in epidemiology, forensic and clinical psychiatry, criminology, sociology, and law, in close cooperation with experienced practitioners, the final aim is to increase our understanding of the developmental trajectories of crime and mental illness.

F10. THE INFLUENCE OF EXPOSOMIC AND POLYGENIC LIABILITY FOR SCHIZOPHRENIA ON THE PERSISTENCE OF DISTRESSING PSYCHOTIC EXPERIENCES IN EARLY ADOLESCENCE

Thanavadee Prachason*¹, Matteo Di Vincenzo², Gaia Sampogna², Angelo Arias-Magnasco³, Bochao D Li⁴, Lotta-Katrin Pries³, Jim van Os⁵, YOUTH-GEMs Investigators⁶, Bart P. F. Rutten³, Sinan Guloksuz⁷

¹ Ramathibodi Hospital, Mahidol University, ²University of Campania "Luigi Vanvitelli", ³School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands, ⁴UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, ⁵Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, the Netherlands; King's College London, King's Health Partners, Institute of Psychiatry, ⁶YOUTH-GEMs Investigators, ⁷School for Mental Health and Neuroscience, Maastricht University Medical Centre, Yale University School of Medicine

Background: Psychotic experiences (PEs) are a significant risk factor for both psychotic and non-psychotic disorders with a peak incidence in adolescence. When persisting, PEs, especially those associated with distress, are linked with poor outcomes. However, research on risk factors for the persistence of distressing PEs is still limited. In this study, we aimed to examine the influence of genomic and exposomic liability for schizophrenia on persistent distressing PEs in early adolescence.

Methods: The data were derived from the Adolescent Brain and Cognitive Development (ABCD) Study release 5.0. This study included 5,122 European participants who had genetic data and underwent annual assessments starting from baseline (ages 9 – 10) until the 3-year follow-up (ages 12 – 13). The Prodromal Questionnaire-Brief Child Version was used to assess past-month PEs and associated distress. Binary variables indicating lifetime distressing PEs were generated at different cutoff thresholds of persistence, varying from one to four waves. Polygenic risk score for schizophrenia (PRS-SCZ) was calculated. Conforming to our previous study exposome score for schizophrenia (ES-SCZ) was calculated using lifetime exposure to childhood adversity domains, cannabis use, winter birth, hearing impairment, and bullying reported up to the 2-year follow-up (ages 11 – 12). PRS-SCZ and ES-SCZ were dichotomized at the 75th percentile (hereafter PRS-SCZ75 and ES-SCZ75, respectively). Finally, the associations of PRS-SCZ75 and ES-SCZ75 with distressing PEs at varying degrees of persistence were tested using multilevel logistic regression analysis. All models were adjusted for age and sex, with additional adjustment for family income and parental education as sensitivity analyses.

Results: PRS-SCZ75 was significantly associated with distressing PEs at a threshold of one (OR 1.28 [95% CI 1.08, 1.53], $p = .004$), and two (OR 1.34 [95% CI 1.08, 1.65], $p = .007$) out of four waves. On the contrary, ES-SCZ75 was significantly associated with distressing PEs at all thresholds of persistence (all p LESS THAN .001). Notably, the influences of ES-SCZ75 tended to increase at higher thresholds of persistence (one wave: OR 2.94 [95% CI 2.38, 3.62];

two waves: OR 3.56 [95% CI 2.79, 4.56]; three waves: OR 4.86 [95% CI 3.44, 6.94]; four waves: OR 4.61 [95% CI 2.94, 7.23]). Sensitivity analyses, incorporating family income and parental education, confirmed all significant findings including the gradient influences of ES-SCZ75 on persistent distressing PEs.

Discussion: Exposomic liability for schizophrenia was more strongly associated with distressing PEs than genomic liability for schizophrenia in early adolescence. There was evidence of increasing influences of ES-SCZ on the persistence of distressing PE, highlighting an important role of accumulating exposure to environmental risks for schizophrenia on the persistence of subclinical psychosis expression in the young population.

F11. APPLYING VISUAL METHODS TO STUDY VIOLENCE AND PSYCHOSIS IN FEMALE PRISONERS AND FORENSIC PATIENTS: A PILOT STUDY

Christine Friestad*¹, Danielle Arlanda Harris², Anja Vaskinn¹, Unn Haukvik³

¹*Oslo University Hospital*, ²*Griffith University*, ³*University of Oslo*

Background: There has been a disproportionate growth in the number of women in correctional and forensic systems during the last decade. This is a cause for concern given the lack of knowledge about the background of women convicted of violent crime. Risk factors for violence seem to be similar for both men and women, also in forensic samples characterised by severe mental illness. What remains to be seen, however, is whether the timing, ordering, and duration of events can be differentiated by gender. For example, the onset and duration of psychosis and its treatment might be distinct for men and women. The emerging field of visual criminology provides an approach that is particularly suited to investigate this question, but it has yet to be applied to the study of violence and mental illness. In this study, and for the first time, we create and present individual Life History Plots for a pilot sample of women with an intersecting history of criminality and mental illness. This project represents a novel cross-disciplinary approach to the study of this vulnerable group.

Methods: The current study employs a data visualisation tool called the Life History Plot to explore and examine the criminal and psychological histories of a small sample of women. The aim of the visualization is to plot the temporal ordering of a selection of officially recorded information such as arrests, convictions, diagnoses, and periods of custody or hospitalisation. This approach allows for the identification of connections and relationships between events and situations at the individual level, providing a dynamic view of a single person's life course. We include illustrations for three separate women that were constructed using criminal conviction data, sentencing remarks, and archival files/records.

Results: Cases 1 and 2 were women in their twenties who were sentenced for attempted homicide. Case 3 was 41 years of age and charged with a series of criminal offences ranging from drug crimes and vandalism to violence against public officials. The backgrounds of all three women were characterised by childhood adversity and drug abuse, but there were important differences in their criminal histories. For the women with severe mental illness, their engagement in criminal activity was highly concentrated. In contrast, the woman sentenced to preventive detention revealed a longer and much more diverse criminal history.

Discussion: Plotting the timing and ordering of criminal events against other noteworthy periods of a person's life history allows for the observation of potentially important patterns of criminal development with relation to the progression of their mental ill-health. Our results suggest that the Life History Plot is a useful visualisation technique that holds promise for the further study of female clients in the forensic and correctional system.

F12. INVESTIGATING THE COGNITIVE AND ENVIRONMENTAL CORRELATES OF PRODROMAL SYMPTOMS IN CHILDREN WHO WERE BORN VERY PRETERM: A PILOT STUDY

Zeyuan Sun^{*1}, Laila Hadaya¹, Lucy Vanes¹, Andrew Lawrence¹, David Edwards¹, Paola Dazzan¹, Chiara Nosarti¹

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London,*

Background: Very preterm birth (LESS THAN 33 weeks' gestation) has been associated with an elevated risk of neurodevelopmental impairments in cognition and behaviour, and with a greater likelihood of receiving a psychiatric diagnosis, including psychosis, compared to term birth. This study aimed to investigate the association between very preterm children's self-reported psychotic-like experiences, their cognitive outcomes and individual-level and area-level environmental factors, namely parenting style and neighbourhood disadvantage.

Methods: Participants were very preterm children (n=101; median gestational age 30.00 weeks; range=24.00–33.27) drawn from the ongoing Brain, Immunity and Psychopathology following very Preterm birth study. All children completed a comprehensive neurodevelopmental assessment at a median age of 10.17 years (range=7.42–13.17). The association between self-reported prodromal symptoms (Prodromal Questionnaire–Brief Child Version; PQ-BC), IQ (Wechsler Intelligence Scale for Children-fourth edition), temperament (Temperament In Middle Childhood Questionnaire), general mental health (Strengths and Difficulties Questionnaire), parenting style (Arnold's Parenting Scale), emotion regulation (Emotion Regulation Checklist), emotion recognition (Emotion Recognition Task, developed in-house) and autism traits (Social Responsiveness Scale-Second Edition) was investigated using stepwise linear regression. Our dependent variable was PQ-BC distress weighted symptom score, while all cognitive and behavioural measures listed above, sex, socioeconomic status (Index of Multiple Deprivation 2019) and age at assessment, were included in the model as independent variables.

Results: Reduced distress-weighted symptom scores was associated with better emotion regulation (b=-0.74 [95%CI: -1.25 to -0.22], se=0.26, t=-2.83, p=0.006), higher effortful control (b=-5.53 [95%CI: -11.50 to -0.43], se=3.01, t=-1.84, p=0.069) and more neighbourhood disadvantage (b=-0.61 [95%CI: -1.36 to -0.15], se=0.38, t=-1.60, p=0.113).

Discussion: Our results suggest that better emotion regulation and effortful control (encompassing attentional focusing, attentional shifting, inhibitory and activational control of behaviours) were associated with less distressing psychotic-like experiences among preterm children. These self-regulatory strategies may protect very preterm children from experiencing distressing psychotic-like symptoms.

F13. DEVELOPMENT AND PRELIMINARY VALIDATION OF THE POSTPARTUM PSYCHOTIC EXPERIENCES SCALE (PPES)

Feten Fekih-Romdhane^{*1}, Diane El Hadathy², Covadonga González-Nuevo³, Diana Malaeb⁴, Habib Barakat², Majda Cheour¹, Souheil Hallit²

¹*Tunis El Manar University, Faculty of Medicine of Tunis,* ²*Holy Spirit University of Kaslik, Jounieh, Lebanon,* ³*University of Oviedo, Oviedo, Spain,* ⁴*Gulf Medical University, Ajman, United Arab Emirates*

Background: If not promptly detected and treated, postpartum psychosis carries the potential for detrimental consequences, including the risk of infanticide or suicide. Making available a valid and reliable self-report measurement instrument for postpartum psychotic experiences (PEs) opens future research to measure psychosis proneness and the clinically relevant subclinical psychosis phenotype during this critical period, and may offer novel perspectives for prevention and early intervention strategies in postnatal care. In addition, large-scale, multi-country longitudinal research is warranted to elucidate the processes underlying the postpartum PEs construct, as well as its various correlates and outcomes. Such research is expensive to perform and, consequently, a cost-effective strategy for identifying postpartum women at-risk for PP is required. The contribution of this work is to design and validate a novel self-report measure, the Postpartum Psychotic Experiences Scale (PPES), to screen for attenuated psychotic symptoms during postpartum.

Methods: This cross-sectional study was conducted from September 2022 until June 2023, enrolling 438 women 4-6 weeks after delivery (mean age: 31.23 ± 5.24 years).

Results: Starting from an initial pool of 22 items, both Exploratory Factor Analysis and Confirmatory Factor Analysis suggested that all remaining 15 items loaded into a single factor with an excellent internal consistency (Cronbach α of .95 and a McDonald ω of .95). The PPES showed good convergent validity against another validated measure of PEs, i.e. the Prodromal Questionnaire-Brief (correlations of GREATER THAN 0.8). In addition, PPES scores correlated with measures of postpartum depression and perinatal anxiety, thus attesting for its good concurrent validity. A PPSE score of 8.5 (sensitivity=85.2%, specificity=78.6%) was defined as the optimal cutoff point. According to this cutoff value, 47% of women in our sample were considered at possible risk for postpartum psychosis.

Discussion: This study provides, for the first time, a specific self-report measure to assess postpartum PEs reliably and validly. The PPES appears to be a convenient-to-use and economic screening tool to detect signs and symptoms of attenuated psychosis in the postpartum women populations at risk for psychosis. While postnatal and postpartum care tends to be typically more focused on the mother and baby's physical health, routine screening for signs of psychosis during postpartum should also be highly recommended, as this may enhance the ability to timely manage the condition and prevent its potential harmful outcomes for both mother and baby. We believe that using the PPSE in maternity healthcare services could potentially result in a significant increase in detection of postpartum, relative to standard referral methods and will hopefully raise exciting prospects for future research in the field.

F14. THE RELATIONSHIP BETWEEN CLIMATE CHANGE ANXIETY AND PSYCHOTIC EXPERIENCES IS MEDIATED BY DEATH ANXIETY

Feten Fekih-Romdhane^{*1}, Diana Malaeb², Alvaro Postigo³, Fouad Sakr⁴, Mariam Dabbous⁴, Sami El Khatib⁵, Sahar Obeid⁶, Majda Cheour¹, Souheil Hallit⁷

¹Tunis El Manar University, ²Gulf Medical University, Ajman, United Arab Emirates,

³University of Oviedo, ⁴Lebanese International University, ⁵Lebanese International University,

⁶Lebanese American University, ⁷Holy Spirit University of Kaslik

Background: As climate change persists, accelerates, and intensifies, and since mitigating factors are absent, mental health impacts are expected to follow the same patterns. Therefore, it appears of utmost importance to deepen and broaden the knowledge and understanding of how and through which mechanisms climate change anxiety (CCA) may interplay with mental health outcomes. Based on the stress-vulnerability model of psychosis, the present study

proposed to examine the relationship between CCA and psychotic experiences (PEs), and to test the theoretically-driven hypothesis that death anxiety acts as a mediator in this relationship. **Methods:** This study adopted a cross-sectional approach involving a sample of young adults aged 18 to 35 years (mean age = 24.56 ± 22.49 years; 63.9% females) originating from and residing in Lebanon.

Results: The results of the mediation analysis showed that death anxiety partially mediated the association between CCA and PEs. Higher CCA was significantly associated with higher death anxiety; higher death anxiety was significantly associated with more PEs. Finally, higher CCA was directly and significantly associated with more PEs.

Discussion: Analyses revealed that the relationship between CCA and PEs is both direct and indirect. The indirect relationship is verified through the intermediary role of death anxiety. To be specific, young people could experience greater degree of death anxiety with the increase of their CCA level, resulting in more severe psychotic symptoms. These findings make important contributions to the existing literature in a relatively new and evolving field of research. The threat of climate change has been described as “existential”, shedding light on its potential danger to social system and humans’ life itself. Being confronted with the reality and inescapability of death as a result of climate change is the essence of death anxiety. Death anxiety is suggested, in turn, to play a certain role in triggering or exacerbating PEs, which replicates findings from earlier studies that death anxiety is likely to exist as a risk factor for psychotic symptoms in young adults from the general population. The key tentative recommendation is that addressing death anxiety might alleviate the association between CCA and PEs. In addition, government decision-makers need to recognize the necessity of considering climate change implications on mental health in policy and decision-making. To some extent, our study can also offer some enlightenment and possible future research directions for researchers in both climate change and early intervention in psychosis fields.

F15. COGNITIVE IMPAIRMENTS AND CLINICAL SYMPTOMS AMONG ADOLESCENTS WITH A HISTORY OF CHILD MALTREATMENT: CLINICAL CONCERNS

Caroline East-Richard^{*1}, Catherine St-Pierre¹, Gabriel Demers¹, Élisabeth Anderson¹, Marie-Michèle Champagne¹, Élisabeth Thibaut², Amélie M Achim³, Danielle Nadeau⁴, Caroline Cellard⁵

¹Université Laval, ²McGill University, Douglas Mental Health University Institute, ³Université Laval, CERVO Brain research center, ⁴Centre de recherche universitaire sur les jeunes et les familles (CRUJeF), ⁵Université Laval, Centre de recherche universitaire sur les jeunes et les familles (CRUJeF), CERVO Brain research center

Background: Child maltreatment history is highly prevalent among people with psychotic disorder and is a major risk factor for the development of such disorders. Child maltreatment is also associated with cognitive impairments, both in children and adults who have experienced child maltreatment. However, recent meta-analyses have highlighted the lack of research in the adolescent population. More specifically, few studies have investigated broad cognitive and clinical profiles in the adolescent population with a history of child maltreatment, while cognitive and clinical difficulties may represent relevant intervention targets in this at-risk population. This study aimed to assess the cognitive and clinical profiles of adolescents with a history of child maltreatment.

Methods: Forty adolescents with a history of child maltreatment were recruited from two child welfare service centers in Quebec, Canada. Inclusion criteria for this group were the following: (1) aged between 12 and 17, (2) having been exposed to child maltreatment. These adolescents were compared to 40 adolescents recruited from the general community without a history of child maltreatment. Clinical and cognitive assessments were carried out over three sessions. Several cognitive measures were used to assess the cognitive profile. Regarding the clinical measures, they assessed self-esteem (Culture Free Self-Esteem Inventories - 3rd Edition) and clinical symptoms or problems (Achenbach's Youth Self-Report). For the group with a history of child maltreatment, data on child maltreatment were collected from their records at the welfare service centers.

Results: Differences between groups were significant on cognitive outcomes ($p < .001$), with lower performance in the group with a history of child maltreatment in processing speed, verbal and visuospatial working memory, verbal and visual episodic memory, visuospatial abilities, and executive functioning. Increased internalized symptoms ($p = .009$), such as anxious/depressed symptoms and somatic complaints, were observed in the group with a history of child maltreatment, as well as externalized symptoms ($p < .001$), such as rule-breaking and aggressive behaviors. Attention and social problems were also more severe in the group with a history of child maltreatment ($p < .05$), as well as thought problems such as obsessive thoughts and auditory or visual hallucinations. Additionally, this group showed lower self-esteem ($p < .001$).

Discussion: Overall, adolescents with a history of child maltreatment showed several cognitive impairments and clinical symptoms. Such impairments may have negative impacts on many areas of their lives and deserve clinical attention. Since child maltreatment represents a risk factor for the development of psychotic disorders, the presence of child maltreatment should be an indication for preventative clinical measures such as addressing cognitive and psychological difficulties in trauma informed care. Clinical assessment aimed at the detection of psychotic symptoms may also be relevant. Finally, the use of neuroeducational tools may also be of relevance to promote better detection of cognitive difficulties and the implementation of strategies aimed towards the reduction of associated repercussions in daily life.

F16. CANNABIS-INDUCED PSYCHOSIS: INCIDENCE AND TRANSITION TO SCHIZOPHRENIA

Eline Rognli^{*1}, Heidi Taipale², Carsten Hjorthøj³, Ellenor Mittendorfer-Rutz⁴, Jørgen Bramness⁵, Ina Heiberg⁶, Solja Niemelä⁷, Bjarne Jacobsen⁸, Anne Høy⁶

¹Oslo University Hospital, ²Karolinska Institute, ³Copenhagen University Hospital, Mental Health Center Copenhagen, ⁴Karolinska Institutet, Sweden, ⁵Norwegian Institute of Public Health, ⁶UiT - Arctic University of Norway, ⁷University of Turku, Finland, ⁸Center for clinical documentation and evaluation

Background: Cannabis use is increasingly viewed as a risk factor for schizophrenia. The incidence of cannabis-induced psychosis, and the transition rate from cannabis-induced psychosis to schizophrenia, is less investigated.

Methods: National patient registries from Denmark and Sweden for the years 2000 to 2016, and from Norway from 2010 to 2015, were used to estimate annual incidence of different types of substance-induced psychosis including cannabis-induced psychosis. In a separate Norwegian study we estimated the cumulative hazard and the adjusted hazard ratios for transition from cannabis-induced psychosis to schizophrenia.

Results: The annual incidence rate of cannabis-induced psychosis increased from 2000 to 2016 with 113% in Denmark and with 265% in Sweden, and from 2010 to 2015 with 69% in Norway.

The six-year cumulative hazard for transition from cannabis-induced psychosis to schizophrenia in Norway was 36% (95% CI 31.4-41.0). The risk of transition from substance-induced psychosis to schizophrenia increased with lower age in men and with more episodes of substance-induced psychosis in both genders.

Discussion: The incidence of cannabis-induced psychosis has increased, and cannabis-induced psychosis is a considerable risk factor for later schizophrenia.

F17. LIFE HISTORY OF AGGRESSION IN A SOUTH AFRICAN STUDY OF XHOSA PEOPLE LIVING WITH SCHIZOPHRENIA

Olivia Wootton^{*1}, Christine Friestad², Christina Bell³, Jaroslav Rokicki⁴, Natalia Tesli⁵, Anja Vaskinn⁶, Gabriela Hjell⁷, Thomas Fisher-Vieler⁸, Ruben Gur⁹, Ezra Susser¹⁰, Unn K. Haukvik¹¹, Dan Stein¹

¹University of Cape Town, ²Institute of Clinical Medicine, University of Oslo, Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, ³University of Oslo, Oslo University Hospital, ⁴Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁵University of Oslo and Oslo University Hospital, ⁶Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, ⁷University of Oslo and Østfold Hospital, ⁸University of Oslo, Oslo University Hospital, ⁹University of Pennsylvania, ¹⁰Columbia University, ¹¹NORMENT, Norwegian Centre for Mental Disorders Research, Institute for Clinical Medicine, University of Oslo, Institute of Clinical Medicine, University of Oslo, Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital

Background: People living with schizophrenia (PLS) are at increased risk of committing acts of violence as well as experiencing violence themselves. The causes of violence in psychosis are multifactorial and many risk factors for violent behaviour have been identified, including adverse childhood experiences and social cognitive impairments. However, few studies have investigated the risk factors for violence in psychosis in low- and middle-income settings where differences in the socioeconomic context may affect the interaction between known risk factors and violent behaviour.

Methods: A subsample of participants (PLS = 179; controls = 357) from The Genomics of Schizophrenia in The South African Xhosa People Study completed The Childhood Trauma Questionnaire (CTQ), Life History of Aggression (LHA), Penn Emotion Identification Test, and Structured Diagnostic Interview for DSM-IV Axis I Disorders. Between group differences for childhood trauma, LHA, social cognition, and selected demographic and clinical factors were assessed using t-tests and chi-square tests. We tested if total scores for the LHA or CTQ were able to predict current social cognitive performance using multivariable linear regression.

Results: Scores for the CTQ and LHA were significantly higher for PLS and social cognitive performance was significantly worse for PLS compared to the control group. Current social cognitive performance was significantly associated with childhood trauma but not with aggressive behaviour over the lifetime.

Discussion: The null relationship between current social cognition and lifetime aggression may be due to the relatively low rates of aggression reported in our sample. The significant relationship between social cognition and childhood trauma in this sample provides evidence that the effect of childhood trauma on social cognition in adulthood persists even in environments where adverse childhood experiences are relatively prevalent.

F18. INSUFFICIENT PSYCHIATRIC TREATMENT IN 74% OF SEVERELY MENTALLY ILL OFFENDERS

Gitte Ahle*¹, Trine Arnglim², Tina Gram-Larsen², Mette Brandt-Christensen², Dorte Sestoft⁵

¹*Mental Health Center Amager*, ²*Forensic Psychiatric Department* ³*Ministry of Justice*, *Clinic of Forensic Psychiatry*

Background: The number of forensic psychiatric patients in Denmark has been increasing dramatically from 300 in 1980 to 4300 in 2014. A similar tendency has been seen in comparable countries, however, not to nearly the same extent. The aim of the study was to investigate if the patients had been offered sufficient psychiatric treatment prior to the committed crime.

Methods: The study is a retrospective, descriptive study based on the extraction of data from forensic mental assessment reports where sentence to psychiatric treatment was recommended. The sample includes all forensic mental assessment reports from all of Denmark conducted in the second half of year 2016. Data were extracted from the reports by a specialist in forensic psychiatry. The evaluation of the psychiatric treatment before the crime was made according to a consensus agreement of what constitutes sufficient treatment by the whole research group. Every tenth of the reports and all the reports where the crime was murder or attempted murder was evaluated by 4-6 specialists in forensic psychiatry and tested with Cohens kappa.

Results: There were 218 forensic mental assessment reports, The examined persons had a mean age of 38 years and 78% were men. 18% were homeless and 54% have previously been convicted. 70% had previously committed violence. Half of the persons were in psychiatric in- or out-treatment at the time of the intended crime. 7% had never been in contact with psychiatric services. Before the forensic mental assessment 118 were diagnosed with a non-affective psychosis. 18% more patients (139 versus 118) were diagnosed with a non-affective psychosis at the forensic mental examination than at the last contact with general psychiatry before the crime. We assessed 74% to have received insufficient treatment during the time leading up till them committing the crime. Insufficient treatment included not being admitted to the hospital when needed, a wrong diagnosis was allocated to the patient, or the patient was unstable at the time of the discharge from the hospital. 13 of the cases were charged of murder or attempted murder. We estimated that in 11 of these cases the patient had received insufficient psychiatric treatment during the time leading up to the intended crime.

Discussion: The finding of insufficient treatment in the majority of cases at the time of the crimes might indicate a link between the criminal behavior and inadequate treatment. Almost all the patients were known by the psychiatric services, many had previously been convicted and many had demonstrated violent behavior. These are all well-known risk factor for committing a crime. Moreover, psychosis were significantly under-diagnosed in the sample. It is critical that 18% more is diagnosed with a non-affective psychosis at the forensic mental assessment as untreated psychosis is also a risk factor for committing a violent crime. Our finding points to the importance of correct assessment of psychosis and of offering treatment to individuals with psychosis, especially when they have additional risk-factors for criminal behavior.

F19. INVESTIGATING THE CORRELATES OF PSYCHOTIC-LIKE EXPERIENCES DURING COVID-19 PANDEMIC IN SIX DIFFERENT COUNTRIES AMONG YOUNG ADULTS: A DATA MINING STUDY

Helin Yılmaz Kafalı*¹, İnanç Kabasakal², Sheikh Shoib³, Dmytro Martsenkovskyi⁴, Irfan Ullah⁵, Joan Soler Vidal⁶, Oluseun Peter Ogunnub⁷, Paola Fuentes Claramonte⁶, Gamze Erzin⁸, Özge Kılıç⁹, Mireia Solerdelcoll¹⁰, Chonnakarn Jatchavala¹¹, Victor Pereira Sanchez¹², Timothea Touloupoulou¹³

¹Işık University, ²Ege University, ³Director Health Services Kashmir, ⁴Bogomolets National Medical University, ⁵Kabir Medical College, University, Peshawar, ⁶FIDMAG Hermanas Hospitalarias Research Foundation, ⁷University of Lagos, Nigeria, ⁸Dışkapı Yıldırım Beyazıt Training and Research Hospital, ⁹Koç University, Department of Psychiatry, ¹⁰King's College London, ¹¹Prince of Songkla University, ¹²Stavros Niarchos Foundation Global Center for Child and Adolescent Mental Health, ¹³Bilkent University,

Background: By using association rule mining method, this study aimed to investigate the correlates of psychotic-like experiences (PLEs) during the SARS-CoV-2 pandemic in six different countries among the young adults.

Methods: 1466 participants aged between 18-24 from six different countries consisting of Indian (n=356), Ukraine (n=320), Pakistan (n=292), Turkey (n=264), Spain (n=135), and Nigeria (n=99) were recruited between July 2020 and July 2021. Community Assessment of Psychic Experiences-42 (CAPE-42-Pos), Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder-7 (GAD-7), and Pittsburg Sleep Quality Index (PSQI) were filled out by using an online questionnaire to evaluate PLEs, depressive symptoms, anxiety symptoms, and sleep problems, respectively. Data regarding the presence of a diagnosed psychiatric disorder, chronic disease, cigarette and alcohol usage within the last 30 days, lifetime drug use, history of SARS-CoV-2 infection (yes/no), and psychiatric disorders in the first degree relatives were also collected. RuleGenerator Software was used to execute the association rule mining algorithm and obtain association rules. Rule mining was repeated for each country separately. The rules were evaluated through measures for interestingness, such as confidence and lift.

Results: In Turkey, 7.6% of the participants had both suicidal thought and had previous suicidal attempt. The ratio of having both a psychiatric disorder and a high CAPE score (≥ 38) in such patients was 6.19 times higher than the entire group of participants from Turkey. 75% of the participants using cigarette everyday and having suicidal thoughts in had high-CAPE score (OR=5.19). 7.6% of the participants from Turkey had both a psychiatric disorder and suicidal attempt. 40% of these individuals had high CAPE score (≥ 38) (OR=5). 40% of the participants using alcohol 3-5 times in a month and having suicidal thought had high CAPE score (≥ 38) (OR=4.8). In Pakistan, the 64.2% of the participants with severe anxiety (GAD ≥ 10) and having a psychiatric disorder in family had high CAPE score (≥ 38) and a psychiatric disorder (OR=18.7). 57.1% of these participants had both high CAPE-score and have medium-level sleep problems (PSQI from 6 to 10) (OR=16.6). 3.44% of the participants from Pakistan had both psychiatric disorder in family, had severe depression (PHQ ≥ 10) and severe anxiety level (GAD ≥ 10). 90% of these participants had high CAPE score (≥ 38) (OR=16.1). All of the participants with a psychiatric disorder, had a psychiatric disorder in family, and severe anxiety (GAD ≥ 10) had high CAPE score (≥ 38) (OR=16.1). Moreover, all of the participants with psychiatric disorder in family, medium PSQI score (6-10) and high GAD (≥ 10) had high CAPE score (OR=16.1). In Nigeria, 50% of the participants with severe sleep problems (PSQI GREATER THAN 11) had both high CAPE score (≥ 38) and severe depression (PHQ ≥ 10) (OR=6). 60% of the male participants with severe depression (PHQ ≥ 10) had high CAPE-score (OR=5.8). 9.2% of the participants from Nigeria had a psychiatric disorder, severe depression (PHQ ≥ 10), and severe anxiety (GAD ≥ 10). 44.4% of these participants had high CAPE score (OR=4.3). In Ukrain, 35.7% of the participants with chronic disease and severe anxiety (GAD ≥ 10) had high CAPE score (≥ 38) (OR=6.3). 25% of the participants with suicidal thought and severe anxiety (GAD ≥ 10) had both psychiatric disorder and high CAPE-score (OR=6.6).

23.8% of the participants with a psychiatric disorder and having suicidal thoughts had both high CAPE score (≥ 38) and severe anxiety level ($GAD \geq 10$) ($OR=5.4$). In India, 13% of the participants had severe sleep problems ($PSQI \geq 11$). 47.3% of these participants had high CAPE score (≥ 38) ($OR=3$). 81% of the participants with psychiatric disorder, suicidal thought, and severe sleep problems ($PSQI \geq 11$) had high CAPE score ($OR=5.1$). In Spain, 6% of the participants were using psychopharmacological treatment. 37.5% of the participants using psychopharmacological treatment had high CAPE score (≥ 38) ($OR=9.9$). 7.5% of the participants had severe sleep problems ($PSQI \geq 11$). 30% of the ones with the severe sleep problems had high CAPE score ($OR=7.9$). 17.6% of the participants who had Covid-19 infection in family and had severe anxiety ($GAD \geq 10$) had both high CAPE score (≥ 38) and severe depression ($PHQ \geq 10$) ($OR=7.8$).

Discussion: Our results showed us that in Turkey having suicidal thoughts/attempts and using cigarette (everyday), and alcohol (3-5 times in a month); in Pakistan having a psychiatric disorder, psychiatric disorder in family, severe depression, and severe anxiety; in Nigeria severe sleep problems, being a male, severe depression, having a psychiatric disorder, and severe anxiety; in India having a chronic disease, severe anxiety, having a psychiatric disorder, suicidal thoughts; in Spain using psychopharmacological treatment, severe sleep problems, Covid-19 infection in family, and severe anxiety were associated with PLEs. Association rule mining model allowed us to find country-specific risk factors regarding PLEs.

F20. AN EXAMINATION OF THE RELATIVE ROLE OF STATIC AND DYNAMIC FACTORS IN PREDICTING RISK FOR REHOSPITALIZATION IN INDIVIDUALS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS: HIGHLIGHTING THE ROLE OF AGGRESSION AS A PRIMARY RISK FACTOR

Shreya Jagtap^{*1}, Cory Gerritsen², Jessica D'Arcey³, Hanna Hamzai⁴, Sylvia Romanowska⁵, Michael Best⁵

¹Centre for Addiction and Mental Health, University of Toronto, ²Centre for Addiction and Mental Health, The University of Toronto, ³University of Toronto Scarborough, Centre for Addiction and Mental Health, ⁴University of Toronto, ⁵University of Toronto Scarborough

Background: Individuals with schizophrenia spectrum disorders (SSDs) typically require a high level of intensive treatment service, such as inpatient hospitalization, with rates of rehospitalization ranging from 52% to 64% between one to five years after discharge. Existing literature has focused on largely static demographic variables such as sex, age, employment status, and education as key factors associated with rehospitalization rates in individuals with SSDs. Dynamic clinical risk factors such as comorbid substance use, aggression, self-harm, impairments in activities of daily living, and length of initial hospitalization have received less attention but are also associated with subsequent rehospitalization. The primary aim of this study was to determine which of these factors are related to subsequent hospital admissions. The secondary aim was to elucidate the incremental changes in the strength of that relationship with dynamic less-established clinical factors related to aggression, functioning, and self-harm beyond the traditionally-established demographic contributors.

Methods: This retrospective chart review study assessed demographic and clinical variables in a sample of 883 individuals with an SSD admitted to an inpatient psychiatric unit from 2015-2020. Demographic data and admission-related incidents (e.g., aggression; need for restraint/seclusion) were obtained from electronic medical records. Clinical variables were obtained from Resident Assessment Inventory, as well as calculated using electronic medical record data (e.g., length of stay). To investigate the factors associated with the event of

rehospitalization, a Cox proportional hazards regression analysis was performed. To examine their incremental predictive capacity, a negative binomial regression analysis was performed.

Results: In our Cox regression model, only scores on the RAI: Harm to Others scale were associated with the event of rehospitalization ([OR] = 1.18, 95% [CI], 1.01 to 1.37). We conducted two negative binomial models with Model 1 consisting of static demographic variables and Model 2 consisting of static demographic and dynamic clinical variables. A chi-square likelihood ratio test comparing deviance scores between both indicated that Model 2 provided a significantly stronger model fit ($p = \text{LESS THAN } .001$). Model 1 was significant, χ^2 likelihood ratio = 119.19, $p = \text{LESS THAN } .001$. Sex (male) was found to significantly predict the number of rehospitalizations ($B = -.25$, $p = .041$). Model 2 was also significant. In this model, identifying as male ($B = -.26$, $p = .045$), the number of aggressive incidents ($B = .03$, $p = .004$), a shorter length of initial rehospitalization ($B = \text{LESS THAN } .001$, $p = .036$), lower RAI: Self Harm scale scores ($B = -.18$, $p = .023$), and not being referred for concurrent disorders treatment services ($B = .57$, $p = .041$) was shown to significantly predict a greater number of subsequent hospitalizations.

Discussion: Our findings highlight that dynamic clinical factors are better predictors of rehospitalization outcomes than static factors. Notably, factors related to aggression and harm are particularly associated with rehospitalization outcomes, while there was no relationship found between positive symptoms and hospitalizations. It may be that a propensity towards aggressive behaviour is more greatly associated with instability in the community upon discharge compared to symptom severity, leading to an increased likelihood of rehospitalization. Thus, the implementation of treatment interventions that target and mitigate aggressive behaviour may be important adjuncts alongside treatment for the stabilization of symptoms, to reduce rehospitalization rates for individuals with SSDs.

F21. DYNAMIC ASSOCIATIONS AMONG NEGATIVE SCHIZOTYPY, ANTICIPATORY PLEASURE, AND SUICIDAL IDEATION

Rebecca Salzano*¹, Richard Linscott¹

¹*University of Otago*

Background: Negative schizotypy is a major risk factor for suicidal ideation. According to previous literature, deficiencies in pleasure are evident in negative schizotypy and suicidal ideation, suggesting a possible link. In particular, low levels of anticipatory pleasure predict negative symptoms and suicidal ideation more strongly than consummatory pleasure. We investigated whether anticipatory pleasure mediated the associations of negative, positive, and disorganised schizotypy to suicidal ideation.

Methods: Psychology undergraduates ($n = 532$) underwent baseline assessments for schizotypy, pleasure capacity, and suicidal ideation, followed by nine follow-up assessment waves at three-day intervals over 30 days. Baseline assessments included self-report measures of schizotypy (Brief Revised Updated version of the Schizotypal Personality Questionnaire, SPQ-BRU), suicidal ideation (Columbia-Suicide Severity Rating Scale, C-SSRS), and anticipatory and consummatory pleasure (Temporal Experiences of Pleasure Scale, TEPS; and Dimensions of Interpersonal Pleasure Scale, DIPS). Follow-up assessments included measures of anticipatory and consummatory pleasure (State Experience of Pleasure Scale, SEPS) and suicidal ideation (C-SSRI). Baseline data were analysed using a structural equation model, and longitudinal data using a general linear mixed-effects model. Bias-corrected bootstrapped confidence intervals were used to assess statistical significance.

Results: Interpersonal (standardised beta $c1 = .11$; bootstrapped 95% confidence interval = [.01, .21]), disorganised ($c3 = .17$ [.08, .27]), and cognitive-perceptual schizotypy ($c4 = .12$ [.17, .28]) had significant total relationships with ideation at baseline. In cross-sectional analyses, anticipatory pleasure fully mediated the relationship between interpersonal schizotypy and suicidal ideation ($c1' = -.03$ [-.13, .08]) and partially mediated the relationship between disorganised schizotypy and suicidal ideation ($c3' = .13$ [.04, .22]). Interpersonal ($c1 = .06$ [.02, .13]), social anxiety ($c2 = .10$ [.02, .17]), disorganised ($c3 = .10$ [.02, .17], and cognitive-perceptual schizotypy ($c4 = .08$ [.01, .17]) had significant total effects on changes in ideation over time. In longitudinal analyses, changes in anticipatory pleasure fully mediated the association of interpersonal schizotypy ($c1' = .01$ [-.02, .13]) and social anxiety ($c2' = .05$ [-.02, .12]) with changes in ideation and partially mediated the relationship of disorganised schizotypy with changes in ideation ($c3' = .08$ [.00, .15]). Cognitive-perceptual schizotypy was neither cross-sectionally ($c4' = .17$ [.07, .28]) nor longitudinally ($c4' = .08$ [.002, .16]) related to ideation through anticipatory pleasure. Consummatory pleasure did not have any mediatory effects on any cross-sectional or longitudinal relationships.

Discussion: Across 10 time points, all subtypes of schizotypy were significantly associated with the emergence of suicidal ideation. Cross-sectional and longitudinal findings indicated that anticipatory but not consummatory pleasure mediated the relationship between interpersonal schizotypy and suicidal ideation and partially mediated the relationship from disorganised schizotypy to suicidal ideation. Our findings echo prior research indicating elevated suicidal ideation in individuals with lower pleasure levels and reduced anticipatory pleasure in negative schizotypy. Addressing deficits in anticipatory pleasure may help to develop targeted prevention and intervention strategies among individuals displaying negative schizotypy.

F22. LONGITUDINAL TRAJECTORIES OF BRAIN DEVELOPMENT IN CHILDREN AND ADOLESCENTS AT FAMILY RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Isabel Valli^{*1}, Mireia Masias², Angels Calvert³, Jose Pariente⁴, Elena De la Serna⁵, Eduard Vieta⁶, Gisela Sugranyes⁷, Josefina Castro-Fornieles⁸

¹*Instituto de Investigaciones Biomedicas de Barcelona, CSIC-IDIBAPS-CIBERSAM*, ²*BCN-Medtech, Universitat Pompeu Fabra*, ³*IDIBAPS*, ⁴*Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS), Barcelona, Spain*, ⁵*Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM*, ⁶*Bipolar Disorder Program, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.*, ⁷*IDIBAPS (August Pi i Sunyer Biomedical Research Institute) / Hospital Clínic Barcelona*, ⁸*Hospital Clinic de Barcelona. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM Barcelona*

Background: Subcortical brain abnormalities are among the most robust findings in schizophrenia and bipolar disorder. Similar yet subtler abnormalities have been observed in youth at clinical or family risk for both disorders. These abnormalities are considered neurodevelopmental in origin and their investigation can contribute to the understanding of neurobiological changes that precede illness onset. However, evidence in high-risk populations has mainly been cross-sectional, whereas the brain is undergoing important maturational

changes over the years before symptoms emerge. A limited number of longitudinal studies therefore examined whether those observed are stable trait structural abnormalities or rather differences that emerge during brain maturation. However, the available evidence largely focused on late adolescence and early adulthood. It remains thus unclear when these abnormalities emerge and how they progress. We therefore sought to investigate an earlier segment of the neurodevelopmental pathway, longitudinally examining children and adolescents at family risk. We tested whether and when their trajectories of subcortical brain development might diverge from those of healthy control participants. In the hippocampus we also examined the longitudinal development of anatomically distinct subfields, to assess whether potential volumetric abnormalities are widespread or rather initially localised and subsequently generalise.

Methods: We examined a total of 385 scans from 194 participants: 52 children of parents with schizophrenia (SZO), 75 children of parents with bipolar disorder (BDO) and 67 children of healthy control parents (HCO) aged 6 to 20 years. Each participant underwent 3T structural MRI imaging at 1 to 3 time points, each two years apart. Mixed models were used to compare groups in terms of volumetric longitudinal trajectories of lateral ventricles, thalamus, caudate, putamen, pallidum, nucleus accumbens, amygdala, the hippocampus and its subfields.

Results: We observed that high risk participants, taken together, showed diverging trajectories of hippocampal development compared to HCO, with significantly accelerated volumetric decline in the left hippocampus and at trend level in the right. When examining the two offspring groups separately, we observed overlapping trajectories of hippocampal development for SZO and BPO compared to HCO in the left hippocampus, whereas in the right hippocampus the divergence from HCO trajectories was more pronounced in SZO compared to BPO. When examining hippocampal subfields, we observed trend level volume differences in the subiculum and CA1 but no interaction with age, with no differences in terms of slope between high-risk individuals and HCO. No significant between-group differences were observed in the other subcortical structures examined.

Discussion: Our results suggest that dynamic changes occur across childhood and adolescence in individuals at family risk for psychosis. These are most pronounced in the hippocampus and especially in its anterior portions, similarly to what has been observed soon after symptoms emergence in first episode psychosis. Future studies, conducted once participants reach the mean age of onset for the examined disorders, will clarify whether diverging trajectories are most pronounced in those who will develop a psychotic disorder, and thus elucidate whether the observed differences are correlates of family proneness or could rather be used as predictors of future illness.

F23. ADOLESCENT MEDIA USE AND ITS ASSOCIATIONS WITH PSYCHOTIC EXPERIENCES

Vincent Paquin^{*1}, Manuela Ferrari¹, Soham Rej¹, Michel Boivin², Isabelle Ouellet-Morin³, Marie-Claude Geoffroy¹, Jai L. Shah¹

¹McGill University, ²Laval University, ³University of Montreal

Background: Adolescent media use has been associated with mental health problems and is thought to influence brain development. However, whether it is associated with psychotic experiences (PEs) remains unclear. The association between media use and PEs may vary according to the types of media involved and time-sensitive changes in the amounts of use over adolescence. We thus aimed to examine longitudinal trajectories of adolescent media use

between 12 and 17 years of age and their associations with PEs at 23 years. We considered four types of media use: TV viewing, video gaming, computer use, and reading.

Methods: The sample included 1226 participants (n=713 [58.2%] female) from the Québec Longitudinal Study of Child Development, a population-based cohort of children born in 1997 and 1998 and followed up annually or biannually from 5 months through 23 years of age. Participants reported their weekly amount of TV viewing, video gaming, computer use, and reading at 12, 13, 15 and 17 years of age. Lifetime occurrence of psychotic experiences was measured at 23 years of age with the 15-item Community Assessment of Psychic Experiences. Covariables included sociodemographic, genetic, and psychosocial characteristics between 5 months and 12 years of age. We used latent class mixed modeling to identify trajectories of media use. Associations between media use trajectories and PEs were examined with Gamma models.

Results: Between 12 and 17 years of age, participants followed lower, medium, or higher trajectories of TV viewing, video gaming, and reading. For computer use, they followed a lower, curved, or higher trajectory. In all types of media, a minority of participants followed trajectories of higher use: TV viewing, n=128 (10.4%); video gaming, n=145 (11.8%); computer use, n=353 (28.8%); and reading, n=140 (11.4%). Relative to lower video gaming (n=891 [72.7%]), a trajectory of higher video gaming was preceded by higher levels of mental health and interpersonal problems at 12 years, and adjusting for these factors explained the association of higher video gaming with PEs at 23 years. A curved trajectory of computer use (n=189 [15.4%] participants), characterized by increasing levels of use until 15 years of age followed by a decrease, was associated with higher PEs (estimated difference, +5.3%; 95% CI, +1.5%-+9.3%) relative to lower use (n=684 [55.8%] participants). This association was robust to covariable adjustment. Trajectories of TV viewing and reading were not associated with PEs, and there were no significant sex differences in the associations of media use trajectories with PEs.

Discussion: A sharp decline in computer use during late adolescence, as found in the curved trajectory, may be a marker of risk for future PEs. This association may reflect the onset of PEs during adolescence that lead to, or are concurrent with, a time-sensitive decrease in the amount of computer use. The higher video gaming trajectory was associated with more PEs at 23 years of age, however this association was explained by higher childhood mental health and interpersonal problems among higher video gamers. It is possible that some adolescents at risk for PEs turn to video games in response to psychosocial adversity, for example as a way of coping or because of the greater accessibility of video games relative to other activities. Overall, trajectories of adolescent media use and their psychosocial antecedents may be informative for the early identification of PEs. Better understanding the motivations for and mental health determinants of adolescent media use may contribute to the development of digital approaches to detect and prevent PEs.

F24. COMPENSATORY UPREGULATION OF C4 MEDIATES THE DEVELOPMENT OF ADULT BRAIN PATHOLOGY AFTER TRANSIENT PREFRONTAL MICROGLIA DEFICIENCY IN ADOLESCENCE

Sina-Maria Schalbetter*¹, Anja Krütli¹, Ron Rabin¹, Anina Sara von Arx¹, Olga Krzyzaniak¹, Han-Yu Lin¹, Johanna Furrer¹, Tina Notter¹, Urs Meyer¹

¹University of Zurich

Background: We have recently shown that microglia, the brain's resident immune cells, contribute to functional and structural maturation of the prefrontal cortex (PFC). Using a mouse

model of cell-specific, transient and local depletion of microglia, we found that deficiency of prefrontal microglia during adolescence is sufficient to induce an adult emergence of PFC-associated impairments in cognitive functions, dendritic complexity, and synaptic structures and functions. However, the precise molecular mechanisms mediating the long-term effects of adolescent microglia deficiency remain elusive. Based on the emerging role of the complement component 4 (C4) in physiological and pathological pruning of synapses, we explored the role of C4 in this novel mouse model of transient prefrontal microglia depletion during adolescence.

Methods: Brain region-specific and transient depletion of prefrontal microglia during adolescence was induced by a single, bilateral stereotaxic injection of clodronate disodium salt (CDS) into the medial portion of the PFC in 6-week-old C57BL/6 mice. Control mice received a bilateral stereotaxic injection of phosphate-buffered saline (PBS). The magnitude and specificity of microglia depletion were ascertained by post-mortem immunohistochemistry at 1, 5, 10, and 40 days post-injection (dpi), whereas mRNA levels of C4b were quantified at these dpi intervals using quantitative real-time PCR (qRT-PCR). RNAscope in situ hybridization was used to co-localize C4b gene expression with different cell populations, including microglia, astrocytes and neurons. PFC-specific downregulation of C4 during adolescence was used to explore whether compensatory upregulation of C4 mediates the development of adult brain pathology after temporary microglia deficiency in adolescence. This was achieved by bilateral injections of an AAV expressing a small hairpin RNA (shRNA) against murine C4, coupled with GFP (AAV-shRNA), in 3-week-old C57BL/6 mice. The control group received an AAV expressing GFP with a scramble shRNA sequence (AAV-Co). A battery of mPFC-dependent cognitive tests, including social recognition memory and temporal order memory, was conducted to probe C4's involvement in disputing adult cognitive functions.

Results: A single intra-PFC injection of CDS led to a robust (~ 80% depletion) but temporary (~ 1 week) microglia deficiency in the adolescent PFC without depleting other cell types, such as astrocytes and neurons. The expression of C4b was markedly (2-3 fold) upregulated in mice that were subjected to transient microglia depletion, starting from 5 dpi and persisting into the 40 dpi interval. This upregulation emerged mostly in astrocytes and, to a lesser extent, in neurons, but not in microglia. Pre-administration of shRNA targeting C4 expression effectively attenuated the upregulation of prefrontal C4b after microglia depletion. Importantly, blocking the compensatory upregulation of C4b by anti-C4 shRNA prevented the subsequent emergence of social recognition memory and temporal order memory deficits in adulthood.

Discussion: Using a selective and transient loss-of-function approach, our study identified compensatory upregulation of C4 in response to transient prefrontal microglia deficiency in adolescence. Furthermore, our data suggest that this upregulation of prefrontal C4 mediates the subsequent emergence of cognitive dysfunctions pertaining to schizophrenia and other PFC-related disorders.

F25. COGNITIVE FUNCTIONING IN PEOPLE WITH SUBCLINICAL PSYCHOTIC SYMPTOMS: A SYSTEMATIC REVIEW AND META-ANALYSIS STUDY

Sai Ting Chu^{*1}, Ivan Wai Lok Chu², Esther Wing-Chi Yip², Joe Kwun Nam Chan², Corine Sau Man Wong³, Wing Chung Chang⁴

¹*The University of Hong Kong*, ²*Department of Psychiatry, the University of Hong Kong*, ³*School of Public Health, LKS Faculty of Medicine, The University of Hong Kong*, ⁴*Department of Psychiatry, School of Clinical medicine, LKS Faculty of Medicine, The University of Hong Kong*

Background: Cognitive deficit is widely observed in schizophrenia patients and is associated with negative functional outcomes. However, comprehensive review and sources of heterogeneity in cognitive functioning in individuals with subclinical psychotic symptoms (PS) are lacking in previous meta-analysis. We conducted a systematic review and meta-analysis with an aim to evaluate the presence, degree, and patterns of cognitive impairment among individuals experiencing subclinical PS relative to those without subclinical PS. Meta-regression analyses were performed to examine sources of heterogeneity.

Methods: We systematically searched four electronic-databases until 6-July-2023 and conducted meta-analysis to synthesize estimates of cognitive functioning for individuals with subclinical PS relative to non-PS counterparts. Subgroup analyses and meta-regression models stratified by sex, age, study design (cross-sectional vs longitudinal), individual cognitive tasks used (i.e., MMSE vs IQ vs others), PS instrument (i.e., PSQ vs others) were conducted when applicable.

Results: Twenty-seven and 6 studies were included for meta-analysis of cognitive functioning with (n=82,561; 10,251 individuals with subclinical PS) and without (n=8,062; 813 individuals with subclinical PS) dichotomous PS cutoff. People with subclinical PS exhibited larger cognitive deficit in general cognition (Hedges' $g=-0.10$ [95% CI: -0.18 to -0.02]), verbal fluency (Hedges' $g=-0.05$ [95% CI: -0.10 to -0.00]), visual learning and memory (Hedges' $g=-0.21$ [95% CI: -0.38 to -0.03]) and working memory (Hedges' $g=-0.16$ [95% CI: -0.28 to -0.04]) relative to non-PS controls. Subgroup analysis in general cognition suggested more severe deficit was observed in both study designs with longitudinal design showing significantly larger deficit ($z=-2.83$, $p=0.005$), and cognitive instruments other than MMSE and IQ (-0.11 [-0.20 to -0.01]). Meta-regression in general cognition revealed subclinical PS was associated with age ($Q_m=11.34$, $p < 0.001$), sex ($Q_m=6.71$, $p=0.010$) and study design ($Q_m=8.01$, $p=0.005$). When concerning cognitive sub-domain, poorer performance in working memory was observed in subclinical PS compared to the counterparts without PS using Digit Span task (-0.18 [-0.32 to -0.05]) and with cross-sectional design (-0.26 [-0.41 to -0.12]). Exploratory analysis examining subclinical PS using scales without dichotomous PS cutoff revealed absence of significant difference in cognitive performance.

Discussion: Taken together, subclinical PS is associated with subtle cognitive deficit. Future studies should examine the underlying biological mechanism for cognitive functioning in subclinical PS.

F26. VISUAL PROCESSING OF SOCIAL AND NON-SOCIAL STIMULI IN SCHIZOPHRENIA: EXPLORING THE LINK TO PSYCHOPATHOLOGY

Hana Kutlikova^{*1}, Natália Čavojská², Vladimír Ivančík², Alexandra Straková³, Vanda Valkučáková², Ján Pečeňák⁴, Anton Heretik³, Michal Hajdúk²

¹Comenius University, ²Comenius University in Bratislava, ³Department of Psychology, Faculty of Arts, Comenius University, Bratislava, Slovak Republic, ⁴Department of Psychiatry, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic

Background: Attentional deficits in the processing of socially salient cues are well established in schizophrenia. However, less is known about how they are related to the specific symptoms of schizophrenia. This study therefore aims to investigate the link between visual processing of social versus non-social scene components, in individuals with schizophrenic spectrum disorder (SZ) and in the healthy controls (HC) with specific focus on the role of positive and negative symptoms.

Methods: Using a free-viewing eye-tracking paradigm, we tested 30 individuals with SZ (52 % female, Mage = 40.60, 95% CI [37.01, 44.19]) and 31 HC (61 % female, Mage = 33.25, 95% CI [29.27, 37.23]). The task consisted of 12 complex scenes drawn from the IAPS database. Each scene contained both social and non-social components and the images were selected to balance arousal and valence, ensuring equal representation of high and low intensities in both dimensions. Participants were instructed to look at any part of the screen, and there was no secondary task involved. We measured eye-tracking parameters capturing both attentional engagement (time to first fixation, peak velocity of the first saccade) and attentional maintenance (number and duration of fixations and saccades). Psychopathology was assessed using Brief Psychiatric Rating Scale (BPRS) and Community Assessment of Psychic Experiences (CAPE-42).

Results: GLMMs of the eye-tracking parameters did not reveal any main effect of the group (SZ/HC), nor its interaction with the type of scene component (social/non-social). When taking into account the arousal and valence of the presented stimuli, SZ (M = 2709 ms, 95% CI [2333.7, 3085]) compared to HC participants (M = 2125 ms, 95% CI [1785.6, 2465]) showed significantly slower ($t(176) = -2.276, p = .024$) attentional engagement toward non-social aspects of the highly arousing negative scenes (Group x Valence x Arousal x Type interaction: $F(1, 917.89) = 5.50, p = .019$). Furthermore, in SZ, slower attentional engagement (i.e., longer time to the first whole fixation) toward non-social scene components was significantly associated with more severe negative symptoms measured by BPRS ($\rho = .467, p = .009$). On the other hand, the positive symptoms were related to slower attentional engagements in the social components of the presented scenes ($\rho = .538, p = .002$).

Discussion: Our study highlights the link between negative symptoms and attentional deficits in processing of the non-social information. More specifically, we show that individuals with SZ need longer time to engage with non-social aspects of highly arousing negative scenes, and that this delay is related to the severity of negative symptoms. Such results point to impaired cognitive processing of contextual information among SZ individuals, particularly in scenarios that are highly distressing. On the contrary, the positive symptoms in SZ seem to be related to the delayed attentional engagement toward central social aspects of the environment. While acknowledging the need for cautious interpretation due to multiple comparisons, our study provides preliminary evidence of a distinct role of negative and positive symptoms in the visual processing of non-social and social stimuli.

F27. PSYCHOEDUCATIONAL PROGRAMS FOR YOUNG WITH ULTRA HIGH RISK: TOOLS SUPPORTING DEPLOYMENT EARLY INTERVENTION IN FRANCE

Marion Feron¹, Trang Nu Thuy TON^{*2}

¹Service CRISALID CHI Clermont de l'Oise, ²none

Background: Early intervention occurs during cerebral adolescence, a period of opportunity for preventive support and a change of paradigm with a transdiagnostic, prospective view, development and implantation. It authorizes the ambition to be able to change the clinical trajectory of young users with clinical situations (high risk mental states) through targeted tools. Psychoeducation is considered as an efficient care tool for established and persistent psychiatric disorders. In the context of early intervention, users show low engagement in care.

Methods: A modular and adaptable program, based on cooperative pedagogy, free choice and concerted objectives is an integral part of the care pathway and a key element of recovery. These elements appear in description of this care pathways and this specific program, led by a

trained multidisciplinary team (including peer health mediator) and evaluated by mixed qualitative and quantitative indicators.

Results: "Cultivate your strengths and live fully"; consists of 2 basic sessions and then 6 optional sessions developed with the young people according to their needs (emotional regulation, psychosocial skills, rights, sexuality, health life, etc.). The objective is to preserve their self-determination, to choose their pathway, in a dynamic of partnership with health professionals.

Discussion: In a preliminary study, this program helps to increase Mental Well-Being (WEMWBS, Trousselard et al., 2016), Emotional regulation (DERS, Dan-Glauser et al., 2013), and use of coping strategies (problem-solving - WCC-R, Cousson et al., 1996), commitment to care, to support a change of vocabulary (verbatim analysis), and to reduce school and care dropout rates.

Psychoeducational programs based on adaptability according to needs are efficient to support recovery and free diffusion helps to develop early intervention in France.

F28. THE IMPACT OF EARLY LIFE STRESS ON SCHIZOPHRENIA-LIKE COGNITIVE DEFICITS IN MICE HETEROZYGOUS FOR A MUTATION IN GLUTAMATE DEHYDROGENASE: A GENE X ENVIRONMENT MODEL

Brigitte Baransi^{*1}, Kfir Asraf², Inna Gaisler-Salomon³

¹*School of Psychological Sciences, University of Haifa, The Integrated Brain and Behavior Research Center (IBBRC), University of Haifa,* ²*University of Haifa,* ³*University of Haifa*

Background: Schizophrenia (SZ) pathology has been associated with glutamate dysfunction, and its developmental trajectory is affected by stress exposure. One of the most coherent findings in psychiatric epidemiology is that early life stress (ELS) is a powerful determinant of mental health issues over a lifetime. In SZ, ELS is hypothesized to affect hypothalamic-pituitary-adrenal (HPA) axis function, which in turn impacts glutamate and dopamine transmission. Glutamate dehydrogenase1 (GDH in humans, Glud1 in rodents), is a mitochondrial enzyme involved in glutamate metabolism, and alterations in GDH mRNA expression have been found in the prefrontal cortex (PFC) of patients with SZ. Our previous studies showed that mice with a homozygous deletion of Glud1 in CNS (CNS-Glud1^{+/+} mice) or mice with a heterozygous deletion (CNS-Glud1^{+/-} mice) exposed to acute mild stress in early adulthood show significant behavioural abnormalities that mimic different aspects of SZ-like symptomatology. In the present study, we tested the impact of ELS on SZ-like behavioural deficits in heterozygous CNS-Glud1^{+/-} mice and their CNS-Cre⁺ controls. We assessed behavior in the open field, novel object recognition (NOR) and Water T-maze tasks. We also assessed performance in a novel overshadowing task, which measures salience attribution that is impaired in SZ and is associated with dopamine dysfunction. Following behavioral tasks, we quantified mRNA expression of glutamate and dopamine markers in the hippocampus and nucleus accumbens.

Methods: We used the limited bedding and nesting material (LBN) paradigm to induce ELS between postnatal days (PND) 3-9. Adult CNS-Glud1^{+/-} and CNS-Cre⁺ mice exposed to ELS or adequate bedding and nesting material (no-stress controls) were tested for behavioral alterations between PND70-90. Twenty days after the overshadowing test, we assessed mRNA expression changes of glutamate and dopamine markers using RT-PCR. We hypothesized that CNS-Glud1^{+/-} mice that undergo the ELS condition will show deficits in all behavioural tests

and abnormalities in glutamate and dopamine markers that mimic findings in patients with schizophrenia.

Results: We find that while ELS does not induce long-term changes in weight or general health conditions, ELS-exposed CNS-Glud1+/- mice display hyper-locomotion in the open field as well as impaired spatial acquisition and reversal in the Water T-Maze Task. Furthermore, we found that LBN disrupted overshadowing regardless of genotype. Our ongoing studies will reveal whether these behavioral alterations are accompanied by gene expression changes.

Discussion: Our findings indicate that ELS affects CNS-Cre+ and CNS-Glud1+/- mice differently, leading to cognitive abnormalities in adult mutant mice that resemble SZ symptomatology. ELS also has a long-term impact on salience attribution. The neural mechanisms of these findings remain to be determined.

F29. COGNITIVE REMEDIATION COMBINED WITH AEROBIC EXERCISE TO FURTHER IMPROVE COGNITION IN SCHIZOPHRENIA

Jacopo Sapienza*¹, Giulia Agostoni², Federica Repaci¹, Margherita Bechi¹, Irene Calzavara Pinton³, Mariachiara Buonocore¹, Marco Spangaro¹, Francesca Martini¹, Federica Cocchi¹, Carmelo Guglielmino¹, Antonio Vita⁴, Roberto Cavallaro⁵, Giacomo D'Este³, Marta Bosia⁵

¹San Raffaele Hospital, ²San Raffaele hospital, ³Spedali Civili of Brescia, ⁴University of Brescia, ⁵Vita-Salute San Raffaele University

Background: Cognitive impairment is a core feature of schizophrenia, on which pharmacological interventions have a limited impact. Cognitive remediation (CR) is the gold standard for addressing cognitive deficits, yet its effect sizes vary and often remain in the low-to-medium range, thus enhanced treatment approaches are needed. Emerging evidence supports the cognitive benefits of Aerobic Exercise (AE), suggesting that a combined intervention involving both AE and CR could result in greater cognitive enhancements, while granting additional advantages to physical health.

Methods: The sample included sixty clinically stabilized patients with schizophrenia recruited at:

Schizophrenia Research and Clinical Unit of IRCCS San Raffaele Hospital (Milan, Italy)

- Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia (Brescia, Italy).

Patients were randomly assigned 1:1:1 ratio to 3 groups:

- AE: 2 weekly 45 min-cycle ergometer sessions + 15 min stretching for 3 months.
- CR: 2 weekly sessions with Cogpack software.
- CR+AE.

MATRICES Consensus Cognitive Battery (MCCB) was used to evaluate cognition:

- T0 = baseline.
- T1 = after training.
- T2 = 3-month follow-up.

Results: CR+AE group compared to CR group (ANCOVA) showed significant improvements in:

- Attention ($F=6.85$; $p=.02$)
- Working Memory ($F=4.41$; $p=.04$)
- Verbal Learning ($F=4.80$; $p=.03$).

In addition, the comparison between CR+AE group and AE group (ANCOVA) highlighted significant improvements in:

- Processing Speed ($F=10.59$; $p=.002$)
- Working Memory ($F=4.14$; $p=.05$)
- Verbal Learning ($F=4.69$; $p=.03$).

Considering results at T2 (three-month follow-up) CR+AE group compared to CR group showed significant differences in:

- Processing Speed ($F=5$; $p=.03$)
- Social Cognition ($F=8.47$; $p=.01$).

CR + AE: the cognitive improvements achieved at T1 remained stable in the other domains, as shown by the lack of significant differences from T1 to T2.

Concerning the comparison between CR+AE vs AE groups at 3-month follow-up, results showed no significant improvement at T2 compared to T1, showing the stability of the improvements achieved after the intervention by the CR+AE group.

Discussion: The CR+AE group showed substantial cognitive improvements in various domains, including attention, verbal learning, working memory, and processing speed compared to the other groups, thus offering greater benefits with respect to CR or AE alone. While preliminary, these results are promising and underscore the potential value of implementing aerobic exercise in rehabilitative approaches aimed at addressing cognitive dysfunction in schizophrenia.

F30. STRATIFICATION OF THERAPY RESPONSE TO SHORT COMPUTERIZED COGNITIVE INTERVENTION: INVESTIGATING DIFFERENCES IN IMPAIRED AND SPARED COGNITIVE SUBTYPES IN RECENT ONSET PSYCHOSIS

Öznur Bastürk^{*1}, Julian Wenzel², Shalaila Haas³, Joseph Kambeitz⁴, Nikolaos Koutsouleris⁵, Dominic Dwyer⁶, Lana Kambeitz-Illankovic²

¹University Hospital of Cologne, ²University Hospital of Cologne, Department of Psychiatry and Psychotherapy, ³Icahn School of Medicine at Mount Sinai, New York, USA, ⁴University of Cologne, Department of Psychiatry and Psychotherapy, ⁵Ludwig-Maximilian-University, ⁶Ludwig Maximilian University

Background: Previous studies have identified two distinct cognitive subtypes in individuals with psychosis, one characterized by impaired cognitive performance across multiple cognitive domains and the other by spared cognitive performance similar as one seen in healthy individuals. Cognitive training (CT) has been shown to enhance the cognitive and functional abilities of patients with psychosis. Despite a large proportion of patients that benefits from the

training, considerable heterogeneity in response is present possibly due to distinct cognitive and neurobiological subtypes exhibiting characteristic features. This study aims to assess the effectiveness of cognitive training in individuals with recent-onset psychosis (ROP) and compare its efficacy across different cognitive subtypes. The primary outcome was cognitive performance, and the secondary outcome was functional outcome.

Methods: The sample in this study included in total of 90 patients with ROP (54 male, 36 females; Mean age = 27.4, SD = 6.6) 40 from the Department of Psychiatry and Psychotherapy at the University Hospital of Cologne in Cologne, Germany, and 50 from the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University (LMU) in Munich. The participants were randomly assigned to either the CT group (26 male, 18 females; Mean age 28.2, SD = 6.5) who were trained with the Social Cognitive Training from Posit Science for 10 hours over 6 weeks of admission to the hospital or the treatment as usual (TAU) group (28 male 18 female; Mean age 26.7, SD = 6.7). To assess cognitive performance and functioning, both groups underwent clinical assessments and completed a comprehensive neurocognitive battery before and after the intervention. Moreover, we utilized previously established cluster models based on their performance in eight cognitive domains to derive distinct cognitive subtypes.

Results: Our findings revealed a significant improvement in the cognitive domain of Processing Speed and Global Functioning (GF) role scores within the CT group, in comparison to the TAU group in which such improvements were absent ($F(1, 88) = 4.7, p = .03$; $F(1, 85) = 4.6, p = .03$). However, these results did not remain statistical significance after applying the false discovery rate (FDR) correction. Additionally, the cognitive subtypes of Wenzel et al. (2021) were validated in differences in distinct cognitive subtypes across attention ($t(81) = 5.19, p \text{ LESS THAN } .001$), executive functioning ($t(65) = 3.83, p \text{ LESS THAN } .001$), processing speed ($t(85) = 4.1, p \text{ LESS THAN } .001$), working memory ($t(88) = 2.72, p \text{ LESS THAN } .001$), and Positive and Negative Symptoms of Schizophrenia Scale (PANSS) scores (PANSS Positive: $t(79) = -2.41, p \text{ LESS THAN } .01$; PANSS Negative: $t(82) = -3.09, p \text{ LESS THAN } .001$; PANSS General: $t(84) = -2.6, p \text{ LESS THAN } .01$). Furthermore, the training group showed increase in the working memory scores for subtypes with impaired cognitive abilities, while those with spared cognition experienced a slight decline ($F(1, 75) = 6.2, p = .015, \eta^2 = .06$). Nevertheless, when accounting for baseline differences in the working memory domain between clusters the effect of the intervention did not maintain statistical significance.

Discussion: We were able to show differences in several primary and secondary outcomes in CT group as compared to TAU. The validation of two distinct cognitive subtypes was taken one step further by showing differences in cognitive training gains in the domain of working memory. However, these differences did not show to be robust after covering for baseline performance levels. These findings provide insights into the relationship between cognitive subtypes and cognitive training outcomes, however, still questioning the potential advantages of stratification based on cognitive data and leaving space to further research.

F31. DIFFERENTIAL EFFECTS OF AGE ON WORKING MEMORY PERFORMANCE IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Catherine Barnes-Scheufler^{*1}, Melek Öyküm Yalçın², Carmen Schiweck¹, Benjamin Peters³, Jutta Mayer⁴, Lara Rösler⁵, Michael Wibral⁶, Robert Bittner¹, Andreas Reif¹

¹University Hospital Frankfurt, ²Institute of Medical Psychology, Goethe University,

³Zuckerman Mind Brain Behavior Institute, Columbia University, ⁴Goethe University Hospital

Background: Working memory (WM) is a core cognitive function which is involved in other crucial constructs of human cognition. Cognitive impairment including WM is a central syndrome in persons with schizophrenia (PSZ) and bipolar disorder (PBD) and is associated with functional outcome. Impairments in visuospatial WM have been observed in PSZ and PBD across illness phases and even before illness onset. A gradient of reduced working memory capacity (WMC) in bipolar disorder and schizophrenia has been observed, with PSZ showing the strongest degree of impairment. WM declines with increasing age in individuals without mental illness, but it is unclear if the same decline is present in PSZ and PBD.

Methods: 189 participants, ranging from 20 to 61 years old participated in this study. Participant groups were matched in age, years of education, and parental years of education. Two cognitive tasks were employed: a visuospatial change detection task to measure attentional control (AC) during WM encoding with four conditions: flickering-bias/predictive cue (F/P), flickering-bias/non-predictive cue (F/NP), non-flickering-bias/predictive cue (NF/P), non-flickering-bias/non-predictive cue (NF/NP) and a canonical color change detection task to assess WMC. All patients were diagnosed according to DSM-5 based on a clinical interview while healthy controls (HCS) were screened using Structural Clinical Interview SCID-I from the Diagnostic and Statistical Manual (Version IV, in German).

A multivariate General Linear Model (GLM) was used with post-hoc analyses to investigate the effect of age on AC and WMC. Two-tailed Spearman correlation analyses were conducted to investigate possible associations between age and information stored in each condition of AC or WM in each group.

Results: The GLM revealed a significant group by age interaction effect on both WMC (p LESS THAN 0.01) and AC (p LESS THAN 0.01). The least amount of information was stored by PSZ in WMC (mean = 2.96 items), and overall AC (0.90 items), followed by PBD (WMC = 3.13 items, AC = 0.97 items), and the most information was stored by HCS (WMC = 3.39 items, AC = 1.23 items). Post-hoc analyses showed significant differences in WMC between PSZ and HCS (p LESS THAN 0.01), as well as PBD and HCS (p = 0.040), and in AC between PSZ and HCS (p LESS THAN 0.001), as well as PBD and HCS (p LESS THAN 0.001). WMC scores correlated significantly negatively with age in HCS (r_s = -.311, p = 0.009), PBD (r_s = -.282, p = 0.033), but not in PSZ (r_s = -.114, p = 0.377). Significant negative correlations between age and three conditions of the AC task in PBD: F/P (r_s = -.301, p = 0.023), F/NP (r_s = -.282, p = 0.034), NF/NP (r_s = -.345, p = 0.009). Significant correlations between age and the same three conditions were observed in HCS: F/P (r_s = -.469, p LESS THAN 0.001), F/NP (r_s = -.315, p = 0.008), NF/NP (r_s = -.426, p LESS THAN 0.001). However, age did not correlate with information stored any conditions of the AC task in PSZ.

Discussion: We observed a differential effect of age on WMC and AC in PBD and PSZ. WMC and AC both declined with increasing age in WMC and most conditions in AC in PBD and HCS, but not in PSZ. These findings indicate that changes in WMC and AC performance across age vary between PSZ and PBD and HCS. This suggests different patterns of cognitive functioning across these groups, with performance in PBD closest to HCS which is compatible with the neurodevelopmental continuum theory. Furthermore, the results match previous studies suggesting earlier cognitive effects on aging in PSZ. Overall, our findings further our understanding of cognitive functioning across age and across mental disorders.

F32. THE DIE IS CAST: DECISION-MAKING UNDER RISK AND UNDER AMBIGUITY IN PATIENTS WITH PSYCHOTIC DISORDERS AND ALCOHOL USE DISORDER

Sarah Stumpp*¹, Alexander Wolber¹, Natascha Büchele¹, Leonie Lipinski¹, Stephanie N.L. Schmidt¹, Michael Odenwald¹, Brigitte Rockstroh¹, Daniela Mier¹

¹*University of Konstanz*

Background: Patients with alcohol use disorder tend to make disadvantageous decisions in tasks involving risk (Game of Dice Task, GDT) and ambiguity (Iowa Gambling Task, IGT). The literature on patients with psychotic disorders however is more heterogeneous, and only a few studies simultaneously investigated both decision-making tasks. This study aimed to explore whether patients with psychotic disorders and alcohol use disorder differ in decision-making under risk and ambiguity conditions.

Methods: In a preregistered study (<https://osf.io/n7z6y>), 40 patients with psychotic disorders, 50 patients with alcohol use disorder, and 36 healthy individuals completed the GDT and IGT. Net scores were calculated for both decision-making tasks (advantageous decisions minus disadvantageous decisions).

Results: The GDT net score was highest in healthy controls, followed by patients with alcohol use disorder and patients with psychotic disorders. The GDT net score significantly differed between groups ($p = .011$, $\eta^2 = .055$), with pairwise comparisons showing significant differences between patient groups and the control group, but not between patient groups. Regarding the IGT net score, the healthy controls achieved the highest score, followed by patients with psychotic disorders and those with alcohol use disorder. The IGT net score also differed significantly between groups ($p = .027$, $\eta^2 = .057$). Pairwise comparisons revealed a significant difference between patients with alcohol use disorder and the control group but not between patients with psychotic disorders and the control group.

Discussion: Both patient groups make disadvantageous decisions under risk conditions, but only patients with alcohol use disorder also make disadvantageous decisions under ambiguity conditions. This suggests more comprehensive impairments in decision-making behavior in alcohol use disorder. Since various studies have shown a link between disadvantageous decisions under risk and in the later blocks of the IGT with executive functions, further investigation should explore whether impairments in executive functions could explain the differences between individuals with psychotic disorders and those with alcohol use disorder.

F33. STIGMA MEDIATES THE RELATIONSHIP BETWEEN SOCIAL COGNITION AND SOCIAL FUNCTIONING IN A CLINICAL HIGH-RISK FOR PSYCHOSIS COHORT

Francesca Crump*¹, Tom Dinzeo², Kristen Woodberry³, Bruce Link⁴, Cheryl Corcoran⁵, Caitlin Bryant⁶, Donna Downing³, Ragy Girgis⁷, Gary Brucato⁷, Debbie Huang⁷, Grivel Margaux⁸, Drew Blasco⁸, Larry Seidman⁹, William McFarlane¹⁰, Lawrence Yang⁸

¹*Cambridge Health Alliance*, ²*Rowan University*, ³*Maine Medical Center*, ⁴*University of California at Riverside*, ⁵*Icahn School of Medicine At Mount Sinai*, ⁶*Beth Israel Deaconess/Harvard Medical Center*, ⁷*Columbia University*, ⁸*New York University*, ⁹*BIDMC*, ¹⁰*Center for Psychiatric Research, Maine Medical Center Research Institute*

Background: The clinical high-risk state for psychosis (CHR-p) was established as part of a movement to reduce duration of untreated illness and improve outcomes in schizophrenia-spectrum disorders. Although entering into early intervention programs has proven beneficial in curtailing threshold psychosis, many CHR-p individuals may face increased rates of stigmatization and discrimination due to accessing early treatment programs without ever developing a full psychotic disorder. Although research suggests that being labeled as CHR-p may elicit positive experiences, such as relief, individuals may employ negative coping strategies in response to early identification, such as secrecy and withdrawal, to conceal their mental health condition. Due to this increased awareness and motivation for concealment, CHR-p individuals may exhibit elevated social preoccupation that may hinder social cognitive performance and negatively impact social functioning.

Methods: This study examined stigma, social functioning, and social cognition in 173 CHR-p individuals recruited as part of a multi-site study conducted at Columbia, Harvard, and Maine Medical Centers. Pearson correlations and mediation analyses were performed to delineate potential causal mechanisms.

Results: Pearson correlations revealed several significant findings. Increased secrecy ($p=0.029$) and experiences of discrimination related to CHR-p status ($p=0.028$) was associated with impaired Theory of Mind (ToM) while increased stereotype agreement ($p=0.009$) was associated with more accurate social relationship perception. Additionally, increased positive emotions related to CHR-p symptoms was associated with impaired ToM ($p=0.023$) and social relationship perception ($p=0.021$). Mediation analyses demonstrated a positive direct effect between ToM and social functioning. Stigma mediated this relationship and was negatively associated with ToM and social functioning. Specifically, secrecy related to the CHR-p label and experiences of discrimination related to CHR-p symptoms fully mediated the direct effect ($p=0.032$) between ToM and social functioning.

Discussion: This study is the first to hypothesize a causal mechanism by which social cognition, stigma, and social functioning are related. A potential explanation for the relationship between stigma, ToM, and social functioning can be viewed through the interpersonal rejection sensitivity model whereby past experiences of rejection and exclusion impact future social perceptions. CHR-p individuals often face stigma and bullying due to their experiences, which may heighten their threshold of rejection sensitivity and lead to altered threat perception in social interactions. Therefore, CHR-p individuals who exhibit heightened rejection sensitivity due to higher instances of stigma may tend to be more secretive and have increased experiences of discrimination, which could negatively impact ToM and social functioning. These findings can help inform early intervention strategies aimed to reduce stigma, which could ultimately lead to improvements in ToM and social functioning if individuals are provided care that increases accurate threat perception.

F34. FACIAL EXPRESSIONS DURING SOCIAL INTERACTIONS IN INDIVIDUALS WITH SCHIZOPHRENIA

Vladimír Ivančík^{*1}, Natália Čavojská¹, Alexandra Straková¹, Vanda Valkučáková¹, Hana Kutlíková¹, Jakub Szabó¹, Ján Pečeňák¹, Anton Heretik¹, Michal Hajdúk¹

¹*Comenius University in Bratislava*

Background: Flat facial affect is a common negative symptom in individuals with schizophrenia. It is often rated based on the clinical judgments from structured interviews. Modern software provides opportunities to measure more objective, automated, and precise assessment of facial expressions. The goal of the study is to understand the role of facial affect

expression during social interactions. More specifically, to explore potential links to objective social skills and symptoms of schizophrenia.

Methods: The sample consisted of 40 patients with schizophrenia spectrum disorders (55 % female, mean age $M = 41.63$, $SD = 9.15$) and 32 healthy controls (66 % female, mean age $M = 32.42$, $SD = 10.16$). Social skills were measured by Conversation Probe, a performance-based measure. Participants were instructed to have a 3-minute unstructured conversation (meeting a classmate at a language course) with a research assistant. Interactions were videotaped and later rated by an independent rater on several domains (e.g. fluency, clarity, affect, overall social skills). In addition, dynamic and objective expressions of facial affect (e.g., happiness, anger, sadness) along with valence and arousal during interaction were examined by FaceReader, a software for analysis of facial affect recognition. Symptoms were measured by Brief Psychiatric Rating Scale and Community Assessment of Psychiatric Functioning. Mann-Whitney U-tests were used to compare patients and controls in social skills domains, as well as intensity of facial expressions. Pearson correlation coefficients were used to determine relationship strength between social skills domains, symptoms, and facial expressions during the interaction. Stepwise linear regression was used to test if valence and arousal of facial expressions predict overall social skills for each group.

Results: Overall, patients had lower global social skills than controls ($U = 1018.50$, $p < 0.001$). In terms of observer-rated affect, controls expressed significantly more emotions during interaction ($U = 983.00$, $p < 0.001$) and their affect was more appropriate ($U = 914.00$, $p < 0.001$). Using FaceReader, patients showed more neutral facial expressions than controls ($U = 346.00$, $p = 0.017$). Overall valence of facial expressions was lower in patients ($U = 841.00$, $p < 0.001$). This difference was driven mainly by less frequently expressed happiness ($U = 866.00$, $p < 0.001$) and surprise ($U = 769.00$, $p = 0.001$). In addition, patients' facial expressions contained less arousal ($U = 711.00$, $p = 0.016$). In the schizophrenia group, patients with dominant positive symptoms expressed more disgust during interaction ($r = 0.346$, $p < 0.05$). Severity of depression-anxiety related to increased expression of fear ($r = 0.499$, $p < 0.01$) and anger ($r = 0.374$, $p < 0.05$). For self-report symptoms, patients with more severe positive symptoms increasingly expressed fear ($r = 0.453$, $p < 0.01$). Specifically in schizophrenia group, arousal measured by facial expressions predicted overall social skills ($\beta = 0.361$, $p = 0.039$).

Discussion: We found evidence of aberrant facial expressions of emotions in individuals with schizophrenia, manifested by decreased expressions of positive emotions. Overall, as expected, patients showed more blunted affect, as evidenced both by ratings made by researcher observations, as well as by facial expression reading software. Emotions with negative valence, such as fear and disgust, were specifically linked to positive symptoms suggesting that different symptom domains might modulate the valence of facial expressions that might consequently impact quality of social interaction. Overall results warrant exploration of potential links between positive symptoms and facial expressions.

Funded by: APVV: 20-0185; UK/114/2023

F35. AEROBIC EXERCISE IMPROVES DORSAL HIPPOCAMPAL CA1 SYNAPTIC PLASTICITY AND NOVEL OBJECT MEMORY IN THE SUB-CHRONIC PHENCYCLIDINE RAT MODEL FOR SCHIZOPHRENIA

Ningyuan Sun^{*1}, Michael Harte¹, John Gigg¹

Background: Evidence suggests that aerobic exercise improves neurocognition and hippocampal function in patients with schizophrenia. Here, we introduced chronic exercise to the sub-chronic phencyclidine (scPCP) rat model for schizophrenia to investigate its effect on the cognitive impairment associated with schizophrenia.

Methods: 50 Female Lister Hooded rats were dosed with either saline or PCP (2 mg/kg, i.p.) twice daily for seven days. Running wheels were provided for aerobic exercise, 1 hour daily for 30 days. Novel object recognition memory was measured after 6 weeks of exercise. Synaptic plasticity in the dorsal hippocampus was then assessed via acute in vivo electrophysiology under urethane anaesthesia (30% w.v.; 1.4g/kg i.p.). The hippocampal CA1 Schaffer- evoked field excitatory postsynaptic potential (fEPSP) was analysed to measure short and long-term synaptic plasticity. Data were analysed with Student t-test and mixed-effect three-way ANOVA.

Results: Behavioural testing after exercise showed improved novel object recognition memory in the exercised scPCP group. Moreover, Exercise increased long-term potentiation after high-frequency stimulation, prevented depression after low-frequency stimulation in the scPCP group, and improved baseline short-term plasticity in both groups. In conclusion, chronic exercise appears to affect cognitive and hippocampal synaptic deficits in the scPCP rat model.

Discussion: Object recognition memory

- The sedentary scPCP group showed the expected deficit in the NOR task.
- The exercised scPCP group NOR performance increased and was not significantly different to the exercised vehicle group.

-This partial recovery of NOR performance after wheel running may be due to some exercised scPCP animals showing apparent neophobia while exploring, so they showed preference to the familiar object; this is still an improvement of object memory. Repeated NOR tasks with different objects might negate this confound.

CA1 hippocampus synaptic plasticity

- Exercise augmented short-term synaptic plasticity in both vehicle and scPCP groups
- This suggests a general effect of exercise on presynaptic release processes. Further analyses will investigate presynaptic differences between the vehicle and scPCP group (e.g. SV2A).
- Exercise increased post-HFS long-term synaptic responses only for the scPCP group.
- This effect was stronger for amplitude rather than slope, which implies that it might reflect altered feed-forward network inhibitory rather than monosynaptic excitatory response components.
- LFS produced a smaller reduction in fEPSP amplitude in the exercised scPCP group.
- The larger depotentiation effect of LFS in sedentary scPCP rats in reducing responses to near baseline (pre-HFS) values was rescued by exercise. As depotentiation is considered a synaptic model for forgetting, this result suggests that exercise may improve memory retention in scPCP animals by stabilizing synaptic weights in CA1.

F36. PEOPLE WHO PRESENT WITH DIMINISHED VOCAL EXPRESSIVITY ARE PERCEIVED AS LESS INTERESTING: CONVERGENT EVIDENCE FROM TWO STUDIES IN PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS AND COMMUNITY CONTROLS

Amélie Achim*¹, Marion Fossard², Audrey Cayouette¹, Caroline Cellard³, Marc-André Roy⁴, Marie-France Demers⁵, Dominique Knutsen⁶

¹Université Laval, ²Université de Neuchâtel, ³École de Psychologie, Université Laval, ⁴Université Laval Faculty of Medicine, ⁵Pharmacy Faculty, Laval University, ⁶Université de Lille

Background: Most of the scientific literature on schizophrenia spectrum disorders (SSD) has thus far focused on the patients themselves; their symptoms, their cognitive deficits, their everyday functioning, etc. But one question that has received much less attention is that of the impact of these symptoms and deficits from the perspective of the people with whom people with SSD interact in the context of social interactions. Our objective was to examine the link between the level of expressivity perceived in the voice of people with SSD and how much interest they generated when they told stories in the context of a joint task.

Methods: In two independent studies, people with SSD and healthy participants performed a joint task with an interaction partner (a research assistant). During the task, the participant held a set of 6 images forming a story, and their task was to tell the story to the interaction partner. The interaction partner held the same images in a random order and had to place them in the correct order as the participant told the story. They could not see each other as they were separated by an opaque panel, but interaction partner could provide feedback (e.g. “ok” or “hum-hum”) or ask for clarifications if needed. The images differed between the two studies, such that in study 1 participants were telling movie scenes whereas in study 2 they were telling cartoon stories. The verbal interactions were tape recorded, and 4 independent judges subsequently listened to all the stories, blind to the participant’s group, and had to provide their subjective appreciation (scale of 1-10) regarding how easy it was to place the images in order (Facility ratings), how interesting the story was (Interest ratings) and how expressive the voice was (Expressivity ratings).

Results: 25 participants with a SSD and 22 community controls (CO) participated in study 1 while 51 participants with SSD and 68 CO participated in study 2. In both studies, very strong correlations were observed between how expressive the participants were perceived (Expressivity ratings) and how interesting their stories were rated (Interest ratings). In study 1, the correlation was of $r = .79$ ($p < .001$) in the SSD group and of $r = .79$ ($p < .001$) in the CO group. In study 2, the correlation was of $r = .89$ ($p < .001$) in the SSD group and of $r = .77$ ($p < .001$) in the CO group. Participants with SSD were rated as significantly less expressive (study 1: $F(1,45) = 12.2$, $p = .001$; study 2: $F(1,115) = 53.4$, $p < .001$) and less interesting (study 1: $F(1,45) = 5.1$, $p = .029$; study 2: $F(1,115) = 46.57$, $p < .001$) than the CO in both studies.

Discussion: These results suggest that the reduced expressivity observed in people with SSD could have an important impact on their social interactions. If the people with whom they interact in their everyday life find them less interesting, these people could be less motivated to interact with them again in the future, hindering social interactions both from the patient’s side (e.g. social avoidance) and from the side of the people with whom they could interact (decreased interest). While the correlational nature of this study prevents from drawing firm conclusions about the causal effect of voice’s expressivity on the interest generated by people with SSD, the strength of the associations and the fact that the results were replicated in two studies should already lead us to be even more proactive when it comes to trying to minimize the reduced expressivity symptoms of people with SSD, for instance through fine adjustment of medication dosages to avoid such side effects.

F37. THE MORE YOU EXPECT, THE MORE YOU'LL HEAR - COGNITIVE EXPECTANCIES AND AUDITORY HALLUCINATIONS IN PATIENTS WITH SCHIZOPHRENIA

Joachim Kowalski*¹, Małgorzata Dąbkowska², Adrianna Aleksandrowicz¹, Michał Jarkiewicz³, Frank Laroi⁴, Łukasz Gawęda⁵

¹*Institute of Psychology, Polish Academy of Sciences*, ²*Institute of Psychology, Polish Academy of Sciences and SWPS University of Social Sciences and Humanities, Warsaw, Poland*, ³*Institute of Psychiatry and Neurology, Warsaw, Poland*, ⁴*University of Oslo*, ⁵*Polish Academy of Sciences, Institute of Psychology*

Background: Various neurocognitive models explore the causes and mechanisms of perceptual distortions and hallucinations in both patients diagnosed with schizophrenia and the general population. One of the variants of the predictive coding account suggests that strong priors, like cognitive expectancy, may influence perception. The current study aimed to examine if stronger cognitive expectancies result in more auditory false percepts in groups of patients diagnosed with schizophrenia – with and without current auditory hallucinations – and healthy controls. We investigated group differences and explored the associations between false percepts, clinical hallucinations and hallucinatory-like experiences.

Methods: Study design: Patients diagnosed with schizophrenia or schizoaffective disorder with current auditory hallucinations (n=51) and without hallucinations (n=66) and healthy controls (n=51) underwent the False Perception Task under various expectancy conditions. All groups were examined for the presence and severity of hallucinations (PANSS, The Psychotic Symptom Rating Scale, Revised Hallucination Scale) and hallucinatory-like experiences (Multi-Modality Unusual Sensory Experiences Questionnaire). We examined the relationships between the susceptibility to false percepts in experimental task and measures of hallucinations and hallucinatory-like experiences.

Results: Study results We observed a main effect of condition across all groups, i.e., the stronger the cognitive expectancy, the greater the number of auditory false percepts. However, there were no group differences in the number of auditory false percepts. The number of auditory false percepts was positively correlated with measures of hallucinations and hallucinatory-like experiences in the currently hallucinating group and with self-report perceptual distortions in the healthy controls. However, no correlations were observed within the non-hallucinating group.

Discussion: Conclusions: The current study demonstrates that strong priors in the form of cognitive expectancies affect perception and play a role in perceptual disturbances. There is also a tentative effect suggesting that overreliance on strong priors is associated with clinical hallucinations. Future studies could explore whether the impact of cognitive expectancies is associated with other postulated mechanisms of hallucinations.

F38. THE PARANOIA PARADOX: THE ROLE OF TRUST, CONFIDENCE, AND PARANOIA IN E-HEALTH USAGE

Emma Palmer-Cooper*¹, Frances Greenway¹, Elena Nichele², Tayyaba Azim¹, Emma Gentry³, Mohamad Armouch³, Mohammad Naishe⁴, Mark Weal¹, Ann-Marie Hughes¹, Liz Dowthwaite³

Background: e-Health is the delivery of healthcare using digital information and communication technologies. Effective deployment of e-Health can support and improve attendance and engagement with psychosis and other mental health services. As such, developing appropriate e-Health interventions is a key research and clinical priority for mental health service provision. An essential consideration when developing e-Health systems for people with serious mental health problems is the potential role of internet- and technology-related delusions, which are increasingly common. Research has also recently highlighted specific constructs of cyber-paranoia and cyber-fear that are distinct from general trait paranoia in the general population. Delusional beliefs about digital systems must be considered alongside trust and confidence in e-Health systems when developing such interventions for mental health purposes. Our research aimed to better understand attitudes towards e-Health services among people with experience of psychosis and depression, as well as the general population, to inform responsible and ethical intervention development. We hypothesised that 1) people with experience of psychosis or depression (serious mental illness; SMI) would have higher levels of trait paranoia, cyber-paranoia, and cyber-fear, and less trust in digital and e-Health systems, 2) positive current and future attitudes towards digital systems and e-Health would be associated with more trust and confidence in digital systems, and less trait and cyber-paranoia. We also sought to explore attitudes towards e-Health using free-text written responses and interviews.

Methods: We recruited 476 participants (Controls=267; SMI= 209; mean age= 39.35, SD = 14.16; 62.18% female). In our 2-part mixed methods study, we first investigated attitudes, alongside current and future use of digital and e-Health systems, including the Digital Confidence Scale, Trust Index, Paranoia Scale, Prodromal Questionnaire-16, and the Cyber-Paranoia and Fear Scale. Participants were also able to provide written responses about their views on using e-Health. We then interviewed 30 individuals across participant groups to better understand their attitudes, beliefs, and motivations towards using e-Health systems. Quantitative data was analysed using group comparisons and correlations between variables of interest. Qualitative results were investigated using linguistic analysis for written responses, and thematic analysis of interview transcripts.

Results: We found no group differences in digital confidence, although the SMI group had slightly lower frequency of online activity and digital technology use. As expected, the SMI group scored significantly higher on trait paranoia and symptoms of mental ill-health. However, whilst there was a small significant difference in cyber-paranoia, there was no difference in cyber-fear. Those willing to use e-Health systems across groups to support mental health were significantly more confident using digital applications generally, and used e-Health services more often. They had slightly more trust in these services, and slightly less cyber-paranoia and fear. Digital confidence was positively associated with frequency of digital technology use, and a small negative association with cyber-paranoia across groups. Analysis of written responses about willingness to use e-Health systems highlighted that comfort in using these systems was attributed to accessibility, ease of use, reduced waiting times and anonymity. Discomfort was related to trust, fear of judgement, security and privacy concerns, usability, and cost.

Interviews highlighted the complicated relationship between trust and attitudes towards digital technology, and actual use. We identified a ‘paranoia paradox’, whereby people continued to use online and e-Health systems, and accept data usage agreements (e.g. cookies) for

convenience and ease of use, regardless of their overall attitudes of (mis)trust towards them and/or their developers. This was present in both clinical and control populations.

Discussion: Results demonstrate that use and attitudes towards e-Health systems do not differ greatly between people with serious mental health problems like psychosis and depression and the general public. Findings highlight the relatively small role that reported attitudes and paranoia play towards actual use of e-Health systems, and openness to use in the future. There are clear ethical implications for developers and prescribers of e-Health interventions, as individuals may use them despite lacking trust. To improve this situation, it is important that new technology and online systems are developed ethically, and responsibly, to be more trustworthy. This involves us all collectively imagining and considering the impact and consequences of new systems, and addressing them. Further, prescribers should themselves understand data usage and privacy, and be confident in and trust in systems they are recommending to patients.

F39. SOCIAL RELATIONS AND QUALITY OF LIFE 20-YEARS AFTER A FIRST EPISODE PSYCHOSIS

Marie Starzer*¹, Helene Gjervig Hansen², Carsten Hjorthøj³, Nikolai Albert⁴, Louise Birkedal Glenthøj⁵, Merete Nordentoft⁶

¹Gentofte University Hospital, University of Copenhagen, ²Copenhagen Research Centre for Mental Health, University of Copenhagen, ³Mental Health Center Copenhagen, University of Copenhagen, Denmark, ⁴Copenhagen Research Center for Mental Health – CORE, ⁵Mental Health Centre Copenhagen University of Copenhagen, ⁶Mental Health Services - Capital Region of Denmark, Mental Health Centre Copenhagen, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, University of Copenhagen

Background: Life satisfaction transcends both symptoms and functioning, and for disorders with limited curative potential this outcome is highly important. Self-rated quality of life is lower in patients with schizophrenia compared to the background population, and poor quality of life has been associated with the severity of psychotic and negative symptoms and global functioning. Despite quality of life being a very important outcome for patients with psychosis, very few studies have examined it in long-term follow-up studies. Another important outcome are social relations. This is a less well-defined subdomain of social functioning which refers to the ability to adapt in social situations, engage in relationships and interact in a meaningful way with other people. Social relations is strongly associated with relapse, global functioning, mortality and quality of life and early intervention programs have specific treatment modalities such as family interventions or social skills training designed to improve this outcome. Despite this there is no consistently used measure to assess social relations, and often a dichotomous milestone outcome such as marital status is the only reported outcome. In general there are only a few long-term follow-up studies of first episode psychosis patients with follow-up of 20-years or longer, the Danish OPUS study is one of them. So far no other of these studies have reported long-term quality of life or social relation outcomes. The aim of the study was to determine self-reported quality of life and social relations 20-years after first episode psychosis and furthermore, to investigate if these outcomes were associated with each other. We also sought to examine differences in outcome depending on underlying psychosis diagnosis and identify possible predictors of poor outcome.

Methods: This study is a 20-year follow-up of the OPUS trial, a clinical trial that included 578 patients first diagnosed with a schizophrenia spectrum disorder between 1998 to 2000 578.

Patients were randomized to early specialized intervention treatment or treatment as usual. All participants were invited to participate in follow-up assessments 2, 5, 10 and 20 years after inclusion. In semi-structured interviews using validated rating scales symptom level, cognitive function, global level of functioning along with sociodemographic factors such as employment and family life, suicidal ideation and substance use were assessed. We used questionnaires to assess self-rated social relations and quality of life. We used ANOVA with post hoc Tukey test to determine associations between main outcomes and baseline diagnosis. Paired students t-tests were used to assess differences in social functioning and quality of life scores at the 10- and the 20-year follow-up assessments.

Results: Physical quality of life and environmental quality of life along with social dysfunction worsened over time. Higher physical quality of life was significantly associated with better subjective sense of social support, better cognitive functioning, lower social dysfunction, and fewer negative and psychotic symptoms. Higher psychological, social, and environmental quality of life were also associated with fewer negative psychotic symptoms, with better global functioning, with less social dysfunction and more social support.

Discussion: Examining the associations between quality of life and social relations with other poor outcomes highlights the importance of assessing these outcomes individually and with accurate measures. They are important treatment outcomes that merit targeted interventions.

F40. DELIVERING COGNITIVE REMEDIATION REMOTELY: FEASIBILITY, ACCEPTABILITY, AND COST EVALUATION

Matteo Cella¹, Lois Parri^{*1}, Kang Wang¹, Roisin Quinn¹, Nike Oyeleye¹, Huajie Jin¹, Til Wykes¹

¹*Institute of Psychiatry, Psychology, and Neuroscience King's College London,*

Background: Individuals with psychosis commonly experience cognitive difficulties impacting memory, attention, and planning abilities, hindering functional recovery in employment, education, and daily living. Cognitive Remediation (CR) is shown to address these issues effectively and is recommended internationally for schizophrenia. Despite proven efficacy, implementing CR in clinical settings poses challenges. The COVID-19 pandemic accelerated remote therapy adoption, and remote CR offers benefits like reduced time and cost, yet there is limited evidence on feasibility and acceptability. In this study, we aim to evaluate the acceptability and feasibility of remote therapist-supported CR in people with psychosis and estimate its cost and potential benefits.

Methods: A case series of participants aged 18-65 with non-affective psychosis who were provided therapist-supported remote CR using CIRCuITS™. Participants were assessed before and after therapy with measures of personal goal attainment (primary outcome), cognition, functioning and symptoms (secondary outcomes). Acceptability was assessed with post-therapy feedback interviews with data collected and analysed by service users. Feasibility was assessed using proportions and confidence intervals on pre-specified parameters. Indication of benefits was assessed with exploratory analyses comparing baseline and post-therapy scores on the pre-specified outcomes. The cost of providing remote CR was assessed from both healthcare and societal perspectives.

Results: Twenty-nine participants started therapy, with two dropping out; on average, participants attended 25.5 sessions. Interviews suggested that remote CR had good acceptability and led to perceived benefits. Significant and large improvements were observed in the primary outcome ($d=2.97$; 95%CI, 2.1 - 3.86). Cost analyses suggested that remote CR

has the same health care cost as face-to-face therapy but a lower societal cost (saving £263 per person).

Discussion: This study revealed remote CR's high engagement (~10% dropout), high acceptability, low societal costs, and significant treatment effects indicating meaningful benefits, notably in personal goal attainment. These results support the use of remote CR in psychosis services as an alternative delivery modality that may improve adherence, attendance, and user convenience. Barriers, such as poor digital literacy or device ownership, should be addressed before starting therapy. Further research, including the direct comparison between remote and in-person CR, will facilitate wider implementation.

F41. ASSOCIATIONS BETWEEN MOMENTARY SYMPTOMS AND DAILY-LIFE SOCIAL FUNCTIONING AFTER REMISSION OF FIRST EPISODE PSYCHOSIS: A HAMLETT ECOLOGICAL MOMENTARY ASSESSMENT STUDY

Matej Djordjevic^{*1}, Hannah Jongsma², Claudia Simons³, Priscilla Oomen⁴, Lieuwe De Haan⁵, Nynke Boonstra⁶, Martijn Kikkert⁷, Sanne Koops¹, Chris Geraets¹, Marieke Begemann¹, Machteld Marcelis⁸, Wim Veling¹

¹University Medical Center Groningen, ²Center for Transcultural Psychiatry 'Veldzicht', ³GGzE, ⁴University of Groningen, University Medical Center Groningen, ⁵Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, ⁶NHL Stenden University of Applied Science/ GGZ Friesland, ⁷Arkin Mental Health Care Amsterdam, ⁸Maastricht University Medical Center

Background: Symptom severity and social functioning are important outcomes after first-episode psychosis (FEP), yet current evidence about associations between them is inconsistent and lacks momentary insights.

Methods: The current Ecological Momentary Assessment (EMA) study was conducted in 58 people in remission of FEP, as part of the HAMLETT (Handling Antipsychotic Medication: Long-term Evaluation of Targeted Treatment) trial. At baseline, participants were prompted to report symptoms and social context 10x/day for eight consecutive days. We employed multilevel mixed-effects regressions to investigate associations between self-reported momentary symptoms and concurrent social activity or company and subjective appraisal thereof. We also conducted retrospective clinical assessments of symptoms (PANSS) and social functioning (WHODAS 2.0) and investigated their cross-sectional associations using multivariable linear regression.

Results: Analyses of 3,101 EMA-questionnaires showed that momentary negative symptoms were associated with less proactive social activity and company (OR=0.96 [95%CI: 0.96; 0.97], OR=0.95 [95%CI: 0.93; 0.96], N.B. ORs per 1-point symptom-score change). Momentary positive and general symptoms were associated with more proactive social activity (OR=1.02 [95%CI: 1.00; 1.03], OR=1.02 [95%CI: 1.01; 1.03]). Each symptom domain was associated with lower activity appraisal overall, though activity-specific associations differed. Positive and general momentary symptoms were associated with lower company appraisal (B=- 0.25 [95%CI: -0.36; -0.14], B=-0.15 [95%CI: -0.23; -0.06]). When assessed retrospectively, only general symptoms were associated with poorer functioning (B=2.52 [95%CI: 1.69; 3.34]).

Discussion: Self-reported momentary symptoms are associated with daily-life functioning after remission of FEP. Retrospective observer-rated and momentary self-report assessment Methods: do not measure the exact same aspects or intensity of psychopathology.

F42. REGIONAL MEDIAL TEMPORAL VS. GLOBAL INTRA- AND INTER-NETWORK FUNCTIONAL CONNECTIVITY ACROSS THE PSYCHOSIS SPECTRUM: A TRANSDIAGNOSTIC COMPARISON

Igor Nenadic^{*1}, Jonas Hoffmann², Christian Gaser³

¹Philipps-Universität Marburg / UKGM, ²Philipps-Universität Marburg, ³Jena University Hospital

Background: Schizophrenia is characterised by changes in structural and functional connectivity. Most transdiagnostic comparisons involving schizophrenia and affective disorders or “affective psychoses” consider DSM categories, for example comparing schizophrenia with unipolar or bipolar disorders. However, this approach might fall short as it does not account for the vast phenotypic heterogeneity within these categories. In this study, we analysed both regional (medial temporal lobe) functional connectivity as well as global (brain-wide) connectivity and intra- vs inter-network connectivity of particular resting-state networks relevant to schizophrenia (esp. default mode network DMN, salience network SN, and frontoparietal network FPN) in a carefully selected cohort of patients with psychosis: we narrowed down the clinical phenotype to contrast patients with stable schizophrenia (GREATER THAN 2 years duration) and currently euthymic bipolar I disorder patients with previous psychotic features. This allowed us to test regional, intermediate and global network level connectivity between two diagnostically (and phenotypically) distinct but closely related phenotypes.

Methods: We used 3T MRI to obtain resting-state fMRI time series for a total of 155 subjects: 41 DSM-IV/5 schizophrenia patients (in remission after psychotic episodes), 19 currently euthymic (HAMD LESS THAN =2, YMRS LESS THAN =2) patients with bipolar I disorder and previous psychotic features (as assessed by SCID-I interview with a board-certified psychiatrist), and 95 psychiatrically healthy control subjects. Groups were matched for age and gender. RS fMRI data were pre-processed and analysed using the CONN toolbox. Analyses were implemented in general linear models in CONN, applying cluster-level FDR correction for multiple-comparisons across the brain / ROIs. First, we used simple seed-based functional connectivity analysis defining the anterior, middle, and posterior hippocampi as regions of interest (ROI), effectively correlating across the rest of the brain. Second, we tested a medial temporal lobe model, using anatomical ROIs from the Glasser atlas (entorhinal cortices, parahippocampal areas, presubiculum) and graph-theory based measures to characterise functional connectome changes between groups at the level. Third, we used independent component analysis (ICA) to extract resting-state network based on a data-driven approach, thus deriving DMN, SN, and FPN regions for subsequent analysis of intra-network and inter-network functional connectivity differences. Fourth, we used a global functional connectome analysis to contrast groups for differences across all 360 Glasser neocortex ROIs.

Results: First, seed-based functional connectivity of hippocampal subregions showed significant F-test effects for left and right anterior hippocampal regions, for which follow-up tests showed a significant effect for the schizophrenia vs. healthy control (HC) group-wise comparison; these group differences in connectivity included connections to the thalamus, precuneus, as well as right supramarginal gyrus / temporoparietal junction. Second, the medial temporal lobe model showed significant network parameter changes for global efficiency as well as cost and degree for the right parahippocampal cortices. Third, ICA analysis of intra- and inter-network level group differences showed no significant effects for intra-network connectivity for DMN, SN or FPN, but a group-difference for SN-to-FPN inter-network

connectivity, with post-hoc testing showing that this was driven by the schizophrenia group. Fourth, global-level analysis of between-ROI functional connectivity showed a complex pattern of mostly prefrontal, superior temporal, and cingulate areas.

Discussion: Addressing group heterogeneity remains a major focus, both problem and opportunity, in identifying brain-level changes associated with schizophrenia. Our approach of contrasting schizophrenia with bipolar I disorder with (previous) psychotic features (both in remission, and in euthymic state) demonstrates that schizophrenia seems to have a more profound impact on disturbed network, both at the regional level of the hippocampus as well as intermediary resting-state networks and global connectome changes. Of particular interest, the anterior hippocampus shows aberrant connectivity only in schizophrenia, but not bipolar disorder with psychosis. This area has recently been suggested as an “epicenter” for the development of (early) schizophrenia. Our findings characterise the functional connectome difference in schizophrenia and demonstrate changes that are unrelated to mere expression of psychotic symptoms (in the past) and distinguish schizophrenia patients from phenotypically similar affective disorder patients within the psychosis spectrum.

F43. THERAPEUTIC IMPORTANCE OF COMPLEMENT PATHWAY PROTEINS IN EARLY INTERVENTION IN PSYCHOSIS: A PROTEOMIC BASED VALIDATION STUDY IN CLINICAL HIGH RISK AND FIRST EPISODE PSYCHOSIS PATIENTS

Subash Raj Susai*¹, David Mongan², Melanie Föcking¹, Jonah Byrne³, Rachel Davis¹, Rodrigo Bressan⁴, Patrick McGorry⁵, Cristiano Noto⁶, G. Paul Amminger⁷, David Cotter⁸

¹Royal College of Surgeons in Ireland, ²Queen's University Belfast, ³RCSI University of Medicine and Health Sciences, ⁴Laboratório Interdisciplinar de Neurociências Clínicas(LiNC), Universidade Federal de São Paulo(UNIFESP); Programa de esquizofrenia-UNIFESP, São Paulo, ⁵Orygen, The National Centre of Excellence in Youth Mental Health, The University of Melbourne, ⁶Laboratório Interdisciplinar de Neurociências Clínicas(LiNC), Departamento de Psiquiatria, Universidade Federal de São Paulo, São Paulo, Brasil, ⁷Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Australia, ⁸Royal College of Surgeons in Ireland, Dept. Psychiatry, Education and Research Center, Beaumont Hospital, Dublin Ireland

Background: Our previous research have noticed the relationship between complement pathway proteins with psychopathology in clinical high-risk population (CHR). Based on these observations, we investigated the blood samples from cohorts of early psychosis and found that baseline complement pathway proteins not only associate with worsening of clinical symptoms in CHR but also useful in identifying responders to anti-psychotic treatment in first episode of psychosis (FEP) [doi: 10.1016/j.bbi.2021.09.018, doi:10.1016/j.bbi.2022.03.013 and DOI: 10.1093/schbul/sbac201]. Since these findings have high clinical value in early intervention of psychosis, in the current study we validated our previous observations in a different clinical cohort of CHR and drug naïve FEP patients.

Hypothesis: The current study hypothesizes that high levels of baseline complement pathway proteins in the blood predicts the worsening of functioning in CHR patients and predict the good clinical response to antipsychotics in FEP patients. To test these hypotheses, first we explored the relationship between complement pathway proteins at baseline and functional scores at follow-up in CHR population; Second in FEP patients, we tested whether the baseline

complement proteins associate with change in functioning or change in psychotic symptom severity before and after treatment.

Methods: Our team performed protein quantification of the blood samples from two clinically unique cohorts namely the STEP (n~175) clinical trial of CHR patients from Australia and the Gapi (n~85) clinical trial of FEP patients from Brazil. The complement pathway proteins were quantified using immune-assays and state of the art Mass-Spectrometry (MS) approaches. Linear regression models were used to investigate the relationship between protein levels and clinical symptom scores for the analyses. These models were adjusted for potential covariates.

Results: First, discovery based mass spectrometry study revealed that in UHR population (STEP study) showed a positive association of complement proteins with psychotic symptoms and inverse association with functional status. Second, in the GAPI clinical trial, we noticed a similar cross sectional association for complement proteins with psychopathology at baseline. Above all, these baseline complement proteins C4a and C1r demonstrated a significant relationship with improvement in psychotic symptoms and functioning after 2 months of risperidone. Overall, these findings strongly validated our previous observations in both CHR and FEP patients.

Discussion: We for the first time identified the relationship of complement proteins with functional deterioration in CHR subjects and with functional improvement after anti-psychotics. We have now replicated in three independent cohorts of psychosis patients by showing the relationship of complement proteins especially C4a with psychotic symptoms and functioning. These findings suggest that complement protein levels could be a strong markers for predicting the course of the disease in high-risk state. Furthermore, in FEP patients, these baseline complement protein levels could be clinically useful to identify the responders from non-responders to anti-psychotics. Since anti-psychotics are effective only in 50-60% of the patients, these markers of treatment response would be novel to modify the early intervention strategies to maximize the treatment response in psychosis. Further validation studies are underway which are funded by HRB, ORYGEN and Future Neuro-2.

F44. METABOLIC PARAMETERS AS A PREDICTOR FOR RELAPSE IN PATIENTS WITH SCHIZOPHRENIA TAPERING ANTIPSYCHOTICS

Sofie Mølgaard*¹, Alexander Nøstdal², Mette Ødegaard³, Jimmi Nielsen²

¹Psychiatric Center Glostrup, Unit for Complicated Schizophrenia, Mental Health Services in the Capital Region of Denmark, ²Psychiatric Centre Glostrup, Unit for Complicated Schizophrenia, Mental Health Services in the Capital Region of Denmark, ³Mental Health Centre Glostrup, Mental Health Services of the Capital Region, Unit for Complicated Schizophrenia

Background: Patients suffering from schizophrenia are at risk of relapse when tapering off their antipsychotic medication. Long-term observations report that following each relapse, patients become more difficult to treat. However, early interference during psychotic relapses seems to be of great importance since a brief relapse in well-monitored patients may have less severe consequences for long-term morbidity. To avoid severe psychotic relapses, markers predicting relapses have been requested. Only a few studies have investigated whether biological markers may predict psychotic relapses. Based on recent findings of a distinct molecular signature in serum in patients with schizophrenia compared to healthy controls, it has been suggested that the level of HDL and LDL may be used to predict symptom

improvement and time to relapse. An increase in serum lipids during initial antipsychotic treatment has been associated with symptom improvement, and one study found baseline HDL to predict later relapse despite continuous treatment with long-acting injectables. In the present study, we aim to investigate whether baseline metabolic parameters, such as LDL and HDL, can predict psychotic relapses in the tapering process.

Methods: The data are from an uncontrolled intervention study including patients undergoing gradual, closely monitored, antipsychotic dose reduction. The antipsychotic medication was tapered for 6 months, after which patients were followed up for an additional 6 months. Relapse status was defined according to hospital admission, symptomatic worsening on the Positive and Negative symptoms scale (PANSS), or a decline in Global Assessment of Function (GAF). Baseline values were compared between stable and relapsed patients using independent t-test. Hypothesized predictors, in this case HDL and LDL were analyzed using binary logistic regression, including other parameters with group differences. Thus, we ended up with a model with relapse status as the dependent variable, and LDL, HDL, and Chlorpromazine equivalent doses as independent variables.

Results: Of the 88 patients who entered the program, blood samples and relapse status after one year were available for 78 individuals (43 females). Their mean age was 37 (range 20 – 64) years. baseline PANSS total score was 62 (34-106), and GAF was 46 (31-82). They received on average 403 (32 – 1267) mg Chlorpromazine equivalent.

After 12 months, 29 (37 %) of the patients had experienced a psychotic relapse. This group of patients had a higher level of LDL ($3.15 \text{ nmol/L} \pm 0.94$) than the stable patients ($2.51 \text{ nmol/L} \pm 0.79$, $t_{76}=3.4$, $P=0.001$). Further, stable patients received higher Chlorpromazine equivalent doses (466 ± 322) at baseline than the patients relapsing (296 ± 259 , $t_{76}=2.4$, $P=0.009$). Our predictive model was significant ($P=0.025$) explaining 27% of the variance, with a significant effect of LDL ($P=0.002$) and Chlorpromazine equivalent doses ($P=0.018$)

Discussion: In the present post hoc analyses of data from an observational cohort, we found a higher baseline level of LDL in patients experiencing a relapse during tapering of antipsychotic medication. Previous studies have reported an antipsychotic-induced increase in serum LDL, particularly in patients responding to antipsychotic treatment, but the underlying mechanism behind this association is still poorly understood. It may, however, be the same mechanism that can explain why patients with increased LDL levels were more likely to relapse during tapering of antipsychotics. To increase the understanding of the association between biomarkers, and relapse during antipsychotic tapering we need longitudinal measures which we are now collecting in our new tapering cohort.

F45. METABOLOMIC SIGNATURES DIFFERENTIATING PSYCHOSIS SPECTRUM DISORDERS FROM HEALTHY CONTROLS AND ASSOCIATION WITH WEIGHT GAIN

Kristoffer Panganiban^{*1}, Jiwon Lee¹, Kenya Costa-Dookhan¹, Nicole MacKenzie², Quinn Casuccio-Treen², Araba Chintoh¹, Gary Remington¹, Daniel J. Mueller¹, Sanjeev Sockalingam¹, Philip Gerretsen¹, Marcos Sanches², Alla Karnovsky³, Kathleen Stringer³, Vicki Ellingrod³, Ivy Tso³, Stephan Taylor³, Sri Mahavir Agarwal¹, Margaret K. Hahn¹, Kristen Ward³

¹Centre for Addiction and Mental Health, University of Toronto, ²Centre for Addiction and Mental Health, ³University of Michigan - Ann Arbor

Background: Psychosis spectrum disorders (PSDs) are a series of debilitating mental illnesses associated with intrinsic metabolic dysfunction, with the pathophysiological mechanisms of both the mental and physical symptom domains being largely unknown. Antipsychotics, the main treatment of PSDs, are known to exacerbate the metabolic problems seen in patients with PSDs. One approach to help understand these mechanisms is through metabolomics which is the study of the complete set of metabolites in the body called the metabolome.

Methods: This 12-week prospective naturalistic study used untargeted metabolomic data and included 37 minimally antipsychotic-treated PSD patients and 18 non-psychiatrically ill controls in the baseline analysis. 19 patients completed the study and changes between baseline and endpoint were compared. Finally, patients with PSDs were grouped based on whether they gained a clinically significant amount of weight (GREATER THAN 7%, N = 6) at endpoint when compared to baseline to identify whether metabolomic signatures could predict antipsychotic-induced weight gain.

Results: The baseline comparison between patients with PSDs and controls showed two reduced metabolites in patients with PSDs: lysophosphatidylcholine (20:0), and carnitine (20:0) (FDR LESS THAN 0.05). Fold change analysis at the 2.0x level showed that oleamide and serotonin were decreased in patients with PSDs. For the baseline-to-endpoint analysis, we found that for the 2.0x fold change levels, oleamide and inosine were lower at endpoint. For patients who gained a clinically significant amount of weight (GREATER THAN 7%), we found 5 metabolites that had an increased 2.0x fold change in patients who gained GREATER THAN 7% weight: 3-hydroxyphenyl valeric acid, monoacylglycerol 16:0, oleamide, 2-piperidinone and bilirubin. We also found that 3 metabolites had a decreased 2.0x fold change in patients who gained GREATER THAN 7% weight: L-urobilin, 2-acetylpyrrolidine, and glycohyodeoxycholic acid.

Discussion: Using metabolomics to understand the pathophysiological mechanisms that underly the mental and physical symptoms of PSDs is a promising technique. Identifying early changes in metabolomic signatures may be able to help predict which patients with PSDs are prone to antipsychotic-induced weight gain and possibly clinical/functional outcomes. However, more research is needed to help identify these potential signatures.

F46. EVENT-RELATED SPECTRAL PERTURBATION AND SPECTRAL ANALYSIS OF TREATMENT RESISTANT AND ULTRA-TREATMENT RESISTANT SCHIZOPHRENIA

Andor Bodnár^{*1}, Yifan Mo¹, Claire McCaulley¹, Arlene Cuerdo¹, Lilian Zhong¹, Chloe Bethany¹, Malaka Harper¹, Jay Leonard¹, Frederick Nucifora¹, Christopher Ross¹, Russell Margolis¹

¹*Johns Hopkins University School of Medicine*

Background: Approximately 30% of patients with schizophrenia do not respond to standard antipsychotic medicines (treatment-resistant schizophrenia, TRS), and of these, 30% or more do not respond to clozapine (ultra-treatment-resistant schizophrenia, UTRS). We hypothesize that neurobiological differences underlie these subtypes.

Methods: To explore potential neural correlates distinguishing these patient categories, we conducted electroencephalographic (EEG) recordings during rest-state and various cognitive tasks involving visual and auditory stimuli. 32 electrodes were mounted in a fitted cap with a standard 10-20 layout. Electrodes on the cap were referenced to the electrode at the vertex (FCz). Average electrode impedance was LESS THAN 20 kΩ. The EEG data were sampled at 1000 Hz. In EEG preprocessing steps, electrodes were average referenced, and spherical

interpolation was limited to 10-15% of electrodes. After epoch rejection, high (0.5 Hz) and low (60Hz) pass filtering was applied to the EEG data.

Results: Eyes-closed resting-state EEG revealed significantly increased gamma band activity at frontal electrodes in UTRS patients compared to TRS patients. Disparity in gamma band activity between eyes-open and eyes-closed states was only significant in TRS patients. In the visual Stroop experiment, UTRS patients exhibited diminished gamma power at frontal-central and occipital electrode sites from stimulus onset to 800ms post-stimulus. Reduction in theta power at occipital electrode sites was also observed from stimulus onset to 100ms. In the auditory oddball experiment, UTRS patients displayed significantly reduced theta and alpha band activity during oddball sounds at frontal and parietal electrodes within the 0-200ms post-stimulus onset time window. Central electrodes recorded diminished alpha power from 50-600ms post-stimulus onset while passively listening to oddball sounds.

Discussion: In summary, our preliminary findings suggest that UTRS patients exhibit decreased neural oscillations across both auditory and visual stimulation, encompassing both high-frequency (gamma-band) and low-frequency (alpha/theta) bands when compared to TRS patients. Conversely, during resting-state EEG recordings, UTRS patients demonstrate heightened gamma band activity. These observations open avenues for further investigation into the neurobiological underpinnings of treatment-resistant schizophrenia subtypes and may inform potential targets for therapeutic interventions.

This work was funded by T32MH015330, the Abramson Fund, and ABCD Charitable Trust.

F47. LONGITUDINAL INFERENCE OF MULTIMODAL HIPPOCAMPAL AND CORTICAL NETWORK CONNECTIVITY IN PSYCHOTIC DISORDERS

Jana Totzek^{*1}, Mallar Chakravarty², Ridha Joobar², Ashok Malla², Jai Shah², Alexandra Young³, Martin Lepage², Katie Lavigne²

¹*McGill University*, ²*McGill University, Douglas Mental Health University Institute*,

³*University College London*

Background: The hippocampus shows the largest volume reduction in psychosis. Further, machine-learning approaches identify two subtypes of volume atrophy in psychosis distinctly related to antipsychotic treatment response, one of which begins in the hippocampus. Beyond volume, a dysconnectivity between the hippocampus and larger-scale brain networks is central to psychosis, and reductions in morphometric hippocampal-cortical connectivity predict negative symptoms as mediated by verbal memory impairments. However, it remains unclear whether multimodal hippocampal dysconnectivity precedes or follows deviations in large-scale cortical networks across subtypes of psychosis.

Methods: We measured morphometric and resting-state functional connectivity in 175 patients with first episode (FEP) and enduring psychosis, and 117 non-clinical controls. To derive morphometric connectivity, 18 hippocampal and adjacent white matter volumes were acquired through MAGeT, while cortical thickness was extracted through CIVET 2.1.1, and parcellated into 62 Desikan-Killiany-Tourville regions. Subject-specific structural covariance matrices were derived through the jackknife bias estimation procedure. To derive functional connectivity, we sampled resting-state functional MRI data from 66 FEP patients, and 51 controls. We used the CONN toolbox to extract correlation matrices between the 18 MAGeT regions and 46 cortical regions of the Harvard-Oxford atlas. In both modalities, the hippocampal regions were grouped into a hippocampal module while the cortical regions were grouped into the 7 Yeo modules, and we estimated the graph-theoretical participation

coefficient as a measure of intermodular connectivity. We used the average participation coefficients of all 8 morphometric and 8 functional modules as input for two separate Subtype and Stage Inference (SuStaIn) analyses. SuStaIn is a machine-learning algorithm which unites disease progression modeling and clustering, allowing us to derive connectivity progression patterns across psychosis subtypes.

Results: Following 10-fold cross-validation, SuStaIn resulted in two models with three subtypes each. In both analyses, Subtype 0 included individuals with normal-range connectivity on all markers. In the morphometric analysis, Subtype 1 progressed from decreased somatomotor network connectivity to decreased dorsal-attention (DAN), frontoparietal (FPN), visual, salience, and hippocampal network connectivity, followed by increased limbic and default mode network (DMN) connectivity, while Subtype 2 progressed from increased DMN and limbic network connectivity to decreased hippocampal, salience, DAN, FPN, visual, and somatomotor network connectivity. Different patterns emerged in the functional SuStaIn analysis. Subtype 1 progressed from decreased FPN, limbic, visual, DMN, and hippocampal network connectivity toward increased DAN, somatomotor, and salience network connectivity, while Subtype 2 progressed from increased somatomotor, salience, and DAN connectivity toward decreased hippocampal, DMN, visual, limbic, and FPN connectivity.

Discussion: We identified a subtype in which hippocampal connectivity was the first to decrease after an increase in cortical connectivity across both modalities. These findings extend prior work on volume atrophy into the field of multimodal connectivity, while underlining the role of bidirectional modeling in psychosis. Future work should address the relationship between the identified subtypes and clinical features of psychosis. In line with previous work, associations with antipsychotic treatment response would be of particular interest in order to evaluate the clinical utility of our connectivity subtypes.

F48. ANTIPSYCHOTIC-INDUCED PROLACTIN ELEVATIONS AND GONADAL HORMONES IN MEN WITH SCHIZOPHRENIA: DIVERGENT EFFECTS OF TESTOSTERONE AND ESTROGEN ON COGNITION AND SYMPTOM SEVERITY

Iris Hamers^{*1}, Bodyl Brand², Marieke Begemann², Cynthia Shannon Weickert³, Thomas W Weickert³, Iris Sommer²

¹University of Groningen, University Medical Center Groningen (UMCG), ² of Groningen, University Medical Center Groningen (UMCG), ³Neuroscience Research Australia, Schizophrenia Research Laboratory; School of Psychiatry, University of New South Wales, Upstate Medical University

Background: Schizophrenia spectrum disorders (SSD) exhibit important sex differences with males being more affected in terms of earlier onset, initial clinical progression, and treatment response. The gonadal hormones, testosterone and estrogen, have been implicated in these sex differences. Understanding the effects of gonadal hormones is complicated by the influence of antipsychotic medication, as it can increase prolactin levels, which in turn may result in a reduced production of gonadal hormones. Previous studies have mainly reported beneficial effects of testosterone on negative symptoms in men, but the effects on cognitive functioning remain inconsistent. In addition, it remains unclear whether the protective role of estrogen in women with SSD can also be extrapolated to men. Therefore, this study aims to investigate how antipsychotic-induced prolactin elevation influences levels of testosterone and estrogen, and how these levels affect symptom severity and cognitive functioning in men with SSD.

Methods: This cross-sectional study included baseline data from two clinical trials including 128 men with SSD and 44 healthy control men. Based on their medication use, patients were divided into a prolactin-sparing (n=53) and prolactin-raising group (n=75). Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) using the total score and five subscales: positive, negative, cognitive, depression/anxiety, and excitement/hostility. Cognitive functioning was measured using the Wechsler Adult Intelligence Scale-3rd edition (Wechsler, 1997) and the Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004) and combined into three domains: verbal fluency (VF), working memory (WM) and processing speed (PS). Hormone levels were compared between the prolactin-raising, prolactin-sparing and the control group. Then, the relationships between prolactin, testosterone and estrogen were investigated. Finally, backward linear regression analyses were conducted to examine the relationship between hormones, cognition and symptom severity.

Results: Prolactin levels were highest in the prolactin-raising group, followed by the control group, and lowest in the prolactin-sparing group ($H=45.279$, $p < .001$). We found no differences in testosterone and estrogen levels among the prolactin-raising, prolactin-sparing and the control group. Testosterone and estrogen were positively correlated in both the control group ($r(42)=.409$, $p=.006$) and in men with SSD ($r(126)=.240$, $p=.007$). In the prolactin-raising group, prolactin was negatively correlated with testosterone ($r(73)=-.32$, $p=.005$). In men with SSD, higher testosterone was a significant predictor for better cognitive functioning (WM: $\beta=.20$, $F(2, 119)=5.16$, $p=.007$, VF: $\beta=.30$, $F(3,118)=5.70$, $p=.001$) and lower symptom severity (total: $\beta=-.21$, $F(4, 117)=4.82$, $p=.001$, negative: $\beta=-.24$, $F(5, 116)=4.01$, $p=.002$). Conversely, higher estrogen levels were linked to slower processing speed ($\beta=-.22$, $F(5,116)=5.35$, $p < .001$) and higher symptom severity (total: $\beta=.23$, $F(4,117)=4.82$, $p=.001$, negative: $\beta=.25$, $F(5, 116)=4.01$, $p=.002$) in men with SSD.

Discussion: The results provide support for antipsychotic-induced prolactin elevations and suggest that prolactin-sparing medication may also result in lower prolactin levels compared to healthy controls. High prolactin levels could negatively impact testosterone levels and indirectly worsen cognition and symptom severity in males with SSD. This highlights the importance of maintaining optimal gonadal hormone levels in men with SSD, especially concerning negative and cognitive symptoms.

F49. IS ACCELERATED AGEING LINKED TO COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA?

Vid Mlakar^{*1}, Ibrahim Akkouch², Torill Ueland³, Viktoria Birkenæs⁴, Daniel S. Quintana⁵, Nils Eiel Steen⁶, Srdjan Djurovic⁷, Ole A. Andreassen², Monica Aas⁸

¹King's College London, Institute of Psychiatry, ²NORMENT Centre for Psychosis Research, Oslo University Hospital and University of ³NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, University of Oslo, ⁴NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, Norway., ⁵NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, University of Oslo, NevSom, Oslo University Hospital, ⁶NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, Diakonhjemmet Hospital, ⁷NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, NevSom, Oslo University Hospital, Oslo University Hospital, ⁸SGDP, Institute of Psychiatry, Psychology, and Neuroscience King's College London

Background: Contemporary research suggests that individuals with schizophrenia spectrum disorders experience a biologically faster rate of ageing compared to age adjusted non-affected individuals. However, whether such accelerated ageing contributes to cognitive abnormalities seen in schizophrenia is yet to be established.

Methods: The study sample consisted of 758 participants (schizophrenia spectrum [$n = 357$] and healthy controls [$n = 401$]) collected as part of the Norwegian TOP study. All participants underwent a standardised neuropsychological test battery assessing five cognitive domains (working memory, verbal fluency, processing speed, verbal memory and verbal learning). Leukocyte telomere length was measured via blood and determined by quantitative real-time Polymerase Chain Reaction (qPCR) providing a telomere to single copy ratio (T/S ratio), used to estimate the mean telomere length of each participant. Telomerase activity was assessed by the expression levels of the Telomerase Reverse Transcriptase (TERT) and Telomerase RNA Component (TERC) genes. All analyses were adjusted for age, sex and ethnicity.

Results: Patients had shorter telomere lengths than healthy controls ($F = 6.22$, $p = 0.01$) and reduced expression levels of TERT ($F = 5.03$, $p = 0.03$), but not TERC ($F = 1.04$, $p = 0.31$). The mean age was twenty-nine years of age and sixty percent of the participants were males. Patients with shorter telomere lengths did nominally better on processing speed ($\beta = -0.17$, $p = 0.002$). For the remaining cognitive domains, no association was observed between telomere length or telomerase activity (working memory, verbal fluency, verbal memory and verbal learning, all p GREATER THAN 0.1). Compared to the controls group, patients performed lower on all cognitive domains (p LESS THAN 0.001).

Discussion: Patients had significantly shorter telomere lengths and reduced telomerase activity, compared to the control group. However, our preliminary results do not support telomere length or telomerase activity's involvement in the mechanisms underlying cognitive impairments in a relatively young group of patients with schizophrenia.

F50. SPEECH CONNECTIVITY IN SCHIZOPHRENIA: A STRUCTURAL APPROACH IN AN ITALIAN-SPEAKING COHORT

Francesca Magnani^{*1}, Matteo Tonna¹, Julianna Olah², Carlo Marchesi¹, Kelly Diederer², Thomas Spencer²

¹University of Parma, ²King's College London

Background: Language abnormalities in schizophrenia are putative pathogenic and risk biomarkers, often preceding clinical diagnosis. Clinical scales for language assessment, such as the Thought Language and Communication scale (TLC) and the Clinical Language Disorder Rating Scale (CLANG), have limitations, prompting the search for alternative methods. Mota's Speech Graph Analysis uses graph theory to objectively quantify structural features of speech connectedness, providing an indirect tool for characterizing thought through language, nearly independent of linguistic rules. The SpeechGraphs software converts text into graph and computes Speech Graph Attributes (SGA), which discriminate patients with schizophrenia from controls and predict diagnosis. It also allows to quantify structural disorganization of speech by comparing original verbal reports' graphs with purposely generated randomized graphs. This study applied Speech Graph Analysis for the first time in an Italian-speaking cohort using free-speech recordings, aiming to confirm its validity in detecting schizophrenia-related speech alterations, and to provide concurrent validity for SGA measures through correlations with clinical scales assessing language.

Methods: Thirty patients with schizophrenia (SCZ) and thirty healthy controls (HC) engaged in spontaneous dialogues, recorded and transcribed. SpeechGraphs software generated original

and random graphs for each transcript, producing connectedness measures (SGA). Participants underwent PANSS (Positive and Negative Syndrome Scale), CLANG and TLC Scales. Independent samples t-test and Mann-Whitney U test were used where appropriate to compare groups on all parameters, including similarity of verbal reports to randomized speech (Z-Scores). The Benjamini-Hochberg test controlled for multiple comparisons. Non-parametric correlations were performed between SGA measures and clinical scales scores in SCZ.

Results: SCZ showed lower levels of speech connectedness (p LESS THAN .001 for most SGA measures) and a higher number of loops and recurrent/parallel edges, suggesting increased repetition and redundancy. Differences between groups held after controlling for verbosity and multiple comparisons. SCZ' verbal reports were significantly more random-like than HC' (p LESS THAN .001 for most Z-Scores). There were significant between groups differences in CLANG and TLC scores (p LESS THAN .001). In patients, SGA measures of connectedness controlled for verbosity correlated negatively with CLANG/TLC total and production and disorganization subscales (p LESS THAN .001). SGA measures of recurrence correlated with higher CLANG/TLC total and disorganization subscales scores. Further correlations emerged between SGA and negative PANSS items.

Discussion: The significant differences in SGA between groups after controlling for verbosity, and the observed random-like speech pattern in SCZ, demonstrate the method's ability to detect subtle structural changes in patients experiencing language impoverishment or disorganization. These results confirm existing literature and hint for the applicability of Speech Graph Analysis for diagnostic discrimination and quantitative detection of speech alterations in schizophrenia, even with Italian language and free speech recordings. Correlations between SGA measures and CLANG/TLC scores suggest a link between thought impoverishment and reduced speech connectedness, extending beyond word production to structural thought qualities. SGA measures demonstrated concurrent validity with clinical scales, providing a complementary approach to the study of language in patients. Collaterally, we also confirmed the association between negative symptoms and reduced speech connectivity.

F51. EEG SENSORY GATING DEFICITS AND BLOOD REDOX MARKER DYSREGULATION: A KEY COMBINATION IN STRATIFYING AND PREDICTING MID-TERM OUTCOME IN EARLY PSYCHOSIS

Ines Khadimallah¹, Guillaume Marillier², Jean-François Knebel³, Chrysa Retsa³, Philippe Golay², Martine Cleusix², Luis Alameda², Micah Murray³, Paul Klauser¹, Kim Do⁴, Philippe Conus², Raoul Jenni*¹

¹Center for Psychiatric Neuroscience, Lausanne University Hospital and University of Lausanne, ²Service of General Psychiatry, Lausanne University Hospital and University of Lausanne, ³Radiodiagnostic Service, Lausanne University Hospital and University of Lausanne, ⁴University of Lausanne

Background: Electroencephalographic (EEG) low-level sensory processing alterations in psychosis may be an important state biomarker. Sensory gating is a crucial mechanism filtering out unnecessary or redundant information, certainly avoiding the overloading of high-level functions. Whereas auditory evoked potentials (AEPs) to sensory gating (mainly indexed by the P50 component in paired-click paradigms) have shown prominent abnormalities in chronic psychosis, inconsistent results have been reported in early psychosis. Isolated biomarkers certainly do not account for the complexity of disease progression, suggesting the need to combine them to increase the predictive potential of clinical and functional outcome. Grouping

AEP sensory gating and redox markers may be relevant given the following triangulation: first, AEP sensory gating alterations have been related to cognitive dysfunction (particularly attentional deficits); second, redox dysregulation may interfere with cognitive outcomes, notably through underpinned GABAergic activities; third, GABAergic interneuron activities are assumed to underlie the sensory gating effects. Thus, we explored the P50, N100 and P200 sensory gating AEPs in combination with COX6A2, as a marker of parvalbumin and redox status.

Methods: 43 early psychosis patients (EPP) and 46 age and gender matched healthy controls (HC) were recorded with high-density EEG during a passive sensory gating paradigm (paired-clicks); blood samples were collected from which exosome levels of COX6A2 were determined at baseline. For EPP, psychopathological, functional, and cognitive assessments were realized at baseline and longitudinally (up to 2.5 years). K-means clustering stratified EPP into two sub-groups based on EEG P50, N100 and P200 suppression values and COX6A2 levels.

Results: Considering all patients together, we observed a significant impairment of N100 suppression and COX6A2 compared to HC, but also negative correlations between N100 on one side and P50 and COX6A2 on the other. HC exhibited a strong positive correlation between P50 and COX6A2. EPP clustering based on P50*P200*COX6A2 differs from models including N100, by allowing patients to be stratified into two sub-groups with significant different cognitive profiles at baseline (including attention, processing speed, working memory). Interestingly, EPP clustering based on this model showed persistency of cognitive differences between groups in longitudinal analyses, but revealed also additional emerging significant differences at functional (GAF) and psychopathological levels (excitability, YMRS and CGI).

Discussion: EEG sensory-gating AEP and oxidative stress markers are key biomarkers in the pathophysiology of psychosis. Both theoretical underpinnings and current data suggest they should be considered together. Whereas P50 has been related to pre-attentional filtering of sensory information, the N100/P200 complex has been considered for triggering and allocating attention. In view of the present results, stratifying EPP by combining P50*P200*COX6A2 without N100 may help to point out current cognitive status, but also mid-latency clinical and functional outcome. By extension this raises questions about the underlying mechanisms subserving AEP. Defining specific sets of biomarkers on precise circuitry-based approaches are crucial for better identification and prediction of clinical, functional and cognitive outcome of EPP. This would have implication in optimizing management treatment.

F52. VISUAL BACKWARD MASKING IS A STABLE AND STATE-INDEPENDENT ENDOPHENOTYPE OF SCHIZOPHRENIA: RESULTS FROM A 10-YEAR LONG LONGITUDINAL STUDY

Melissa Faggella^{*1}, Simona Garobbio¹, Maya Roinishvili², Eka Chkonia³, Andreas Brand¹, Michael Herzog¹

¹Laboratory of Psychophysics, Brain Mind Institute, EPFL, ²Laboratory of Vision Physiology, Beritashvili Centre of Experimental Biomedicine and Institute of Cognitive Neurosciences, Free University of Tbilisi, ³Tbilisi State Medical University

Background: Endophenotypes are physiological, anatomical or cognitive traits that lie along the causal pathway between genetic risks and clinical syndromes. They are of great interest to investigate the pathology of psychiatric disorders as their closer proximity to the condition risk

factors allows to narrow down the heterogeneity and complexity of the phenotype. In previous studies, visual backward masking (VBM) has emerged as a promising candidate endophenotype of schizophrenia. Clear-cut VBM deficits and N1 differences were not only found in chronic patients but also in first-episodic patients, in unaffected first-degree relatives, and in schizotypal individuals. Here, we evaluate the stability of the deficit over a period of 10 years.

Methods: To this end, we examined VBM behavioural performance and EEG response from a cohort of 57 schizophrenia patients, 31 first-degree relatives, and 61 healthy controls. We retested those participants after 5 years and a subsample was retested again after 10 years.

Results: We found that group differences in behavioural performance between patients and controls were maintained over 10 years. In the EEG data, the group-averaged global field power (GFP) time series remained highly reliable over time for patients, relatives and controls. Moreover, we found pronounced inter-individual differences but high intra-individual reliability in the ERP waveforms. Finally, our results suggest that VBM behavioural performance and ERP response is independent from disorder covariates such as disorder duration, medication, and symptom severity.

Discussion: To our knowledge, this is the first time that a candidate endophenotype of schizophrenia is successfully shown to be state-independent and stable over such a long time period.

F53. ANTIPSYCHOTIC-INDUCED PROLACTIN ELEVATION IN PREMENOPAUSAL WOMEN WITH SCHIZOPHRENIA: ASSOCIATIONS WITH ESTROGEN, DISEASE SEVERITY, AND COGNITION

Bodyl Brand*¹, Janna de Boer¹, Elske Willemse², Cynthia Shannon Weickert³, Iris Sommer⁴, Thomas Weickert⁵

¹University Medical Center Groningen, ²University of Groningen, University Medical Center Groningen, ³Neuroscience Research Australia: Schizophrenia Research Laboratory, ⁴UMC Groningen, ⁵State University of New York Upstate Medical University

Background: Antipsychotic-induced prolactin elevation may impede protective effects of estrogens in women with schizophrenia-spectrum disorders (SSD). Our study sought to confirm whether the use of prolactin-raising antipsychotics is associated with lower estrogen levels, and to investigate how estrogen and prolactin levels relate to symptom severity and cognition in premenopausal women with SSD. To disentangle antipsychotic-induced hormone alterations from those that may be inherent to SSD itself, a sample of women receiving prolactin-sparing antipsychotics and a sample of women receiving prolactin-raising antipsychotics were compared. In addition, we include a sample of age-matched women without SSD for comparison.

Methods: This cross-sectional study included 79 premenopausal women. We separated women with SSD into those treated with prolactin-sparing antipsychotics (n=21) or prolactin-raising antipsychotics (n=27), and we included age-matched women without SSD (n=31). Circulating 17 β -estradiol was compared between groups. In patients, we assessed the relationship between prolactin and 17 β -estradiol, and the relationships of these hormones to symptom severity and cognition, using correlation analyses and regression models.

Results: In women receiving prolactin-raising antipsychotics, 17 β -estradiol levels were lower as compared to both other groups ($H(2) = 8.34$; $p = 0.015$), and prolactin was inversely correlated with 17 β -estradiol ($r = -0.42$, $p = 0.030$). In the prolactin-raising group, 17 β -estradiol

correlated positively with verbal fluency ($r = 0.52$, $p = 0.009$), and 17β -estradiol and prolactin together explained 29% of the variation in processing speed ($\beta(17\beta\text{-estradiol}) = 0.238$; $\beta(\text{prolactin}) = -0.446$; $F(2,25) = 5.98$, $p = 0.008$). In the prolactin-sparing group, 17β -estradiol correlated negatively with depression/anxiety ($r = -0.57$, $p = 0.014$), and explained 26% of the variation in total symptom severity together with prolactin ($\beta(17\beta\text{-estradiol}) = -0.406$; $\beta(\text{prolactin}) = 0.324$; $F(2,18) = 4.44$, $p = 0.027$).

Discussion: In premenopausal women with SSD, antipsychotic-induced prolactin elevation was related to lower estrogen levels. Further, estrogens negatively correlated with symptom severity and positively with cognition. Our findings indicate that while premenopausal women should benefit from the natural protective actions of estrogens, those beneficial effects may be impeded by prolactin-raising antipsychotics. Our findings emphasize the clinical importance of maintaining healthy prolactin and estrogen levels in women with SSD of premenopausal age.

F54. OLFACTORY FUNCTION AND ADVANCED BRAIN AGE IN CLINICAL HIGH RISK AND FIRST-EPISODE PSYCHOSIS

Lejia Fan^{*1}, xiaoqian Ma², Liangbing Liang³, Liu Yuan², Lijun Ouyang², Yujue Wang², Xiaogang Chen², Lena Palaniyappan⁴

¹Central South University, Changsha, ²The Second Xiangya Hospital, Central South University, ³Western University, ⁴Douglas Mental Health University Institute

Background: Schizophrenia is an illness where both aberrant olfactory function and accelerated brain aging are seen. We require further exploration, particularly in the context of pre-psychotic clinical high risk (CHR) state for psychosis before the onset of the first psychotic episode. This study aims to investigate olfactory identification function and brain age in individuals with first episode schizophrenia (FES) and those at CHR, examining the interplay between these factors.

Methods: A total of 215 participants, comprising 77 drug-naïve individuals with FES, 71 CHR, and 67 healthy controls (HC), underwent assessment of olfactory identification function using the odor stick identification test. T1-weighted anatomical images were obtained, and the XGboost method was employed to estimate individual brain age. Brain age, corrected by chronological age, was quantified as the brain age gap (BAG), representing the difference between predicted brain age and chronological age. A General Linear Model was applied, with olfactory function and BAG as independent variables, considering education levels and gender as covariates for BAG, and education levels and age as covariates for olfactory function. The relationship between olfactory function and BAG was also explored.

Results: Individuals with FES exhibited lower olfactory function ($F(2,210) = 5.66$, $p = 0.014$, partial $\eta^2 = 0.036$; mean(SD) in FES = 6.06(2.20); CHR = 6.88(2.35); HC = 7.69(1.83)) and higher BAG ($F(2,210) = 3.86$, $p = 0.022$, partial $\eta^2 = 0.051$; mean(SD) in FES = 3.17(8.88); CHR = 1.46(7.76); HC = 0.001(7.38)) compared to HC, with CHR showing no significant difference from the other two groups. Lower olfactory function was associated with higher BAG for HC ($r = -0.37$, $p = 0.002$), CHR ($r = 0.26$, $p = 0.031$), and CHR plus HC ($r = -0.31$, $p < 0.001$), but not for FES ($r = 0.04$, $p = 0.711$) or FES plus CHR ($r = -0.13$, $p = 0.116$).

Discussion: Impaired olfactory functions and advanced brain aging are characteristic of schizophrenia, distinguishing it from CHR. The observed association between lower olfactory function and higher BAG remains consistent in individuals with normal olfactory function and brain age. However, this relationship is disrupted once abnormalities emerge.

F55. RETINAL NERVE FIBER LAYER AND ITS RELATIONSHIP WITH COGNITIVE VARIABLES IN YOUNG SPANISH PATIENTS WITH EARLY-COURSE SCHIZOPHRENIA SPECTRUM DISORDERS

Jairo Gonzalez-Diaz*¹, Silvia Amoretti², Sergi Salmerón³, Anaid Pérez², Florencia Forte⁴, Maria Serra⁴, Bernardo Sanchez-Dalmau⁵, Anna Camos-Carreras⁶, Salut Alba⁷, Miquel Bernardo⁸

¹*Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clinic of Barcelona, Neuroscience Institute, Barcelona, Spain; School of Medicine and Health Sciences, Institute of Neurosciences (UBNeuro), University of Barcelona (UB), Barcelona, Spain; UR Center for Mental Health—CERSAME, School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia; Clinica Nuestra Señora de la Paz - OHSJD, Bogota, Colombia,*
²*Barcelona Clinic Schizophrenia Unit (BCSU). Hospital Clinic of Barcelona. University of Barcelona. IDIBAPS, CIBERSAM,*
³*Institute of Neuroscience, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Biomedical Research Networking Centre Consortium on Mental Health (CIBERSAM), Instituto de Salud Carlos III, School of Medicine and Health Sciences, Institute of Neurosciences (UBNeuro), University of Barcelona (UB),*
⁴*Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM,*
⁵*Hospital Clínic de Barcelona, Barcelona University, Institut d'Investigacions Mèdiques August Pi i Sunyer (IDIBAPS),*
⁶*Ophthalmology Service, Hospital Clínic Barcelona,*
⁷*Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), University of Barcelona,*
⁸*Hospital Clinic Barcelona. Universitat Barcelona. IDIBAPS. CIBERSAM*

Background: Several studies have suggested that the retina structure is affected in schizophrenia spectrum disorders (SSD). However, most of these studies have included patients with mean ages 36-44 years and disease duration GREATER THAN 12 years (González-Díaz et al., 2022). This study aims to validate the hypothesis that Spanish individuals diagnosed with SSD within five years after diagnosis exhibit distinct retinal structures compared to matched healthy controls. These structural differences are expected to correlate with various cognitive-related variables.

Methods: Employing a cross-sectional design, individuals diagnosed with SSD were compared to age- and gender-matched healthy controls (HCs). Participants with pre-existing retinal/ocular pathology, a history of craniocerebral or ocular trauma, previous ocular surgery, diabetes, or high blood pressure were excluded. The Peripapillary Retinal Nerve Fiber Layer (pRNFL) was assessed with Optical Coherence Tomography, and data from each eye (i.e., right eye [OD] and left eye [OS]) were analyzed independently. The relationship between cognitive performance and pRNFL thickness was only analyzed in cases. The neuropsychological battery measured the following cognitive domains: 1. Estimated intelligence quotient (IQ), assessed with the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1955) vocabulary subtest; 2. Working memory index of the WAIS-III, derived from the performance on the Digit Span, Arithmetic, and Letter-Number Sequencing subtests; 3. Processing speed index of the WAIS-III (Digit Symbol and Symbol Search subtests); 4. Verbal learning and memory, assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1993); 5. Logical memory was evaluated using the Wechsler Memory Scale, 3rd edition (WMS-III) (Wechsler, 1997); 6. Executive function was assessed using the Wisconsin Card Sorting Test (WCST) (Berg, 1948);

7. Sustained attention, tested with the Continuous Performance Test–II (CPT-II), version 5 (Conners, 2005); and 8. Verbal fluency (phonemic and semantic) was assessed with the Controlled Oral Word Association Test (COWAT) (Benton, 1967). All scores were standardized by the patient's age/educational level. Higher scores correspond to better performance in all cognitive domains except for attention.

Results: Two HCs were included for each case to increase the power of the study (n=18 vs 36), with a similar proportion of genders in each group (n male cases: 10 (55.6%) vs. n male HCs: 20 (55.6%); $p=0.61$) and comparable age (Cases Mean age in years (SD): 30.17 (1.36) vs. Cases Mean age in years (SD): 30.11 (0.96); $p=0.96$). Surprisingly, a statistically significant thickening in global pRNFL was observed in SSD patients compared to healthy controls (OD: Mean (SD): 106.89 μm (9.64) vs. 100.11 μm (8.10), $t=2.720$, $p=0.009$; OS: 04.89 μm (9.00) vs. 99.08 μm (8.21), $t=2.373$, $p=0.021$). Negative correlations were found between global pRNFL thickness and Estimated IQ (OD: $r=-0.54$, $p=0.030$; OS: $r=-0.48$, $p=0.057$), Processing Speed (OD: $r=-0.72$, $p=0.002$; OS: $r=-0.63$, $p=0.008$), Working Memory (OD: $r=-0.55$, $p=0.032$; OS: $r=-0.52$, $p=0.048$), Verbal Memory (OD: $r=-0.59$, $p=0.015$; OS: $r=-0.54$, $p=0.031$), Logical Memory (OD: $r=-0.58$, $p=0.039$; OS: $r=-0.69$, $p=0.008$), and Sustained Attention (OD: $r=0.56$, $p=0.026$; OS: $r=0.63$, $p=0.009$). Other cognitive variables showed no correlation with pRNFL thickness.

Discussion: Previous studies in the Spanish population have yielded analogous paradoxical findings, suggesting the absence of thinning in recent psychotic episodes (compared with HCs) and implicating potential localized retinal inflammation. Our results suggest characteristics resembling papilledema, indicating possible retinal inflammation at the first stages of the illness in young patients. In this way, several significant correlations between cognitive variables and retina structure in a homogeneous sample suggest that pRNFL might aid in identifying cognitive dysfunction as it has been proposed in other diseases such as Multiple Sclerosis, Alzheimer's, and Parkinson's. These findings underscore the complexity of retinal alterations in early-stage SSD, highlighting unexpected pRNFL thickening and its relationship with cognitive performance.

F56. HEAD CIRCUMFERENCE TRAJECTORIES ASSOCIATED WITH PSYCHOTIC EXPERIENCES

Sarah Ashley¹, Kate Merritt², Francesca Solmi¹, Yanakan Logeswaran¹, Pedro Luque Laguna³, Avi Reichenberg⁴, Anthony David^{*5}

¹UCL, London, ²Institute of Mental Health, UCL, ³CUBRIC, Cardiff, ⁴Icahn School of Medicine At Mount Sinai, ⁵University College London

Background: Schizophrenia is associated with reduced total brain volume in adulthood, however the timing and trajectory of these volume changes are not well understood. Head circumference offers a simple but highly effective proxy measure of brain size, and when studied longitudinally it may provide important insights into developmental biomarkers of psychosis.

Methods: Using longitudinal data from a UK-based birth cohort (Avon Longitudinal Study of Parents and Children: ALSPAC), we modelled head circumference trajectories for the first time in relation to psychotic experiences across 22 timepoints from birth to age 15 years. We compared trajectories in those with subclinical psychotic experiences (N = 339) elicited at interview at age 18, and to those of controls without such experiences from the same cohort (N = 3,527). We used multilevel linear mixed regressions, iteratively controlling for a series of important confounders and provide results split by sex. To assess whether differences in head

circumference are related to generic growth factors, height was included as a covariate of interest.

Results: Psychotic experiences in females (n=218) were associated with reduced head circumference across childhood and adolescence compared to controls in univariable (mean difference = -0.27, 95% CI: -0.49 to -0.05) and multivariable models (fully adjusted: mean difference = -0.25, 95% CI: -0.46 to -0.04, $p = 0.02$). In contrast, psychotic experiences in males (n=121) were associated with increased head circumference across this period in univariable (mean difference = 0.35, 95% CI: 0.05 to 0.65, $p = 0.02$) and multivariable models (fully adjusted: mean difference = 0.40, 95% CI: 0.12 to 0.69, $p = 0.006$). When height was included in the model, results remained significant for males (increased head circumference), whereas there were no significant group differences in females. This suggests there may be divergent growth-related factors associated with psychotic experiences in males compared to females.

Discussion: Head growth is atypical in individuals who have psychotic experiences, suggesting that brain development may also be atypical early in development. Psychotic experiences occur in 5-10% of the general population and are associated with an increased risk for developing a range of adverse mental health outcomes including clinical psychotic disorder. Results differed by sex, with reduced head circumference in females and increased head circumference in males. Our results provide support for the neurodevelopmental hypothesis of schizophrenia, and highlight the possibility of opposing growth-related risk factors based on sex associated with the development of psychotic experiences.

F57. BIOLOGICAL SUBSTRATE OF COGNITIVE FUNCTIONS IN ADOLESCENT POPULATION WITH EARLY ONSET PSYCHOSIS: N-ACETYL ASPARTATE LEVELS DURING THE FIRST 5 YEARS OF ILLNESS

Belén Taulero^{*1}, Marta de la Torre², Chao Suo³, Joost Janssen², Josefina Castro-Fornieles⁴, Elena de la Serna⁴, Mara Parellada², Dolores Moreno⁵, Montse Graell⁶, Inmaculada Baeza⁴, Manuel Desco³, Andreas Meyer-Linderberg⁷, Murat Yucel³, Celso Arango², Marta Rapado-Castro⁸

¹Hospital Gregorio Marañón, ²Hospital General Universitario Gregorio Marañón. Complutense University, ³School of Psychological Sciences, Monash Clinical and Imaging Neuroscience (MCIN) Laboratory, MONASH University, ⁴Neurosciences Institute, Hospital Clinic de Barcelona, IDIBAPS, CIBERSAM, University of Barcelona, ⁵Hospital General Universitario Gregorio Marañón. Complutense University. Hospital Universitario del Sureste, ⁶Hospital Infantil Universitario Niño Jesús, CIBERSAM, ⁷CIMH Medical Faculty Mannheim, Heidelberg University (Germany), ⁸Hospital General Universitario Gregorio Marañón. Complutense University, Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health,

Background: Subjects with Early Onset Psychosis (EOP) present with alterations in early cognitive development [4]. These cognitive impairments are indicators for severity of the illness which are strongly associated with poor community outcome [1], and one of the most important prognostic variables [2]. While these cognitive deficits tend to remain stable over time in subjects with EOP, their cognitive functions have shown to continue to develop at a lower rate than their control counterparts [3][4][5]. Cognitive functions that have consistently shown to be most disrupted include executive functions, global attention, verbal and visual-spatial working memory, most of them have been related to functions of the dorsolateral

prefrontal cortex (DLPFC) region [5]. However, there is scarce knowledge about the biological substrate of cognitive function in psychoses. Some studies have pointed to biochemical alterations as the underlying causes of cognitive dysfunction. For instance, lower concentrations of N-Acetyl-Aspartate (NAA), a marker for neural integrity, have been found in psychosis [6]. In particular, previous studies have shown reduced levels of NAA/water ratio in the DLPFC in subjects with EOP compared to their control counterparts [7, 8]. The search for associations between biological substrate and neuropsychological functioning is essential for the pathophysiology of the psychotic disorders. Therefore, the main objective of this study is to analyse the relationship between the variation in NAA levels in the DLPFC in adolescents with EOP and cognitive functions over the first five years after the onset of the disease, compared to a paired sample of controls.

Methods: The study sample consisted of 65 subjects with EOP and 67 controls derived from the original sample (N=110 EOP and N=98 controls) of the Child and Adolescent First Episode Psychosis Study (CAFEPS) [9], who completed both neuroimaging and cognitive assessments over time with a mean age of 15.59 ± 1.82 . The study of neuropsychological domains function was performed by neuropsychological assessment at baseline, 2 years and 5 years follow up. The cognitive functions related to DLPFC region were grouped in DLPFC index: global attention (Continuous Performance Test; Wechsler Adult Intelligence Scale; Trail Making Test A; Stroop Test 1 and 2), verbal and visual-spatial working memory (WAIS-III digits backward and letter-number sequencing) and executive functioning (Trail Making Test B; Stroop Test 3; Verbal Fluency and Wisconsin Card Sorting Test). In vivo NAA levels were obtained by single-voxel MR spectroscopy in the left DLPFC region at baseline, 2 years and 5 years follow up. The statistical analysis was performed using a mixed model, in which the variation of NAA levels over the five years follow-up was introduced as covariate to determine its plausible effect on cognitive function. The direction of the associations was analysed using Pearson's correlation.

Results: The index of cognitive functions associated with the DLPFC region: global attention, verbal and visual-spatial working memory and executive functioning, was higher in controls counterparts compared to EOP subjects, throughout the follow-up. In controls, there was a significant rise of cognitive index when NAA was considered as covariate, from baseline to 5-years follow-up (difference: 0.406, $p < 0.01$) and from 2-years to 5-years (difference: 0.327, $p=0.002$). The difference of cognitive index at 5 years follow-up, between EOP subjects and their counterparts, became statistically significant taking into account NAA (difference: 0.458, $p=0.007$ NAA). In terms of global attention, the difference between groups at 5-years follow-up became statistically significant with NAA (difference: 0.722, $p=0.002$). The same applied to the difference in working memory in controls from baseline to 5-years (difference: 0.437, $p=0.010$ NAA). Finally, executive functions variation from baseline to 5 years in EOP subjects was associated with NAA (coefficient: 0.24, $p=0.05$), and did not show it in controls (coefficient: 0.139, $p=0.198$).

Discussion: The decrease of NAA levels in the DLPFC area in EOP subjects is related to a deficit in the development of cognitive functions over the 5-years follow-up. This brain metabolite would be a specific marker of deficit of neurodevelopment or continued cellular disruption that may contribute to the impairment of cognitive functions. It may be explained on the basis of an abnormal maturation process before or in the first steps towards the onset of the disease.

F58. CORTICAL REACTIVITY AND TASK-RELATED ACTIVITY MODULATION IN SCHIZOPHRENIA AND HEALTHY CONTROLS: A TMS-EEG STUDY

Inés Fernández-Linsenbarth*¹, Gema Mijancos-Martínez², Alejandro Bachiller², Rosa M. Beño-Ruiz-de-la-Sierra¹, Antonio Arjona-Valladares¹, Alejandro Roig-Herrero¹, Miguel Ángel Mañanas², Vicente Molina¹

¹Universidad de Valladolid, ²Polytechnic University of Catalonia

Background: Schizophrenia has been associated with a reduced task-related modulation of cortical activity assessed through electroencephalography (EEG) by means of Shannon Entropy, i.e., a global index of EEG signal irregularity [1–3]. However, to the best of our knowledge, no study so far has assessed the underpinnings of this decreased EEG modulation in schizophrenia. This lower modulation has been associated with higher pre-stimulus connectivity strength, revealing a basal hypersynchrony [4, 5], and with an increased density of theta spectral power at baseline [6]. A possible substrate of these findings could be a decreased inhibitory function, a replicated finding in the field [7–9]. In recent years, the combination of transcranial magnetic stimulation (TMS) and EEG has emerged as a powerful tool for assessing inhibitory and excitatory functions of the cerebral cortex. In this study, our aim was to explore the association between EEG modulation during a cognitive task and the inhibitory system function in a sample including healthy controls and schizophrenia patients. We hypothesized that the replicated decreased task-related activity modulation during a cognitive task in schizophrenia would be related to a hypofunction of the inhibitory system.

Methods: 27 healthy controls and 22 patients with schizophrenia (of them 13 first episodes) performed a three-condition auditory oddball task from which the spectral entropy modulation was calculated. Additionally, cortical reactivity -as an indirect index of the inhibitory function- was assessed by the administration of 75 monophasic transcranial magnetic stimulation single pulses over the left dorsolateral prefrontal cortex. Finally, to assess potential auditory-evoked potentials that could confound the genuine TMS cortical reactivity findings, 40 participants (of them 20 healthy controls) received sham TMS pulses.

Results: In line with previous studies, schizophrenia patients showed significantly lower spectral entropy modulation compared to healthy controls during the three-condition auditory oddball task ($t = 2.87$, $p = 0.006$). Moreover, our study revealed that patients displayed higher cortical reactivity following TMS single pulses applied over the left dorsolateral prefrontal cortex than healthy controls ($t = 3.01$, $p = 0.004$). Active stimulation resulted in significantly higher cortical reactivity compared with sham stimulation ($t = 10.21$, $p < 0.001$). Finally, our data revealed that cortical reactivity was significantly related to spectral entropy modulation ($r = 0.336$, $p = 0.018$) when considering both healthy controls and schizophrenia patients.

Discussion: Compared to healthy controls, schizophrenia patients showed a deficit in EEG activity modulation during a cognitive task and higher cortical reactivity following TMS single pulses. Our key finding implies that spectral entropy modulation is associated with the amplitude of the evoked response to TMS single pulses in the left dorsolateral prefrontal cortex when considering the entire sample. This may suggest the idea that this relationship would be better considered dimensional rather than categorical. These findings provide novel insight into the neurophysiological underpinnings of potentially different subgroups of schizophrenia patients.

F59. COGNITIVE PROFILING IN SCHIZOPHRENIA: WHO IS TO BLAME BETWEEN INFLAMMATORY AND KYNURENINE PATHWAY MARKERS?

Giulia Agostoni^{*1}, Jacopo Sapienza², Stefano Comai³, Sofia Nasini³, Stefano Dell'Acqua³, Stefania Sut³, Margherita Bechi², Marco Spangaro², Francesca Martini², Roberto Cavallaro¹, Marta Bosia¹

¹Vita-Salute San Raffaele University, ²IRCCS San Raffaele Hospital, ³University of Padua

Background: Cognitive impairment is a core feature of schizophrenia and its heterogeneity is a typical hallmark, both from the biological and clinical point of view. Several biomarkers of cognitive impairment have been described, including neuroinflammatory indexes and metabolites derived from the kynurenine pathway (KP), which gained attention as they are at the crossroad between inflammation and neurotransmission. However, the specific interplay between cognitive deficits and both neuroinflammatory biomarkers and KP metabolites is far from being elucidated. Our aim is to disentangle the specific neuroinflammatory and KP markers related to different cognitive profiles in schizophrenia.

Methods: 68 patients with schizophrenia were enrolled and evaluated for cognition (MATRICS). Serum levels of inflammatory factors (i.e., IL-6, IL-1 β , IL-1ra, IL-8, IL-9, IL-10, IL-13, IL-17A, IFN α , IP-10, MCP-1, MIP1 α , MIP1 β , PDGF-BB, RANTES e TNF- α e ANP) and KP metabolites (i.e., Trp, KYN, KYNA, 3-HK, QUIN, KYN/Trp ratio, KYNA/KYN ratio, and 3-HK/KYN ratio) were extracted. To characterize different cognitive profiles, we performed a two-step cluster analysis, considering MATRICS subscores as clustering variables. Then, we separately performed Pearson's correlations in each cluster, to evaluate the interplay between cognitive domains and both the plasma levels of inflammatory markers and KP metabolites.

Results: Cluster analysis produced two groups of patients: Cluster 1 (low neurocognitive profile) and Cluster 2 (high neurocognitive profile).

As for Cluster 1, correlations were found between processing speed and ANP levels ($r=0.566$; $p=.003$), KYN ($r=-0.4$; $p=.02$), KYNA ($r=0.40$; $p=.023$), 3-HK ($r=-0.42$; $p=.015$), and KYN/Trp ratio ($r=-0.44$; $p=0.01$). Visual learning resulted associated to 3-HK ($r=-0.40$; $p=.002$) and KYN levels ($r=-0.40$; $p=.002$). Lastly, attention was related to 3-HK/KYN ratio ($r=0.52$; $p=.01$). Concerning Cluster 2, correlations showed associations between working memory and IL-17A ($r=-0.56$; $p=.04$), IL-9 ($r=-0.56$; $p=.04$), TNF- α ($r=-0.64$; $p=.01$), MIP1 α ($r=-0.58$; $p=.035$), PDGF-BB ($r=-0.69$; $p=.009$) and RANTES ($r=-0.62$; $p=.02$). Attention was related to MIP1 α ($r=-0.58$; $p=.04$) and QUIN ($r=-0.56$; $p=.018$), while reasoning resulted related to KYNA ($r=-0.40$; $p=.04$).

Discussion: Results support previous literature showing correlations between both inflammatory and KP markers and cognitive abilities in schizophrenia. Noteworthy, they shed new light on possible differential impact of the two pathways, suggesting specific patterns of association according to the cognitive profile. In patients with a higher cognitive profile (Cluster 2), neuroinflammatory cytokines are mostly and adversely related to cognition, with limited effects of KP metabolites. These results may be due to a greater susceptibility to the oxidative stress and cytotoxicity exerted by neuroinflammation in patients with a more preserved cognition. In contrast, in patients with a lower cognitive profile (Cluster 1), KP metabolites have a greater impact on cognition compared to cytokines. We can argue that in patients already cognitively compromised, KP metabolites might impact cognition due to a wide range of neuromodulatory, neurotoxic and neuroprotective properties, while the action of inflammatory factors seemed less impactful. Although preliminary, our findings highlight the dissociated effects of inflammatory and KP markers on cognition, depending on the patients' cognitive profile. In particular, a predominant effect of inflammation is observed among patients with relatively preserved cognitive abilities, while the KP plays a major role in patients with more severe deficits.

F60. IMMUNOPHENOTYPING SCHIZOPHRENIA SUBTYPES STRATIFIED BY ANTIPSYCHOTIC RESPONSE

Yanhui Li^{*1}, Jocelyn Wen Xin Ong², Yuen Mei See¹, Jie Yin Yee¹, Charmaine Tang¹, Shushan Zheng¹, Boon Tat Ng¹, Bernett Teck Kwong Lee³, Anand Kumar Andiappan², Jimmy Lee¹

¹*Institute of Mental Health, Singapore*, ²*Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Singapore*, ³*Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*

Background: Immune dysfunction has been proposed to play a role in the pathophysiology behind the development and persistence of psychosis, apart from well-established dopaminergic mechanisms. Studies have shown immunological changes in schizophrenia ranging from proteins to genomics and immune cell types. However, current immunophenotyping studies are limited by small sample sizes and the number of immune markers investigated. In this study, we perform comprehensive immunophenotyping of 196 subjects comprising 147 schizophrenia patients stratified by antipsychotic response (49 antipsychotic-responsive, 70 clozapine-responsive, 28 clozapine-resistant) and 49 healthy controls. We aim to identify significant immune cell populations associated with schizophrenia and increasing treatment resistance, as potential modulators of underlying psychosis.

Methods: Patients with schizophrenia were recruited from inpatient and outpatient settings at the Institute of Mental Health, Singapore. Patients were categorised based on antipsychotic response, defined as positive symptom remission after at least 8 weeks of respective antipsychotic treatment. 49 healthy controls with no prior medical and psychiatric history were recruited from the community. Demographic data including age, sex, ethnicity, body mass index and smoking status were collected. Data regarding antipsychotic treatment history was collected via patient interviews and medical records. All participants were assessed on the Positive and Negative Symptom Scale (PANSS) while schizophrenia patients were rated on the Clinical Global Impression (CGI) scale by trained clinicians. Peripheral blood mononuclear cells (PBMCs) were collected from participants, stained with antibodies from a panel of 34 immune markers and put through flow cytometry. Manual gating was performed on flow cytometry data and proportions of each cell population relative to CD45⁺ cells (total leukocyte population) were analysed. Median centering was performed to correct for batch effects and cell population proportions across all 4 groups were compared using the Kruskal-wallis test. Post-hoc Dunn tests and Bonferroni correction were subsequently performed for pairwise comparisons between groups.

Results: As expected, PANSS and CGI scales increased with increasing treatment resistance. Mucosal-associated invariant T (MAIT) cells ($p = 3.20 \times 10^{-5}$), plasmablasts ($p = 3.60 \times 10^{-4}$), IgG⁺ B cells ($p = 7.38 \times 10^{-3}$), IgD⁺ CD27⁺ Memory B cells ($p = 0.042$), CD8⁺ T cells ($p = 2.60 \times 10^{-3}$), exhausted CD8⁺ T cells (CD57⁺ CD8⁺) ($p = 9.35 \times 10^{-3}$), (CD69⁺ KLRG1⁺ CD8⁺) ($p = 1.20 \times 10^{-3}$) and CD8⁺ memory T cells (CD45RA⁺ CD27⁺ CD8⁺) ($p = 0.0286$), were among the top cell populations to be downregulated in schizophrenia, with lower proportions seen with increasing treatment resistance. Conversely, CD4⁺ memory T cells (CD69⁺ KLRG1⁺ CD4⁺) ($p = 0.0331$) and naïve CD4⁺ T cells (CD45Ra⁺ CD27⁺ CD4⁺) ($p = 0.0336$) were found to be upregulated in schizophrenia, with higher proportions seen with increasing treatment resistance.

Discussion: Our results corroborate higher CD4⁺/CD8⁺ ratios previously found in psychosis. We have also explored immune cell populations not previously investigated, and present novel findings. Most significant populations were downregulated rather than upregulated in

schizophrenia, suggesting attenuated immune function modulated by those cell populations in psychosis. This study represents a first attempt at comprehensive immunophenotyping of patients with varying antipsychotic response. Future research may build on our findings with further mechanistic studies, and immune markers identified may serve as potential biomarkers of treatment resistance and disease severity.

F61. IDENTIFYING INDIVIDUALS AT RISK OF PSYCHOSIS USING MODELLED DECISION-MAKING PARAMETERS

Franziska Knolle*¹, Elisabeth F. Sterner¹, Rick Adams², Michael Moutoussis², Graham Murray³

¹Technical University of Munich, ²University College London, ³University of Cambridge

Background: In psychosis, alterations in value-based action selection and action-outcome learning can be observed often even before disease onset. Computational models of decision-making allow the investigation of whether and how these impairments contribute mechanistically to psychotic symptoms and, thus, have great potential to improve early identification and intervention. The active inference framework conceptualizes decision-making as a process of Bayesian inference in which the brain predicts the consequences of an action based on both past experiences and the structure of the task to choose the action to produce the most preferred outcomes. Using active inference modelling, we wanted to explore (1) whether AI parameters of a modelled orthogonalized Go/NoGo task differ between at-risk-mental-state (ARMS) individuals, first-episode psychosis (FEP) patients and healthy controls and (2) whether task performance and modelling parameters would be suitable for identifying group associations.

Methods: 23 ARMS individuals, 26 patients with FEP and 31 healthy controls completed a probabilistic decision making task in which action choice (go/no-go) was dissociated from outcome valence (gain or loss). We evaluated group differences in performance and active inference model parameters and performed receiver operating characteristic (ROC) analyses to assess group classification.

Results: We observed reduced performance in patients with specific deficits in punishment learning. In addition, active inference modelling showed that FEP patients displayed increased forgetting and less optimal general choice behavior, with poorer action-state association (1). Using ROC analysis, we were able to demonstrate that combining the specific expression of modelling parameters and the individual performances measures revealed fair-to-good classification performances of all groups which is especially relevant for the distinction of controls and ARMS individuals (2).

Discussion: Taken together, our findings show that active inference modelling of an orthogonalized Go/No-Go task does not only provide further explanation for dysfunctional mechanisms underlying decision-making in psychosis, but may also be highly relevant for future research on the development of diagnostic biomarkers.

F62. DECIPHERING SEX-SPECIFIC NEURODEVELOPMENTAL TRAJECTORIES VIA THE SULCAL PITS

Noemí Hostalet¹, Pilar Salgado-Pineda², Yasser Alemán-Gómez³, Erick J Canales-Rodríguez⁴, Raymond Salvador⁵, Edith Pomarol- Clotet⁵, Mar Fatjó-Vilas*⁵

¹FIDMAG Sisters Hospitaliers Research Foundation and CIBERSAM, ²FIDMAG Research Foundation and CIBERSAM, ³Connectomics Lab, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), ⁴Signal Processing Lab (LTS5), École Polytechnique Fédérale de Lausanne, ⁵FIDMAG Research Foundation and CIBERSAM

Background: Sulcal pits are the deepest points of the brain cortex. They are located in each sulcal basin along the bottom sulcal lines, regularly arranged in chains of shallower and deeper pits. Their apparition begins prenatally, with the first cortical folds, and they span with the formation of the secondary and the tertiary sulci through gestation and early childhood. The spatial distribution of sulcal pits is stable once they are formed and highly reproducible across individuals. Therefore, sulcal pits are proposed as suitable markers of neurodevelopmental alterations that occur during the first stages of embryo development. Neurodevelopmental disorders, such as autism, attention deficit hyperactivity disorder and bipolar disorder, have been associated with specific patterns of sulcal pits. However, no study has evaluated sex-specific differences related to the patterns of sulcal pits in healthy adult individuals. We aimed to explore differences in the quantitative patterns of sulcal pits between males and females, separately in each hemisphere. This novel approach can shed light on the biological mechanisms underlying neurodevelopmental sex differences in the health-psychopathology spectrum.

Methods: The sample was composed of 93 healthy males and 97 healthy females whose age range was between 18 and 65 years old. No significant differences in age between groups were found. For all participants, structural magnetic resonance images (MRI) were acquired in a 1.5T scanner. First, we proceeded to segment white matter surfaces from the MRI using the FreeSurfer pipeline. From the white matter surfaces, sulcal pits were extracted using the implemented function in BrainVisa “Sulcal pits Extraction”. Subsequently, individual sulcal pits were projected to fsaverage FreeSurfer template to perform group comparisons and obtain a group parcellations map applying a watershed algorithm. The maximum depth of the sulcal pits was calculated using the depth potential function (DPF) and the parcels were clustered in three groups (shallow, middle, deep) using a k-means algorithm based on sulcal pits depth. The frequency of sulcal pits was assessed in males and females considering the total number of sulcal pits separately in each hemisphere (hemispheric level) and the total number of pits on each depth cluster (cluster level). Furthermore, differences in the depth of sulcal pits were also assessed in each parcel (parcel level). Comparisons between groups were performed by applying linear regressions including IQ as a covariate. Regional comparisons were corrected by applying False Discovery Rate (FDR).

Results: At the hemispheric level, males showed a higher frequency of sulcal pits in both hemispheres (right: $p=0.0002$; left: $p=2.47 \times 10^{-8}$). At the cluster level, males showed more sulcal pits than females in the deep clusters of both hemispheres and in the shallow cluster of the left hemisphere ($p < 0.05$). At the parcel level, females had significantly deeper pits than males ($pFDR < 0.05$) in two deep parcels of the left hemisphere comprising the insula and the central sulci. On the other hand, males had deeper pits than females in two shallow parcels of the right hemisphere comprising the marginal and pericallosal sulci.

Discussion: Our findings suggest the potential role of sulcal pits as suitable markers of neurodevelopmental sex differences. Furthermore, differences between hemispheres suggest asymmetrical neurodevelopmental trajectories between sexes. These results underscore the need to adopt a perspective considering sex when analysing neurodevelopmental disorders.

Acknowledgements: ISCIII (FI21/00093-NH, CP20/00072-MFV, project PI20/1002; ERDF/ESF “Investing in your future”); 2021SGR01475-AGAUR.

F63. MECHANISM OF AUTOANTIBODIES IN SCHIZOPHRENIA

Ryan McLean^{*1}, Nicole Brace¹, Philomena Halford¹, Jun Wei¹, Antonia Pritchard¹

¹*University of the Highlands and Islands*

Background: The causes and pathomechanisms of schizophrenia are unclear despite many years of dedicated research. A series of observations has indicated autoimmune dysregulation is present in people with schizophrenia, including increased levels of specific circulating antibodies. The targets for the antibodies identified to date include neurotransmitter receptors such as the N-Methyl-D-Aspartate Receptor (NMDAR), intracellular proteins such as TRANK-1 and dietary proteins such as gliadin (from gluten). The role of schizophrenia-associated antibodies in the development of schizophrenia is, however, not yet understood. Studies of Anti-NMDA-Receptor Encephalitis suggest that autoantibody binding may disrupt receptor function and result in psychiatric symptoms, however the contribution of autoantibodies to neuroinflammation, immune cell activation and complement-mediated synaptic pruning, all with relevance to Schizophrenia, have not been examined. The contribution of an autoantibody to these processes are likely to depend on antibody isotype, possibly more importantly than antibody target. This study examined the hypothesis that antibody target and IgG subtype has different effects on a range of Schizophrenia-relevant cellular processes in mixed CNS cultures derived from Mouse neural precursor cells (NPC).

Methods: Mouse NPCs were differentiated into mixed populations of neurons, oligodendrocytes and astrocytes, using standard protocols. Differentiation was confirmed using Flow Cytometry markers against O4, Nestin and GFAP respectively. Commercially available monoclonal antibodies against a range of targets, including schizophrenia-relevant receptors including NMDAR and Voltage-Gated Calcium Ion Channels, were selected on the basis of the availability of different IgG isotypes, against these targets. The antibodies were incubated with mouse mixed mouse neuronal populations, for 24 hours before the impact of different IgG isotypes and different IgG targets on Schizophrenia-relevant cellular processes were examined. As complement-mediated synaptic elimination is a plausible mechanism by which autoantibodies may contribute to the pathology of Schizophrenia, the impact of IgG, by target and isotype, on Complement Protein expression was examined using immunohistochemistry with antibodies against C3 and C4.

Results: The NPC derived mixed population neuronal cells were confirmed as being of three different types, with median percentage populations of 61% neurons, 29% oligodendrocytes and 9% astrocytes. While results are still being collected, to date the impact of IgG target and IgG isotype on cell death has been examined in the first of three independent replicates of the in vitro experiments. Flow cytometry with Annexin-V-APC/PI in conjunction with O4, Nestin and GFAP have been used to characterise the impact of IgG incubation on apoptosis in individual cell types. Immunohistochemistry comparison of C3 and C4 expression elicited by each cell type has similarly been performed on the first of the replicate experiments.

Discussion: This study is testing the hypothesis that antibodies contribute to Schizophrenia-processes in a class specific manner, which has as an important of an impact as the antibody target, -As this study required multiple different classes of antibodies raised to a specific target, this approach required the use of murine derived antibodies and cell line. This does, however, present the opportunity to assess target-independent mechanisms of antibody classes, as well as relevant target antibody effects on vital cells of the central nervous system, using mixed populations of central nervous system cells.

F64. EARLY LIFE ADVERSITY AND HIPPOCAMPAL VOLUME AS RISK FACTORS FOR PSYCHOTIC-LIKE EXPERIENCES IN ADOLESCENTS

Svenja Kretzer^{*1}, Rebecca Pollard², Andrew J. Lawrence², Pei Jung Chen³, Xuemei Ma², Nare Amasi-Hartoonian², Corentin Vallée², Olivia Johnson Trewick², Craig Morgan⁴, Seeromanie Harding⁵, Gunter Schumann⁶, Carmine Pariante², Mitul Mehta⁷, Giovanni Montana⁸, Chiara Nosarti⁹, Sylvane Desrivieres¹⁰, Ana Rodriguez-Mateos⁶, Michael Meaney¹¹, Paola Dazzan¹²

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London; Agency for Science, Technology and Research (A*STAR)* ²*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ,* ³*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, Chang Gung Memorial Hospital,* ⁴*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ESRC Centre for Society and Mental Health, King's College London,* ⁵*School of Life Course and Population Health Sciences, King's College London, School of Life Course and Population Health Sciences, King's College London, ,* ⁶*School of Life Course and Population Health Sciences, King's College London, ,* ⁷*Centre of Neuroimaging Sciences, King's College London, National Institute for Health Research (NIHR) Mental Health Biomedical Research,* ⁸*University of Warwick, WMG, University of Warwick,* ⁹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, Centre for the Developing Brain, School of Biomedical Engineering and Imaging Sciences, King's College London,* ¹⁰*Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London,* ¹¹*McGill University, Agency for Science, Technology and Research (A*STAR),* ¹²*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, National Institute for Health Research (NIHR) Mental Health Biomedical Research*

Background: Sub-clinical psychotic-like experiences are relatively common in the general population, and in young people they have been established as a risk factor for a wide range of mental health problems. Early life adversities (ELA), capturing negative and stressful experiences in childhood, have been consistently associated with the onset of psychosis later in life. Furthermore, a history of ELA has also been associated with volumetric reductions in the hippocampus, and lower hippocampal volumes have been reported in psychiatric disorders, including early-onset psychosis. Yet, it is unclear whether exposure to ELA and reductions in hippocampal volume interact to increase the risk towards psychotic-like experiences in young people. Here, we investigated ELA and hippocampal volume as risk factors that potentially interact to heighten the vulnerability to psychotic-like experiences in young adolescents.

Methods: We recruited n=228 adolescents (mean age=12.4 years, SD=1; 54% female). We assessed ELA experiences using the Adolescent Life Experiences questionnaire, and psychotic-like experiences with the Adolescent Psychotic Symptom Screener, creating a weighted score of frequency and perceived distress. We acquired structural MRI in a 3T GE scanner (IR-SPGR, 32Ch head coil, res=1.2x1x1mm). T1-weighted images were processed with Freesurfer (v7.3.2) to estimate hippocampal volume. We used linear regression models predicting psychotic-like experiences, modelling main effects of ELA and total hippocampus volume, and an interaction between the two predictors. We adjusted all models for age, sex, and estimated Total Intracranial Volume (eTIV) as potential covariates.

Results: A linear regression model with total score of ELA and total hippocampal volume explained variance in psychotic-like experiences ($F(5,222)=5.44$, $p < .001$; adjusted $R^2=0.09$), above and beyond the covariates (change in adjusted $R^2=0.08$; model comparison $F(2,222)=10.92$, $p < .001$). ELA had a positive association with

psychotic-like experiences ($\beta=0.45$, 95%CI [0.33;0.57], p LESS THAN .001), whereas total hippocampus volume was negatively associated with psychotic-like experiences ($\beta=-0.36$, 95%CI [-0.5;-0.21], $p=.014$). The interaction between ELA and total hippocampus volume did not significantly improve model performance (change in adjusted $R^2=0.01$; model comparison $F(1,221)=2.13$, $p=.146$).

Discussion: Exposure to adverse and stressful experiences in childhood and adolescence and hippocampal volume were independently associated with higher weighted scores of frequency and distress of psychotic-like experiences. This suggests that both, ELA and hippocampal structure represent risk factors for psychotic-like experiences that develop early in life. The hippocampus is a structure highly sensitive to neurodegenerative effects of chronic stress, such as that induced by ELA, and plays a main role in regulating the stress responses through a negative feedback loop with the hypothalamic-pituitary-adrenal (HPA) axis. Hippocampal volume reductions may be related to dysregulated HPA-axis activity, representing a shared mechanism relevant to development and maintenance of psychiatric disorders. Future longitudinal investigations capturing a wider age range could explore whether there is an interaction at specific developmental periods, or if ELA and hippocampal structure could be considered independent risk factors.

F65. ANTENATAL PSYCHOPATHOLOGY AND INFANT OUTCOMES: THE ROLE OF MATERNAL ANTENATAL IMMUNE SYSTEM

Catriona Curl^{*1}, Katie Hazelgrove¹, Alessandra Biaggi¹, Rebecca Bind¹, Susan Conroy¹, Susan Pawlby¹, Lavinia Rebecchini¹, Kristi Sawyer¹, Carmine Pariante¹, Vaheshta Sethna¹, Paola Dazzan¹

¹*King's College London, Institute of Psychiatry*

Background: Prospective cohort studies have shown that maternal mental illness during pregnancy can have long lasting negative consequences on the developing child. Research to understand the potential mechanisms underlying this association, such as developmental programming, has begun to attract attention. More specifically, immune activation, indicated by higher levels of Interleukin-6 (IL-6) has been reported in association with risk for major psychiatric disorders. Here, we investigated the relationship between maternal antenatal psychopathology and infant outcomes, and whether maternal antenatal IL-6 levels might help explain this relationship.

Methods: We included 253 women comprising $n=103$ healthy controls; $n=32$ women with a history of Major Depressive Disorder (MDD); $n=67$ women with MDD in current pregnancy; and $n=51$ women at risk of Postpartum Psychosis (PP). They were recruited in pregnancy and followed up until 12 months postnatally. Blood was obtained from the mothers during the early third trimester of pregnancy to measure a biological marker of immune system function, serum interleukin 6 (IL-6). Neonatal behaviour and infant development were assessed at 6 days and 12 months postpartum respectively across all four groups using the Neonatal Behavioural Assessment Scale (NBAS) and the Bayley Scales of Infant Development (BSID).

Results: Mothers in the “history of MDD” and “MDD in pregnancy” groups had significantly higher levels of serum IL-6 during pregnancy than controls and “at risk of PP” women ($p=$ LESS THAN .05).

At 6 days postpartum, newborns of women in the “MDD in pregnancy” and “at risk of PP” groups scored significantly lower than controls ($p=$ LESS THAN .001) in the autonomic stability cluster which records signs of stress related to the homeostatic adjustments of the

central nervous system. Newborns of women in the “MDD in pregnancy” group also scored significantly lower than those of controls for social interaction ($p=.008$). At 12 months postpartum, infants of mothers in the “at risk of PP” scored lower than controls for cognitive development ($p=.015$), and lower than all groups for motor development ($p=.004$). Infants of mothers “at risk of PP” also scored lower for language development than controls and “MDD in pregnancy” ($p= \text{LESS THAN } .001$). Finally, higher levels of serum IL-6 during pregnancy were negatively correlated with infant cognitive scores at 12 months postnatal across all groups ($r= -.185$, $p= .01$).

Discussion: Maternal antenatal psychopathology is associated with activation of the immune system in pregnancy and less optimal neonatal and infant development. It is possible that higher maternal levels of immune system function could be due to poor regulation of cytokine-glucocorticoid feedback, leading to overactive Hypothalamic-Pituitary-Adrenal (HPA) Axis regulation of immune response. These are in turn associated with poorer infant cognitive development, which supports the premise that stress-induced maternal immune activation may contribute in part to prenatal programming of risk. Future regression models will test whether these associations represent mechanistic pathways.

F66. PARENTAL STRESS AND GENERAL FAMILY FUNCTIONING IN FIRST-ONSET CHILD AND ADOLESCENT PSYCHOSIS: PRELIMINARY RESULTS FROM THE OPUS YOUNG TRIAL

Naja Kirstine Andersen¹, Caroline Friis Nielsen², Mathilde Søndergaard Madsen², Natascha Larsen², Thomas PL Andersen², Louise Berthram Bay², Lene Halling Hastrup³, Ditte Lammers Vernal⁴, Lis Raabæk Olsen², Jacob Rydkjaer², Martin Rimvall², Jens Richardt Møllegaard Jepsen², Birgitte Fagerlund², Anne Amalie Elgaard Thorup², Pia Jeppesen⁵, Merete Nordentoft⁶, Marianne Melau⁶, Anne Katrine Pagsberg², Anne Katrine Pagsberg*⁷

¹*Child and Adolescent Psychiatric Center, Capital Region of Denmark*, ²*Child and Adolescent Mental Health Center Capital Region of Denmark*, ³*Psychiatric Research Unit, Psychiatry Region Zealand*, ⁴*Aalborg University Hospital, Psychiatry, Research Unit for Child and Adolescent Psychiatry*, ⁵*Region Zealand Psychiatry, Research Unit*, ⁶*Mental Health Centre Copenhagen, Copenhagen University Hospital*, ⁷*Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark*

Background: Few studies have investigated the stress and burden on parents associated with having a child or adolescent experiencing first-onset of a psychotic disorder. However, studies in adult psychosis has demonstrated the need for Early Intervention Services (EIS) to target the burden of disease that parents and families experience. Parental stress and family function is therefore expected to correlate with changes in child illness severity and functioning during the course of treatment. OPUS YOUNG (OY) is a randomised clinical trial comparing the effects of two years of EIS (the OY intervention) to treatment as usual (TAU). The present study outlines parent stress and family functioning at baseline before treatment is initiated.

Methods: Parents of 290 youths aged 12-17 years participating in the OY trial were invited for baseline assessment with Parental Stress Scale (PSS) and the McMaster Family Assessment Device – General Functioning Subscale (FAD-GF). The PSS measures stress as experienced by the parents. The questionnaire includes 18 statements to which the parent rate their response on a 5 point Likert scale from strongly disagree to strongly agree. Ten of the statements address negative and stressful aspects of parenting, while 8 statements address positive aspects of

parenting. The FAD-GF measures the overall general family function assessed by 12 questions addressed to the parents. Responses are rated on a 4 point Likert scale from strongly disagree to strongly agree.

Results: We will present characteristics of the patient sample and preliminary results of PSS and FAD-GF of the OY sample at baseline.

Discussion: We will discuss our findings of the perceived level of burden compared to findings from other similar and other patient samples.

F67. THE ROLE OF IL-18 AND CHILDHOOD TRAUMA IN EARLY-ONSET PSYCHOSIS

Cecilie Funderud^{*1}, Anette Fjeldstad², Ingrid Agartz³, Nils Eiel Steen⁴, Ole Andreassen⁵, Monica Aas⁶, Anne Margrethe Myhre⁴

¹Østfold Hospital Trust, ²NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, ³Østfold Hospital Trust, Norway, ⁴Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Region Stockholm, Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Diakonhjemmet Hospital, ⁵NORMENT Centre for Psychosis Research, Oslo University Hospital and University of Oslo, ⁶NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, University of California, San Diego, Oslo University Hospital and University of Oslo, , ⁶Institute of Psychiatry, Psychology, and Neuroscience, Kings College London

Background: There is evidence for immunological dysregulation and low-grade inflammation as a part of the pathogenesis of psychosis-spectrum disorders. Furthermore, studies in adults indicate a link between low-grade inflammation and early trauma. The proinflammatory interleukin-18 (IL-18) has been found elevated in psychosis-spectrum disorders. IL-18 is to a large degree bound to IL-18's binding protein (IL-18BP), forming a complex which blocks IL-18's biological activity. This interleukin is an important modulator of the immune system, but there are few studies examining IL-18 in adolescents with Early-Onset Psychosis. The purpose of this study is increased understanding of the association between childhood trauma and low-grade inflammation (IL-18) in adolescents with an Early-Onset Psychosis. We will specifically investigate whether childhood trauma exposure and higher levels of IL-18 and IL-18/IL-18BP-ratio are more often observed in adolescents (aged between 13-18 years) with an Early-Onset Psychosis, compared to age- and sex-matched healthy controls (HC).

Methods: Serum levels of IL-18 and IL-18BP were measured using venous blood samples from adolescents with Early-Onset Psychosis (n=22) and HC (n=44). Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ) and analyzed as a continuous variable (total and subgroup CTQ-score). As the immune markers (IL-18 and IL-18/IL-18BP-ratio) were skewed, they were log transformed prior to being entered into the statistical models. Logistic regression was used to investigate differences in trauma exposure and IL-18 levels in patients and controls. Linear regression was used to investigate the relationship between IL-18 and childhood trauma experiences in patients and controls separately. All analyses were controlled for age and sex.

Results: Patients experienced significantly more childhood trauma (Odds ratio, OR: 1.25; 95% CI: 1.08-1.45; p=.003) and had higher IL-18-levels (OR: 2.28; 95% CI: 1.08-4.82; p=.03) compared to the controls, but no significant differences were observed for IL-18/IL-18BP-ratio

(p GREATER THAN .1). We did not find a significant association between reported childhood trauma experiences (total CTQ-score) and serum IL-18 in either group (p GREATER THAN .1). However, there was a trend-level association between reported childhood trauma (total CTQ-score) and the IL-18/IL-18BP-ratio within the patient group ($\beta=.40$, $t = 1.77$, $p=.09$). Investigating trauma-subscales, we found within the patients a significant association between emotional abuse and the IL-18/IL-18BP-ratio ($\beta=.47$, $t = 2.40$, $p=.03$). No association was observed between childhood trauma and the immune markers (IL-18 and IL-18/IL-18BP ratio) in the control group (p GREATER THAN .1).

Discussion: Our findings support an association between childhood trauma and low-grade inflammation (IL-18) in adolescents with an Early-Onset Psychosis. Our preliminary analyses suggest higher occurrence of childhood trauma in patients with an Early-Onset Psychosis than in the age- and sex-matched healthy adolescence group. Our preliminary findings may suggest an association between the IL-18 system and specific types of childhood trauma experiences in the Early-Onset Psychosis group, but not in the healthy adolescents. While taking the small sample of these preliminary analyses into consideration, our findings indicate an interplay between low-grade inflammation and childhood trauma in adolescent psychosis deserving further attention.

F68. EXAMINING THE ASSOCIATION BETWEEN PRENATAL AND PERINATAL ADVERSITY AND THE PSYCHOTIC EXPERIENCES IN CHILDHOOD

Lorna Staines*¹, Niamh Dooley¹, Colm Healy², Ian Kelleher², David Cotter¹, Mary Cannon¹

¹Royal College of Surgeons in Ireland, ²University of Edinburgh

Background: Prenatal and perinatal complications are an established risk factor for psychotic disorder, but far less is known about the association between prenatal and perinatal complications and psychotic experiences (PEs). PEs in childhood are relatively common, but distressing and/or repeated PEs (persistence), have been associated with adverse outcomes including higher rates of mental disorders and substance disorders. We aimed to examine the longitudinal effects of prenatal/perinatal risk factors on frequency and persistence of distressing PEs across late childhood (age 9/10 - 11/12). Prenatal risk factors were maternal behaviours during pregnancy (smoking/substance use/alcohol consumption) and eleven medical complications (e.g. pre-eclampsia, maternal diabetes). Perinatal risk factors included birth weight and eight medical complications (e.g. born jaundiced, convulsions at birth). We examined the cumulative risk of prenatal/perinatal risk factors on frequency of distressing childhood PLE, and differences between transient PEs, persistent PEs, and controls.

Methods: The Adolescent Brain Cognitive Development study is a large USA based child cohort (age 9-10 at baseline; n=11872 with PE data). PEs were measured at 3 time points (baseline, T1, T2) using the Prodromal Questionnaire-Brief, Child version, and included only if reported as distressing (score $\geq 3/5$). Mixed effect models were used for analysis, controlling for random-effects, and a substantial number of fixed-effects covariates which have been previously associated with PEs, including; family history, socio-economic status, maternal health and age.

Results: Urinary tract infection ($\beta=0.11, 95\%CI[0.03, 0.19]$), and severe anaemia ($\beta=0.18, 95\%CI[0.07, 0.29]$) increased frequency of distressing PEs in childhood. Number of prenatal complications increased frequency of PE ($\beta=0.03, 95\%CI[0.01, 0.06]$) and risk of persistent PEs (OR=1.08, 95%CI[1.01, 1.15]). Maternal smoking was associated with an increased frequency of PEs ($\beta=0.11, 95\%CI[0.04, 0.18]$), and were 31% more likely to report

persistent PEs (OR=1.31,95CI[1.04,1.66]). Maternal substance use was associated with a 48% increased risk of persistent PEs (OR=1.48,95%CI[1.08,2.01]). Perinatal complications showed no effect on frequency or persistence of distressing childhood PEs.

Discussion: This study provides evidence that specific prenatal medical complications (urinary tract infection, severe anaemia) and maternal behaviours (smoking during pregnancy), increased frequency of distressing PEs in childhood. Cumulative number of prenatal medical complications also increased frequency of PEs. Maternal smoking and substance use, as well as cumulative number of prenatal complications, increased risk of persistent PEs. These findings support the evidence of the importance of addressing maternal behaviours for the long term health of the child. Additionally, it demonstrates that public health services currently not freely available in the USA (e.g. sexual health services for pregnant people) could have long-term adverse consequences on children.

F69. DEVELOPMENT OF PSYCHOPATHOLOGY IN ADOLESCENTS BORN TO PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Doris Helena Bjarnadóttir Olsen^{*1}, Maja Gregersen², Mette Falkenberg Krantz², Carsten Hjorthøj³, Sinnika Birkehøj Rohd⁴, Marta Schiavon⁴, Anette Faurskov Bundgaard⁵, Andreas Færgemand Laursen⁵, Jessica Ohland⁴, Aja Greve⁵, Ole Mors⁵, Nicoline Hemager², Merete Nordentoft⁶, Anne Amalie Elgaard Thorup⁷

¹CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, ²CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; BFOR - Child and Adolescent Mental Health Centre, ³CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; University of Copenhagen, Section of Epidemiology, ⁴CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; ⁵Psychosis Research Unit, Aarhus University Hospital Psychiatry, ⁶CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; Faculty of Health and Medical Sciences, University of Copenhagen, ⁷CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark; BFOR - Child and Adolescent Mental Health Centre; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen

Background: Schizophrenia spectrum disorder (SZ) and bipolar disorder (BP) are severe mental disorders. Although these disorders vary in terms of character and severity, they are highly associated with periods of disability and suffering on a personal as well as a societal level. SZ and BP tend to cluster in families in which familial high-risk (FHR) offspring constitute a vulnerable risk group. Compared to individuals without affected parents, FHR offspring of a parent with either a psychotic disorder or BP have a more than a five-fold risk of developing the same disorders as the parent. Furthermore, FHR offspring of SZ and BP have an increased risk of mental disorders already in childhood, indicating that vulnerability to psychopathology is founded early in life. However, it is not clear whether this vulnerability is significant for development of severe mental illness later in life. By comparing adolescents with familial high-risk of SZ and BP with population-based controls, we aim to examine and describe: 1. Mental disorders and psychiatric comorbidity, Prevalence of mental disorders and

psychiatric comorbidity by age 15, Cumulative incidence of mental disorders and psychiatric comorbidity from age 7 to age 15.

2.Diagnostic changes over time, Stability of mental disorders from age 7 to age 15, Proportion of offspring with persistent, incident, remittent, or no mental disorder at age 15.

3.Global functioning: Overall global functioning in FHR offspring from age 7 to age 15, Global functioning in relation to offspring psychopathology.

Methods: The Danish High Risk and Resilience Study is a nationwide prospective cohort study consisting of 522 children born to parents with SZ, BP, or none of these disorders (population-based controls). The families were recruited from the Danish registers and the population-based controls were matched to the children of FHR-SZ on municipality, sex, and age. The first assessment was performed from 2013–2016 when the children were 7 years old (the VIA 7 study). The second wave (the VIA 11 study) was carried out when the children were 11 years old from 2017-2020 with an 89% retention rate. In the third wave (the VIA 15 study) the children have turned 15 years old, data collection started in 2021 and will be finalized in spring 2024. Face-to-face interviews are conducted by trained professionals blinded to parental illness with the gold-standard diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (KSADS-PL). All diagnoses are confirmed at clinical conferences with a child and adolescent psychiatrist.

Results: Results are expected in autumn 2024.

Discussion: As our study is based on a large nationwide prospective sample observing the same individuals from early childhood to adolescence during three waves of comprehensive assessment, we expect it to provide valuable data of the development of psychopathology. Furthermore, we enhance the accuracy of data by including offspring within a narrow age range. As in our previous follow up study we expect a high retention rate. We use clinical interviews where data is based on the participants' memory, entailing a risk of reporting bias. Furthermore, we are aware of the risk of selection bias, as participants with poorer functioning may find it more difficult to participate in the project. To eliminate this, we facilitate flexible interview scheduling and durations. Cohort studies following FHR offspring contribute to an increased knowledge of which FHR offspring are at most risk of severe mental illness, and thus improving which FHR offspring to target for preventive services.

F70. COMPARING PARENT AND CHILD COGNITION IN FAMILIES WITH PARENTAL SCHIZOPHRENIA OR BIPOLAR DISORDER: A DEVELOPMENTAL PERSPECTIVE FROM SEVEN TO 11 TO 15 YEARS OF AGE

Anette Faurskov Bundgaard*¹, Arndis Simonsen², Andreas Færgemand Laursen², Nanna Lawaetz Steffensen², Merete Birk², Sinnika Birkehøj Rohd³, Martin Wilms³, Marta Schiavon³, Doris Helena Feodora Bjarnadóttir Olsen³, Jens Richardt Møllegaard Jepsen³, Nicoline Hemager³, Merete Nordentoft³, Anne Amalie Elgaard Thorup³, Ole Mors², Aja Neergaard Greve²

¹Psychosis Research Unit, Aarhus University Hospital Psychiatry, ²Psychosis Research Unit, Aarhus University Hospital Psychiatry, ³Copenhagen University Hospital

Background: Schizophrenia (SZ) and bipolar disorder (BD) are severe mental disorders, and offspring of parents with SZ or BD are at increased risk of developing the same or other mental disorders. Growing evidence has indicated that SZ and BD share clinical, cognitive,

neuroimaging, and genetic characteristics, an overlap which might also be present in their offspring. Neurocognitive deficits are core features of both SZ and BD. In both groups, neurocognitive impairments have been found to negatively impact the level of functioning and some studies have suggested that cognitive impairments are early vulnerability markers or endophenotypes for these disorders. Familial high-risk (FHR) studies have demonstrated that children born to parents with SZ or BD display a wide array of neurocognitive deficits that lie in between the respective patient group and healthy controls. These studies highlights the importance of assessing and understanding the presence and development of neurocognition in offspring at FHR. High heritability estimates of cognition have been demonstrated in SZ as well as in healthy populations. Heritability of general cognitive ability increases significantly and linearly with age, suggesting a genotype-environment correlation. However, the intergenerational transmission of cognitive abilities is still an under-researched field both in general and in families with severe mental disorders. Few studies have investigated the association and only cross-sectional data has been reported. This study aims to assess the transmission of intelligence, processing speed and verbal working memory from both biological parents to their offspring from the child was seven to 11 to 15 years of age in a cohort of families where a least one parent was diagnosed with schizophrenia og bipolar disorder, or none of these disorders.

Methods: This study is part of The Danish High Risk and Resilience Study – VIA, a longitudinal nationwide cohort of children with no (PBC; 200), one or two parents diagnosed with SZ (FHR-SZ; 202) or BP (FHR-BP; 120). At age seven, 522 children and both their biological parents were assessed (VIA 7). Parents and children underwent the same battery of tasks from validated neurocognitive measures. Intelligence was estimated using The Reynolds Intellectual Screening Test. Processing speed and verbal working memory was assessed respectively with Coding and Letter-Number Sequencing in children from Wechsler Intelligence Scale for Children – fourth edition, and in parents from Wechsler Adult Intelligence Scale – fourth edition. At age 11, the children were assessed using the same tests, with a follow-up rate of 89% (VIA 11). Now at age 15, the children are assessed for the third wave of the study (VIA 15).

Results: Data collection is ongoing and will be finalized in the spring of 2024.

Discussion: To our knowledge this is the first longitudinal study to assess cognition between parents and children in in the same study with the same measurements. This provides a unique opportunity to investigate the relationship between parent and child cognition and how cognition might be modulated by having a parent with a severe mental disorder such as SZ or BP. This will enrich our understanding of neurocognitive deficits as endophenotypes for SZ and BD which is important to enhance our understanding of the etiological mechanisms underlying the development of the disorders.

F71. AMPHETAMINE SENSITISATION IN HEALTHY VOLUNTEERS LEADS TO INTERNALISING ATTRIBUTION BIAS AND INCREASED STRESS SENSITIVITY TO LOSS OF CONTROL

Nace Mikus^{*1}, Federico Mancinelli², Claus Lamm³, Mathäus Willeit⁴, Christoph Mathys¹

¹Aarhus University, ²University of Bonn, ³University of Vienna, ⁴Medical University of Vienna

Background: Hypersensitivity of the dopaminergic system is believed to be the core biological abnormality in patients with psychosis and an important risk factor in various other

neuropsychiatric disorders. Endogenous dopamine sensitization is characterized by an increased response to dopamine-releasing drugs as well as stressful environments. Yet, the mechanisms through which dopamine dysregulation leads to increased stress sensitivity are largely unknown. Stressors that result from perceived uncontrollable negative events are particularly likely to elicit a larger response in vulnerable individuals, especially those that have a self-blaming causal attribution bias. Here, we present preliminary data from an experiment investigating the effects of dopamine sensitization on causal attribution in experimentally induced loss of control.

Methods: Healthy male volunteers were subjected to an amphetamine sensitisation procedure in which they received three repeated low doses of D-amphetamine ($n = 8$) or mannitol ($n = 2$) two days apart. After a two-week sensitisation period, both groups received another dose of D-amphetamine. Blood pressure and heart rate were measured several times during each experimental session. Stress sensitivity and attribution bias were measured using a novel behavioural task in which participants had to exert effort to either gain monetary rewards or avoid monetary losses. Throughout the task, the degree of control participants have over the outcome of each trial is reduced. After each trial, participants are asked about their subjective sense of control, perceived stress and whether they attribute the outcome of the trial to chance or to their performance. Participants perform the loss of control task several times during the experiment: at baseline (B1), after the first amphetamine administration (A1), after sensitisation without drug administration (B2) and after sensitisation with amphetamine administration (A2).

Results: We found stronger responses to amphetamine after the sensitisation procedure, as indicated by a significant difference in systolic blood pressure in response to amphetamine between the last and the first amphetamine administration ($p = 0.03$, mean difference = 8.75 mmHg). Using a linear model predicting self-reported stress from perceived control as a random and fixed effect, and sensitisation and amphetamine administration as fixed effects, we found that loss of control led to higher self-reported stress across the study ($p < 0.001$) and that this effect was more pronounced after sensitisation ($p < 0.001$). Looking at session comparisons within the sensitisation group only, we found that stress sensitivity was higher under amphetamine after sensitisation (A2) compared to before sensitisation (A1) and to baseline (B1, all $p < 0.01$). We defined attribution bias as a linear effect of success or failure in each trial on attribution. We found that participants generally show a positive attribution bias, by attributing failures to luck and successes to their own performance ($p < 0.001$), and that a positive attribution bias reduced the effect of loss of control on stress. A mixed linear model predicting attribution from trial outcome as a fixed and random effect and sensitisation and amphetamine administration as fixed effects, we found that sensitisation led to stronger internal attribution, regardless of trial outcome ($p < 0.001$).

Discussion: The preliminary results of this study support the notion that repeated exposure to psychostimulants leads to increased stress sensitivity in response to loss of control. Our data suggest that the psychological mechanism that underlies the heightened stress response is a higher internalising attribution style. The strength of this study is a novel paradigm that is administered repeatedly within subjects; however, the findings are preliminary, with low sample sizes, and should be interpreted with this in mind.

F72. PRELIMINARY DATA FROM THE CONNEX-X EXTENSION TRIAL EXAMINING THE LONG-TERM SAFETY OF ICLEPERTIN (BI 425809) IN

PATIENTS WITH SCHIZOPHRENIA WHO COMPLETED PHASE III CONNEX TRIALS

Corey Reuteman-Fowler^{*1}, Zuzana Blahova², Stephen R. Marder³, Satoru Ikezawa⁴, Peter Falkai⁵

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Boehringer Ingelheim RCV GmbH and Co. KG, ³Semel Institute for Neuroscience at UCLA, David Geffen School of Medicine, ⁴International University of Health and Welfare, Mita Hospital, ⁵Ludwig Maximilians University Munich

Background: Cognitive impairment associated with schizophrenia (CIAS) is an important unmet need as there are no effective treatments available. Iclepertin (BI 425809), a glycine transporter-1 inhibitor, has been shown to improve CIAS in Phase II trials, and Phase III trials are underway. The ongoing CONNEX-X extension study aims to collect additional safety data relating to iclepertin treatment in patients with CIAS.

Methods: CONNEX-X (NCT05211947/1346-0014) is a multinational, multicentre, open-label, single-arm extension study in patients with CIAS who completed 26 weeks of treatment (iclepertin 10 mg or placebo) in one of 3 Phase III CONNEX parent trials (NCT04846868/1346-0011, NCT04846881/1346-0012, NCT04860830/1346-0013). An estimated 1400 clinically stable outpatients will be treated (iclepertin 10 mg daily) for 1 year, irrespective of previous treatment (iclepertin/placebo). Patients are excluded if any of the following circumstances occur during the parent study and up to Visit 1 of CONNEX-X: suicidal behaviour or ideation (type 5 on the Columbia-Suicide Severity Rating Scale), diagnosis with moderate/severe substance use disorder, diagnosis other than schizophrenia (according to Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition), development of any condition preventing participation, a haemoglobin level decrease (GREATER THAN 25% or LESS THAN 100g/L from baseline in parent trial) or haemoglobinopathies. The primary endpoint is the occurrence of treatment-emergent adverse events. The secondary endpoints include change from baseline (CfB) in Clinical Global Impressions-Severity (CGI-S) and CfB in haemoglobin. Further efficacy endpoints include CfB in MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score, CfB in Schizophrenia Cognition Rating Scale total score and CfB in Virtual Reality Functional Capacity Assessment Tool (VRFCAT) total times.

Results: Currently, 460 patients have been enrolled and randomised from the parent trials with 0% screening failures (~80% roll-over rate, 30 August 2023). Current study status, including recruitment, screening failures and data collection experiences, are presented.

Discussion: Patient enrolment rates from the CONNEX trials to the CONNEX-X open-label extension study are stable. CONNEX-X will allow the exploration of long-term safety, as well as descriptive analyses of cognitive and functional endpoints of iclepertin in the treatment of CIAS.

This study is funded by Boehringer Ingelheim (NCT05211947/1346-0014).

F73. LEVEL AND CHANGE IN SYMPTOM CLUSTERS AND INSIGHT AFTER COMMENCING ANTIPSYCHOTIC TREATMENT

Lena Stabell^{*1}, Erik Johnsen¹, Rune Kroken¹, Else-Marie Løberg¹, Eirik Kjelby², Inge Joa³, Solveig Klæbo Reitan⁴, Rolf Gjestad⁵

¹Haukeland University Hospital, University of Bergen, ²ReHaukeland University Hospital, ³TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital, Network for Medical Sciences, University of ⁴St. Olavs Hospital; Norwegian University of Science and Technology, ⁵Haukeland University Hospital, Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital

Background: Impaired clinical insight is common in schizophrenia spectrum disorders. Impaired insight may influence both treatment motivation and adherence. This has effects on prognosis. Most studies lack multiple assessments in the initial phase after commencing antipsychotic treatment to capture the relationship between insight and symptom changes. In this study, we aim to disentangle the effects of fluctuations in different symptom cluster on insight. We examined changes in symptoms and insight during the first six weeks of antipsychotic treatment.

Methods: Using data from the BeSt InTro trial, 144 patients were assessed with the Positive and Negative Syndrome Scale (PANSS) at baseline, week 1,3, and 6 after commencing antipsychotic treatment. We predicted change and end level of insight in separate latent growth curve models based on the following symptom clusters: Positive (P1, P3, G9, P5, P6), negative (N4, N2, N1, N3, G7, G16), disorganised/cognitive (G11, P2, N5, G10, N7, G13, G5), hostility (P7, G8, G4, G14), and a total PANSS score excluding the insight item (mPANSS).

Results: Mean insight improved from 3.4 at baseline to 2.5 after six weeks of AT, range 1-6 at both time points. However, more than one fifth of the participants had a score of four or more after six weeks use of antipsychotics. Change in several of the predictors corresponded with change in outcome within the following intervals: week 0-1, week 1-3 and week 3-6. The end level of insight was predicted by baseline level and change in the 3-6 weeks interval in all symptom models. Change in positive ($b = 2.06$, $p = 0.007$), hostility ($b = 1.62$, $p = 0.028$) and mPANSS ($b = 1.89$, $p = 0.014$) in the 1–3-week interval were also significant predictors of the end level of insight.

Discussion: Our analyses display time-specific relations between improvements in symptoms, and

improvements and the end level of clinical insight after six weeks of antipsychotic treatment. Accordingly, ongoing symptom reduction is associated with continuous improvement in insight. This aligns with previous findings based on longer follow-up or less frequent assessments in the initial phase. Lack of significant findings in negative and cognitive symptoms clusters in the week 1-3 interval, may be due to the internal relationships between the predictors in their individual models. Our results suggest close monitoring of treatment effects, including insight. Although mean insight was improved, a notable group of participants displayed persistent impaired insight after commencing antipsychotic treatment. This has been reported in previous studies, and the literature has identified both state and trait properties of insight. Therefore, some patients may benefit from other treatments aimed at improving insight, particularly the trait aspect. Lately, interventions aimed at improving metacognitive functions have shown promising results.

F74. LONG-TERM SAFETY OF KARXT (XANOMELINE AND TROSPIMUM) IN SCHIZOPHRENIA

Ronald Marcus¹, Rishi Kakar², Andrew C. Miller¹, Amy Claxton*¹, Steven M. Paul¹, Stephen K. Brannan¹, Inder Kaul¹

Background: A high unmet medical need exists for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action. All currently approved treatments for schizophrenia have D2 dopamine receptor blocking activity; the efficacy and tolerability limitations of these therapies are well known. KarXT, an investigational medication, combines the dual M1/M4 preferring muscarinic acetylcholine receptor agonist xanomeline and the peripherally restricted muscarinic receptor antagonist trospium chloride. KarXT is designed to preserve the beneficial central nervous system effects of xanomeline while reducing adverse events (AEs) due to peripheral muscarinic receptor activation. The efficacy and safety of KarXT in schizophrenia was demonstrated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. Long-term safety and tolerability of KarXT in adults living with schizophrenia is being assessed in the Phase 3, multicenter, 52-week, outpatient, open-label extension EMERGENT-4 (NCT04659174) study and 52-week, open-label EMERGENT-5 (NCT04820309) study in de novo participants.

Methods: Safety and tolerability measures from EMERGENT-4 and EMERGENT-5 were pooled to assess the long-term safety and tolerability of KarXT in participants with schizophrenia. The EMERGENT-4 trial enrolled participants who previously completed the treatment period of one of the two Phase 3 double-blind studies, and the EMERGENT-5 trial enrolled de novo adult subjects with schizophrenia without prior exposure to KarXT and with a Positive and Negative Syndrome Scale total score ≤ 80 , a Clinical Global Impression–Severity score ≤ 4 . Data from an interim analysis of the EMERGENT-4 and EMERGENT-5 trials were pooled, and all safety analyses were conducted in the safety population, defined as all participants who received ≥ 1 dose of trial drug. Data are continuing to be recorded in these ongoing studies, and updated analyses will be available at the time of the meeting.

Results: A total of 674 participants were included in the long-term safety interim analyses. Across the EMERGENT-4 and EMERGENT-5 trials, approximately 60% of patients reported ≥ 1 treatment-related AE. The most common treatment-related AEs occurring in $\geq 5\%$ of participants receiving KarXT were nausea, vomiting, constipation, dry mouth, dyspepsia, dizziness, hypertension, and diarrhea. Of the most common treatment-related AEs the majority were mild or moderate in severity with low rates of severe AEs reported for nausea and vomiting. KarXT was not associated with clinically meaningful changes in prolactin levels and a mean decrease in weight was observed from baseline to Week 52.

Discussion: The interim pooled analyses from the long-term, open label trials indicated KarXT was generally well tolerated in individuals with schizophrenia in an outpatient setting across 52 weeks. These findings, together with the long-term efficacy results showing improvements in efficacy measures across the 52-week trial, support the potential of KarXT to be the first in a new class of antipsychotic medications based on muscarinic receptor agonism and a well-tolerated alternative to currently available antipsychotics.

F75. INCORPORATING DIGITAL HEALTH TECHNOLOGY TOOLS IN STUDY DESIGN TO ASSESS MEDICATION ADHERENCE IN SCHIZOPHRENIA TRIALS

Reuben Fan^{*1}, Elizabeth Hanson², Rich Christie³, Deshana Desai³, Tingting Ge¹, Leah Aluisio¹, Shaolei Feng³, Mahnaz Asgharnejad², Satjit Brar¹, Eduardo Dunayevich¹, Lei Guan³, Venkatesha Murthy², Jaskaran Singh¹, Ni Aye Khin¹

Background: In CNS trials, study design is crucial to mitigate high drop-out rates and poor treatment adherence. Digital health technology tools have been used as part of the study design to monitor and support medication adherence. A smartphone-based application (the Platform), that utilizes video analysis technology to monitor study medication intake was employed in a clinical study evaluating investigational TAK-831/NBI-844 (luvadaxistat) as an adjunctive treatment for negative symptoms of schizophrenia (the INTERACT Study). Here, we sought to understand the impact of including adherence support with the Platform in the single blind lead-in (SLBI) phase as part of the eligibility requirement for inclusion in the double-blind (DB) (post-randomization) period. We also investigated how DB Platform adherence values correlated with pill-count and detectable luvadaxistat plasma levels in subjects assigned to take luvadaxistat during the DB period.

Methods: The INTERACT Study was a phase 2, 12-week, randomized, DB, placebo-controlled, efficacy, safety, and pharmacokinetic study of 3 doses (50, 125 and 500 mg) of luvadaxistat. There was a 2-week (Day -14 to Day -1) SLBI period where adherence to study drug intake was measured using the Platform. During the SLBI period, all subjects received placebo tablets, that appeared identical to the study drug to be given during the 12-week DB period (Day 1 to Day 84). To enter the DB portion of the study, subjects needed to complete the SLBI period with at least 75% adherence to Platform use. Platform adherence is defined as the number of pills successfully logged on the Platform against the expected number of pills. Pill count adherence is defined as the number of pills dispensed corrected for number of returned pills. For measuring concordance between pill-count and Platform use, we set adherence thresholds of 90% and 75% respectively between the final two visits (Day 70 and Day 84). Concordance with detectable luvadaxistat plasma level is based on samples collected at final DB study visit (Day 84).

Results: Of the 304 enrolled subjects, 256 subjects were randomized and 169 subjects were assigned to take luvadaxistat. Of the 256 randomized subjects, 254 (83.5%; 254/304) have Platform data for analysis. Within the SLBI period, the average adherence to Platform use of those who did not qualify for the DB period was ~71%. The average SLBI adherence to Platform use of those who did qualify for the DB period was ~94%. The overall adherence to Platform use for subjects participating in both the SLBI and DB periods was ~92%. The adherence to Platform use for the DB portion alone was also ~92%. There were 160 subjects assigned to the take luvadaxistat in the DB that also maintained a $\geq 75\%$ overall Platform use adherence and 144 (90%; 144/160) of those subjects had quantifiable plasma concentrations of luvadaxistat. In addition, 154 subjects assigned to a luvadaxistat arm had Platform data to compare with pill count data and 151/154 (98.1%) of those subjects had both 75% adherence to Platform use and 90% or greater pill count adherence. Overall, among all 3 measures, we found 88% met all 3 thresholds ($\geq 75\%$ adherence to Platform use, $\geq 90\%$ pill-count adherence, and quantifiable plasma concentrations of luvadaxistat).

Discussion: Preliminary analysis indicates subjects who demonstrated adherent behaviors in the SLBI period tended to maintain such behaviors through the DB. This also indicates that thoughtful integration of a technology platform in the study design (that considers markers of medication adherence) can lead to a desirable confluence of measures indicative of subjects who are able to maintain intake of investigational product throughout a protocol. Further analysis to be discussed.

F76. METACOGNITIVE TRAINING FOR NEGATIVE SYMPTOMS

Linda Swanson*¹, Jonas Persson², Benjamin Rask², Simon Cervenka²

¹*Centre for Clinical Research Sörmland, Uppsala University SE, ,* ²*Uppsala University,*

Background: The cognitive model proposes that negative symptoms (NS) in schizophrenia might be caused/maintained by dysfunctional beliefs about social affiliations, performance, expectations of pleasure, success, and acceptance as a consequence of repeated failures and setbacks, where individuals adopt coping strategies by ‘shutting down’ the cognitive-affective experience. This allows individuals to cope with overwhelming situations in the short-term, but leads to a reliance on NS in the longer-term. Longitudinal studies have shown support for the model as defeatist performance attitudes and asocial beliefs are found to predict future NS. In addition, there is evidence that suggests a link between metacognition and NS as limitations in complex metacognitive processes are associated with concurrent and future NS. These limitations predict NS in first episode psychosis and in more chronic samples. This suggests that NS reduction may partially depend on improved metacognitive capacity, and that a metacognitive intervention specifically targeting the cognitions listed in the cognitive model may be beneficial. We (Swanson et al. 2022) therefore adapted a metacognitive training programme (MCT) to NS to examine variable change over the course of the intervention and to carry out a preliminary investigation of putative mechanisms of change.

Methods: We adopted a mixed methods case series design (N=15) where detailed quantitative data on changes over time were combined with exit interviews. The triangulation of quantitative and qualitative results also facilitated a thorough exploration of the feasibility of the intervention. The study used a combination of interviews (Brief Negative Symptom Scale; Positive and Negative Syndrome Scale; Calgary Depression Scale for Schizophrenia; Metacognition Assessment Scale; the Global Assessment of Functioning) and self-rated questionnaires (Personal Belief about Illness Questionnaire; Reflective Function Questionnaire). Non-parametric tests were used to evaluate changes at pre, post and follow-up due to the limited sample size and the repeated-measure nature of the data whilst multilevel modelling (MLM) was used to assess change over time and across cases and thematic analysis to analyse the qualitative data.

Results: Improvements on NS were observed following the intervention (with large effect sizes post intervention/follow-up) as well as on reflective functioning and stigma with similar patterns seen in the qualitative results. The intervention showed good feasibility as demonstrated by the attendance rate and the positive feedback from participants and the multidisciplinary team. MLM showed that depression, internalized stigma and reflective functioning best explained the variance in NS. In a follow-up analysis (Swanson et al. 2023), we found that there were two specific NS underlying the improvement: asociality and blunted affect. The overall results suggest that NS is related to intrapersonal functioning in terms of cognitive and emotional experience and that NS may develop in part as a consequence of diminished capacity for self-other mental state processing.

Discussion: The study shows that MCT could be adapted to target NS, thereby holding the promise of a brief and structured intervention to reduce NS. In addition, the analysis allowed us to identify potential mechanisms and how these could interact to influence NS expression, facilitating the future refinement of the intervention to target specific psychological processes that may underpin NS. The refined intervention will be systematically assessed in future research with a larger sample, utilizing a more robust randomized controlled design by including a control group, independent assessors as well as brain scans (see poster by Rask et al 2024).

F77. COMPARING COGNITIVE REMEDIATION APPROACHES IN SCHIZOPHRENIA: PRELIMINARY RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL

Matthew Kurtz*¹, Bryan Gu¹, Maeve Hoffman¹, Grace Melville¹, Alexia Pollock¹, Jennifer Rose¹

¹*Wesleyan University*

Background: Cognitive remediation (CR) is a type of behavioral intervention that addresses cognitive deficits in schizophrenia by restoring lost cognitive skills or providing strategies for bypassing deficits through task practice. Meta-analyses (Vita et al., 2021; Lejeune et al., 2021) have revealed that cognitive remediation is a validated approach to improving cognitive function in schizophrenia, however a lack of precision regarding the active elements of the intervention have prevented its recommendation as a standard treatment for the illness (Dixon et al., 2010). The present study sought to identify cognitive training mechanisms that are most effective at improving cognitive function in schizophrenia by comparing two different systematic programs of CR with different foci: drill-and-practice exercises vs. compensatory strategies. Both programs have strong preliminary empirical support.

Methods: In this ongoing, single-blind, randomized, controlled and pragmatic clinical trial, participants were randomly assigned to one of three groups according to a 2 (drill-and-practice computerized CR): 2 (compensatory cognitive skills group) :1 (computer games control) randomization strategy. Participants were assessed with a comprehensive battery consisting of well-validated measures of cognition, social cognition, self-efficacy, and functional outcomes before, during, and after treatment. Assessments were conducted by an administrator blind to group assignment. Treatment consisted of 12 weeks of compensatory cognitive training groups (Twamley et al., 2012), 20-40 hours of computerized drill-and-practice cognitive exercises (Kurtz et al., 2007; 2015), or 20-40 hours of computer games depending upon group assignment.

Results: To date 24 participants with schizophrenia-spectrum-illness meeting all inclusion/exclusion criteria have been enrolled in the study. Analysis of data collected to date in the 8 participants who have completed treatment, revealed a trend towards improvement in working memory as measured by the Digit Span Backwards test, when data from both the drill-and-practice and strategy-based forms of CR were combined. Preliminary results from the Digit Span Backward Test revealed a pre-treatment mean raw score of 6.00 vs. a post-treatment mean raw score of 7.33 in the two CR-treated groups (Hedge's $g=.48$). Data from approximately 15 participants on cognitive, social cognitive, attitudinal and functioning measures before and after treatment will be available for presentation in April.

Discussion: These preliminary findings suggest that both forms of CR, drill-and-practice and compensatory training, improve working memory skills at a trend level relative to scores at baseline. As our sample size increases we will evaluate the relative efficacy of these two empirically-supported cognitive interventions across a broader array of outcome measures and as compared to a computerized games control condition.

F78. A SYSTEMATIC REVIEW AND META-ANALYSIS OF TRANSCRANIAL MAGNETIC STIMULATION IN TREATING POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: PRELIMINARY RESULTS

Konstantinos Pallis^{*1}, Anahita Fazel Dehkordi¹, Charles Laidi², Philippe Huguelet¹, Stefan Kaiser¹, Indrit Bègue¹

¹University Hospitals of Geneva, ²INSERM U955, Institut Mondor de la Recherche Biomédicale (IRMB), Univ. Paris Est Créteil, Equipe 15 Neuropsychiatrie Translationnelle La Fondation Fondamental, Créteil, France NeuroSpin, Neuroimaging Platform, CEA, UNIACT Lab, PsyBrain Team,

Background: Transcranial magnetic stimulation (TMS) has emerged as a promising therapeutic approach for addressing symptoms in individuals with schizophrenia. Preliminary results indicate encouraging outcomes, but the evidence suggests nuanced efficacy across different symptom categories. This systematic review and meta-analysis explore the effectiveness of TMS in alleviating positive and negative symptoms associated with schizophrenia. Our study aims to comprehensively understand the patterns of TMS effectiveness, considering the distinct challenges posed by each symptom domain. We sought to identify factors contributing to variations in outcomes and contribute to a better understanding of TMS as a potential intervention for schizophrenia.

Methods: We systematically searched Pubmed, EMBASE, Web of Science, and PsycINFO for double-blind, randomized sham-controlled trials (RCTs) of TMS in patients with schizophrenia. We specifically included trials where the symptom of interest was a primary outcome. To quantify the impact of TMS relative to sham, the standardized mean difference (SMD, using Cohen's d) along with 95% confidence intervals (95%CI) were calculated. An inverse variance random effects model was utilized to aggregate data across the selected studies. Additionally, subgroup analyses were carried out to assess the effects of different stimulation locations and protocols.

Results: We performed a meta-analysis on 3'111 participants across the spectrum of schizophrenia symptoms. Regarding NS (N = 1654, 39 studies) analysis revealed an overall positive effect size (SMD = 2.02, confidence intervals [1.32; 2.7191], p LESS THAN 0.0001), indicating a substantial impact of TMS vs. sham, regardless of the stimulation protocol. However, the high heterogeneity ($I^2 = 92.9\%$) suggests notable variability in effect sizes across studies. Regarding positive symptoms (N = 859, 21 studies) we found a positive but statistically not significant trend in the overall effect size (SMD = 0.2735, confidence intervals [-0.06, 0.61] with high heterogeneity among the studies ($I^2 = 97.5\%$)).

Discussion: Our study highlights the potential efficacy of TMS in mitigating negative symptoms of schizophrenia, evident from the significant overall effect size observed. The next step involves detailed subgroup analysis to understand how different stimulation protocols and other factors contribute to this effect. The absence of statistical significance in the improvement of positive symptoms, coupled with substantial heterogeneity across studies, emphasizes the need for continued research in this domain. These findings collectively aim to inform future research and shape intervention strategies that are more effectively customized to meet the varied requirements of individuals with schizophrenia.

F79. A RANDOMIZED CONTROLLED CLINICAL STUDY OF HIGH-DEFINITION TRANSCRANIAL DIRECT CURRENT STIMULATION (HD-TDCS) TO IMPROVE COGNITIVE FUNCTION IN PATIENTS WITH SCHIZOPHRENIA

Xiangyang Zhang*¹

¹*Institute of Psychology, Chinese Academy of Sciences*

Background: Cognitive impairments serve as a critical component among schizophrenic symptoms and effective pharmacologic treatments for this dysfunction have lacked consideration. Transcranial direct current stimulation (tDCS) appears to be a potential clinical add-on treatment to improve clinical symptoms and cognitive functions in schizophrenic patients. The present study aimed to investigate the clinical efficacy of high-definition tDCSv(HD-tDCS) in improving the cognitive function in patients with schizophrenia.

Methods: We recruited 46 schizophrenic patients and allocated them randomly to the HD-tDCS real/sham stimulation group. Patients were treated with 20 sessions (once a day, five times a week) of 1.5 mA stimulation of the left dorsolateral prefrontal cortex (DLPFC) using the HD-tDCS technique. Cognitive functioning was measured using the Repetitive Battery of Neuropsychological Status (RBANS) with clinical symptoms measured by the Positive and Negative Symptom Scale (PANSS).

Results: Compared to the sham stimulation group, the real stimulation group demonstrated a significantly greater improvement on clinical symptoms and cognitive function. In real stimulation groups, patients receiving twenty sessions showed better improvement in cognitive function than those receiving ten sessions, indicating that the efficacy of twenty sessions was significantly better than that of ten sessions.

Discussion: Our results showed that HD-tDCS had significant efficacy in the treatment of cognitive impairment in schizophrenia patients, in which such phenomenon was better in long sessions than in short sessions. Our study presented a great practical significance to provide more treatment options for the clinical intervention of schizophrenia, particularly emphasizing concerns on patients' cognitive function.

F80. TREATMENT WITH EVENAMIDE FOR 1 YEAR IN TRS PATIENTS NOT BENEFITTING TO CURRENT ANTIPSYCHOTICS IS ASSOCIATED WITH SUSTAINED, CLINICALLY IMPORTANT BENEFIT: RESULTS FROM A PROSPECTIVE, PILOT, 1 YEAR, RANDOMIZED, OPEN-LABEL TRIAL

Ravi Anand*¹, Alessio Turolla², Giovanni Chinellato³, Francesca Sansi², Rodolfo Giuliani², Richard Hartman⁴

¹*Anand Pharma Consulting*, ²*Newron Pharmaceuticals SpA*, ³*Newron Pharmaceuticals*, ⁴*NeurWrite LLC*

Background: Treatment resistant schizophrenia (TRS) leads to reduced life-expectancy, frequent hospitalizations, indigent status, and increasing costs for families and society (Kennedy et al., 2014). Many strategies have been pursued for its management like the off-label prescription of more than one antipsychotic (AP) despite the absence of benefit (Galling et al., 2017), and the usage of clozapine (Kane et al., 1988) that, although exceptionally efficacious, is vastly underutilized due to its safety concerns (agranulocytosis, myocarditis, sedation). Evenamide, a selective inhibitor of voltage-gated sodium channels, devoid of biological activity at GREATER THAN 130 CNS targets, normalizes glutamate release without affecting its basal levels. Preclinical experiments have indicated that it is likely to benefit patients responding inadequately or resistant to AP. Evenamide was evaluated as monotherapy or add-on to APs in animal models in which pre-pulse inhibition was impaired using amphetamine, scopolamine, phencyclidine, MK-801, ketamine, or sleep deprivation. It

demonstrated efficacy across a broad spectrum of experiments, including models of mania, depression, impulse control loss, and obsessive-compulsive behavior (Anand et al., 2018).

Methods: This 1 year, randomized, open-label, rater-blinded international study (study 014/015) aims to assess safety, tolerability, and efficacy of evenamide added on to AP orally at three fixed doses (7.5, 15 and 30 mg bid) in patients with documented TRS. After an initial treatment period of 6 weeks, patients had the opportunity to continue for up to 1-year.

Selection criteria for the study require patients to meet standardized criteria for TRS: non-response to two APs, baseline PANSS total score 70-90 with predominant positive symptoms, at least two moderate core symptoms and functional deficits. Efficacy data (PANSS, CGI-S/C, and LOF) were collected regularly every 10/12 weeks and were analyzed using paired t-test for changes from baseline to endpoint and descriptively for each dose group and for the responder analyses. Safety was assessed at all visits throughout the 1-year period.

Results: Scheduled review of safety data by an ISMB did not detect any pattern of motor or CNS symptoms, weight gain, sexual dysfunction or laboratory/EKG abnormalities, indicating the good tolerability of evenamide at all doses in addition to low incidence of ADOs (1.9%). Furthermore, the attrition rate was extremely low (~25% at 1-year) in contrast to published TRS studies (Homman et al., 2021). After 1 year of treatment, the overall improvement in symptoms from baseline was -20% (PANSS total), with a clinically important benefit in the positive subscale (-26%). ~45% of the patients were considered at least “much improved” on the CGI-C, and the severity of disease improved by more than 1 point on average, with 30% of the patients improving by 2 categories or more on the CGI-S. Furthermore, the benefit seen in all efficacy scales (including functioning), is sustained and long-lasting, as seen in the first cohort (Aanand et al., 2023), with the largest improvement in the 15 and 30 mg bid dose groups. Validated and final, 1-year, efficacy and safety results, available by the time of the Congress, will be presented demonstrating remarkable efficacy of evenamide at 1-year.

Discussion: This is the first international 1-year trial of evenamide add-on to any AP (except clozapine) in patients with TRS. Encouraging results of this study have expedited the conduct of a potentially pivotal, phase 3, randomized, double-blind, placebo-controlled, 1-year, international study to demonstrate the profound, multi-domain, long-lasting efficacy of the combination of evenamide and AP. These data demonstrate the unique benefits of glutamate modulation when added to APs.

F81. INVESTIGATING ASSOCIATIONS BETWEEN ANTIPSYCHOTIC DOSAGE, MOVEMENT DISORDERS, BODY MASS INDEX, AND WAIST CIRCUMFERENCE IN PATIENTS AFTER A FIRST EPISODE OF PSYCHOSIS

Yinzhaio Liu^{*1}, Dr. P. Roberto Bakker², Dr. Sanne Kooops¹, Prof. Dr. Iris Sommer¹

¹University of Groningen, University Medical Center Groningen, ²Arkin, Institute for Mental Health, Amsterdam,; Maastricht University Medical Center, School for Mental Health and Neuroscience

Background: Side effects of antipsychotic medication (APS) include movement disorders and metabolic syndrome. It is unclear how antipsychotic dose and dose reduction/discontinuation are related to these side effects. The present study aims to investigate the associations between antipsychotics dose and movement disorders, body mass index (BMI), and waist circumference, at 6 months and 12 months follow-up.

Methods: Patients in remission after a first-episode psychosis (FEP) were selected from the single-blind randomized controlled trial: Handling Antipsychotic Medication: Long-term

Evaluation of Targeted Treatment (HAMLETT). 267 were followed for 6 months, from whom 225 patients were followed for 12 months. Of them, approximately 30% of patients used aripiprazole, 40% of patients used olanzapine, and the last 30% of patients used various APS at the baseline. Over the course of 6 and 12 months, 63.67% and 52% of patients gradually reduced/discontinued their APS doses respectively, to a variable extend. For some, after an initial dose reduction, the previous dose needed to be reinstalled upon worsening of psychotic symptoms. Movement disorders including parkinsonism, dyskinesia, dystonia and akathisia were assessed with St. Hans Rating Scale (SHRS), and Barnes Akathisia Rating Scale. Olanzapine equivalent doses (OLZE) were used for standardizing doses of antipsychotics. Data were analyzed using a mixed-effects model, adjusting for sex, age, psychotic symptoms, treatment duration, adjunctive antipsychotic, SSRI/SNRI, lithium, anticonvulsants, benzodiazepine, glucose-lowering medication, antihypertensive medication, drinking coffee, alcohol, and smoking status.

Results: For the APS with the movement disorders risk, the mixed effects model yielded significant coefficients linking parkinsonism to OLZE over both the 6- and 12-month follow-up ($B=0.158$, $p < 0.001$ and $B=0.120$, $p=0.013$, respectively), meaning that 1mg of OLZE increment was associated with increases of 0.158 and 0.120 points on the SHRS total parkinsonism scores over 6 and 12 months. There was also a significant association between decreased parkinsonism and OLZE reduction/discontinuation across 12 months ($B=-2.720$, $p=0.007$). No significant associations between other domains of movement disorders and OLZE were found. Besides, 1mg of aripiprazole dose was significantly related to a 0.121 increase in parkinsonism ($B = 0.121$, $p=0.033$) across 6 months, but not for 12 months. No other significant relationship was found between aripiprazole doses or dose reduction/discontinuation and other domains of movement disorders. For the change in metabolic measures across 6 and 12 months, the mixed effects model did not show significant associations between OLZE of APS with the risk of weight gain and either BMI or waist circumference. Olanzapine doses were not associated with BMI and waist circumference change across 6 and 12 months either. However, olanzapine dose reduction/discontinuation was significantly associated with BMI decreasing over 12 months ($B = -3.348$, $p=0.0493$).

Discussion: For APS with the movement disorder risk, parkinsonism was associated with OLZE at 6- and 12-month follow-up, and with OLZE reduction/discontinuation at 12 months. Olanzapine dose reduction/discontinuation was associated with BMI decreases after 12 months. No significant association with the other movement disorders or metabolic measures and OLZE nor OLZE reduction/discontinuation was observed. This shows that a dose reduction in maintenance treatment is associated with reduced movement disorders at a scale, and a reduced risk for weight gain in olanzapine of 6 to 12 months follow-up.

F82. COGNITIVE BEHAVIORAL GROUP TREATMENT FOR LOW SELF-ESTEEM IN PSYCHOSIS: A PROOF OF CONCEPT STUDY

Elise van der Stouwe^{*1}, Chris Geraets¹, Mirjam Rutgers¹, Wim Veling¹

¹*University Medical Center Groningen*

Background: Patients with a psychotic disorder often suffer from low self-esteem, which has been related to higher suicidal risk, poor quality of life and, the maintenance of psychotic and depression symptoms. However, intervention studies are scarce and reported interventions

concern individual therapies provided by highly educated psychologists. Both the individual setting and the required qualifications of the therapist may contribute to a low level of availability of an intervention. Therefore, we aimed to investigate the efficacy of an easily accessible psychological group treatment targeting self-esteem in patients with a psychotic disorder.

Methods: Thirty patients with a psychotic disorder were included in this pilot study. All participants received nine weekly group sessions of 90 minutes. The therapy was offered in groups of six to eight patients and was provided by a psychiatry nurse and a graduate psychologist. To assess self-esteem the Rosenberg Self-esteem Scale and the Self-Esteem Rating Scale were used, to measure depression symptoms the Beck Depression Inventory-II was administered. Questionnaires were completed at baseline and post-treatment.

Results: Twenty-seven patients (90%) completed treatment. At post-treatment, self-esteem was significantly increased, and depression symptoms were significantly decreased compared to baseline.

Discussion: This pilot study demonstrates the feasibility and treatment potential of a self-esteem group treatment provided by a psychiatry nurse and graduate psychologist in a patient population that receives little psychological treatment. Results suggest that this easily accessible intervention may be effective in improving self-esteem and reducing depression symptoms.

F83. COMPUTATIONALLY DISSOCIABLE ABNORMALITIES IN SEMANTIC REPRESENTATION AND SEMANTIC RETRIEVAL IN SCHIZOPHRENIA AND FORMAL THOUGHT DISORDER

Isaac Fradkin^{*1}, Rani Moran², Beth Jefferies³, Rick Adams⁴, Raymond Dolan⁴

¹Max Planck UCL Centre for Computational Psychiatry and Ageing Research, ²Queen Mary University of London, ³University of York, ⁴University College London

Background: Abnormalities in language and semantic cognition are suggested as biomarkers for schizophrenia. Such abnormalities are particularly evident in patients with Formal Thought Disorder (FTD) - diagnosed based on atypicality in discourse. However, the precise components of semantic cognition that go awry in schizophrenia, including those distinguishing patients who have FTD from patients without FTD, have yet to be specified. We combine computational modeling with neural decoding of semantic representation to disaggregate core abnormalities in semantic structure from abnormal retrieval and executive dysfunction, and detail how they interact in schizophrenia and FTD.

Methods: Thirty-one patients with schizophrenia and thirty-one matched controls completed a word association task during MEG. Patients varied in the degree of FTD symptoms, assessed using the thought and language disorder scale (TALD). We characterized abnormalities in semantic structure by modeling the subjective strength of participants' associations and by mapping semantically meaningful spaces to participants' neural representations of cues (using representation similarity analysis). These measures were then used to characterize participants' personalized associative structures, allowing us to investigate the retrieval and control processes operating on these structures by modeling free association as a controlled accumulation of internal evidence.

Results: As expected, patients produced more atypical associations (Odds ratio [OR] Credible Interval; CI = [1.11, 1.36]), and association atypicality was positively correlated with FTD scores among patients (OR = [1.001, 1.71]). A stark dissociation emerged with respect to participants' subjective ratings of the strength of their associations, which were decreased in

patients (CI=[-0.14,-0.01]) but showed a non-significant, positive correlation with FTD (CI = [-0.02, 0.09]). A computational analysis of the personalized associative structures underlying these behavioral findings suggested that patients' semantic structures are characterized by weakened connectivity (CI = [-0.03, -0.006]). However, this weakening is not found in patients with notable FTD, whose semantic structures are, instead, characterized by more atypical connections (CI = [0.04, 0.26]). Neural representation similarity analysis provided further support for these abnormalities in semantic structures (Cohen's d = [-1.49, -0.40]). Finally, consistent with the idea that atypical associations in FTD can be exclusively explained by abnormal semantic structure, only diagnosis (Adjusted R^2 = 0.24) but not FTD symptoms (Adjusted R^2 = 0.02) predicted abnormal retrieval and control processes, as indicated by a computational analysis of retrieval dynamics.

Discussion: Mechanisms of FTD can be partially dissociated from those explaining general semantic cognition abnormalities in schizophrenia. Whereas patients exhibit more noisy semantic structure and retrieval, FTD was exclusively explained by abnormalities in semantic structure. The formation of an abnormal semantic structure in FTD may reflect a compensatory response to a fundamental loss of precision in structure and retrieval.

F84. RECONSIDERING EVIDENCE FOR PSYCHEDELIC-INDUCED PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF HUMAN STUDIES

Michel Sabe^{*1}, Natacha Perez¹, Adi Sulstratova¹, Akram Elrhaoussi², Alban Glangetas¹, Marco De Pieri¹, Luc Mallet³, Logos Curtis¹, Helene Richard-Lepouriel⁴, Katrin Preller⁵, Louise Penzenstadler⁶, Federico Seragnoli⁶, Gabriel Thorens⁶, Daniele Zullino⁶, Kerem Boge⁷, Stefan Leucht⁸, Marco Solmi⁹, Stefan Kaiser¹, Matthias Kirschner¹

¹University Hospitals of Geneva, ²University of Geneva, ³Univ Paris-Est Créteil, DMU IMPACT, Hôpitaux Universitaires Henri Mondor - Albert Chenevier, Assistance Publique-Hôpitaux de Paris, ⁴Mood Disorder Unit, Psychiatric Specialties Service, Geneva University Hospital, ⁵Neuroscience, and Psychology Yale University, Psychiatric University Hospital Zurich, ⁶University Hospitals of Geneva, ⁷Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin; and Freie Universität Berlin; and Humboldt-Universität zu Berlin; and Berlin Institute of Health, Germany, ⁸School of Medicine, Technical University of Munich, ⁹University of Ottawa,

Background: Patients with schizophrenia are currently contraindicated for psychedelic-assisted therapy due to concerns about the potential for psychedelic-induced acute or persistent psychotic symptoms. However, meta-analytic evidence of the precise risk for psychedelic-induced de novo and exacerbation of psychotic symptoms in pre-existing psychotic disorders remains scarce.

Methods: We conducted a systematic review and meta-analysis to examine the prevalence of psychedelic-induced psychosis in the general population and the exacerbation of psychotic symptoms in schizophrenia following our protocol (CRD42023399591). Classical psychedelics were considered: LSD, psilocybin, peyote, DMT, salvia, MDMA, and ecstasy. Embase, PubMed, PsyARTICLES, and PsynFO, and different trial registries were searched from inception until July 2023. Results were limited to human studies. The prevalence of psychedelic-induced psychosis and its variance was computed using a random effects meta-analysis model. Risk of Bias in Non-randomized Studies-of Interventions, Cochrane risk-of-bias, and AMSTAR-2 tools were used to assess the quality of studies.

Results: We retained 113 publications published from 1947 to date: 14 systematic reviews, 21 reviews, 25 randomized-controlled trials (RCT), 8 case-control studies, 26 non-randomized controlled trials (NRCT), and 18 cohort types of studies. Most articles studied LSD. Nine studies were included in our meta-analysis. The prevalence of psychedelics-induced psychosis found in population studies was 0.002% (95%; CI 0- 0.006) in absence of heterogeneity ($I^2=0\%$) ($N=123800$; $n=2$); 0.2.% (95%; CI 0.1- 0.3)($I^2=0\%$) in NRCT including healthy individuals ($N=6535$; $n=6$); 0.6% (95% CI 0.2-1.8)($I^2=0\%$) in RCT including healthy population and patients with depression ($N=563$; $n=3$); 0.4% (95%; CI 0.1-2.8)($I^2=0\%$) for healthy population and patients with depression in RCTs ($N=563$; $n=3$); 3.8%(95%; CI 1.6-8.9)($I^2=0\%$) for NRCT including patients with schizophrenia ($N=133$; $n=2$); and 13.1% (95%; CI 9.4-17.9) ($I^2=24\%$) for conversion from psychedelics-induced psychosis to schizophrenia ($N= 353$; $n=3$). Sensitivity analyses confirmed the main findings.

Discussion: Prevalence for psychedelic-induced psychosis is low in all populations and slightly raised when including patients with schizophrenia. Dose-finding trials for patients with schizophrenia who benefit from maintenance treatment and exhibit treatment-resistant or residual depressive and negative symptoms should be considered.

F85. LINKING CEREBELLUM AND CEREBELLAR PROCESSES TO PSYCHOSIS PHENOTYPES

Alexandra Moussa-Tooks^{*1}, Jonathan Tsay², Jinyuan Liu³, Kristan Armstrong³, Baxter Rogers⁴, Richard Ivry², Neil Woodward³, Stephan Heckers³

¹Indiana University Bloomington, ²University of California Berkeley, ³Vanderbilt University Medical Center, ⁴Vanderbilt University Institute of Imaging Sciences

Background: Motor disturbance, including psychomotor slowing, has been identified as a key feature of psychotic disorders, with motor signs observed in upwards of 66% of unmedicated, first-episode patients, and present even before formal onset of the disorder. While recent work has linked cerebellum to sensorimotor processing deficits, the brain-behavior-symptom relationships have been difficult to establish. This may be due in part to a muddling of distinct processes in our current tasks, inhibiting our ability to capture disturbances in the various subprocesses and their relationships to brain and symptoms. A more complete understanding becomes exceedingly important as the field continues to develop and refine novel mechanistic approaches for treatment, including TMS-based interventions.

Methods: To address these gaps, we first (Study One) present findings from a sample of 339 psychosis patients (242 schizophrenia-spectrum, 97 bipolar with psychotic features) and 217 controls where we evaluated the relationship between cerebellar grey matter volume in the Yeo sensorimotor network and processing speed (assessed via the Screen for Cognitive Impairment in Psychiatry [SCIP]). We tested the role of these variables in predicting psychomotor disturbance (mannerisms and posturing, retardation, excitement of the Positive and Negative Syndrome Scale [PANSS]) using a mediation analysis for an a priori model in the psychosis group: predictor=cerebellar sensorimotor volume; mediator=processing speed; outcome=psychomotor disturbance. Since tasks of “processing speed” incorporate various psychological processes, we secondarily (Study Two) present a new line of work leveraging a computerized motor learning task that has not yet been utilized in the psychiatry literature. Participants ($N=10$) completed a brief computerized motor learning task that allows us to capture directly measured and computationally modeled latent constructs (motor speed, planning time, learning rate, motor system noise). During the task, participants make reaching movements to a target with and without an angular visual perturbation to their reach. Change,

or lack thereof, across metrics are characterized and relationships with cerebellar subregions and psychosis symptom features were assessed. Cerebellar volumes were calculated using optimized processing through the Spatially Unbiased Infratentorial (SUIT) toolbox. Statistical analyses were performed in R. As appropriate, models included total intracranial volume, age, sex, chlorpromazine equivalents as covariates.

Results: In study one, as expected, sensorimotor cerebellar volume was positively associated with processing speed in the whole sample ($t=3.428$, p LESS THAN 0.001, $d=0.30$). Effects were present in both the control sample ($t=2.345$, $p=0.020$, $d=0.32$) and the psychosis sample ($t=2.188$, $p=0.029$, $d=0.24$). Within the psychosis group, no significant direct effect (cerebellar volume $\square$ psychomotor disturbance) was observed in this mediation model ($\beta=-0.035$, $p=0.59$, $d=0.06$). Rather, the indirect path (average combined effect: $\beta=-0.043$, $p=0.014$) showed a significant partial mediation by processing speed, with a small effect of cerebellum on processing speed ($\beta=0.172$, $p=0.029$, $d=0.24$) and medium effect of processing speed on psychomotor disturbance ($\beta=-0.254$, p LESS THAN 0.001, $d=0.60$). In study two, we observed no differences between groups in any metrics of motor speed (initiation or execution of the reach). Psychosis participants did exhibit higher modeled motor noise ($d=0.6$). Moreover, implicit adaptation was positively correlated with cerebellar volume in the psychosis group ($d=0.54$).

Discussion: The current findings suggest a critical role of cerebellar circuitry in sensorimotor aberration in psychosis (processing speed) and the presentation of related psychomotor phenotypes within psychosis. Our follow-up study begins to provide evidence that the slowing observed may not be due to mechanical limitations of the motor system, but noise present in the motor system and an inability to update internal motor models, driven by cerebellum. We plan to continue this work, increasing our sample and tracking symptoms and task performance longitudinally so that we may more effectively linking these brain-behavior relationships to symptoms in psychosis. Future research may also determine the magnitude of these relationships within subtypes of psychosis (e.g., disorganized behavior or catatonia) as well as the specificity to motor, versus non-motor (e.g., cognitive, social), cerebellar functions and cerebellar connectivity with cerebrum.

F86. DEVELOPMENT OF A POPULATION PHARMACOKINETIC MODEL TO DESCRIBE THE PHARMACOKINETICS OF ARIPIRAZOLE 2-MONTH READY-TO-USE, A NOVEL LONG-ACTING INJECTABLE FORMULATION OF ARIPIRAZOLE FOR ADMINISTRATION ONCE EVERY 2 MONTHS

Yanlin Wang¹, Matthew Harlin*¹, Frank Larsen², Xiaofeng Wang¹, Wansu Park³, Benjamin Rich⁴, Jogarao V. Gobburu⁵, Arash Raoufinia¹

¹Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC), ²H. Lundbeck A/S, ³Alnylam Pharmaceuticals, ⁴InnoMx Inc., ⁵University of Maryland

Background: Compared with oral antipsychotics, long-acting injectable (LAI) antipsychotic formulations are associated with greater treatment adherence and a reduced risk of hospitalization or relapse. Aripiprazole 2-month ready-to-use (Ari 2MRTU) 960 mg is a novel LAI formulation of aripiprazole monohydrate for gluteal intramuscular administration once every 2 months. Ari 2MRTU 960 will offer an extended dosing interval versus aripiprazole once-monthly 400 mg (AOM 400). As part of the development of Ari 2MRTU 960, population pharmacokinetic (popPK) modelling was undertaken to characterize the pharmacokinetics (PK) of this formulation. The final popPK model is described here.

Methods: A previously developed and validated popPK model for characterizing aripiprazole plasma concentrations following administration of oral or AOM 400 (gluteal or deltoid intramuscular injection) formulations was expanded to include the novel Ari 2MRTU formulation. Overall, 8,899 aripiprazole PK samples from 1,191 adults (schizophrenia, schizoaffective disorder, or bipolar I disorder [BP-I], n=1,139; healthy individuals, n=52) from ten Phase 1 and 3 trials were included in the final combined analysis dataset; of these, 240 patients with schizophrenia or BP-I received Ari 2MRTU across three trials. All fixed-effects parameters from the prior model remained fixed throughout the model development, as did random-effects parameters for the first-order absorption rate constant of the oral and AOM routes, apart from CL/F and Vc/F, which were re-estimated. Covariate effects from the original model were retained, with additional potential effects related to the absorption and relative bioavailability of the Ari 2MRTU formulation formally tested using a modified stepwise approach. Data were analyzed using non-linear mixed effects modeling software (NONMEM v7.4.2).

Results: A 3-compartment model with linear elimination and different absorption models for each formulation best described the data. Absorption of the Ari 2MRTU formulation was modeled by a parallel zero-order and lagged first-order process that accounted for an identified double peak in plasma concentrations of aripiprazole post-administration of Ari 2MRTU. All disposition parameters were shared between the formulations except Vc/F (oral and AOM formulations, 93.4 L; Ari 2MRTU formulation, 2035 L); the different Vc/F value for the Ari 2MRTU formulation was attributed to the terminal half-life being absorption driven. Sex was a significant covariate on the absorption of the Ari 2MRTU formulation (90.7% higher absorption rate constant and 56.0% lower fraction of first-order absorption in males versus females); however, simulated C_{avg,ss} values were identical in both sexes, indicating no clinically relevant effect. As expected, simulated aripiprazole concentrations were higher in poor versus extensive metabolizers of CYP2D6; the effect of CYP2D6 metabolizer status was thus retained as a covariate from the prior model.

Discussion: The final popPK model was considered fit for purpose, adequately describing aripiprazole PK following administration of Ari 2MRTU 960. The model also established estimates for key popPK parameters and identified sources of variability in drug exposure. The model will be used to perform simulations to support dosing of Ari 2MRTU 960 across multiple realistic clinical scenarios.

F87. IDENTIFYING SCHIZOPHRENIA SPECTRUM DISORDERS FROM HEALTHY CONTROLS USING ACOUSTIC FEATURES

Elif Kizilay¹, Berat Arslan¹, Emre Bora^{*1}

¹*Dokuz Eylül University, School of Medicine*

Background: In the diagnosis and assessment of schizophrenia spectrum disorders (SSD), speech plays a crucial role as it reflects formal thought disorder. Acoustic characteristics of speech, such as rate, pauses, articulation, duration of speech, pitch, and tone, can serve as important indicators of formal thought disorder as well as negative symptoms present in patients with SSD. In this study, we aimed to analyze acoustic features from speech recordings obtained from patients with SSD and healthy controls (HC) using the extended Geneva Acoustic Minimalistic Parameter Set (eGeMAPS) and to differentiate patients from HC using these features with a machine learning approach.

Methods: Speech samples were obtained from 41 Turkish-speaking patients with SSD and 36 HC during The Discourse in Psychosis Speech Bank Protocol, a semi-structured interview on

different topics, including free conversational speech, personal narrative, health narrative, picture descriptions, storyboard, dream reports, and reading-recall task sections. Speech pre-processing was carried out using PRAAT, resulting in only speech segments of participants. Acoustic features were acquired through the use of OpenSMILE, utilizing the eGeMAPS parameter set, yielding a grand sum of 88 parameters. A random forest classifier with ten-fold cross-validation method was performed using 88 acoustic parameters to assess the role of these acoustic features in identifying SSD from HC. The receiver operator curve (ROC) and area under the curve (AUC) are obtained after the random forest classification.

Results: The random forest classifier using 10-fold cross-validation with 300 n-estimators achieved a mean accuracy of 73.9% with an AUC of 0.77 in classifying patients with SSD and HC. Seventeen significant acoustic parameters were identified. Two of these were temporal and are described as increased variation of voiced segment length per second and increased average unvoiced segment length ($p = 0.035$ and 0.036 , respectively), suggesting fragmented speech segments and extended pauses in patients with SSD. Patients diagnosed with SSD exhibited a higher average spectral slope in the voiced section ($p=0.029$), and a reduced average spectral slope in the unvoiced section ($p=0.045$). Additionally, individuals diagnosed with SSD had higher mean F1 bandwidth and frequency ($p= 0.026$ and $p= 0.006$, respectively). Furthermore, within the SSD group, there was a decrease in the mean relative energy of the first, second and third formants' center frequency to the energy of the spectral peak at pitch (F0) ($p= 0.003$, $p= 0.016$ and 0.016 , respectively) while the variations of these features increased ($p=0.002$, $p= 0.015$ and $p= 0.016$, respectively), suggesting differences in intonation attributes and voice quality compared to HC. Patients with SSD exhibited lower mean jitter ($p=0.018$) and reduced mean shimmer ($p=0.029$), indicating diminished voice quality. Additionally, the mean Hammarberg index of the unvoiced segment and variation in loudness were found to be higher in SSD ($p= 0.044$ and $p= 0.038$, respectively). Moreover, the decreased loudness peaks per second feature was highly significant (p LESS THAN .001).

Discussion: In this study, we found the acoustic analysis of speech had an accuracy of 73.9% in identifying within a small sample of Turkish-speaking patients with SSD from HC. Furthermore, our analysis revealed a highly significant decrease in loudness peaks per second, suggesting that this aspect of speech may serve as a crucial indicator for distinguishing SSD from HC among Turkish individuals. Our analysis showed that acoustic features of speech can be a potential biomarker in SSD.

F88. INSIGHTS ON THE ROLE OF E/I BALANCE IN NETWORK DYNAMICS UNDERLYING REMISSION FROM PSYCHOTIC EPISODE: INTERPRETING PHENOMENOLOGICAL MODELS

Ludovica Mana^{*1}, Manel Vila-Vidal¹, Gustavo Deco¹

¹*Universitat Pompeu Fabra*

Background: In Mana et al. 2023, we investigated the functional-structural interplay underlying remission and relapse following a first psychotic episode, by means of a phenomenological whole-brain model applied to fMRI and DTI data of 128 healthy controls and 88 early psychosis patients. We investigate the interplay between global and local dynamics, shedding light on a potential compensatory mechanism involved in clinical remission. Intriguingly, in fact, we observe opposite alterations in functional connectivity (FC) between remitting and non-remitting patients compared to controls. We provide evidence suggesting that these alterations may arise due to the loss of heterogeneity in regional stability, a crucial property for filtering out irrelevant stimuli and preventing excessive network

synchronization while maintaining functional flexibility by relaxing structural constraints. Consequently, we propose that this could represent a compensatory response to the reduced structural conductivity observed in patients. However, the biological mechanisms underlying this phenomena cannot be understood by such a phenomenological model.

Methods: The current work therefore aims to deepen our understanding and interpretation of these findings employing a more biophysically constrained model based on Wilson-Cowan equations. Specifically, we explored the hypothesis that an excitatory/inhibitory (E/I) imbalance underlies this compensatory mechanism. Dysregulation of this balance is in fact considered to be crucially implicated in psychotic disorders, and glutamate and GABA levels have been found to vary in individuals at high genetic risk and in patients at different stages of psychosis (Gonzalez-Burgos and Lewis 2012; Liu et al. 2021). To test our hypothesis, we utilized a biophysically constrained model based on the Wilson-Cowan equations. Through a detailed characterization of model properties and a direct comparison with properties of the Stuart Landau model, we explored the impact of E/I modulation on network synchronization and stimulus processing.

Results: The findings of our model simulations revealed that alterations in E/I balance influenced both local and global network properties, mirroring the effects of changes in the bifurcation parameter as observed in previous analyses. E/I balance regulates the local behaviour of nodes, affecting their stability, their level of activation and the frequency and amplitude of oscillations. Moreover, we show that local E/I is influenced by global coupling of structural connectivity and that in turn local values of E/I modulate nodes' synchronization, thereby affecting functional global dynamics. In particular, lower values of E/I in critical nodes allow for the emergence of complex patterns of functional connectivity and modulate the response to incoming stimuli preventing excessive network synchronization. Disinhibition arising from increased local values of E/I in such nodes could therefore represent a possible mechanism to explain the functional over synchronization observed in patients remitting from a first psychotic episode. These results are consistent with recent literature suggesting that hyperactivity may be recruited as compensation for connectivity deficiencies in psychotic disorders.

Discussion: While future studies will be needed to provide definitive proof for these hypotheses, the current study serves as an initial exploration of the possible network dynamics underlying remission from psychotic episode and suggest a crucial role of E/I balance.

F89. COGNITIVE CONTROL IN EARLY PSYCHOSIS: COMPARING OBSERVED AND MODELED PERFORMANCE OF THE TRANSLATIONAL ORIENTATION PATTERN EXPECTANCY TASK (TOPX)

Jessica Arend*¹, Zoe Liu¹, Olivia Calvin¹, Kaylee Enevold¹, Sadrisha Pandit¹, Anita Kwashie², Caroline Demro¹, Angus MacDonald, III¹

¹University of Minnesota, ²Icahn School of Medicine at Mount Sinai,

Background: The translational orientation pattern expectancy (TOPX) task is an AX-expectancy task variant (also related to AX-CPT and DPX) designed to investigate proactive and reactive cognitive control in individuals with early psychosis and healthy controls. Participants must identify a predominant target sequence (known as AX) of gabor stimuli among more rare, non-target sequences (AY, BX, and BY). BX trials require greater proactive control, whereas AY trials require greater reactive control.

Methods: 121 participants (60 controls, 61 patients; M = 25.5 years old, 55% female, 71% white) completed TOPX as part of a larger ongoing neuroimaging study. We examined

accuracy and response time (RT) by trial type across groups. d' -context and d' -expectancy were calculated to assess use of proactive and reactive control, respectively. We hypothesized that patients would demonstrate lower d' -context (BX/proactive control sensitivity), as well as higher RTs, compared to controls.

Results: Significant effects of trial type were found for accuracy ($F(3,484) = 34.36$, $p < .001$) and response time ($F(3, 484) = 152.9$, $p < .001$). Group effects were present for accuracy ($F(4, 484) = 7.973$, $p = .005$), such that patients had lower accuracy on BX and AY trials compared to controls. Interaction effects were not observed. However, patients demonstrated lower d' -context than controls ($t(155.84) = -18.733$, $p < .001$) as well as lower d' -expectancy ($t(161.65) = -17.144$, $p < .001$). These results held constant at a one-month follow-up visit.

Discussion: Preliminary analyses suggest a partial replication of established cognitive control patterns, largely in support of our hypotheses. Data collection is ongoing as is data analysis, including hierarchical drift diffusion modeling (hDDM). hDDM is a singular analysis that integrates accuracy and reaction times to model within-subject variability. Previous literature shows that people with psychosis have slower drift rates (the rate at which evidence is accumulated to make a decision) and longer non-decision times (response delay) than controls. We will present these data, seeking to replicate previous findings in our early psychosis sample.

F90. A NORMATIVE MODELING APPROACH TO INVESTIGATE ALTERATIONS IN BRAIN ACTIVITY DURING WORKING MEMORY IN SCHIZOPHRENIA

Gabriele De Agazio^{*1}, Thomas Wolfers², Francesco Massari³, Roberta Passiatore¹, Giuseppe Stolfi¹, Giuseppe Blasi³, Leonardo Fazio¹, Teresa Papolizio⁴, Antonio Rampino³, Alessandro Bertolino³, Giulio Pergola⁵, Pierluigi Selvaggi¹

¹University of Bari "Aldo Moro", ²University of Tübingen, ³University of Bari "Aldo Moro", Bari, Italy; ³U.O.C. Psichiatria Universitaria, A.O.U. Consorziale Policlinico di Bari, ⁴IRCCS Casa Sollievo Della Sofferenza, ⁵University of Bari "Aldo Moro", Lieber Institute for Brain Development

Background: Working Memory (WM) impairments are a consolidated finding in Schizophrenia (SCZ) at the level of cognitive performance and related brain activity. Functional Magnetic Resonance Imaging (fMRI) studies found that the patients with SCZ show a shift of the physiological inverted-U-shape response of the Dorsolateral Prefrontal Cortex during WM tasks, associated with inefficient task performance. Case-control studies in psychiatry, however, tend to introduce an artificial symmetry between groups, often assuming variance homogeneity within groups. Instead, ample heterogeneity characterizes SCZ at the level of risk factors, neurobiology, phenomenology, and treatment response. Normative Modeling (NM) addresses heterogeneity by estimating features as functions of a set of covariates, returning "deviations", i.e., the difference between real and estimated feature values. Applications of NM on brain structural metrics have shown that deviations are frequent in patients with SCZ, but highly heterogeneous, occurring largely in non-overlapping regions. Here, we aimed to study WM inefficiency in SCZ via NM for the first time. We hypothesized that SCZ patients would show a pattern of extreme deviations in the WM network when compared to healthy controls (HC). While we did expect a degree of heterogeneity in the deviation distribution, we also hypothesized that SCZ patients would show deviations in brain activity to occur more frequently in the Cognitive Control Network (CCN).

Methods: A sample of 923 subjects (791 HC, 132 SCZ; 483 M, 440 F; aged 14 - 63 years, with a mean age of 28 ± 7.9 years) with fMRI data during the 2-Back task WM, no excessive head motion and task performance above 25% was used to estimate and test WM NM. For each subject, we estimated functional connectivity networks using the Neuromark Independent Component Analysis parcellation. Forty-nine networks were used as features for NM estimation, after removing cerebellar networks. Age, sex, scanner, performance at the 2-Back task and reaction times were used as covariates. NMs were estimated independently for each network using Bayesian Linear Regression and 10-fold cross-validation. We then applied the resulting coefficients to our clinical cohort to calculate the deviation of each subject in each component from the estimated NM, expressed as Z-scores (Zs). Positive Zs indicate increased activity, while negative Zs indicate decreased activity. We defined “extreme deviations” (XZ) as Zs GREATER THAN $|1.96|$. We used permutation-based t-tests to compare XZs and mean Zs between HC and SCZ.

Results: Patients with SCZ had globally more positive XZs than HCs (pFDR = 0.02). The highest rates of overlapping XZs in SCZ were observed in the middle cingulate cortex and in the middle frontal gyrus (MiFG), with an overlapping rate of 7.5% in both regions. Patients also showed significantly more positive XZs than HCs in the whole CCN (pFDR = 0.014). No significant difference between groups was found on negative XZs. We observed significantly increased mean positive deviations in CCN regions such as the inferior frontal gyrus (pFDR = 0.02) and the MiFG (pFDR = 0.04) in SCZ. No significant difference between groups was found on mean negative deviations.

Discussion: Our preliminary findings suggest that the NM framework can parse heterogeneity in SCZ at the functional level using a working memory task. Our results suggest an equal or greater degree of overlap of functional deviations from the norm as compared to NM studies using structural metrics. Further studies with larger sample sizes will help validate these insights and explore fMRI abnormalities in SCZ at the level of individual.

F91. NATURAL LANGUAGE PROCESSING TO DETECT MENTAL STATE EFFECTS OF KETAMINE IN DEPRESSION

Farida Zaher^{*1}, Nicolas Garel², Stephane Richard--Devantoy², Alban Voppel³, Lena Palaniyappan²

¹McGill University, ²Douglas Mental Health University Institute, ³McGill University, Department of Psychiatry

Background: In current psychological practices, mental states are mostly detected through self-reports. This means that individuals only receive help when they actively pursue it and that means we have no objective way of assessing internal mental state changes. In cases of psychosis, this can lead to significant health and economic consequences, because a relapse is only detected when mental states and symptoms become overt. Natural Language Processing (NLP) is a technique that aims to assess the mental states of individuals through text and spoken word. NLP data can be collected from sources such as social media and clinical interviews to examine markers in speech to provide an objective way to identify subtle changes in mental states. Ketamine is a well-established treatment for depression in unipolar and bipolar disorder and is regarded as a model for symptoms of psychosis. Ketamine has been shown to induce difficulties in abstract thinking and speech disturbances, including lack of spontaneity and flow of conversation, as well as formal thought disorder. NLP is highly sensitive to psychedelic states and has the ability to partially predict individual therapeutic outcomes and collect information important for early diagnosis. We propose to use NLP to detect ketamine speech

markers to test: (1) whether ketamine therapy can reduce depression-related features of language, to further studies establishing NLP speech markers as an objective marker of mental states; and (2) the validity of ketamine use as a model of psychosis.

Methods: Speech samples will be collected from 20 patients with depression undergoing ketamine treatment at the Douglas Institute's Ketamine Clinic. A speech sample consisting of story-reading and recall, a picture description task, and a short semi-structured interview will be administered during the baseline and final treatment sessions, before and after ketamine administration, for a total of 4 recordings. The recorded speech will then be transcribed and preprocessed to extract acoustic (pauses in speech, pitch), semantic (word choices), and syntactic (complexity of expressed ideas) markers of speech. Sentiment analysis will also be carried out on the semi-structured interview, to assess the frequency of various mental state clusters (positive and negative emotional tones).

Results: Preliminary results to be determined

Discussion: To date, no study has examined the potential effect of ketamine on objective speech-based markers. This study will help advance the development of objective markers of mental states, further the applications of NLP which can eventually be used to detect relapse before it occurs, test the efficacy of treatment through language analysis, reliably diagnose mental illness, and even contribute to early diagnosis. This study will contribute to future studies examining the linguistic features of treatment-resistant depression in individuals undergoing ketamine treatment and will determine if regular speech recording can help in therapeutic monitoring for depression and psychosis.

F92. COMPLEX SEIZURE DISORDER SYMPTOMS MANIFESTING IN TREATMENT-RESISTANT SCHIZOPHRENIA SPECTRUM DISORDERS IN YOUNG ADULTS WITH PRIOR CANNABIS USE: A CLINICAL OVERVIEW

Sophia Walker^{*1}, Katharine Cutts Dougherty¹, Howard Weiner¹, Suma Srishaila¹, David Rowe¹, Lisa Mann¹, Rocco Marotta²

¹*Silver Hill Hospital*, ²*Silver Hill Hospital, Yale University*

Background: In the last decade, a notable surge in admissions of young adults to our private psychiatric hospital has revealed an intriguing trend. A significant cohort of these individuals, predominantly comprising college students or recent graduates, presents with severe psychiatric symptoms meeting the criteria for Schizophrenia Spectrum Disorder. These cases share a common history of cannabis use, alongside a substantial portion having received treatment for Attention-Deficit/Hyperactivity Disorder and other attentional spectrum disorders, employing stimulants and other medications during their academic tenure. Surprisingly, formal mental status assessments unveil intact cognitive faculties, often demonstrating a high intellectual aptitude, with some individuals functioning at advanced levels, such as completing graduate school. Paradoxically, upon establishing trust, these patients divulge idiosyncratic convictions of embodying special beings, assuming roles like messiahs or even deities.

Methods: Regrettably, conventional treatments, including second-generation antipsychotics and varied medication combinations, have yielded poor responses, necessitating referral to our team specializing in treatment-resistance. As part of the preliminary evaluation, these individuals underwent a comprehensive twenty-question Complex Partial Seizure Checklist (Krusz, 1987), exhibiting response patterns consistent with cases of partial complex seizure disorder, akin to temporal lobe epilepsy, outlined in Lishman's seminal work, "Organic Psychiatry" (2009), which stressed that diagnosis of epilepsy is clinical.

Results: The present case series posits several factors contributing to the recent surge in such cases, including prolonged exposure to high-potency cannabis from an early age, concurrent usage of psychostimulants, cultural and societal influences from platforms like social media, and the potential impact of COVID-19 infection on delicate limbic and frontal brain structures. The analysis and treatment outcomes of eight cases will be synthesized herein. All cases demonstrated exposure to marijuana and nearly all had exposure to psychostimulants. All cases had intact intelligence, ability to abstract, limited negative symptoms, positive symptoms marked by paranoia, grandiosity, and philosophical and existential preoccupations. Furthermore, presentations were marked by sleep impairment, including nightmares, marked episodes of mood instability, bizarre sensory experiences, loss of time, and lack of overt sexual activity despite sexual preoccupation. Notably, all patients sought benzodiazepines, claiming they were beneficial to them, along with cannabis and psychostimulant use, leading to classification as substance induced psychosis. Scores on the twenty-point scale described above were greater than 11 out of 20.

Discussion: Noteworthy in our observations is the efficacy of Clozapine as an intervention; however, its usage is impeded by patients' intolerance towards associated side effects. We concede that such presentations are consistent with schizophrenia; however, the clinical insights gained from these cases sheds light on the complex interplay between numerous environmental factors, seizure-like symptoms, and treatment-resistant manifestations of Schizophrenia Spectrum Disorders. The increased density of cases more recently is intriguing and requires a nuanced approach in their diagnosis and management.

F93. IDENTIFYING CASES OF MENSTRUAL PSYCHOSIS USING ELECTRONIC HEALTH RECORDS

Thomas Reilly^{*1}, Edward Chesney², Amelia Jewell², Philip McGuire³, Ian Brockington⁴

¹*Institute of Psychiatry, King's College*, ²*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ³*University of Oxford*, ⁴*University of Birmingham*

Background: Menstrual psychosis has been described by numerous case reports. It has been defined as: (i) episodes of psychosis, mania, catatonia or confusion, (ii) with acute onset, (iii) in synchrony with the menstrual cycle, (iv) showing complete recovery within two weeks. However, case reports rely on clinicians to identify, accurately report, and then publish a summary. This is prone to bias and may be unrepresentative of the underlying patient population. The Clinical Record Interactive Search was used to identify patients from Case Register of South London and Maudsley NHS Foundation Trust with menstrual psychosis.

Methods: Keywords were used to search electronic records of patients within this large mental health trust, for example, 'premenstrual', 'menstrual', 'catamenial', 'menses', 'menarche') adjacent to ('psychosis', 'psychotic', 'mania', 'manic', 'catatonia', 'catatonic'). Next, a search of cases diagnosed with a psychotic disorder was performed, using the search terms 'premenstrual', 'menstrual', 'catamenial', 'menses', 'menarche'. Clinical records, including emergency assessments, progress notes, ward rounds, clinic letters, and discharge summaries were reviewed. Cases were included if they met criteria for menstrual psychosis. Patients who had menstrual exacerbation of a chronic psychotic disorder (without full recovery between episodes) were excluded. Demographic and diagnostic information were extracted from the clinical records.

Results: The initial search returned 472 patient records. Of these, 364 were immediately excluded: 55 had no link with the menstrual cycle, 283 had no evidence of psychotic symptoms, 25 were irrelevant records. Of the 108 records in which a patient, family member or clinician

reported a link between symptoms and the cycle, 68 were exacerbation of an underlying chronic illness, four were likely premenstrual dysphoric disorder or premenstrual syndrome, two did not have enough information, and 34 met criteria for menstrual psychosis. In 16 cases, the clinical team explicitly documented a diagnosis of menstrual psychosis, though none were published in the literature as case reports. The most common diagnosis of cases was schizophrenia spectrum disorder (48.5%), followed by bipolar disorder (27.3%). This was similar to patients with menstrual exacerbation, 68.1% of whom were diagnosed with schizophrenia and 20.8% with bipolar disorder. The modal age of onset of menstrual psychosis was 14, median 17 (interquartile range 14-25.3), while the modal age of onset for patients with a diagnosis of menstrual exacerbation was 16, median 21 (interquartile range 17-27.3). There was a borderline difference in age of onset between groups (Wilcoxon rank sum test with continuity correction $p=0.05$).

Discussion: This study is the first to identify cases of menstrual psychosis using searches of electronic health records from a single mental health trust. This identified 34 cases which met pre-specified criteria, with a larger number of patients identified who had menstrual exacerbation of an underlying disorder. In approximately half of the cases, the treating clinicians recognised the diagnosis of menstrual psychosis, though notably none of these cases were published as case reports. This suggests the published literature is a gross underestimation of the true incidence of this disorder. Some features are consistent with previously published cases. Peak onset was in early adolescence, slightly earlier than the illness onset of patients with menstrual exacerbation. In contrast with the published cases, the most common ICD-10 diagnosis was schizophrenia spectrum disorders.

F94. THE PLEASURE EXPECTANCIES SCALE (PLEX): EXAMINING THE RELIABILITY AND VALIDITY OF A SELF-REPORT MEASURE OF LOW EXPECTANCIES FOR PLEASURE IN SCHIZOPHRENIA

Sarah Saperia^{*1}, Alex Prosserman², Konstantine Zakzanis³, Margaret Hahn⁴, Mahavir Agarwal⁴, George Foussias⁴

¹*Centre for Addiction and Mental Health, University of Toronto Scarborough*, ²*Centre for Addiction and Mental Health*, ³*University of Toronto Scarborough*, ⁴*Centre for Addiction and Mental Health, University of Toronto*

Background: According to the cognitive model, negative symptoms are conceptualized as maladaptive compensatory responses to dysfunctional beliefs, expectancies, and appraisals. Implicated within this model are low expectancies for pleasure, which refer to a set of unhelpful beliefs characterized by low levels of anticipated enjoyment and generally negative expectations for experiences of pleasure. While this hypothesized belief system derives from a growing body of research suggesting that motivational and hedonic deficits in schizophrenia are reflective of reductions in anticipatory pleasure, there is concern that existing measures may actually be tapping into one's disposition towards experiencing pleasure in-the-moment while anticipating future events, as opposed to the beliefs and expectancies one holds regarding their likelihood and/or capacity to experience pleasure. To this end, the goal of the current study is to test the reliability and validity of a new brief measure, titled the Pleasure Expectancies Scale (PLEX), evaluating low expectancies for pleasure in schizophrenia.

Methods: Seventy nine participants with schizophrenia-spectrum disorder have been recruited to date. After excluding invalid responders, the sample consisted of 68 participants. All participants were administered the 8-item PLEX, along with a battery of other self-report and observer-rated measures. Cronbach's alpha was calculated to evaluate the scale's internal

consistency. Convergent validity was assessed using the anticipatory subscale of the Temporal Experience of Pleasure Scale (TEPS), as well as the future anticipation subscale of the Savoring Beliefs Inventory (SBI), while discriminant validity was examined using the positive symptom and excitement subscales of the Brief Psychiatric Rating Scale (BPRS). To confirm the relationship hypothesized by the cognitive model, bivariate correlations were conducted between the PLEX, the negative symptom subscale of the BPRS, as well as the Motivation and Pleasure Scale – Self-Report (MAP-SR). Finally, a hierarchical multiple regression analysis was run to test the predictive value of the PLEX on the MAP-SR, above and beyond the effects of the TEPS and SBI anticipatory subscales.

Results: The reliability of the scale was acceptable at $\alpha = 0.76$. Convergent validity was demonstrated, with significant inverse correlations between low expectancies for pleasure on the PLEX with the anticipatory pleasure subscales of the TEPS ($r = -0.37$, $p = 0.002$) and SBI ($r = -0.42$, $p < 0.001$). Discriminant validity was also demonstrated, as indicated by the non-significant correlations between the PLEX and the BPRS positive symptom subscale ($r = 0.13$, $p = 0.28$) and excitement/mania subscale ($r = 0.04$, $p = 0.77$). Significant correlations also emerged between the PLEX and BPRS negative symptom subscale ($r = 0.33$, $p = 0.006$) and MAP-SR ($r = 0.45$, $p < 0.001$). The results of the hierarchical multiple regression analysis revealed that the PLEX significantly contributed an additional 10% of the variance in MAP-SR scores after accounting for the TEPS and SBI anticipatory subscales, with the final model significantly accounting for 24% of the variance ($F(3,66) = 6.67$, $p < 0.001$), and with only the PLEX emerging as a significant predictor ($\beta = 0.36$, $p = 0.006$).

Discussion: Preliminary results suggest that the PLEX is a promising new brief self-report measure of low expectancies for pleasure, with good reliability and validity. Importantly, the PLEX overcomes the issues with existing measures of anticipatory pleasure by more explicitly tapping into beliefs and expectancies about pleasure, and contributes unique variance to self-reported motivational and pleasure deficits beyond that accounted for by these other measures.

F95. AN OBSERVATIONAL STUDY USING THE RADIOLIGAND [11C]UCB-J FOR IMAGING SYNAPTIC DENSITY IN PATIENTS WITH A PSYCHOTIC DISORDER AND THEIR HEALTHY SIBLINGS

Monique van der Weijden-Germann^{*1}, Erik De Vries², Chris W. J. van der Weijden³, Sanne Brederoo⁴, Carl M. Sellgren⁵, Iris E.C. Sommer⁶

¹University of Groningen, University Medical Center Groningen (UMCG), ²Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, ³Department of Radiology and Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands, ⁴University Center of Psychiatry, University Medical Center Groningen (UMCG), Groningen, The Netherlands, ⁵Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, ⁶Department of Psychiatry, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands

Background: The majority of patients with schizophrenia (SCZ) suffer from global disabling cognitive symptoms affecting multiple cognitive domains. Recent studies assessing the pathophysiology underlying cognitive deficits in SCZ highlight the crucial role of a genetically overexpressed complement compound C4 which leads to excessive complement-mediated

microglial synaptic pruning. Such a faulty programmed pruning process may further result in a decrease of synaptic density, and ultimately leads to impaired cognitive functioning. Whereas a recent [11C]UCB-J PET-study confirmed the consequential loss of synaptic density in patients with SCZ, the effect of the genetic predisposition for SCZ on unaffected relatives remains unclear. In an attempt to disentangle genetic vulnerability from secondary disease and medication related effects, the current investigation assessed synaptic density using [11C]UCB-J PET-scans and cognitive functioning in SCZ patients, their healthy siblings, and healthy controls.

Methods: The present mono-center, cross-sectional observational study enrolled N = 75 participants aged between 26 – 65 years. Patients were diagnosed with schizophrenia, schizoaffective disorder, or a schizophreniform disorder. All participants underwent cognitive testing, an [11C]UCB-J PET-scan, and an T1w-MRI-scan for anatomical reference. PET-images were corrected for motion, co-registered with T1w-images, and segmented. Non-displaceable binding potential (BPND) images were estimated using the Simplified Reference Tissue Model 2 (SRTM2) with the centrum semiovale as a reference region. Per group, regional and whole cortex mean BPND were computed and an ANCOVA with years of education as covariate was used to compare the whole cortex mean BPND between the groups.

Results: Albeit sex ($p = 0.147$) and age ($p = 0.138$) did not significantly differ between the groups, the healthy sibling group significantly differed from the SCZ group in terms of years of education. That is, healthy siblings (15.24 ± 1.3) had significantly higher number of years of education ($p = 0.017$) compared to SCZ patients (13.6 ± 3.3). The whole cortex BPND turned out to be significantly lower in patients with SCZ (2.90 ± 1.42) compared to their healthy siblings (3.08 ± 1.52 , $p = 0.012$) and compared to healthy controls (3.26 ± 1.60 , $p < 0.001$). Strikingly, healthy siblings were found to have a significantly lower whole cortex BPND as compared to healthy controls ($p < 0.001$). Furthermore, the right putamen, left nucleus accumbens, and the right posterior cingulate cortex showed the highest BPND across all groups.

Discussion: The current investigation provides a first in-vivo assessments of synaptic density in patients with psychotic disorders and their unaffected siblings. Our results demonstrate a significantly decreased synaptic density in patients with SCZ as well as in their healthy siblings as compared to healthy controls, which further supports the notion of a genetic vulnerability for SCZ which leads to aberrant complement-mediated microglial synaptic pruning. This renders the pruning machinery as a potential target for early treatment and prevention strategies. Based on the peak of excessive pruning in late adolescence and early adulthood, interventions aimed at preventing over-pruning may prove most beneficial early on in adolescent individuals who are at high risk to develop SCZ. As a crucial next step, future analyses of the present study will provide more insight into whether the loss of synapses may be related to decreased cognitive functioning in SCZ and their healthy siblings.

F96. THE LONGITUDINAL STRUCTURE OF NEGATIVE SYMPTOMS IN TREATMENT RESISTANT SCHIZOPHRENIA

Noham Wolpe^{*1}, Aya Vituri¹, Peter Jones², Moni Shahar¹, Emilio Fernandez-Egea²

¹Tel Aviv University, ²University of Cambridge

Background: The negative symptoms of schizophrenia are strong prognostic factors but remain poorly understood and treated. Five negative symptom domains are frequently clustered into the motivation and pleasure (MAP) and emotional expression (EE) ‘dimensions’, but whether this structure remains stable and behaves as a single entity or not remains unclear.

Methods: We examined a cohort of 153 patients taking clozapine for treatment-resistant schizophrenia in a regional mental health clinic. Patients were assessed longitudinally over a mean period of 45 months using validated scales for positive, negative and mood symptoms. Network analyses were performed to identify symptom ‘communities’ and their stability over time. The influence of common causes of secondary negative symptoms as well as centrality measures were also examined.

Results: Across patients at baseline, two distinct communities matching the clinical domains of MAP and EE were found. These communities remained highly stable and independent over time. The communities remained stable when considering psychosis, depression, and sedation severity, and these causes of secondary negative symptoms were clustered into the MAP community. Centrality measures also remained stable over time, with similar centrality measures across symptoms.

Discussion: Our results suggest that MAP and EE are independent domains that remain highly stable over time in chronic schizophrenia patients treated with clozapine. Common causes of secondary negative symptoms mapped onto the MAP domain. Our results emphasise the need for clinical trials to address either MAP or EE, and that treating causes of secondary negative symptoms may improve MAP.

F97. PROSODIC CUES ARE LINKED TO PECULIAR SUBJECTIVE EXPERIENCES IN SCHIZOPHRENIA: A COMBINED ACOUSTIC AND PHENOMENOLOGICAL ANALYSIS

Valeria Lucarini^{*1}, Martine Grice², Jalal Al-Tamimi³, Francesco Rasmi⁴, Stefano Amorosi⁴, Nikolas Fascendini⁴, Carlo Marchesi⁴, Linda Scoriels⁵, Matteo Tonna⁴, Marie-Odile Krebs¹

¹*Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266*, ²*IfL-Phonetics, University of Cologne, Cologne, Germany*, ³*LLF, CNRS – UMR 7110*, ⁴*University of Parma*, ⁵*Université Paris Cité - Laboratoire de Psychologie du développement et de l'éducation de l'enfant*

Background: Automated linguistic analysis in patients with schizophrenia is an extremely rapidly evolving research field. Peculiarities in patients’ speech have been identified at various levels, including prosody, also referred to as tone of voice. Although there is evidence of different prosodic patterns between patients and healthy controls, results are contradictory, analyses are often limited to few cues, and the association with psychopathological dimensions has been poorly investigated. Moreover, the relationship with experiential anomalies, considered by the phenomenological tradition to be at the core of schizophrenia but still scarcely assessed in clinical and research contexts, has never been explored.

Methods: We enrolled 58 participants, all native Italian speakers (29 healthy controls – HC; 29 patients with schizophrenia – SCZ) at the University Hospital of Parma. We obtained high-quality dual channel audio files from recorded interviews between each participant and a clinician. Praat software was used to extract an extensive range of acoustic features from 4 prosodic domains (temporal profile, intonation range, intonation variability, voice quality). Patients underwent a thorough psychopathological exploration with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), the Examination of Anomalous Self Experience scale (EASE) and the Autism Rating Scale (ARS). (Protocol approved by the AVEN, Emilia-Romagna region ethics committee, 05/05/2021 code:1235/2020/SPER/AUSLPRLANG_20.)

Results: SCZ and HC significantly differed in temporal profile and intonation variability (e.g. speech rate $t = 2.72$, $p < .01$; total nuclei duration $t = 3.32$, $p < .01$; total internuclei duration $t = 4.59$, $p < .001$; total pause duration $U = 169$, $p < .001$; glissando $t = 2.51$, $p < .01$; intrasyllabic trajectory $t = 2.39$, $p < .05$). We did not find differences in intonation range and voice quality patterns. Prosodic patterns were correlated with negative (e.g. pitch range and PANSS negative score $\rho = -0.599$, $p < .001$) and disorganization dimensions (e.g. pitch range and PANSS disorganization score $\rho = -0.510$, $p < .001$, F0 mean and PANSS disorganization score $\rho = -0.421$, $p < .001$) but not with positive symptoms. Moreover, we found significant associations with the EASE and ARS scores, especially with stream of consciousness, ipseity and attunement anomalies (e.g. speech rate and EASE total score $\rho = -0.460$, $p < .01$, total internuclei duration and EASE total score $\rho = -0.486$, $p < .001$).

Discussion: We showed for the first time that Italian-speaking patients with schizophrenia display significant differences from healthy controls in a number of prosodic patterns, prosodic cues being associated with negative and disorganization symptoms. Also, for the first time, we showed significant associations in the relationship between prosody and subjective experiential anomalies. Our results suggest that communication features are deeply intertwined with core symptoms and subtle deep subjective peculiar experiences in schizophrenia. This underscores the need for research projects on speech analyses in psychiatric conditions that are strongly interdisciplinary in both design and conduct, using appropriate linguistic techniques and including accurate psychopathological evaluations.

F98. A SYSTEMATIC REVIEW OF NON-VERBAL CORRELATES ASSOCIATED WITH PARANOID IDEATION

Ron Haarms^{*1}, Hannah Jongsma¹, Chris Geraets¹, Wim Veling¹

¹UMCG

Background: Diagnostic instruments that help classify psychotic disorders, such as paranoid ideations, are heavily reliant on language-based assessments (e.g. interviews or questionnaires). During the florid stage of the illness healthcare professionals rely on their clinical experience for a diagnosis. However, interviews and self-report questionnaires strongly rely on patients' memory, current mental state, self-understanding, and insight. Ideally, auxiliary methods in the form of observations of non-verbal behaviours could provide supplemental evidence for the diagnosis. In order to be able to develop novel non-verbal diagnostic tools that are valid, knowledge about non-verbal correlates and their association with paranoid delusions is needed. The aim of the paper is to create an overview concerning all non-verbal correlates associated with paranoid delusions and to critically review them.

Methods: The systematic literature review followed the PRISMA guidelines and the protocol was registered with PROSPERO (CRD42022288001). Articles were included if they concerned qualitative or quantitative research in people with clinical or subclinical levels of paranoia. Assessed non-verbal correlates were measured using a non-verbal method in a standardised way, thereby excluding (self-report) questionnaires and interviews. Screening was done in duplicate and data was extracted using a standardised format.

Results: The search strategy yielded 4286 potentially eligible titles, from which 21 studies were selected to fit with inclusion criteria. The included studies considered the following non-verbal correlate themes: visual perception ($n=5$), spatial behaviour ($n=7$), physiology and distress ($n=4$), information processing ($n=5$), and other ($n=5$), some studies covered multiple

themes. Patients with paranoid delusions exhibited significant differences in visual perception compared to controls, specifically in ambiguous social scenes. Overall, the evidence suggests that paranoia influences social approach and avoidance behaviours, impacting both proxemics and responses to emotional stimuli (spatial behaviour). However, findings on physiological measures and information processing were mixed.

Discussion: The current evidence emphasizes the multifaceted nature of paranoia, shedding light on its diverse manifestations across various non-verbal domains. These outcomes underscore the potential of a diagnostic framework that assesses behavioural dimensions. Further research is needed, amongst others, to inquire the applicability of non-verbal approaches.

F99. TUNING TO THE VOICE: DISTINGUISHING SUBTYPES OF AUDITORY VERBAL HALLUCINATIONS TO GUIDE TAILORED TREATMENT

Sanne Brederoo*¹

¹*University Medical Center Groningen*

Background: With a lifetime prevalence of around 10%, the experience of auditory verbal hallucinations (AVH) is quite common. For about one third of the people who hear AVH, these cause suffering to the extent that they seek treatment for it. A wide array of psychological therapies exists aimed at decreasing the occurrence and resulting distress of voice-hearing, each through different methods. Examples are cognitive behavioural therapy (CBT)-based therapies (e.g., CBT, Acceptance and Commitment Therapy), and ‘dialoguing’ therapies (e.g., Voice Dialogue and Avatar Therapy). Unfortunately, these one-size-fits-all treatment approaches have not proven sufficiently effective in countering the often-debilitating effects of AVH, as evidenced by their small-to-modest effect sizes. As a result, some voice-hearers enter lengthy treatment trajectories from which they do not profit, causing further distress and damaging their confidence in mental health care. However, arguably each of these therapies in fact does have its own merit, but they are not yet effective to their full potential because they are not prescribed for the type of voices that they best target.

The core shared feature of all AVH is that they are linguistic in nature. Intriguingly, linguistic differences are also what sets AVH apart from each other, but in current clinical practice there is no appreciation of this fact. In a recent study, a data-driven approach showed that linguistic characteristics can be used to distinguish different ‘voice-types’ that align with clinical impressions. Some AVH are ‘compact’ –they are short utterances with little grammatical complexity, sometimes consisting of short commands or swear words. Other AVH are ‘expanded’ –they are longer and more complex utterances, and resemble the way we speak to each other. Not only do these results suggest the existence of different voice-types, they may also explain previous discrepant findings regarding underlying working mechanisms of voice-hearing. Some research posits that AVH originate in the right cerebral hemisphere –which is nondominant for language. This finding aligns with the linguistic presentation of ‘compact’ AVH, as language that the non-dominant right hemisphere can produce is very simple in nature. However, more ‘expanded’ AVH arguably do not originate from the right-hemisphere, as this hemisphere is incapable of such complex language. Different voice-types likely have different neural origins, but, importantly, they also presumably call for different types of treatment. As a case in point, a person who hears short and repetitive utterances may not profit from a therapy based on the principle of engaging in dialogue with the voice in the way that a voice-hearer

with ‘expanded’ AVH will: offering Voice Dialogue or Avatar therapy to a ‘compact’-voice-hearer will likely result in suboptimal treatment. The key to improvement may lie in providing the treatment that is tailored to the type of AVH people hear. The presented study aims to distinguish and characterize different voice-types, examine differential neural working mechanism of voice-types, and evaluate the role of voice-type in treatment effectiveness.

Methods: A sample of $n = 146$ voice-hearers will be recruited. Verbatim repetitions of the AVH will be collected and transcribed, and then subjected to a data-driven clustering analyses based on linguistic features. The assessed linguistic features include pronouns, time references, content, and structure measures, function word classes, and content word classes. In addition, voice-related measures will be collected using the PSYRATS-AHRS and the Revised Beliefs About Voices Questionnaire. Lateralization of cortical language areas will be measured using functional near-infrared spectroscopy (fNIRS) during a dichotic listening task. Finally, voice-hearers will receive their psychological therapy as planned, and a pre- and post-assessment (10 weeks) will be done to evaluate treatment effectiveness using the Voices Impact Scale.

Results: The results are hypothesized to show at least two different voice-types based on the linguistic analyses. A ‘compact’ voice-type is expected to be associated with more right-hemisphere involvement. Dialoguing therapies are expected to be more effective for ‘expanded’ than for ‘compact’ voice-types.

Discussion: The outcomes of the study are expected to yield strong added value for both clinical practice and fundamental research.

F100. A NETWORK ANALYSIS OF PSYCHOSIS SYMPTOMS AND POST-TRAUMATIC SEQUELAE AMONG THERAPY-SEEKING INDIVIDUALS PRESENTING WITH COMORBID PSYCHOSIS AND POST-TRAUMATIC STRESS DISORDER

Rachel Frost¹, Ciaran O'Driscoll², Emmanuelle Peters^{*1}, Amy Hardy¹, STAR (Study of Trauma And Recovery) Research group³

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*University College London*, ³*London, Manchester, Newcastle, Oxford and Sussex*

Background: Post-traumatic sequelae are theorized to contribute to the development and maintenance of psychosis symptoms. There is limited research evaluating the relationship between psychosis symptoms and multiple post-traumatic sequelae simultaneously. Specifically, there has been little investigation of the relative contribution of core post-traumatic stress disorder (PTSD) symptoms (re-experiencing, hyperarousal and avoidance) and those reflective of complex PTSD, operationalized as ‘disturbances of self-disorganization’ (DSO) in ICD-11 (negative self-concept, relationship difficulties, and affective dysregulation). This study employed network analysis to examine interactions between psychosis, core post-traumatic stress, and complex post-traumatic symptoms. It was predicted that trauma-related beliefs would have the greatest predictability in the network, based on previous evidence suggesting they have a stronger role in psychosis relative to other post-traumatic sequelae. Accordingly, it was also hypothesised that the association between voices and trauma-related beliefs would be greater than the association between voices and re-experiencing.

Methods: The study utilized baseline data from a randomized controlled trial evaluating an integrated Trauma-Focused Cognitive Behaviour Therapy for Psychosis, the Study of Trauma and Recovery (STAR trial). The sample comprised 305 individuals meeting criteria for ICD-10 schizophrenia-spectrum disorder (F20-29) and DSM-V PTSD and presenting with

distressing hallucinations and/or delusions. A network was estimated comprising psychosis symptoms (delusions and voices), using the frequency factor items (Woodward et al, 2014) of the Psychosis Symptom Rating Scales (PSYRATs; Haddock et al, 1999); core post-traumatic stress and DSO symptoms, assessed using the International Trauma Questionnaire (ITQ; Cloitre et al, 2018); trauma-related beliefs (negative cognitions about the self and world, and self-blame), assessed using the Post-Traumatic Cognitions Inventory (PTCI-9; Wells et al, 2019).

Results: The hypotheses were not supported. All symptoms had similar predictability scores so it was not possible to discriminate symptom centrality. There was no evidence for conditionally dependent relations between re-experiencing and voices, nor between trauma-related beliefs and voices, suggesting no difference between these associations. However, delusions had a positive direct connection with self-blame whilst voices had positive direct connections with affective dysregulation (including numbing) and avoidance (including internal suppression). Further analysis demonstrated that affective dysregulation predicted hallucinations whilst self-blame predicted delusions.

Discussion: Unlike previous findings, there was no evidence of trauma-related beliefs being of greater centrality in the network, relative to other symptoms; nor was there indication of trauma-related beliefs being linked to voices. Variation in symptom presentation within the sample may hinder accurate representation in networks; identifying subgroups with similar symptom profiles may improve reliability. Notably, there were no direct associations between the ‘core’ re-experiencing symptoms of PTSD and psychosis symptoms either. However, self-blame, a type of trauma-related belief, and affective dysregulation, may be key mechanisms influencing the maintenance of delusions and voices, respectively. The findings may have implications for psychological interventions, as targeting specific post-traumatic stress sequelae could reduce psychosis symptoms, but further research is required to test this hypothesis.

F101. SUBJECTIVE DISTURBANCES OF IMAGINATION IN SCHIZOPHRENIA-SPECTRUM DISORDERS: RECENT EMPIRICAL INVESTIGATIONS

Andreas Rasmussen*¹

¹*Mental Health Center Amager*

Background: Patients often report distressing or functional impairing imaginative experiences such as vivid intrusive images, aggressive fantasies or extensive daydreaming. In 20th century psychiatry, various aberrations of imagination were discussed in the context of schizophrenia. Thus, Bleuler included this domain under the concept of autism defined as a detachment from reality linked with a predominance of the inner life. Jaspers discussed the so-called pseudo-hallucination as an intermediate phenomenon between imagination and hallucination. And, within neurocognitive research, aberrations of imaginative processes have been proposed to underlie development of delusions and hallucinations, most recently articulated under the notion of source monitoring deficits. However, none of these approaches have explored the subjective (experiential) character of imagination in schizophrenia. Psychopathology lacks concepts for this domain, and the rich variety of these complaints is only partly captured by notions such as obsession and rumination.

Methods: An overview of recent empirical research addressing subjective disturbances of imagination in schizophrenia-spectrum disorders.

Results: Phenomenological-qualitative studies of imagination and fantasy life in patients with schizophrenia-spectrum disorders have recently articulated several phenomena that appear to

have received little attention in the previous literature. These include a characteristic spatialization of mental imagery and fantasy experience. Thus, imagery is described as temporally stable with a highly articulated spatial character and autonomous development. Furthermore, patients report a variety of subtle and transient subjective disturbances of the tacit discrimination of fantasy life from other modalities such as memory or an insecurity of such discrimination. These psychopathological concepts have received more systematic support in a recent empirical study that found that these subjective disturbances of imagination aggregate selectively in patients with schizophrenia-spectrum disorders compared to other mental disorders or healthy controls. Moreover, they are retrospectively reported to have an early onset, several years before clinical contact, and to be involved in patients' account of the formation of delusions and hallucinations. A semi-structured interview, the Examination of Anomalous Fantasy and Imagination (EAFI), addressing these disturbances has been developed. This instrument has been found to have good-excellent reliability and internal consistency. Finally, it has been argued that subjective disturbances of imagination reflect the same disorder of subjectivity as disorders of basic self.

Discussion: These notions addressing subjective disturbances of imagination facilitate an awareness of the lived experience of patients with a schizophrenia-spectrum disorder, crucial to clinical work. Moreover, these disturbances have a potential clinical relevance for differential diagnosis and early detection. Future studies should address their temporal trajectory and possible longitudinal associations with self-disorders and other schizophrenia-spectrum psychopathology.

F102. SCHIZOPHRENIA: WHEN NO DIFFERENCES MAKE THE DIFFERENCE

Simona Garobbio^{*1}, Dario Gordillo¹, Maya Roinishvili², Eka Chkonia³, Andreas Brand¹, Michael H Herzog¹

¹*École Polytechnique Fédérale de Lausanne (EPFL)*, ²*Beritashvili Centre of Experimental Biomedicine, Free University of Tbilisi*, ³*Free University of Tbilisi, Tbilisi State Medical University*

Background: The common practice of only publishing significant results often leads to the impression that patients with schizophrenia have deteriorated performance in the majority of paradigms. Identifying intact functions is, therefore, not only important to avoid stigmatization of the patients but also to obtain a clear-cut picture of what is and what is not impaired in the disease.

Methods: We run a battery of tests targeting many aspects of visual information processing to investigate what is and what is not impaired in schizophrenia, and in addition we report some previous results from our group. We tested tasks that require high attention and for which accuracy was measured, as well as tasks addressing the subjectivity of perception and for which bias rather than sensitivity was determined.

Results: In the attention-demanding tasks, schizophrenia patients showed intact performance in two out of three tasks (i.e., in contextual modulation and complex motion processing, but not in visual backward masking). In tasks targeting the phenomenology of schizophrenia, patients showed intact performance in four studies: bodily self-representation during changes in body ownership induced by prolonged multisensory stimulation, perception of illusions, impulsivity as tested by a delay-discounting task, and an occlusion task where participants indicated if a dot traveling from left to right describing a concave-up curved trajectory would

reappear above or below a tick-mark after occlusion. Differences between patients and controls were found in two subjective tasks: ambiguous figures and free viewing.

Discussion: Our findings indicate that there is no general impaired mechanism in schizophrenia, as patients showed both intact and deteriorated visual processing. Although patients with schizophrenia are often thought to perceive the world very differently than controls, such as strongly fragmented in time and space, we show that this is not always the case. It is important for a holistic understanding of schizophrenia to publish null results, i.e., studies where patients are not impaired and hence there are no significant group differences. Understanding the intact mechanisms will help understanding the abnormal ones.

F103. VALIDATION OF SELF-REPORT ITEMS TO ASSESS SELF AND REALITY EXPERIENCES IN PSYCHOSIS

Dan-Andes Bekkering-Bauer*¹, Marieke (Gerdina) Pijnenborg¹, Jasper Feyaerts², Lisette Van der Meer¹

¹University of Groningen, ²Ghent University

Background: Psychosis poses a substantial societal burden, prompting the identification of individuals at ultra-high risk (UHR) for psychosis. However, UHR criteria are grounded in a third-person approach which limits the capturing of nuanced subjective experiential alterations reported by individuals with lived experiences of psychosis. Advocating for a paradigm shift, phenomenological researchers emphasize the active meaning-making process and experiential dimensions of self and reality in psychosis. Self and reality related experiences can be assessed with self-report instruments, such as the Examination of Anomalous Self Experience (EASE) which translates anomalous self and reality experiences into a semi-structured interview. However, the EASE does not allow for the assessment of temporal patterns and changes over time. Therefore, our research aims to systematically explore and document anomalous self and reality experiences reported by individuals at ultra-high risk and those with lived experiences of psychosis. Based on the resulting data, we will develop and validate self-report assessments of anomalous experiences, and elucidate necessary adaptations for deployment in experience sampling methods (ESM) to enable the capture of moment-to-moment fluctuations in anomalous self and reality experiences in a future study.

Methods: This qualitative exploratory study addresses four research questions concerning anomalous self and reality experiences. An interview guide will be developed through discussions with experience-experts from December 2023 to February 2024. Qualitative semi-structured interviews in February and March 2024 will explore self and reality experiences in 10 individuals (UHR and first-episode psychosis), employing thematic analysis with inductive and deductive coding schemes. The identified themes will inform the development of self-report items which will be validated for use in an experience-sampling study.

Results: We will present a set of validated items that can be used to assess self-disturbances in psychotic disorders.

Discussion: Study outcomes will be helpful in enhancing our understanding of the daily self and reality related experiences of individuals with psychosis. These items will be used in future studies, to assess the interplay between these experiences over time and the association between these items and transition to psychosis.

F104. EFFECT OF AEROBIC EXERCISE INTENSITY COMBINED WITH SOCIAL COGNITIVE SKILLS TRAINING ON SOCIAL COGNITION AMONG SCHIZOPHRENIA PATIENTS

Lya Ehrenfeld*¹, Avraham Munitz¹, Yuri Rassovsky²

¹Bar-Ilan University, ²UCLA/Bar-Ilan University

Background: Patients with schizophrenia typically display a wide range of cognitive impairments, including both deficits in social and non-social cognition. While both social and non-social cognitive impairments are associated with poor community functioning, social cognition is more closely related to daily functioning than non-social cognition in schizophrenia. Therefore, interventions designed to improve social cognitive functioning may have important impact on the clinical and functional outcome of these individuals. To this end, a social cognitive skills training (SCST) program for patients with schizophrenia. While showing promising results, individual heterogeneity remains. Aerobic exercise (AE) was suggested as an augment to SCST since it previously showed a positive effect on social cognition. Thus, here we will evaluate the augmenting effect of AE on SCST in patients with schizophrenia.

Methods: Schizophrenia patients were recruited from major psychiatric hospitals and other local community care facilities. Subjects were randomly assigned to one of two conditions: (1) moderate-intensity continuous training (MICT) + SCST, and (2) low-intensity stretching exercise control condition (SE) + SCST. Participants exercised in small groups (4-6 participants), followed by SCST administered in the same group. The intervention was 2 days per week, for a total of 12 weeks. Assessments include the Penn Emotion Recognition Task (ER-40), Hinting Task and The Intentional Bias Task (IBT) and were administered at baseline, at midpoint after 6 weeks, and at completion of 12 weeks of training.

Results: A two-way repeated measures ANOVA was performed for each of the social cognition assessments (ER-40, Hinting Task and IBT). In each model, the within-subjects factor was time (pre vs. post) and the between-subjects factor was condition (MICT vs. SE). While there were no significant effects, each model showed a non-significant trend towards greater improvement in the MICT group.

Discussion: Preliminary results suggest a trend towards a greater improvement in social cognition following the intervention in the MICT group compared to the SE group. Whether this trend becomes statistically significant will be seen upon further data collection. Altogether, this research has the potential to provide a deeper insight into social cognitive remediations for patients with schizophrenia.

F105. SENSE OF ABERRANT SALIENCE AND DELUSIONALITY IN CLINICAL AND NON-CLINICAL POPULATIONS: A SYSTEMATIC REVIEW

Chen Zhu*¹, Suzanne So²

¹Shenzhen University, ²The Chinese University of Hong Kong

Background: Anomalous experience has been theoretically proposed and empirically shown as a relevant factor in the development of delusions. A change of perceived meaning in one's lived experience is commonly reported at the early stage of delusional. Namely, what used to be normal and unremarkable starts to have unusual significance and novelty, and vice versa. Despite the fact that this sense of aberrant salience itself is not a psychotic symptom, it has

been reported to be aggregated in patients with schizophrenia and people high in psychosis proneness. A sense of aberrant salience also tends to be positively associated with the presence of delusions and delusion-like experiences. Its reduction tends to be positively correlated with the likelihood of change in delusions. Of note, such salience is not about hedonic pleasure. While some researchers have proposed that a sense of aberrant salience might be a potential prodromal marker for the development of psychosis, the relationship between a sense of aberrant salience and the severity of delusions remains unclear. Therefore, the current systematic review aimed to collate the empirical evidence on aberrant salience and delusions in clinical and non-clinical samples.

Methods: The systematic review was prepared according to the PRISMA protocol (Liberati et al., 2009; Moher et al., 2009). The inclusion criteria for studies were: measuring and reporting an association between the sense of aberrant salience and delusionality; empirical research; published in peer-reviewed journals; with English text available. Case studies and qualitative studies were excluded. Studies were also excluded if there was insufficient information to compute the effect sizes from their reports and upon request. The inclusion criteria for participants were: adult (aged 18 years or above); with delusions or delusion-like experiences. Clinical participants must be diagnosed with schizophrenia-spectrum and other psychotic disorders. Database search was conducted in November 2018 in PubMed, PsycINFO (1806 -), PsycARTICLES, and Scopus (1823 -) using “aberrant salience AND delusion*”. No limit was applied for the year of application. For all included articles, study characters, participant characters, measures of delusionality, measures of the sense of aberrant salience and effect sizes in Pearson’s r were extracted. The risk of bias was evaluated for each included study.

Results: Out of 451 records, twelve fulfilled the inclusion criteria. Common measures for the sense of aberrant salience included the Aberrant Salience Inventory (Cicero et al., 2010), the Salience Attribution Test (Roiser et al., 2009), the Experience of Aberrant Novelty and Salience (Reininghaus et al., 2016), and the Implicit Salience Paradigm (Katthagen et al. 2016). Overall, the included studies showed an acceptable level of risk of bias. Among six empirical studies that data were available ($N = 2172$), eight effect sizes were extracted (range of Pearson’s $r = 0.45 \sim 0.62$, all ps LESS THAN .05). Patients with higher delusions tended to report a higher sense of aberrant salience. All patients but three in the current review were under antipsychotic treatments at the time of the assessments. However, they still tended to present a sense of aberrant salience.

Discussion: The degree of delusionality and sense of aberrant salience tended to be positively associated in both clinical and non-clinical samples. Considering that most studies focused on the prodromal or early stage of psychosis, the relationship between a sense of aberrant salience and chronic patients awaits further research. There is also limited research on the effect of subtypes of delusional themes and antipsychotics.

F106. USING NATURAL LANGUAGE PROCESSING FOR IDENTIFICATION OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA FROM ELECTRONIC HEALTH RECORDS DATA IN THE UNITED STATES

Pin Xiang^{*1}, Mona Nili¹, James K Nelson², Carrie W Mills², Cory Pack², Randall Thompson², Joe Vasey², Joseph Parks³

¹Boehringer Ingelheim, ²Veradigm Health, ³National Council for Mental Wellbeing

Background: Schizophrenia is a chronic and debilitating condition characterized by a combination of positive and negative symptoms and cognitive impairment. Negative symptoms (NS) significantly contribute to long-term disability and the diminished functional capacity of

affected individuals. The NS domain includes five main components: blunted affect, avolition, asociality, and anhedonia. The objective of this study is to use natural language processing (NLP) to identify NS in the unstructured electronic health records (EHR) of patients with schizophrenia and to describe their characteristics.

Methods: This retrospective cohort study used patient records from the Veradigm Network EHR database spanning from January 1, 2016, to February 28, 2023. The EHR data used were sourced from ambulatory (outpatient) medical facilities throughout the United States. Adult patients (≥ 18 years) with a minimum of two schizophrenia diagnoses and at least 12 months of EHR activity prior to the first schizophrenia diagnosis (index date) were included. All unstructured texts from patient records during the study period were processed for review. A list of key terms for NS was created in collaboration with medical informatics specialists and clinical experts. For the NLP component of the study, Python scripts converted clinical notes into plain text, and Python NLP libraries segmented this text into sentences to extract context around keywords related to NS. Keywords were evaluated for false-positives using regular expressions and rule-based techniques. Patient characteristics were assessed in the 12 months preceding the index date.

Results: This study included 79,326 schizophrenia patients, with 14,992 (18.9%) having documented evidence of NS. Among those with 50 or more notes available, 41.5% had documented evidence of NS, in contrast to only 2.3% for those with 1-5 notes. Avolition was identified most often (44.0%), followed by blunted affect (41.9%), alogia (25.0%), anhedonia (22.0%), and asociality (5.4%). The most common key terms found included “poor hygiene” for avolition, “flat affect” for blunted affect, “poverty of speech” for alogia, “apathetic” and “loss of interest” for anhedonia, and “withdrawn” and “poor eye contact” for asociality. Patients with documented evidence of NS were slightly younger (49.3 vs. 51.0 years, $p < .01$) compared to those without NS and had slightly higher rates of anxiety (18.7% vs. 15.7%, $p < .01$), depression (19.0% vs. 17.3%, $p < .01$), and substance use disorder (17.7% vs. 15.4%, $p < .01$).

Discussion: This study successfully employed NLP to identify NS from an unstructured EHR database, overcoming the limitations of traditional structured databases. These results highlight the importance of advanced data analytics in psychiatric research, offering new insights into the characteristics of NS in schizophrenia. This study detected overall lower rates of documented evidence of NS. This raises the question of whether the presumed missed information using the NLP approach is due to shortcomings in the usual clinical exam for NS, the number of available notes, or the NLP methodology itself. The pattern of most predominant type of specific negative symptom reported in this study is different than several other studies that reported that decreased emotional expression is more uncommon compared to reduced social motivation. Additionally, this study reported slightly higher rates of other mental disorders in patients with documented evidence of NS. This study informs the need for future treatment strategies and healthcare policies for improving management of NS among patients with schizophrenia.

F107. THE SPATIAL LOCATION OF AUDITORY VERBAL HALLUCINATIONS IN PATIENTS WITH SCHIZOPHRENIA: SELF-REPORT AND CLINICIAN-RATING COMPARISON

In Won Chung^{*1}, Hee Yeon Jung², Se Hyun Kim³, Seong Hoon Jeong⁴, Kyuyoung Lee⁵, Yong Sik Kim⁶

¹Yong-In Mental Hospital, ²SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea, ³Seoul National University College of Medicine, ⁴DaeJeon Eulji University School of Medicine, ⁵Nowon Eulji University Hospital, ⁶NoWon Eulji University School of Medicine, Seoul, Korea

Background: The spatial location of auditory verbal hallucinations (AVHs), whether they come from inside the head (internal) or outside (external), has been thought to be one of the cardinal features that defines the phenomenology of AVHs and is associated with the severity of psychopathology in psychotic disorders.

Methods: We categorized subgroups of patients with schizophrenia according to the spatial location of AVHs as assessed by clinician-rated Psychotic Symptom Rating Scale-Auditory Hallucinations (PSYRATS-AH) and self-report Hamilton Schizophrenia Voice Questionnaire (HPSVQ) assessed on the same day. We compared the distribution of patients between groups categorized by internal, bilateral, and external spatial location according to the two scales, and explored the severity and linearity of scores by spatial location for each group of patients reclassified according to each scale. The main inclusion criterion was a score of 3 or higher on the PANSS-P3 item of hallucinations.

Results: The mean age of the 85 patients was 33.51 ± 9.75 years, and the mean duration of illness and AVH experience was 9.89 ± 6.72 and 9.23 ± 6.85 years, respectively. The patient distributions of 15 (17.6%), 44 (51.8%), and 26 (30.6%) by PSYRATS-AH and 23 (27.1%), 22 (25.9%), and 40 (47.1%) by HPSVQ, respectively, showed a significant difference and the agreement of patient distribution in groups of spatial location between the two scales was somewhat lower. The total scores and emotional component scores in three categorized groups were statistically significantly different and showed clear monotonic increase with increasingly outward localization (internal LESS THAN both LESS THAN external).

Discussion: The different patient distributions and low agreement on spatial locations between two scales are likely due to the different response wording and the ambiguity in the definition of spatial location across scales. Patients with external AVHs had more severe scores on the total and emotional component scores, suggesting greater concern about external AVHs.

F108. VALIDATION OF EPICOG-SCH SCREENING BATTERY IN FIRST EPISODE PSYCHOSIS: COHORT STUDY TO FOLLOW UP COGNITION AND FUNCTIONALITY

Rosa Ayesa-Arriola^{*1}, JULIO Bobes², M PAZ García-Portilla², Rebeca Magdalena-Herrero¹, Angel Yorca-Ruiz³, Manuel De Gracia Blanco⁴, Gemma Escartin Martin G⁵, Víctor Ortíz-García de la Foz¹, Jolanda Ruiz⁶, Silvia Zaragoza Domingo⁷

¹Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria, ²CIBERSAM UNIVERSITY OF OVIEDO, ³Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria,, ⁴Faculty of Psychology, University of Girona, Girona, Spain, ⁵Parc Sanitari Sant Joan De Déu, Barcelona, Spain, ⁶Faculty of Psychology, University of Barcelona, Barcelona, Spain, ⁷Neuropsychological Research Organization s.l (Neuropsychro), Barcelona, Spain

Background: Objective the Epidemiological Study of Cognitive Impairment in Schizophrenia (EPICOG-SCH) is a brief battery to screen for cognitive impact of schizophrenia in outpatient settings. The EPICOG-SCH includes well-known subtests available worldwide that cover key cognitive domains demonstrated to be related to a variety of functional outcomes: Letter-

Number-Sequencing-LNS, Category Fluency Test-CFT, Logical-Memory Immediate Recall-LM, and Digit-Symbol-Coding-DSC. A composite score is derived from the battery, which is based on algorithms modelled to predict patient's functionality in daily life. Functional composite scores (FWCS) showed adequate discriminant capacity in identifying patients with up to moderate disability levels with fair discriminant accuracy, areas under the curve (AUC) $\square$ 0.70, p $\square$ 0.0001 from a receiver-operating characteristic (ROC) method. A FWCS cut-off $\geq$ 96 provided the best balance between sensitivity (0.74) and specificity (0.62). We want to confirm the constancy and utility of this method in the context of first episode schizophrenia and at discharge during a follow up period.

Methods: Participants and Methods Data for the present investigation were obtained from the epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Spain. The cohort is composed by 167 patients with a diagnose of Schizophrenia and 160 healthy controls recruited between February 2001 to February 2014. For all analyses, a subset of measures was selected corresponding to the EPICOG-SCH domains as Letter-Number-Sequencing-LNS, Category Fluency Test-CFT Animals, Digit-Symbol-Coding-DSC and for Verbal Memory it was selected the Rey Auditory Verbal Learning Test (RAVLT) in substitution of Logical Memory not available in the cohort. Functional outcomes were measured by the Disability Assessment Scale (DAS) and the General Assessment for Function (GAF) scales. Functional measurements were conducted regarding premorbid, baseline set at clinical stabilization and 1, 3 year follow-up, and cognitive assessments where conducted at baseline and 1, 3 years of follow up.

Results: All patients included at baseline and a total of 122 patients and 114 Controls completed the study with a 3-year follow up were included in the analysis. We present descriptive of cognitive results by subtests and as composite scores. EPICOG-SCH composite scores were validated using Baseline results. Consistency across evaluations is also tested. A regression analysis including the different EPICOG-SCH subtests at baseline as predictors of functionality at the different time points to explore the best predictive algorithms at 1 and 3 years of patient's functionality in daily life following a first-episode. Results on predictive capacity of baseline cognition of functionality will be compared with previous results, and an additional analysis of functional impact is planned by gender and age ranges.

Discussion: Conclusions The EPICOG-SCH brief battery is administered in less than 20 minutes, proved to be a useful first to screen for the cognitive impact of schizophrenia and second to ascertain the associated functionality in daily life, validated in a cross-sectional cohort and from this study its validity at 1 and 3 years predictive capacity is described. This research work will validate the composite scores for a context of use of first-episodes schizophrenia and follow up. To date it has not been described an efficient and straightforward way for clinicians working with schizophrenia to transfer quantitative information about patient cognitive profile into real life. The EPICOG-SCH modelled FWCS global composite score provides valuable information to clinicians which can facilitate disease management, drawing a roadmap for cognitive rehabilitation, and planning of supportive resources from the community and health care system. Future research is needed to ascertain the utility of this new battery to monitor drug adjustments for outpatients and its corresponding impact on patient functionality. In addition, additional validation work and calibration of the algorithm in different world geographical regions is needed. This will provide a more accurate result reflecting variations on cultural attitudes towards patients suffering from severe mental health disorders in the community.

F109. ASSESSING EARLY-STAGE SCHIZOPHRENIA BASED ON PARALINGUISTIC ANALYSIS OF SPEECH - SYSTEMATIC REVIEW AND CASE STUDY

Julianna Olah^{*1}, Kelly Diederer¹, Thomas Spencer¹, Nicholas Cummins¹

¹*King's College London*

Background: Automated analysis of paralinguistic parameters of speech, combined with contemporary machine learning approaches could aid crucial early interventions in schizophrenia and bipolar disorder. However, the literature has not been synthesised on the efficacy of paralinguistic approaches and reported findings have not been replicated.

Methods: In this study, we first systematically reviewed the literature on paralinguistic analyses and machine learning approaches in schizophrenia. We observed that studies typically applied feature engineering and shallow learning approaches without a reproducible code base. Studies tend to report inflated accuracies (GREATER THAN 0.90) when discriminating between the speech of individuals with a full-blown disorder against the speech of healthy controls, a use-case we argue has limited clinical relevance. We then applied conventional modelling approaches and one deep learning approach (Sch-net) on the task of identifying individuals at elevated risk of developing schizophrenia. Finally, to evaluate the potential of clinical application we also tested the bias of the model for gender, age, education and ethnicity.

Results: 34 papers met our inclusion criteria. Studies that aimed to discriminate healthy control from schizophrenia could achieve high performance (highest accuracy reported was 97%), similar to papers that aimed to discriminate schizophrenia from bipolar disorder (highest AUC = 0.92). Papers on discriminating healthy control from bipolar disorder reported good performance (highest AUC = 0.8). When papers aimed to discriminate between more than 2 conditions, performance dropped to 69-77% accuracy. Studies that aimed to discriminate between different states of the same disorder reported moderate to good performance (highest performance was UAR = 0.79 with three classes and 86% accuracy with 2 -classes). Papers both applied conventional machine learning approaches and DNN-s with no clear trend in better performance in any specific algorithm type. Also, patterns of limitations appeared that might hinder the progress of the field. These include the lack of external validation, publicly available code bases and datasets, standardization of measurements, performance metrics and speech elicitation tasks and the limited considerations of applicability and early detection. The Sch-net model achieved a more moderate accuracy (0.70) for identifying individuals at elevated risk of developing schizophrenia tasks while shallow machine learning approaches reached excellent accuracy (0.879). All models were moderately biased toward reaching higher accuracy on white, female and educated individuals.

Discussion: Our work highlighted the lack of data and reproducible code in the field and how it can lead to unreliable results. Increasing reproducibility and publicly available databases could be a potential solution to overcome the vulnerability for biases and provide sufficient training data to experiment with more scalable deep learning approaches in the field to eventually complement human expertise in early mental health care.

F110. CHANGING CITIES IN ORDER TO PROMOTE RECOVERY IN PATIENTS WITH PSYCHOSIS

Philippe Conus*¹, Lilit Abrahamyan Empson¹, Ola Söderström², Marc Wintz¹, Aurora Ruggeri²

¹Lausanne University Hospital, ²Neuchâtel University

Background: The movement of deinstitutionalization has led to a reduction in the duration of hospitalization and the development of community treatment. However, this shift was not always accompanied by a necessary intervention at the population level to facilitate the integration of patients in the community. Patients therefore live in the city but nevertheless feel excluded and have no access to work and leisure activities.

Methods: We conducted video-elicitation interviews of urban walks and ethnographic observations in a community care centre in the city of Lausanne and identified factors that constitute excess of stress for patients in the city. Through a large survey, we also compared first episode psychosis and university students regarding their patterns of use of the city and perception of stress and respite in the urban environment

Results: After a first episode of psychosis, young patients avoid city centers and have no access to many of the positive aspects of the urban environment. Patients identify various domains where adaptations of the environment would facilitate their access to the enrichment cities have to offer.

Discussion: After a first episode of psychosis, patients avoid cities and are deprived of social integrations. Based on these interviews, we currently develop, in collaboration with patients, professionals and the city authorities, a set of interventions that should promote social integration of patients and facilitate their access to the city.

F111. IMPACT OF REFERRAL OUTCOME OF CLINICAL HIGH RISK OF PSYCHOSIS SUBJECTS TO EARLY INTERVENTION SERVICES IN SWITZERLAND: PRELIMINARY DATA FROM THE PSY YOUNG MULTICENTRIC STUDY

Caroline Conchon*¹, Elodie Sprungli-Toffel², Luis Alameda², Martine Cleusix², Logos Curtis³, Anne Edan⁴, Nathalie Nanzer⁴, Ana Liso-Navarro⁵, Remy Barbe⁶, Marco Armando⁷, Kerstin von Plessen⁷, Davina Genoud⁷, Barbara Bailey⁸, Philippe Stertz⁸, Evelyn Herbrecht⁸, Christian Huber⁸, Stefan Borgwardt⁹, Christina Andreou⁹, Philippe Conus¹⁰

¹General Psychiatry Service, Lausanne University Hospital and University of Lausanne,

²Service of General Psychiatry, Lausanne University Hospital and the University of Lausanne,

³Geneva University Hospitals, ⁴Child and Adolescent Psychiatric Service, Geneva University Hospitals, ⁵Medical Pedagogical Office, State of Geneva, ⁶Child and Adolescent Psychiatric Service, Geneva University Hospitals, and ⁷Medical Pedagogical Office, State of Geneva,

⁸Service of Child and Adolescent Psychiatry, Lausanne University Hospital and the University of Lausanne, ⁹University of Basel Psychiatric Hospital, ¹⁰University of Lübeck, ¹⁰Service of General Psychiatry, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL),

Background: Psychotic disorders are one of the main causes of chronic disability in young people. Subclinical symptoms ('clinical high risk for psychosis' (CHR-P)), precede the first psychotic episode by several years in the majority of patients, however, while only about a third of these patients develop full-blown psychosis, most of the CHR-P suffer from psychiatric comorbidities and have unfavourable functional outcomes. Unfortunately, a very small proportion of FEP patients have benefited from treatment in CHR-P early intervention services

(EIS), which shows the deficient pathways to care of this population. The PsyYoung project aims to improve the detection of CHR-P patients by increasing access to specialist care and reducing the pathway to care. The objectives and assumptions of the project are: (i) Increase the flow and speed of treatment by improving pathways to care; (ii) aim to reduce unnecessary referrals; (iii) improve clinical and functional outcomes and quality of life, aim for reduction in the Duration of Untreated Psychosis (DUP).

Methods: The PsyYoung project is a multicentric study involving 6 psychiatric units in three cantons (Basel, Vaud and Geneva)). The project uses a stepped-care model, that proposes an intervention which consist of the application of a standardised pathway to care model for access to EIS, harmonising the assessment batteries and practises across centers, implementing activities to increase the awareness in the general public as well as teaching and network activities targeting professionals in the education and healthcare sector. This intervention aims, among other things, to optimize detection of CHR-P by improving pathways to care, and to reduce unnecessary psychiatric treatments in patient before and during the CHR-P phase. Data are collected over a period of 2 years and 8 months, wIncluding a pre- and post-implementation phase. Each site collects its own data. Inclusion criteria: patients aged between 15 and 35 referred to an early intervention center. Changes before and after the implementation will be measured at several levels ((at service, patient, referring professionals and center levels). In the current report we will present the percentage of referred patients with a CHR-P status and those without CHR-P (ie. CHR-N), before and after the implementation.

Results: We focus on the preliminary results for the treatment and early intervention in one psychosis program (TIPP, one of the 6 centers, based in Lausanne) between March 2021 and August 2023. Before implementation, the number of CHR-P patients was 52.8% for TIPP. After implementation the number dropped to 47.2%. The number of patients with a CHR-N status was 59.2% before implementation and 40.8% after the implementation.

Discussion: These preliminary results showed a decreased percentage of CHR-N referred to TIPP suggesting that stakeholders are better informed about the CHR paradigm and also more familiar with pre-test tools proposed by PsyYoung. Updated results will be presented in SIRS 2024.

F112. ABNORMAL INTER-HEMISPHERIC EFFECTIVE CONNECTIVITY FROM LEFT TO RIGHT AUDITORY REGIONS DURING MISMATCH NEGATIVITY (MMN) TASKS IN PSYCHOSIS

Christian Valt*¹, Francisco José López Caballero², Angelantonio Tavella¹, Brian Coffman², Dylan Seebold², Pierluigi Selvaggi¹, Antonio Rampino¹, Mario Altamura³, Giuseppe Barrasso⁴, Antonello Bellomo³, Filippo Iovine⁴, Alessandro Saponaro⁵, Domenico Semisa⁶, Alessandro Bertolino¹, Giulio Pergola¹, Dean Salisbury²

¹University of Bari 'Aldo Moro', ²University of Pittsburgh School of Medicine, ³University of Foggia, ⁴ASL Barletta-Andria-Trani, ⁵ASL Brindisi, ⁶ASL Bari

Background: Psychosis is currently thought to result from functional dysconnectivity between cortical processing areas that prevents effective communication between brain regions. Accordingly, the abnormal auditory Mismatch Negativity (MMN) observed in psychosis may result from impaired communication between brain regions, even at the perceptual stages of stimulus processing. MMN studies investigating functional or effective connectivity in schizophrenia and psychotic disorders have yielded mixed results regarding the dysfunctional connectivity processes underlying blunted MMN amplitude. The variability in these results

may be due to the limited spatial resolution of electroencephalography (EEG) signals, which affects the precision of source reconstruction of neurophysiological scalp potentials for accurate analysis of connectivity between brain regions. Leveraging the superior spatial resolution of magnetoencephalography (MEG), the present MMN study investigated effective connectivity within and between auditory regions in patients with psychosis.

Methods: Analyses were performed on two different magnetic MMN (MMNm) datasets: one on duration and pitch MMNm in individuals with a first episode of psychosis (FEP, N = 35) and matched neurotypical controls (NC, N = 34); another on duration MMNm in a cohort with various diagnoses within the psychosis spectrum (N = 82) and matched NC (N = 91). We applied spectral Granger causality to MEG source-reconstructed signals to compute effective connectivity within (LL, RR) and between (LR, RL) the left and the right primary auditory cortex in two time windows after stimulus onset (50-150ms and 150-250ms). The Granger value difference between deviant and standard stimuli was considered as an index of MMNm effective connectivity. This index was first contrasted between patients and controls to detect possible group differences. It was then correlated with event-related field (ERF) amplitudes to determine the relationship between effective connectivity and MMNm peak amplitude.

Results: The first experiment showed lower MMNm effective connectivity in the theta frequency band from left hemisphere to right hemisphere auditory regions in FEP compared to NC, $F(1,64) = 4.26$, $p = .043$, especially for duration deviant stimuli, $t(65) = 3.05$, $p = .003$. Interestingly, this directional connectivity also showed the strongest correlation with MMNm peak amplitude for duration deviant stimuli, $r = .66$, $p \text{ LESS THAN } .001$. The evidence for abnormal connectivity from left to right auditory regions was replicated in the second experiment. Again, compared to controls, patients with psychosis or at clinical high risk for psychosis showed lower connectivity from left to right auditory regions, $t(170) = 2.78$, $p = .006$. The correlation between mMMN peak amplitude and effective connectivity was not replicated in this sample.

Discussion: These two experiments suggest that blunted MMNm in psychosis may reflect a deficit in inter-hemispheric communication from the left to the right auditory regions. We interpret these results as evidence for a possible directional “disconnection” in individuals with psychosis. In addition, it appears that the strength of this interhemispheric connectivity may significantly influence the magnitude of the MMNm response to duration-deviant stimuli, although further evidence is needed to substantiate this finding.

F113. PRELIMINARY DATA ON MEDICATION INTAKE IN SWISS INDIVIDUALS REFERRED TO EARLY INTERVENTION SERVICES FOR SUSPICION OF CLINICAL HIGH RISK FOR PSYCHOSIS

Elodie Sprüngli-Toffel*¹, Caroline Conchon¹, Luis Alameda¹, Philippe Golay², Martine Cleusix¹, Logos Curtis³, Anne Edan⁴, Nathalie Nanzer⁴, Ana Liso Navarro⁵, Remy Barbe⁶, Marco Armando⁷, Kerstin von Plessen⁷, Davina Genoud⁸, Barbara Bailey⁹, Philippe Sterzer⁹, Evelyn Herbrecht⁹, Christian Huber⁹, Stefan Borgwardt¹⁰, Christina Andreou¹⁰, Philippe Conus²

¹General Psychiatry Service, Lausanne University Hospital and University of Lausanne,

²Service of General Psychiatry, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), ³Young Adult Psychiatry Unit, Geneva University Hospitals,

⁴Child and Adolescent Psychiatric Service, Geneva University Hospitals, ⁵Medical Pedagogical Office, ² State of Geneva, Geneva, Switzerland, ⁶Child and Adolescent

Psychiatric Service, Geneva University Hospitals, Geneva, Switzerland and Medical Pedagogical Office, 2 State of Geneva, 7Service of Child and Adolescent Psychiatry, Lausanne University Hospital and the University of Lausanne, 8Division of Child and Adolescent, Lausanne Hospital (CHUV), 9University of Basel Psychiatric Hospital, , 10University of Lübeck,

Background: Psychotic disorders are one of the main causes of chronic disability in young people. Attenuated symptoms ('clinical high risk for psychosis' (CHR-P)), precede the first psychotic episode (FEP) by several years in the majority of patients. While only about a third of these patients develop full-blown psychosis, most of the CHR-P suffer from psychiatric comorbidities and have unfavorable functional outcomes. Unfortunately, a very small proportion of FEP patients have benefited from treatment in a CHR-P early intervention service (EIS), which shows the deficient pathways to care of this population. The PsyYoung project is a multicentric study in Switzerland that uses a stepped-wedge design to implement an intervention in Swiss EIS, in order to optimize early detection and intervention in psychosis. Through this intervention, the project wants, among other things, to reduce unnecessary psychiatric treatments in in patient before and during the CHR-P phase. The aim of this study is to assess the impact of the project intervention specifically regarding medication intake in Swiss individuals referred to early intervention services for an evaluation of CHR-P.

Methods: 576 patients aged 15-35 years have been referred to EIS for suspicion of psychosis of the six PsyYoung units. Data is collected at service level and at 4 timepoints (baseline, 4, 6 and 12 months follow-up) over a year to inform about referrals trends. The project is still in the data collection phase, so the current report examines preliminary data on medication intake in individuals referred to EIS for suspicion of CHR-P.

Results: Descriptive analysis showed 576 referrals to a PsyYoung unit between March 2021 and March 2023, of which 505 had completed data for analysis (25% CHR-P, 36.2%FEP and 37.8% CHR-N). 23.6% CHR-P patients were referred from hospitals, 29.6% of CHR-P were already on antipsychotics at referral. Pearson correlations analyses showed that the number of CHR-P patients on antipsychotic medication before referral in EIS significantly decreased over time (before and after the implementation of the PsyYoung strategy) ($r=-.192$, $p=.032$). Updated results will be presented in April 2024.

Discussion: These preliminary results suggest that the PsyYoung strategy is associated with a decrease in the number of referrals for suspicion of CHR-P who take antipsychotic medication, which is important, given the lack of evidence that antipsychotic need to be prescribe for this population. The project also gives the opportunities of a transcantonal and inter-services collaboration regarding early detection and intervention on psychosis.

F114. DOES METACOGNITIVE TRAINING (MCT) IMPROVE NEUROCOGNITIVE PERFORMANCE IN PSYCHOSIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

Clayton Jeffrey^{*1}, Danielle Penney², Genevieve Sauve³, Daniel Mendelson⁴, Steffen Moritz⁵, Martin Lepage¹

¹McGill University, Douglas Mental Health University Institute, ²Douglas Mental Health University Institute and L'Université du Québec à Montréal, ³Douglas Mental Health University Institute, Université du Québec À Montréal, ⁴McGill University, ⁵University Medical Center Hamburg

Background: Previous research has elucidated that metacognitive training (MCT) offers benefits for addressing hallmark deficits and symptoms in schizophrenia spectrum disorders. These benefits include reductions in positive symptoms such as delusions and cognitive biases, improvements in social cognition, and an overall increase in functioning. However, results from individual studies diverge regarding the relationship between MCT and neurocognition, with some showing a positive effect and others none whatsoever. A comprehensive understanding of the nature of this relationship would significantly contribute to the existing literature and provide valuable insights to clinicians regarding the potential added value of MCT as a cognitive capacity enhancing intervention for psychosis. Therefore, this systematic review and meta-analysis aim to determine the efficacy of MCT in improving neurocognitive performance (including speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning, and problem-solving) when compared against control conditions.

Methods: This systematic review and meta-analysis summarizes the existing literature considering the relationship between MCT and neurocognitive performance. Across eleven electronic databases, 1355 sources were identified, and 14 studies were included in this review. Measures of estimated effect sizes were calculated with Hedge's g , moderator analyses used Cochrane's Q statistic and significance tests to measure group differences according to control conditions including treatment as usual (TAU) and active (ACT) control interventions.

Results: Twelve studies, 11 RCT's and 1 non-RCT, were included in the main meta-analyses, consisting of 673 participants ($n_{MCT} = 345$, $n_{control} = 328$). When comparing MCT against control interventions, minimal nonsignificant differences in estimated effect sizes were observed across all six neurocognitive domains when evaluating pre-post, post-follow-up, and pre-follow-up changes in neurocognition ($g \leq 0.1$, p GREATER THAN 0.05). Likewise, moderator analyses demonstrated that no significant differences were demonstrated between TAU or ACT control condition for any of the timepoint comparisons (p GREATER THAN 0.05). Two additional studies were included in a narrative review, corroborating these findings.

Discussion: These results suggest that when compared against both passive and active control conditions, MCT does not pose a statistically meaningful difference compared to control interventions across the six neurocognitive domains assessed. This relationship was demonstrated when evaluating immediate effects (pre-post), maintenance effects (post-follow-up), and sustained effects (pre-follow-up). These findings indicate that general practice/learning effects are likely the main contributor that leads to improvement in neurocognitive performance, and not a difference of intervention allocation when considering MCT. Despite some initial positive findings, improvement of neurocognitive was never an explicit aim of MCT, however these findings help establish the specificity of its effects.

F115. DEVELOPING AND TESTING THE CLINICAL HIGH RISK FOR PSYCHOSIS SERVICES - FIDELITY SCALE (CHRPS-FS)

Mark Savill¹, Lindsay M. Banks¹, Briana Sepulveda¹, Valerie L. Tryon¹, Kathleen E. Nye¹, Christopher Blay², Michelle Carlson², Adrian F. Asbun¹, Sabrina Ereshefsky¹, Kristin LaCross², Stephanie L. Hayes¹, Tara A. Niendam¹, Donald Addington³

¹University of California Davis, ²University of California San Francisco, ³University of Calgary

Background: Fidelity scales measure the adequacy of implementation of an evidence-based practice. They are necessary to inform early stages of model development for promising

practices, support program-level quality improvement, and can facilitate research aimed at identifying, measuring, and improving the components and effectiveness of interventions.

To record what components of care early psychosis (EP) programs deliver to their clients with psychosis, numerous fidelity scales have been developed and validated. However, no tool to date has been validated to assess the specific components of care that are delivered to individuals at clinical high-risk for psychosis (CHRP), despite many EP programs also providing care for individuals with CHRP. This is problematic, as while many shared features of care exist, some treatment recommendations for CHRP do deviate from best-practice care for EP. We detail the steps taken to develop, refine, and validate the Clinical High Risk for Psychosis Services – Fidelity Scale (CHRPS-FS) tool within the EPI-CAL EP learning healthcare network.

Methods: We used a three-step development, measurement, and validation process to develop the CHRPS-FS. First, the items and rating criteria were developed following a review of the literature, focusing on identifying common and contrasting components with the First Episode for Psychosis – Fidelity Scale (FEPS-FS). Next, we explored the face validity of the tool through a Delphi consensus process with clinical and academic experts in the field of CHRP care. Items were amended based on participant feedback and sent out for additional review until consensus was achieved across GREATER THAN 80% of all items and ratings. While the Delphi study was ongoing, we tested and refined measurement practices through piloting the tool in 11 EPI-CAL EP clinics that served individuals experiencing CHRP.

Results: The review identified two components of CHRP care distinct from those detailed in the FEPS-FS. Six FEPS-FS items were removed as they were not considered relevant to CHRP care. In the piloting of the tool, the median CHRPS-FS rating scored across the eight participating clinics was 4.03 (IQR 3.72 – 4.16). The median percentage of items rated at good-to-high fidelity was 68.8% (IQR 65.6 – 78.1). In the Delphi study, 17 clinical and academic experts based in seven different counties participated. Both expert groups achieved a consensus of GREATER THAN 80% within two rounds, with feedback leading to some changes in item wording, and in the addition of an item measuring the stepped care approach. In the final version of the CHRPS-FS, six items of the FEPS-FS 1.1 were removed, three items unique to the CHRPS-FS were added, and for three items the item description remained the same, but their rating criteria were modified.

Discussion: The newly developed CHRPS-FS was found to be feasible to implement in both community and university settings, could be conducted in conjunction with a FEPS-FS assessment and alone, and was able to detect variability in service delivery between programs. Additionally, the scale component and rating criteria was found to have face validity amongst both academic and clinical experts in the field.

The CHRPS-FS could support researchers, providers, and policy makers to assess what components of care are being provided to individuals with CHRP and at what standard, within and across EP programs. This could be critical to supporting a formal validation of the team-based approach to CHRP care, could support the subsequent development of clinical practice guidelines, and could facilitate the benchmarking of CHRP care necessary for improving CHRP care standards worldwide.

F116. PATTERNS OF PRIMARY CARE USE PRIOR TO A FIRST DIAGNOSIS OF PSYCHOTIC DISORDER: A 2-YEAR RETROSPECTIVE COHORT STUDY

Paula Suárez-Pinilla*¹, Nazareth Sánchez-Gallego², Oscar Vallina-Fernández³, Alicia Ruiz-Toca⁴, Javier Vazquez-Bourgon⁵, Rocio Perez-Iglesias⁶

¹University Hospital Maqués de Valdecilla, ²University Hospital Marqués de Valdecilla, ³Hospital Comarcal Sierrallana, ⁴Hospital Comarcal de ⁵University Hospital Marqués de Valdecilla, Institute of Biomedical Research Valdecilla (IDIVAL), CIBERSAM, ⁶University Hospital Marques de Valdecilla

Background: Many patients experience early symptom before the diagnosis of a first episode of psychosis (FEP), suggesting that there may be help-seeking prior to diagnosis. A longer duration of untreated psychosis (DUP) is usually related to worse clinical and functional prognosis. General Practitioners (GPs) may play a role in detecting those subjects, as are often the first point of contact. This study examined patterns of Primary Care use preceding a diagnosis of psychotic disorder.

Methods: We reviewed health administrative records of Primary Care of 35 patients included in the Early Intervention (EI) Clinical Program for Psychosis (ITP-Can-Santander) in Spain during 2020. Patients are consecutively treated in a real-world setting EI program. Inclusion criteria were: aged from 17 to 65, and being affected by a drug-naïve FEP (affective or non-affective). Exclusion criteria were: suffering from a severe neurological disease or traumatic brain injury, severe intellectual disability or/and psychosis directly induced by illicit substances. For this study, we investigated patterns of primary care use in the 2 years prior to first diagnosis of psychosis.

Results: Mean age at diagnosis was 36.6 years, and 57% were females. Mean DUP was 9.02 months. Patients were referred to ITP-Can-Santander through different pathways: 22 from Emergencies (63%), 5 from Primary Care (14.3%), 7 from Specialist Care (20%), and 1 from other departments (2.7%). Out of 35 patients, 28 (80%) contacted with GP during the previous 2 years. Overall, 147 consultations in Primary Care were accounted, with a mean of 5.25 consultations per patient. More than 40% of FEP patients (n=15) asking for mental health related signs and symptoms, being anxiety and social problems the most frequently recorded before psychotic diagnosis. Among patients who asked about physical problems (n=13; 34%), the most common patterns of attention were diseases of the digestive system and musculoskeletal pain. However, the DUP was virtually the same for subjects that did and did not contact with GP, for those referred to the program thorough Primary Care vs other pathways, and for those who did and did not contact for mental health related symptoms. A higher sample size is needed to clarify patterns of Primary Care use prior to FEP diagnosis.

Discussion: During 2 years before the diagnosis of FEP, 8 out of 10 patients consulted their GP, and half of them sought help for mental health-related problems. Improving GP knowledge in identifying patterns of prodromal symptoms may alter to those developing psychosis, facilitating earlier referral to specialist care. Initiatives to support GPs in their role detecting FEP are warranted.

F117. A BETTER UNDERSTANDING OF GAMING DISORDER AND PROBLEM GAMBLING AMONG PEOPLE WITH FIRST-EPISODE PSYCHOSIS: A NEW PATH TOWARDS RECOVERY

Maxime Huot-Lavoie*¹, Olivier Corbeil², Laurent Béchard³, Sébastien Brodeur¹, Charles Desmeules¹, Chantale Thériault⁴, Colombe Claveau⁵, Anne-Marie Essiambre⁴, Michel Dorval⁶, Magali Dufour⁷, Amal Abdel-Baki⁸, Isabelle Giroux⁹, Yasser Khazaal¹⁰, Marie-France Demers¹¹, Marc-André Roy¹²

¹Université Laval Faculty of Medicine, ²Faculty of Pharmacy, Université Laval, ³Pharmacy Faculty, Laval University, ⁴CERVO Brain Research Centre, ⁵Psychology School, Laval University, ⁶Faculty of Pharmacy, Laval University, ⁷UQAM, ⁸Centre hospitalier de l'Université de Montréal, ⁹School of psychology, Laval University, ¹⁰Université de Lausanne, ¹¹Faculté de pharmacie de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, ¹²Faculté de médecine de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec

Background: Treatment approaches for psychotic disorders are shifting to prioritize overall patients' recovery beyond symptom control and emphasizing early intervention for first-episode psychosis (FEP). Despite these changes, comorbid conditions, such as gambling disorder (GD) and problem gambling (PG), still remain neglected and understudied. The first studies on GD and PG in young adults with FEP, conducted by our team, revealed an increased prevalence of these comorbidities compared to the general population and a significant impact on patients' recovery. Building upon this, we obtained research grants to further explore the consequences and correlates of those behavioral addictions in FEP patients.

Methods: A prospective multicenter cohort study is being conducted in two clinics for FEP in Quebec, Canada. This study should include over 600 adults aged 18 to 35, with a diagnosis of FEP (either affective or non-affective), followed for an average period of 36 months. These patients will undergo a systematic screening for GD and PG at admission and every 6 months, which will allow to: 1) quantify the prevalence of these 2 comorbidities among people with FEP and, 2) identify potential risk factors for developing problematic behaviors. Additionally, qualitative interviews will be performed with a sample of individuals with GD and PG to describe motivations underlying video gaming and gambling behaviors, their consequences on patients' lives and the efficiency of available treatment modalities for these conditions.

Results: The findings of this study will lay the groundwork for the development of tailored approaches for enhancing screening, prevention, and treatment of GD and PG adapted to the FEP population. The results will be disseminated through various channels, including a FEP-dedicated website, scientific publications, continuous education programs, and engagement with the media. Being part of an internationally recognized care model enhances the global reach of our findings. A robust network of partnerships, including mental health institutes, caregiver/patient associations, and professional organizations, supports widespread dissemination.

Discussion: FEP is often associated with problematic gambling and video gaming habits, acknowledged as a potential source of concern by the World Health Organization. However, limited data exist regarding both GD and PG in individuals with FEP. This study will help filling this gap by providing essential insights to better support the recovery of young individuals dealing with FEP.

F118. BECAUSE COGNITION EMERGES FROM CULTURE: ETHICAL NEED FOR A TRANSCULTURAL NEUROPSYCHOLOGY AND TREATMENT OPTIMIZATION IN THE PSYCHIATRY OF FIRST EPISODE PSYCHOSIS

Amelie Pavard^{*1}, Alexia Cuisniak², Nicolas FRANCK³, Tasneem Pichori⁴, Julien Plasse², Frederic Haesebaert⁵

¹CH Le Vinatier, Lyon, ²CH Le Vinatier, Lyon (France), ³University of Lyon, Vinatier Hospital, ⁴Abt Brain, Lyon (France), ⁵PSYR2 Team, INSERM U1028, CNRS UMR5292, Lyon

Neuroscience Research Center, Université Claude Bernard Lyon 1, Lyon, France, Lyon, France.

Background: The risk of developing a first episode psychosis (FEP) increases with the experience of migration (Brandt et al., 2019), often due to traumatic events and living conditions in the host country. In our early intervention services nearly 30% of users were born in a non-western country, thus increasing the amount of users in intercultural situations.

As good cognitive functioning plays a decisive role functional recovery in FEP (Lam, 2018), neuropsychological assessment is highly recommended in early intervention settings, to offer recovery and user oriented care. The anticholinergic burden of treatment (ACB) and the cultural considerations (Casaletto and Keaton, 2017) are among the most important factors influencing the interpretation of neuropsychological assessment. Indeed, cognition is a dynamic process (Barsalou, 2008): based on our experiences, we produce inferences to understand our environment, and respond accordingly. Our ways of interacting and reasoning are therefore modulated by cultural determinants. Nevertheless, neuropsychological tests are constructed according to a Western problem-solving logic, including measures of efficiency and speed. Therefore, they are not very suitable for intercultural evaluation. Elsewhere, if ACB is well-known, only moderate concordance was found among anticholinergic scales (Naples et al., 2015) and a very few studies examine the load associated to the treatment dosage. This study aims to assess the impact of both cultural and medication factors on the neuropsychological evaluation of young people with early psychosis.

Methods: We invited FEP users (half of whom were Westerners) to perform executive and attentional assesment, either through classic neuropsychological testing (TMT, Stroop, D2-R), or with Mindpulse©, a new assessment battery using culturally shared stimuli (Suarez et al., 2021). The ACB of their treatment was calculated according to Crideco anticholinergic scale (Ramos et al., 2022), an updated of ACB scale (Salahudeen et al., 2015), and cumulated with a score of low, median, or high antipsychotic defined daily dosage, as we called “total ACB”.

Results: 12 users were recruited. Non-Western group has a higher score at EPICES scale of precarity. Results show a significant test*group interaction, where the non-Western group reaction time was longer for usual neuropsychological test (TMT-B) than the occidental group, but not with Mindpulse flexibility clue (p LESS THAN .05). As total ACB shows no difference between the two cultural groups, total ACB score was correlated with error number (p = .01) and total score in Stroop inhibition test (p = .08), on executive speed (p = .08), and on flexibility clue (Mindpulse, p = .006). Data will be hence by further recruitment in the early 2024.

Discussion: These results highlight the importance of considering both the anticholinergic load and treatment dosage when assessing cognitive impacts in individuals with FEP. Given that cognition plays a crucial role in achieving improved clinical recovery and social functioning (Lam, 2018), early intervention care should incorporate treatment optimization strategies to enhance the cognitive and social functional outcomes. This study shows that classical neuropsychological tests such as TMT are not suitable in intercultural evaluation. Mindpulse© battery seems more appropriate in the executive and attentional assessment for intercultural groups. As migration serves as both a contributor to disengagement from care and a risk factor for psychotic transition, one of the imminent challenges in psychiatry and neuropsychology is the development of intercultural assessments.

F119. COMPUTATIONAL SPEECH AND LANGUAGE FEATURES FOR WITHIN- AND BETWEEN-SUBJECT SYMPTOM CHARACTERIZATION IN FIRST-EPIISODE PSYCHOSIS

Michael Spilka*¹, Anthony Yeung², Mengdan Xu¹, Bertina Jebanesan³, Wishah Khan³, Sarah Ahmed³, William Simpson¹, Jessica Robin¹, Farooq Naeem⁴

¹Winterlight Labs, ²University of British Columbia; Centre for Addiction and Mental Health, ³Centre for Addiction and Mental Health, , ⁴University of Toronto, Centre for Addiction and Mental Health

Background: Alterations in speech and language are evident in psychotic disorders, reflecting core positive, negative, and cognitive symptoms. Speech assessment and analysis using computerized approaches have the potential to enhance clinical care by providing objective and easy-to-deploy symptom screening and monitoring. Digital speech assessment may be particularly useful in first-episode populations, where monitoring symptom exacerbations and predicting relapse is crucial for timely intervention. However, it is unclear whether similar speech and language characteristics are sensitive to symptom severity differences between vs. within individuals, knowledge of which will help determine the most relevant speech-based markers for symptom screening and monitoring. In the current study, we compared between-subject and within-subject associations between speech and symptom severity in a longitudinal study of first-episode psychosis.

Methods: 43 first-episode psychosis outpatient participants underwent clinical assessments (Brief Psychiatric Rating Scale [BPRS], Scale for the Assessment of Negative Symptoms [SANS]) and completed speech tasks from the Winterlight assessment app (journaling, picture description, paragraph reading) at baseline, and at 3-, 6-, 9-, and 12-month follow-up. Participant speech and language were characterized using 74 core acoustic and linguistic features extracted from signal analysis and natural language processing of speech task recordings and transcripts. Associations between speech features and symptom severity (BPRS Total, BPRS Positive, SANS Total) were examined with linear mixed-effects models controlling for demographic characteristics (age and gender), with between-subject effects estimated using participants' subject-level mean across visits, and within-subject effects estimated using participants' visit-specific deviations from their subject-level mean.

Results: 23 unique features were significantly associated with symptom severity differences between participants, with most associations for negative symptoms (14 features), followed by overall symptoms (9 features) and positive symptoms (5 features). In contrast, 15 features were associated with symptom severity changes within participants, with the greatest number of associations with overall (10 features) and positive (9 features) symptoms, followed by negative symptoms (4 features). Both the between- and within-subject results included several linguistic feature categories, while acoustic features were only significantly associated with symptom severity between subjects. Only one feature was consistently associated with symptom severity both between- and within-subjects: greater speech graph connectivity during the journaling task was associated with greater positive symptom severity.

Discussion: Computational speech features are sensitive to symptom severity in first-episode psychosis. Although similar feature categories generally show associations with symptom severity both between and within subjects, there was little overlap in specific features, suggesting different features may be appropriate for patient screening vs. monitoring applications.

F120. SELF-STIGMA AND STIGMA RESISTANCE AFTER A FIRST EPISODE OF SCHIZOPHRENIA: CLINICAL, COGNITIVE, AND FUNCTIONAL CORRELATES AND CHANGE OVER TIME

Thanh Le*¹, Ruth Firmin², Joseph Ventura³, Kenneth Subotnik³, Keith Nuechterlein³

¹University of California, Los Angeles, School of Medicine, ²McLean Hospital/Harvard Medical School, ³University of California, Los Angeles, Department of Psychiatry and Behavioral Sciences

Background: Individuals with mental disorders experience considerable public stigma, which can lead to self-stigma, or applying and internalizing these negative beliefs and stereotypes to oneself. Most research on self-stigma has focused on individuals with multi-episode schizophrenia. Little is known about self-stigma in first-episode schizophrenia (FES), particularly regarding clinical, cognitive, and functional correlates. Moreover, there have been very few investigations on whether stigma changes over time in the context of comprehensive treatment. Of note, stigma resistance is an active process of using one's skills and experiences to challenge stereotypes at the personal level, which is then used to help peers with mental illness and advocate at the public level. This study investigated the: 1) positive and negative symptoms, cognitive, and role and social functioning correlates of self-stigma stigma and stigma resistance in individuals with first-episode schizophrenia, and 2) changes in self-stigma and stigma resistance over a 6-month comprehensive early intervention.

Methods: Ninety-two participants with FES from the UCLA Aftercare Research Program were enrolled in a 6-month comprehensive early intervention program that included medication management, weekly case management and individual supportive therapy, and psychoeducation focused on recovery and life skills. Participants were also enrolled in a 6-month RCT comparing cognitive training plus healthy living training versus cognitive training plus physical exercise. They were administered baseline measures of positive symptoms (SAPS), negative symptoms (SANS), cognition (MATRICS Consensus Cognitive Battery), and functioning (Role Functioning Scale), as well as baseline and 6-month measures of self-stigma (Internalized Stigma of Mental Illness Scale) and stigma resistance (Stigma Resistance Scale; SRS). Paired sample t-tests were used to examine changes between baseline and 6 months for the two self-stigma variables. Pearson correlations were used to investigate the baseline correlates of the self-stigma variables.

Results: Higher baseline self-stigma was associated with greater baseline severity of positive symptoms ($r = .27$, $p < .05$) and anhedonia ($r = .26$, $p < .05$), and approached significance with poorer social cognition ($r = -.19$, $p = .08$). Higher baseline stigma resistance was associated with lower severity of negative symptoms ($r = -.23$, $p < .05$), particularly anhedonia ($r = -.29$, $p < .01$), and greater social functioning with peers ($r = .23$, $p < .05$). These significant associations appear to be largely driven by Personal Identity (finding meaning in life outside their mental illness), Peer Stigma Resistance (use of one's experience to help others with stigma), and Public Stigma Resistance (ways people challenge public stigma) subscales of the SRS. Self-stigma did not significantly change over the 6-month intervention period, $t = .92$, $p = .36$. However, stigma resistance (SRS total score) increased at 6 months compared to baseline values, $t = 2.07$, $p < .05$, Cohen's $d = .27$). This significant gain over time was largely driven by increases in the Personal Cognition (cognitive strategies used to challenge negative mental illness thoughts) and Peer Stigma Resistance subscales of the SRS.

Discussion: These findings provide key information about the correlates of self-stigma of mental illness in FES, which may lead to a better understanding of self-stigma mechanisms to inform treatment development. Stigma resistance also improved over time during comprehensive intervention services. However, the modest effect size observed suggests a need for a more tailored focus on resisting stigma in the early illness stages.

F121. ASSOCIATION BETWEEN EXPOSOME SCORE FOR SCHIZOPHRENIA AND GENERAL FUNCTIONING IN REMITTED FIRST-EPISODE PSYCHOSIS: EARLY RESULTS FROM THE HAMLETT STUDY

Sterre Kamphuis^{*1}, Marieke Begemann², P. Roberto Bakker³, Sinan Guloksuz¹

¹Maastricht University Medical Centre, ²University Medical Center Groningen, ³Arkin, UMCG

Background: Psychosis spectrum disorder is known for its wide range of clinical representations, varying from complete remission to a chronic course with significant functional impairment. Evidence suggests that environmental exposures might be contributing to this variety, not only by increasing the risk for psychosis but also by influencing the course of illness. Recent studies have shown a negative association between general functioning and the exposome score for schizophrenia (ES-SCZ), a weighted score of cumulative environmental liability for schizophrenia, in patients with psychotic disorders. This replication study aims to validate and extend these findings in patients with remitted first-episode psychosis (FEP) and lays the groundwork for further longitudinal investigation of the influence of environmental exposures on psychosis liability and long-term outcomes.

Methods: Data were obtained from the baseline assessments of the ongoing HAMLETT study (Begemann et al., 2020). This multicenter pragmatic single-blind RCT investigates the effects of continuation versus dose-reduction/discontinuation of antipsychotic medication after remission of FEP on functioning, psychotic symptom severity, and health-related quality of life. In total 346 patients were randomised, who were 3–6 months in remission of their first psychotic episode (defined as a score of 3 or below on the positive scale of the PANSS (Positive and Negative Symptom Scale)). The ES-SCZ was calculated based on formerly validated estimates and included data derived from questionnaires on childhood adversity, cannabis use, hearing impairment, and bullying. Childhood adversity was assessed using the Dutch Childhood Trauma Questionnaire Short Form (CTQ-SF). The Global Assessment of Functioning (GAF, range 0-100) was used to measure general functioning. Multiple regression analyses were conducted to examine the association between GAF and ES-SCZ.

Results: Data from 123 patients were available for this analysis, including 83 men and 40 women. In this subsample, the mean age was 28.5 (SD=8.6, range: 17-54) years, mean GAF was 64.04 (SD=11.47), and mean ES-SCZ was 4.3 (SD=1.3) at baseline. The mean time between remission after FEP and enrolment in the study was 139.4 (SD=51.5) days. The ES-SCZ was significantly negatively associated with GAF ($B=-1.929$, $p=0.015$), after adjusting for age and sex. The model accounted for a small proportion of the variance in GAF (Multiple R-squared: 0.065) and was statistically significant in predicting GAF from the combined aforementioned set of predictors ($F(3,119)=2.759$, $p=0.045$).

Discussion: These preliminary results suggest that ES-SCZ shows a significant and independent association with general functioning, with age and sex as covariates. These findings confirm the previously identified negative link between ES-SCZ and functioning, this time in remitted FEP patients. More data on the previously mentioned variables are currently being collected and will allow for further investigation of the association between general functioning and ES-SCZ, whilst adjusting for other environmental factors and important clinical factors in a larger sample with repeated assessments for longitudinal analyses. We anticipate that increasing data points and the number of participants from the ongoing HAMLETT study will strengthen the model. Taken together, the use of ES-SCZ for clinical

purposes might facilitate clinical characterization and subsequently tailor clinical interventions to individual needs.

F122. COGNITIVE RESERVE AND PANSS SYMPTOMATOLOGY IN FIRST EPISODES OF SCHIZOPHRENIA

Mabel Rodriguez^{*1}, Karolina Knížková¹, Barbora Keřková¹, Aneta Siroňová¹, Aleš Hrubý¹, Monika Večeřová¹, Filip Spaniel¹

¹*National Institute of Mental Health*

Background: Heterogeneity in schizophrenia is not yet fully explored. The concept of cognitive reserve (CR) becomes increasingly important in relation to the expression of the disease. As cognitive reserve we understand the individual's ability to optimize their cognitive activity by using alternative neural networks. The relationship between CR and symptomatology has been studied in general terms. The results of the few studies indicate a correlation between CR and negative symptoms. In our study we analyzed in detail the relationship between CR and symptomatology measured with the Positive and Negative Symptom Scale (PANSS)

Methods: We assessed demographic (sex, age, education) and symptoms (PANSS) variables in a sample of 137 stable patients (46 females, aged 25.93 ± 6.47) diagnosed with either schizophrenia F20.XX(N = 77) or acute and transient psychotic disorder with schizophrenia symptoms F23.1, F23.2(N = 60), ICD-10. CR was operationalized by a composite score based on three proxy measures reflecting lifetime cognitive experiences: education, premorbid IQ, and socioeconomic status. Three different approaches were used to assess symptomatology: 1) the positive, negative, general and total symptomatology 2) the five-factor model with positive symptoms, negative symptoms, disorganization, excited, and depressed as variables 3) PANSS Negative sub-factors2: diminished expression and amotivation. To analyze the relationship between CR and PANSS symptoms, we used a Pearson's correlation. In the case of a significant relationship, the results were further explored with a multivariate multiple regression analysis

Results: 1) A significant negative relationship was found between CR and the PANSS negative symptom scale: $r = -0.28$, $p < 0.01$, 95% CI (-0.42;-0.11). No other significant relationships were observed for the other PANSS scales. Specifically, the relationship between CR and the PANSS positive symptom scale was: $r = -0.04$, $p = 0.65$, 95% CI (-0.21; 0.13); for the PANSS general symptom scale: $r = -0.094$, $p = 0.28$, 95% CI (-0.26;0.075); for the overall PANSS scale: $r = -0.17$, $p = 0.05$, 95% CI (-0.33;-0.001)

2) A significant negative relationship was observed between CR and PANSS five-factor model negative symptom scale, $r = -0.23$, $p < 0.01$ (95%CI -0.38; -0.063); Furthermore, a significant negative relationship was found between CR and PANSS excited symptom scale $r = -0.26$, $p < 0.01$, 95%CI(-0.41; -0.10). However, a significant association was not observed between CR and PANSS positive scale, $r = -0.06$, $p = 0.49$, 95%CI(-0.23; 0.11); PANSS disorganized scale $r = 0.01$, $p = 0.93$, 95%CI (-0.16; 0.17); PANSS depressed scale, $r = 0.09$, $p = 0.28$, 95%CI(-0.087; 0.26).

3) For the PANSS negative sub-factors, the diminished expression scale was mildly negatively correlated with CR, $r = -0.2$, $p < 0.05$, 95%CI (-0.36; -0.03). However, a significant association was not observed between CR and amotivation scale $r = -0.16$, $p = 0.063$, 95%CI (-0.32;0.01) The results of linear regression analysis supported CR as significant predictor of PANSS diminished expression scale $F(1, 135) = 5.62$, $p < 0.05$,

indicating that higher levels of CR were associated with lower scores on the PANSS diminished expression scale. However, the model accounted for a small amount of variance in PANSS diminished expression scores ($R^2 = 0.04$, adjusted $R^2 = 0.03$) Multivariate multiple regression analysis was utilized to examine the relationship between CR and both the PANSS negative symptom scale and the PANSS excited symptom scale, considering them as the dependent variables. Multiple multivariate regression analysis revealed that CR is a significant predictor for both PANSS negative symptom scale and PANSS excited symptom scale ($V = 0.09$; $F(2, 134) = 6.23$, $p < 0.01$). The model explained a small proportion of variance in both PANSS negative symptom scale ($R^2 = 0.05$, adjusted $R^2 = 0.045$) and PANSS excited symptom scale ($R^2 = 0.07$, adjusted $R^2 = 0.063$)

Discussion: Although CR is a significant predictor for PANSS negative symptom and excited symptom factors, in both cases it explains a small proportion of the variance. CR is like "a mini puzzle piece" in the level of the expression of symptomatology

F123. SUCCESSFUL PATIENT RECRUITMENT IN PSYCHIATRIC RESEARCH PROJECTS BRIDGING THE GAP BETWEEN RESEARCH AND CLINIC

Marianne Melau^{*1}, Lone Baandrup¹, Mette Ødegaard², Rikke Hilker¹

¹*Mental Health Services in the Capital Region Denmark, Copenhagen University Hospital,*

²*Mental Health Centre Glostrup, Mental Health Services of the Capital Region*

Background: Clinical research serves as a fundamental pillar for the development of novel and enhanced treatment interventions for patients with mental illness. Successful recruitment is vital for any research study. In the Capital Region of Denmark, the proportion of patients recruited to psychiatric research projects amounted to only 3% in 2022 and locally 6% in Mental Health Center Copenhagen. Difficulties in recruitment are common and annual project terminations due to insufficient recruitment is not unusual. This recruitment improvement intervention aims to enhance collaboration between research projects, patients within the target population, and the clinical setting to augment recruitment to research projects. The goal is to enhance the proportion of patients recruited to 20 % of the patient target population in an outpatient clinic for first-episode psychosis (OPUS team).

Methods: In the OPUS team, we aim to intervene at three levels: 1. Organizational; Facilitate collaboration between research and clinical practice by regular intersections to exchange knowledge bidirectionally and involve clinical experts in the early state of protocol drafting. In addition, shared positions for clinicians are recommended. 2. Clinical; Promote research projects through various channels by inviting researchers to present lectures for both patients and staff and provide easy overview of current research projects. 3. Individually; Involving patients and staff directly in the research process by performing interviews to gain more insight into barriers and how to improve.

Results: Data from semi-structured interviews with patients, researchers and clinical staff will be presented alongside data on recruitment success from clinical research projects recruiting from OPUS. We expect an increasing awareness of the importance of patient recruitment for clinical research and a resulting increase in patients referred to and included in clinical research projects.

Discussion: Which recruitment strategies seemed particularly effective? Which strategies can surmount obstacles, and how are their sustainability and maintenance assured?

F124. IS DURATION OF UNTREATED PSYCHOSIS ASSOCIATED WITH COGNITION AFTER FIVE-YEARS OF AN EARLY ONSET OF PSYCHOSIS?

Inmaculada Baeza*¹, Patricia Camprodon-Boadas², Gisela Sugranyes³, Daniel Ilzarbe⁴, Adriana Fortea⁵, María Moya⁶, Yamila Tosetti⁷, Josefina Castro-Fornieles⁸, Elena De la Serna⁹

¹Hospital Clinic de Barcelona, ²Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERSAM, ³Instituto de Investigaciones Biomédicas de Barcelona, CSIC-IDIBAPS-CIBERSAM, ⁴Institute of Neuroscience, Hospital Clinic de Barcelona, ⁵Hospital Clinic / Fundació Clínic per la la Recerca Biomèdica (FCRB) / Universitat de Barcelona, ⁶FCRB-IDIBAPS, ⁷Institut Clínic de Neurociències, Hospital Clínic Universitari, Fundació Clínic per a la Recerca Biomèdica, ⁸Hospital Clinic de Barcelona. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, ⁹Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM

Background: Early-onset psychoses (EOP LESS THAN 18 years of age) are more severe disorders than those with adult-onset (AOP), and age at onset results in specific patterns of cognitive interference, being in EOP worse at first months after the first-episode of psychosis (de la Serna et al, 2023). Also, duration of untreated psychosis (DUP) is longer in EOP than AOP (Baeza et al, 2023). Meta-analyses have not shown a relationship between DUP and cognition, but they included almost only studies with AOP samples (Allot et al, 2018; Bora et al, 2018). The objective of this study is to assess in a sample of adolescents who had an EOP the possible relationship between DUP and cognition after 5-years of evolution, and compare cognition domains in patients with long and short DUP.

Methods: This is a 5-year prospective longitudinal study of patients who had a first episode of psychosis before 18 years of age. A sample of healthy controls (HCs) were also included. At baseline as well as 5-year assessment both a clinical and cognitive evaluation was conducted including intelligence, verbal memory, working memory, attention and executive functions.

Results: Thirty-four patients with an EOP and 31 HC were included with both assessments. At baseline, no differences were found in age between patients and HC (15.8 ± 1.8 vs. 15.3 ± 1.4 years, respectively, $t=1.301$, $p=0.197$) and sex (70 vs 60.8% males, $\chi^2=0.835$, $p=0.386$). Both at baseline and at 5-year follow-up, patients performed significantly worse than HC in all the cognitive domains. From 34 EOP patients at baseline, 23 (67.6%) were diagnosed with schizophrenia and 11 (32.4%) with bipolar disorder at 5-year assessment. Mean DUP for patients with schizophrenia was 60.2 ± 59.4 days and for bipolar disorder: 35.9 ± 30.8 days, without reaching statistically significant differences ($t=1.065$, $p=0.300$). When we divided the sample between those with longer DUP (mean+ 1 SD) for each diagnosis, 25% of the sample had a long DUP (mean of 112.2 ± 66.8 days) vs the others (33.7 ± 24.5 days). No differences in total PANSS or any of the PANSS subscales at 5-year follow-up were shown in both groups. Comparing cognitive domains at 5-year assessment, patients with longer DUP performed worse in the executive function domain ($t=2.460$, $p=0.024$) than the other EOP patients, without significant differences in the other domains.

Discussion: Executive functions are more impaired in EOP patients with longer DUP at 5-years of follow-up, suggesting a possible neurotoxic role of untreated psychosis in younger patients. It's important to study the impact of DUP in long-term cognition in EOP patients to analyze its consequences and try to detect and treat the psychotic symptoms as soon as possible.

This study has been funded by Fundación Alicia Koplowitz, Instituto de Salud Carlos III (ISCIII) through the project PI20/00654 and co-funded by the European Union.

F125. INTEGRATION OF CLINICAL AND EEG PREDICTORS USING MACHINE LEARNING

Livia Dominicus^{*1}, Melissa Zandstra¹, Josephine Franse¹, Wim Otte¹, Arjan Hillebrand², Simone De Graaf¹, Karen S. Ambrosen³, Birte Glenthøj⁴, Andrew Zalesky⁵, Floor Scheepers⁶, Cornelis Stam⁷, Bob Oranje⁸, Bjorn Ebdrup⁹, Edwin van Dellen¹

¹UMC Utrecht, ²Amsterdam UMC, ³Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), ⁴Center for Neuropsychiatric Schizophrenia Research, CNSR, and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, ⁵The University of Melbourne, Melbourne Neuropsychiatry Centre, ⁶University Medical Center Utrecht, Utrecht, ⁷VU University Medical Center, ⁸Center for Neuropsychiatric Schizophrenia research, ⁹University of Copenhagen

Background: Prompt diagnosis and intervention are crucial for first episode psychosis (FEP) outcomes, but predicting response to antipsychotics in FEP remains a challenge. We tested (1) the performance of a prediction model with clinical features and (2) if a prediction model of combined clinical and EEG characteristics outperforms clinical models for treatment response.

Methods: Our study incorporated EEG data from 70 antipsychotic-naïve FEP patients for the clinical model and 45 for the combined model. The clinical model was tested and validated in two separated datasets (N=70 and N=45). Clinical attributes included Positive and Negative Symptom Scale (PANSS) items and sociodemographic details. From the resting state EEG data we derived relative power, functional connectivity, and network organization metrics. Treatment response was assessed via changes in PANSS positive subscale scores from baseline to a 4-6 week follow-up. We applied machine learning algorithms for the prediction of treatment response using a random forest regression model.

Results: The clinical models elucidated a 12-32% variance in symptom reduction. Integrating EEG markers showed 34% variance in symptom reduction, but did not significantly improve the clinical model. High hallucination symptom scores and a more hierarchical organization of alpha band networks (Tree hierarchy) were associated with Δ PANSS+ reduction.

Discussion: We found that both clinical and combined clinical-EEG models can be used for the prediction of treatment response in patient with a first psychotic episode. However, there is no significant difference between the clinical model and the combined model, suggesting that in practice, one can work solely with the clinical model.

F126. CANNABIS WITHDRAWAL ASSOCIATED PSYCHOSIS: CASE SERIES AND SYSTEMATIC REVIEW

Edward Chesney^{*1}, Thomas Reilly², Fraser Scott³, Ikram Slimani¹, Ananya Sarma¹, Daisy Kornblum³, Dominic Oliver², Philip McGuire²

¹Institute of Psychiatry, Psychology and Neuroscience, King's College London, ²University of Oxford, ³South London and Maudsley NHS Foundation Trust

Background: Cessation of heavy cannabis use can cause a withdrawal syndrome which is characterised by irritability, anxiety, insomnia, reduced appetite, restlessness and physical symptoms such as abdominal pain, headache and sweating. Recent reports have described cases

in which cannabis withdrawal has been associated with the acute onset of psychosis. Our objective was to identify cases of psychosis associated with cannabis withdrawal.

Methods: We searched a large electronic database of psychiatric healthcare records in South London using the Clinical Record Interactive Search system. We reviewed entries (n=1,058) which had terms related to both psychosis and cannabis withdrawal. A case was included if two psychiatrists agreed that the patient had an episode of psychosis which was ‘probably’ or ‘definitely’ associated with cannabis withdrawal. All demographic and clinical data were either extracted or reviewed by a psychiatrist. Psychotic symptoms were assessed using the OPCRIT criteria. We also completed a systematic review of previously published case reports, case series and other studies.

Results: In the health record study, we identified 69 cases in which cannabis withdrawal was associated with the onset of acute psychosis. Forty-eight cases involved a first presentation of psychosis while 21 were relapses in people with an existing psychotic disorder. Almost all cases were daily cannabis users who stopped using cannabis abruptly, and many reported severe sleep disturbance before the emergence of psychotic symptoms. Psychosis emerged within 1 week of cessation in 48 (69.6%) of cases, with the highest incidence at four days post-cessation. The symptoms with the highest prevalence were persecutory delusions (76.8%), poor appetite (71.0%), initial insomnia (69.6%), loss of insight (68.1%), and agitated activity (66.7%). A sleep disturbance of any type was identified in 62 (89.9%) of participants. Cases who continued to use cannabis after the acute episode had a much higher risk of subsequent relapse than those who did not (Odds ratio = 14.7 [95% CI: 4.3 to 60.0]; $\chi^2 = 21.1$, $p < 0.00001$). Terms describing cannabis withdrawal or the cannabis withdrawal syndrome were only written in the clinical records in a minority of cases (24; 34.8%). The systematic review identified a total of 28 cases from 16 studies. The demographic and clinical features of these cases were similar to those identified from the health record search, with a high proportion of male patients, frequent histories of heavy cannabis use followed by abrupt withdrawal, and many cases with a history of insomnia prior to psychosis onset.

Discussion: These studies comprise the largest set of cases of cannabis withdrawal associated psychosis collected to date (n=97). They suggest that the cannabis withdrawal syndrome may precipitate the onset of psychosis more often than has been recognised previously. It is important that clinicians are aware that psychotic symptoms can emerge after the cessation of cannabis use, as well as following cannabis use.

F127. CHILDHOOD TRAUMA AND TREATMENT RESISTANCE IN FIRST-EPISODE PSYCHOSIS: INVESTIGATING THE ROLE OF PREMORBID ADJUSTMENT AND DURATION OF UNTREATED PSYCHOSIS

Kristin Wold*¹, Akiah Ottesen², Camilla Bärthel Flaaten³, Trine Vik Lagerberg⁴, Kristin Lie Romm⁵, Carmen Simonsen⁶, Line Widing¹, Gina Åsbø¹, Ingrid Melle⁷

¹NORMENT, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, ²Norwegian Centre for Violence and Traumatic Stress Studies, ³NORMENT Centre for Research on Mental Disorders, University of Oslo and Oslo University Hospital, ⁴NORMENT, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, ⁵Early Intervention in Psychosis Advisory Unit for South East Norway, Oslo University Hospital, ⁶NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, ⁷Early Intervention in Psychosis Advisory Unit for

South East Norway, Oslo University Hospital, ⁷NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical medicine, University of Oslo,

Background: Early identification of treatment non-response in first-episode psychosis (FEP) is essential for outcomes, but the impact of childhood trauma (CT) is not thoroughly investigated. How the interplay between CT and other pre-treatment variables affects outcome is also not comprehensively examined. We use an adaptation of recent consensus criteria to identify FEP without early clinical recovery (no-ECR), an indicator of early treatment resistance, to investigate the relationship between CT and potential treatment resistance at one-year follow-up.

Methods: 141 participants recruited in their first year of treatment for a schizophrenia-spectrum disorder participated in this prospective one-year follow-up study. We investigated clinical status, childhood trauma (CT), premorbid adjustment (PA), and duration of untreated psychosis (DUP) at baseline and clinical status at one-year follow-up. Ordinal regression analyses were conducted to investigate to what extent PA and DUP affected the relationship between CT and one-year outcome in FEP.

Results: 55% of the FEP sample reported moderate to severe CT, with significantly higher levels of CT in the no-ECR group compared to participants with full or partial early recovery. Ordinal regression analysis showed that CT was a significant predictor for belonging to a more severe outcome group (OR=4.25). After including PA and DUP in the model, the effect of CT weakened, suggesting that PA and DUP mediate the effects of CT on early indications of treatment resistance.

Discussion: Our findings support the importance of reducing treatment delay to mitigate adverse effects of CT on clinical outcomes and the inclusion of trauma assessment in FEP services.

F128. EXPLORING MENTAL HEALTH DATA SHARING PRACTICES AND PERSPECTIVES AMONG LATINX SPANISH SPEAKING COMMUNITY PARTNERS IN THE CALIFORNIA EARLY PSYCHOSIS INTERVENTION (EPICAL) NETWORK

Karina Muro^{*1}, Sophie A. McMullen², Kathleen E. Nye¹, Valerie L. Tryon³, Steven R. Lopez⁴, Adrian F. Asbun¹, Vanessa Merino-Castenada¹, Mark Savill¹, Laura M. Tully¹, Sabrina Ereshefsky¹, Tara A. Niendam¹

¹University of California, Davis, School of Medicine, ²University of California - San Francisco, ³UC Davis Medical Center, ⁴University of Southern California,

Background: Despite being the nation's second largest racial and ethnic group in the US, very little is known about the perspectives of mental health data sharing and privacy preferences among Latinx Spanish speaking populations in early psychosis (EP) care programs. Therefore, it is imperative to understand the unique preferences and perspectives of this population if early psychosis researchers and clinicians alike want to be equitable in serving marginalized Latinx populations utilizing eHealth technology tools with end user license agreements (EULAs). This study seeks to explore the specific preferences and concerns around data sharing for Latinx Spanish speaking consumers in California.

Methods: We conducted three qualitative focus groups (provider, service user, and support persons) exploring the attitudes, beliefs, and preferences of Latinx Spanish speaking community partners to address culturally affirming practices for ethical and equitable data use. All three groups were led by bilingual Spanish speaking group facilitators. Participants

included Spanish and English-speaking community partners involved in delivering or receiving EP care within California Early Psychosis Intervention (EPI-CAL), thus, the provider and support person focus groups were conducted primarily in Spanish and the service user group was conducted in English as the language preference for the group. Key themes were identified via a content analysis of focus group transcripts.

Results: Participants included 6 providers, 5 support persons, and 2 service users. Of note, most of the support person participants identified as a mother of a loved one in an EP care program. Across all three groups transparency and provision of relevant information, mental health stigma, control and agency of data, unfamiliarity with data sharing concepts, as well as data security and protections were considered of utmost importance when considering data sharing. Notable themes of the potential to help others, overall general mistrust of data sharing, and mistrust of technology were of significance for both the provider and support person group. Additionally, rapport with clinical providers was a critical theme for service users and their support persons.

Discussion: As the use of electronic and digital tools increases in both research and clinical EP settings, it is urgent to recognize the attitudes, beliefs, preferences, and concerns around data sharing for marginalized groups such as Latinx Spanish speaking communities. To better serve Latinx community partners in EP care during this era of eHealth technology tools we must recognize the concerns of mental health stigma, unfamiliarity with data sharing concepts, and the mistrust of technology that may potentially contribute to their unwillingness to utilize eHealth technology tools. We need to carefully consider how we are introducing mental health data sharing concepts if we want to build trust and promote the involvement of sharing data among Latinx community partners participating in EP programs. Future studies should consider exploring access to available digital tools and technology as well as incorporating educational forums to increase awareness of data sharing concepts.

F129. BRAIN-WIDE DISRUPTIONS OF ANATOMICAL CONNECTIVITY PREDICT LONGITUDINAL FUNCTIONAL OUTCOMES IN ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOSIS

Sidhant Chopra^{*1}, Priscila Levi², Alexander Holmes², Edwina Orchard¹, Shona Francey³, Brian O'Donoghue³, Vanessa Cropley⁴, Barnaby Nelson³, Jessica Graham³, Hok Pan Yuen³, Kelly Allott³, Mario Alvarez-Jimenez³, Susy Harrigan⁵, Christos Pantelis⁴, Stephen J. Wood³, Patrick McGorry³, Alex Fornito²

¹Yale University, ²Turner Institute of Brain and Mental Health, Monash University, ³Orygen, ⁴The University of Melbourne, ⁵Monash University

Background: Disruptions of axonal connectivity are thought to be a core pathophysiological feature of psychotic illness, but whether they are present early in the illness, prior to antipsychotic exposure, and whether they can predict clinical outcome remains unknown.

Methods: We acquired diffusion-weighted MRI to map axonal connectivity between each pair of 319 parcellated brain regions in 61 antipsychotic-naïve individuals with First Episode Psychosis (FEP; 15-25 years, 46% female) and a matched sample of 25 control participants, along with clinical follow-up data in patients 3 months and 12 months after the scan. We used connectome-wide analyses to map disruptions of inter-regional pairwise connectivity, coupled with connectome-based predictive modelling to predict longitudinal change in symptoms and functioning.

Results: Individuals with FEP showed disrupted connectivity in a brain-wide subnetwork linking all brain regions when compared with controls ($p\text{-FWE}=0.03$). Baseline structural connectivity significantly predicted change in functional outcome at 12 months ($r=.44$; $p\text{-FWE}=0.041$), such that lower connectivity within fronto-striato-thalamic systems predicted worse outcomes.

Discussion: Diffuse brain-wide reductions of structural connectivity exist during the early stages of psychotic illness and cannot be attributed to antipsychotic medication. Moreover, baseline measures of structural connectivity can predict change in patient functional outcomes up to one year after engagement with treatment services.

F130. INDIVIDUAL MEDICATION-TAKING BEHAVIOR IN EPI CARE AND SIDE EFFECT REPORTING CONCORDANCE WITH SUPPORT PERSONS

Katherine M. Pierce^{*1}, Kathleen Marshall¹, Regina Graham¹, Kathleen E. Nye¹, Valerie L. Tryon¹, Laura M. Tully¹, Stephania L. Hayes¹, Mark Savill¹, Sabrina Ereshefsky¹, Chelyah Miller¹, Madison J. Miles¹, Merissa Kado-Wilson², Khanh Linh H. Nguyen¹, Nitasha Sharma¹, Amanda P. McNamara², Christopher K. Hakusui¹, Viviana Padilla¹, Maliha Safdar², Rachel Lowey³, Daniel J. Shapiro¹, Khalima A. Bolden-Thompson¹, Karina Muro¹, Yi Zhang¹, Andrew Padovani¹, Leigh Smith¹, Adam B. Wilcox⁴, Lindsay M. Banks¹, Renata M. Botello¹, Rebecca Grattan¹, Joy Melnikow¹, Daniel J. Tancredi¹, Bonnie Hotz¹, Sonya Gabrielian⁵, Lisa Dixon⁶, Cameron S. Carter¹, Tara A. Niendam¹

¹University of California Davis, ²University of California, San Diego, ³University of California, San Francisco, ⁴Washington University in St. Louis, ⁵University of California, Los Angeles, ⁶Columbia University

Background: Medication side effects can impact individuals' perceptions of medication efficacy and subsequent medication taking behaviors. In early psychosis intervention (EPI), taking medications as prescribed and having a support person (e.g. family) involved in care are key factors associated with better outcomes. Facilitating communication regarding medication side effects between care providers, support persons, and individuals receiving care may assist in side effect management, shared decision making, and support healthy medication-taking behaviors. As such, it is important to identify whether individuals in care and their primary support person (PSP) report similar patterns of side effects, and whether there are areas for improved communication. The present study aimed to investigate whether there are differences in PSP and individual report of medication side effects, characterize any patterns in discordance, and identify areas for potential clinical intervention.

Methods: Within the first 6 months of EPI engagement, individuals and their PSPs were asked whether the individual is prescribed any medication. Those who endorsed having at least one prescription medication were administered a modified version of the Glasgow Antipsychotic Side-effect Scale (GASS). Paired samples T-test examined GASS sum scores to determine whether individuals were systematically reporting more side effects than PSPs. Individual and PSP GASS item level endorsement concordance was evaluated utilizing Cohen's Kappa. Finally, bivariate correlations were conducted between GASS scores and measures assessing intent to remain in EPI care and taking medication as prescribed. Concordance between PSP, individual, and clinician agreement on medication status was also examined.

Results: In a total sample of 114, agreement of medication prescription status between individuals and PSPs was high ($k = .84$, $p < .001$ at baseline, $k=1.00$, $p < .001$ at 6 months). Individuals who endorsed prescription medication and completed

the GASS were examined (n=54 at baseline, n=22 at 6 months of EPI engagement). At baseline, 78% of individuals (32 of 41) reported taking any medication as prescribed 0-25% of the time; at 6 months, 93% of individuals (13 of 14) reported taking medication as prescribed 0-25% of the time. Paired sample T-test results indicated that individuals and PSPs report similar rates of side effects; however, which side effects were endorsed differed. Of the 27 side effect items assessed, at baseline individuals and PSPs agreement performed above chance on 16 items (ranging from $k=.19$ to $k=.47$). At 6 months, only 7 items performed above chance (ranging from $k=.22$ to $k=.48$). GASS scores did not significantly correlate with intent to continue or complete EPI services, medication-taking behaviors, or medication related beliefs. However, individuals' distress regarding side effects was significantly correlated with concerns that taking medication will do more harm than good ($r=.32$, $p < .05$).

Discussion: In the present sample, most individuals reported they take medication as prescribed 25% of the time or less. These medication taking behaviors may impact the number of medication side effects individuals experience and reduce overall medication efficacy. Individual and PSP agreement on side effects was moderate to low at baseline and decreased over the course of EPI. Lack of PSP and clinician awareness and communication around individuals' medication taking behavior may contribute to poor outcomes. Therefore, increased communication between individuals, their support systems, and their care teams is crucial to address individuals' concerns regarding medication and increase shared decision making.

F131. CONNECTION LEARNING HEALTHCARE SYSTEM HUB OF THE EARLY PSYCHOSIS INTERVENTION NETWORK: PROGRAM AND PARTICIPANT CHARACTERISTICS

Monica Calkins^{*1}, Megan Jumper¹, Arielle Ered¹, Fanghong Dong¹, Deepak Sarpal², Krista Baker³, Donna Bencivengo¹, Russell Margolis³, Robert Buchanan⁴, Yasmine Boumaiz⁵, Elizabeth Burris⁶, Phillip Campbell¹, Roy Chengappa², Catherine Conroy¹, Akinyi Cooke⁷, Faith Dickerson⁸, Nyasia Flowers⁷, Mandy Fauble⁹, Richard Goldberg¹⁰, Alexander Harvin⁸, Carolyn Howell⁷, Christian Kelly¹¹, Julie Kreyenbuhl¹⁰, Lan Li⁵, Alicia Lucksted⁵, Jill Marsteller¹², Alexander Moxam¹³, Denise Namowicz¹⁴, Swati Nayar², Jamie Oko¹⁵, Jessie Riggs¹, Arunadevi Saravana⁵, Rachel Scheinberg³, William Smith¹, Richard States⁹, Timur Suhail-Sindhu³, Jerome Taylor¹³, Crystal Vatz¹, Max Wolcott⁷, Christian Kohler¹, Melanie Bennett⁵

¹University of Pennsylvania, ²University of Pittsburgh, ³Johns Hopkins School of Medicine, ⁴Maryland Psychiatric Research Center, University of Maryland School of Medicine, ⁵University of Maryland School of Medicine, ⁶Wesley Family Services First Episode Psychosis Program-ENGAGE, ⁷Johns Hopkins Bayview Medical Center Community Psychiatry Program, ⁸Sheppard Pratt, ⁹University of Pittsburgh Medical Center Western Behavioral Health at Safe Harbor, ¹⁰VA Capitol Health Care Network (VISN 5) Mental Illness Research, Education and Clinical Center (MIRECC), ¹¹University of Pittsburgh Medical Center, Western Psychiatric Hospital, ¹²Johns Hopkins Bloomberg School of Public Health, ¹³University of Pennsylvania and Children's Hospital of Philadelphia, ¹⁴Children's Service Center, ¹⁵Children's Hospital of Philadelphia

Background: Connection Learning Healthcare System (CLHS), one of eight hubs of the National Institute of Mental Health funded Early Psychosis Intervention Network (EPINET),

supports uniform data collection, analysis, feedback, and infrastructure development to promote a culture of continuous quality improvement across twenty-five Coordinated Specialty Care (CSC) programs serving young people experiencing first episode psychosis (FEP) and their families in Maryland and Pennsylvania, USA. This presentation describes the CLHS hub and its constituent programs, approach for developing and implementing a hub-wide core assessment battery harmonized with the national EPINET battery, and preliminary program and participant characteristics.

Methods: Twenty-five CLHS programs provide standard components of CSC, including intake assessment, crisis intervention services, pharmacotherapy, psychoeducation, family support, employment and education services, and individual therapy, for up to two years or longer. Program capacity ranges from 15 to GREATER THAN 150 individuals (mean=37). Participant age (minimum range=13-16 years, mean=14.9; maximum range=18-40 years, mean=29.4) and duration of untreated psychosis (DUP; range=12-60 months, mean=21.6 months) are eligibility criteria for all programs. Most programs are overseen by, or embedded within, community mental health centers (57%), hospitals (39%), or academic institutions (22%). Our hub developed and implemented a computerized core assessment battery, harmonized with the national EPINET battery, selecting measures based on domain coverage, clinical utility, reliability/validity, practical utility, and utility to multiple stakeholders. The battery assesses 5 core domains: (1) Socio-Demographic, Pathways to Care, Adverse Events; (2) Symptoms and Diagnosis; (3) Psychosocial Functioning and Recovery; (4) Physical Health, Medication, and Side-Effect Monitoring; and (5) Service Engagement and Satisfaction. The battery is administered by trained program staff at admission and every 6 months thereafter through program discharge. To assist with data monitoring and enhance the CAB's clinical utility, all sites receive licenses for Tableau, a data visualization system.

Results: Between January 2021 and May 2023, 803 participants were admitted to a CLHS program and a total of 912 complete and 1662 partially completed assessment batteries across time-points were collected. Completion rates are higher for clinician administered than participant self-report measures. Admission age ranges from 12.2 to 39.7 years (Mean=20.8, s.d.=4.0). At admission, most participants are male at birth (66%), identify as African American or other minority group (54%), have a high school diploma or less (64%), and have experienced a prior psychiatric hospitalization (80%; mean prior hospitalizations=2.2). Primary diagnoses at admission are predominantly Other Specified/Unspecified Schizophrenia Spectrum Disorders (46%), Schizophrenia (17%), Schizoaffective (11%), and mood with psychotic features (11%). Mean duration of untreated psychosis (defined as time in months between first threshold psychosis symptoms and admission to an FEP program) is 13.5 months. Clinical characteristics at admission reveal moderate psychiatric symptoms, serious to moderate impairment in role and social functioning, mild antipsychotic medication side effects, and relatively high service engagement.

Discussion: As part of our learning healthcare system to improve clinical services and outcomes across two states, CLHS has implemented standardized assessment across twenty-five CSC programs. Our efforts align with those of other EPINET hubs and show that CLHS serves a diverse cohort of young people experiencing FEP. Prospective data are now being analyzed to investigate critical topics in FEP CSC, including treatment engagement, medication prescription practices, substance use, suicidality, trauma, and family involvement. Given our overall success in implementing the battery, the many potential applications in clinical research and practice, and the resources the EPINET initiative provides to CSC programs outside of the network, we recommend CSC programs engage in standardized data collection, despite some challenges. Routine assessment allows programs to track individual and program progress and outcomes and offers the opportunity to discuss this progress with young people, families, administrators, and funders. The national EPINET dataset, aggregating

data from CLHS and the other seven EPINET hubs, constitutes a novel large-scale resource allowing powerful analyses that ultimately should inform and improve FEP practice and outcomes.

F132. ADDRESSING DISCRIMINATION IN A FIRST EPISODE PSYCHOSIS POPULATION: INDIVIDUAL AND PRACTITIONER PERSPECTIVES AT THE BEGINNING OF TREATMENT

Piper Meyer-Kalos*¹, Arundati Nagendra², Grace Owens¹, Melissa Fisher¹, Mara Russell¹, Sophia Vinogradov¹

¹University of Minnesota Medical School, ²Massachusetts General Hospital

Background: Experiences of discrimination for individuals with first episode psychosis (FEP) are common, with estimates ranging from 76% to 98%. These experiences may play a role in long-term outcomes, as international research suggests that illness-related stigma may be associated with demographic, clinical, and functioning variables. Those from minoritized communities (e.g., due to their sexual orientation or race) may experience the effects of compounded forms of discrimination. Such experiences, whether in their communities or in treatment, may contribute to observed poorer outcomes, such as by delaying help-seeking and interfering with treatment engagement. In this study, we aim to understand the impact of discriminatory experiences due both to illness and belonging to a minoritized community when a person is first entering FEP treatment. Secondly, we will evaluate practitioner perspectives on broaching the topic of discrimination in treatment and training needs to address experiences of discrimination.

Methods: The sample is collected from 6 coordinated specialty care (CSC; first episode psychosis) programs in Minnesota as part of the Early Psychosis Intervention Network (EPINET). The sample of 182 individuals includes individuals with schizophrenia spectrum diagnoses, affective disorders with psychosis, and unspecified psychosis diagnoses. When individuals enter treatment in the CSC programs, a routine assessment battery is collected as standard of care at baseline and every 6 months. This project evaluates data from the Intersectional Discrimination Index (InDI) which includes 3 subscales (anticipated, day-to-day, and major discrimination). We will evaluate the relationship between experiences of discrimination and key clinical and demographic variables including race/ethnicity, age, gender, diagnosis, duration of untreated psychosis, symptoms, functioning, and service utilization. Additionally, we developed an 11-item survey to evaluate how providers discuss discrimination in treatment. We will assess how frequently practitioners bring up discrimination compared to clients and how prepared practitioners feel to address experiences of discrimination in treatment. 29 providers from 4 of the 6 FEP clinics completed the survey.

Results: At the beginning of treatment, 68% (n=124) of individuals entering CSC reported an experience of discrimination in the last 12 months and 83% reported an experience of discrimination within their lifetime. The most commonly reported types of discrimination included experiencing jokes/laughter, treated as unfriendly/rude, and treated as less smart/capable. Results from the clinician survey found that 31% (n=9) of clinicians do not feel comfortable being the first to bring up topics related to discrimination and 17% (n=5) of clinicians feel uncomfortable when responding to clients who bring up topics related to discrimination.

Discussion: Our findings associated with lifetime experiences of discrimination align with other studies that have found high rates of discrimination experiences in FEP. Upon entering early intervention treatment, people with FEP are likely to be struggling with concerns about

current or anticipated illness-related discrimination in addition to psychotic symptoms. Beyond this, those from minoritized communities may have compounded discriminatory experiences and may need additional support. As such, assessing experiences of discrimination across groups for individuals entering a CSC program may inform targeted assessment and treatment interventions at entry into a CSC program. When provided with training and support, practitioners in CSC programs could play a pivotal role in addressing the needs of those experiencing multiple types of discrimination, in turn improving outcomes for those with FEP. These data will inform strategies and training for CSC practitioners to broach and address the impacts of discrimination for individuals with FEP.

F133. PARSING INSIGHT IN FIRST EPISODE PSYCHOSIS (FEP): AWARENESS AND JUDGMENT

Hadar Hazan*¹, Vinod Srihari²

¹*Yale Medical School*, ²*Yale University*

Background: Despite the progress made in measuring and quantifying insight, there remains a persistent gap between the theoretical conceptualization and the phenomena of insight. Even after more than three decades, the study of insight in individuals with psychosis continues to present significant challenges for researchers. Despite some correlation among some of the scale, they vary greatly in the aspects they include under the term insight. Insight scales may (or may not) include cognitive aspects (awareness of having a disorder, labeling oneself as ill, awareness of social consequences of illness), need for treatment (need for treatment, its effects and benefit) symptoms-specific aspects (awareness of specific symptoms and their attribution to illness), and temporal-related aspects (whether the three previous components of insight include the present time, the past, and the future course of illness). Scales also differ in their dichotomic vs. continuous view of rating and the rater (self-report vs. clinician-rated).

Methods: We explore the varied definitions and conceptualizations of insight, noting the discrepancy between theoretical constructs and the operationalization of insight measures. We systematically review six prominent insight scales: The Scale to Assess Unawareness of Mental Disorder (SUMD), The Comprehensive Assessment of Insight (CAI), The Insight and Treatment Attitudes Questionnaire (ITAQ), The Scale for Assessing Insight in Psychosis (SAP), The Psychotic Symptom Rating Scale (PSYRATS), and The Assessment of Insight (AOI).

Results: We discuss the strengths and limitations of each scale, including their psychometric properties, theoretical underpinnings, and clinical utility.

Discussion: We conclude by highlighting the need for a more comprehensive and unified approach to measuring insight in psychosis, encompassing both cognitive and affective aspects of insight.

F134. THE ANXIOLYTIC EFFECT OF ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ali Abdolizadeh^{*1}, Maryam Hosseini Kupaie², Yasaman Kambari¹, Aron Amaev¹, Vittal Korann³, Edgardo Torres-Carmona¹, Jianmeng Song¹, Fumihiko Ueno⁴, Teruki Koizumi⁵, Shinichiro Nakajima⁶, Sri Mahavir Agarwal⁷, Philip Gerretsen⁸, Ariel Graff-Guerrero⁸

¹Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), Institute of Medical Science, University of Toronto, ²University of Toronto, ³Institute of Medical Science, University of Toronto, ⁴Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, Keio University School of Medicine, ⁵Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, Toronto, ON, Canada, MD; National Hospital Organization Shimofusa Psychiatric Medical Center, ⁶Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), Keio University School of Medicine, ⁷Institute of Medical Science, University of Toronto, University of Toronto, Campbell Family Mental Health Research Institute, CAMH, ⁸Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), Institute of Medical Science, University of Toronto, University of Toronto, Campbell Family Mental Health Research Institute, CAMH,

Background: Despite the high prevalence of anxiety in schizophrenia (SCZ), no established guideline exists for the management of these symptoms. While adjunctive antidepressants could be useful for depressive and negative symptoms, their effectiveness on anxiety has not been well studied. Moreover, the evidence is limited to support the long-term use of gamma-aminobutyric acid-A (GABA-A) receptor modulator benzodiazepines in patients with SCZ, considering its potential addictive properties; however, GABA-A receptor dysfunction has been related to the neurobiology of SCZ. Furthermore, augmentations with novel agents such as amino acid L-theanine, pregnenolone, and cannabis derivatives require more research to conclude their clinically significant benefits for anxiety in SCZ. For the management of patients with SCZ and concurrent anxiety symptoms, it is suggested to consider treatment options that are effective for both conditions. Atypical antipsychotics (AAPs) are the recommended pharmacotherapy for SCZ, and their efficacy has been reported for the treatment of primary anxiety disorders and comorbid anxiety in mood disorders including bipolar disorder. To our knowledge, the anxiolytic effect of AAP in SCZ has not been systematically reviewed. We aimed to synthesize evidence on anxiolytic effects of AAPs in patients with schizophrenia.

Methods: We systematically searched Medline, Embase, PsycInfo, and Web of Science to identify randomized controlled trials of AAPs reporting anxiety measures in schizophrenia. The search was limited to English-language articles published before January 2023. Data were pooled using a random-effects model.

Results: Among 48 eligible studies, 29 (n=7712) were included in the meta-analyses comparing AAPs to placebo, haloperidol, or another AAP for their effect on anxiety. AAPs had a small anxiolytic effect versus placebo (SMD=-0.28 (95%CI [-0.34,-0.21], p LESS THAN .00001, I²=47%, n=5576), which were associated with efficacy for positive (z=5.679, p LESS THAN .001) and negative symptoms (z=4.490, p LESS THAN .001). Furthermore, AAPs were superior to haloperidol (SMD=-0.44, 95%CI [-0.75,-0.13], p=.005, n=1068) with substantial study-level heterogeneity (I²=85%). Excluding one study of quetiapine in first-episode patients (SMD=-3.05, n=73), AAPs showed a small anxiolytic effect versus haloperidol without heterogeneity (SMD=-0.23, 95%CI [-0.35,-0.12], p=.01; I²=%0). Risperidone's anxiolytic effect was comparable to olanzapine (SMD=-0.02, 95%CI [-.24,0.20], p=.87, I²=45%, n=753) and amisulpride (SMD=0.27, 95%CI [-1.08,0.61], p=.13, I²=50%, n=315).

Discussion: While AAPs showed a small anxiolytic effect, the findings are inconclusive due to scarcity of research on comorbid anxiety in schizophrenia, heterogeneity of anxiety symptoms, and the scales used to measure anxiety. Further studies employing specific anxiety scales are required to explore antipsychotics, considering their receptor affinity and augmentation with serotonin/norepinephrine reuptake inhibitors or benzodiazepines for managing anxiety in schizophrenia.

F135. GLOBAL THICKNESS ADJUSTMENT OF REGIONAL THICKNESS MEASURES YIELDS ERRONEOUS RESULTS IN SCHIZOPHRENIA

Jessica Hua*¹, Susanna Fryer², Barbara Stuart³, Rachel Loewy⁴, Sophia Vinogradov⁵, Daniel Mathalon²

¹San Francisco Veterans Affairs Medical Center, ²University of California, San Francisco,

³Department of Psychiatry, University of California, San Francisco; San Francisco, CA,

⁴University of California - San Francisco, ⁵University of Minnesota Medical School

Background: Recent studies in psychiatric disorders, including schizophrenia and bipolar disorder, as well as the clinical high-risk for psychosis (CHR-P) syndrome, have advocated that analyses of regional thickness covary for global thickness, to support conclusions about disease-related regional specificity. Moreover, recent efforts to disseminate analytic tools to conduct age- and gender-normative modeling have incorporated global brain covariation when deriving normatively-adjusted regional measurements. These analytic approaches have been applied to large datasets, yielding seemingly definitive estimates of disease effects on regional morphometry. The current study challenges this approach on conceptual and statistical grounds, formally demonstrating its misleading impact on psychiatric comparisons. We examined regional thickness profiles from two archival magnetic resonance imaging (MRI) studies and hypothesized that: 1) covarying for global thickness will attenuate or eliminate patient group regional thickness abnormalities, 2) especially when there are patient group abnormalities in global thickness and when global and regional thickness are highly correlated.

Methods: Study 1 consists of 90 healthy control (HC), 51 CHR-P (10 individuals converted to a psychotic disorder, 23 were followed clinically for ≥ 24 months without converting), and 78 early illness schizophrenia (ESZ) participants from the University of California San Francisco. Study 2 consists of 56 HC, 83 non-affective psychosis (NAff-P), and 30 affective psychosis (Aff-P) participants from the Human Connectome Project-Early Psychosis (HCP-EP). We examined global and regional thickness correlations, global thickness group differences, and regional thickness group differences with/without global thickness covariation.

Results: Global and regional thickness were strongly correlated across groups. Global thickness was lower in schizophrenia-spectrum groups versus other groups. Regional widespread schizophrenia-spectrum group differences (large effect sizes) were eliminated with global thickness adjustment. Global thickness adjustment so distorted profiles of schizophrenia-spectrum groups that, paradoxically, adjusted scores for some brain regions were rendered abnormally increased. Further, there was a trend for CHR-P converters to have decreased global thickness versus non-converters, with complete attenuation of regional differences with global thickness covariation. In contrast, CHR-P and Aff-P did not differ from HC in global thickness, and profiles remained similar with global thickness adjustment. This distortion was further demonstrated in permutation analyses in which global thickness was randomly shuffled within groups to attenuate the typical regional-global thickness correlation. This simulation showed that distortion of true group differences only arises when global and regional thickness are highly correlated, which in nature, is most of the time.

Discussion: Depriving regional thickness of the variance it shares with global thickness removes disease-related effects and leads to erroneous conclusions, particularly when widespread cortical deficits are characteristic of the disease. These analytical decisions are important to clarify because conclusions drawn from these studies inform our understanding of disease pathophysiology and identification of prognostic biomarkers. We recommend future studies examining cortical thickness in psychiatric disorders abandon the poorly conceived practice of global thickness adjustment, and that currently disseminated analytic tools provide the option to omit global thickness adjustment.

F136. ALTERED BRAIN ACTIVATION DURING MEMORY RETRIEVAL MEDIATES THE RELATIONSHIP BETWEEN DEVELOPMENTAL TRAUMA AND PSYCHOTIC SYMPTOM SEVERITY

Ava Mason^{*1}, William Palmer², Hengyi Cao², Jean Addington³, Carrie Bearden⁴, Kristin Cadenhead⁵, Barbara Cornblatt⁶, Diana Perkins⁷, Daniel Mathalon⁸, Elaine Walker⁹, Scott Woods², Tyrone Cannon²

¹University College London, ²Yale University, ³University of Calgary, ⁴University of California, Los Angeles, ⁵University of California, San Diego, ⁶The Zucker Hillside Hospital, ⁷University of North Carolina, ⁸University of California, San Francisco, ⁹Emory University

Background: Both developmental trauma and poorer episodic memory performance are associated with an increased risk of psychotic symptoms, but the mechanisms underlying these associations remain to be established. We sought to investigate whether both memory performance and fMRI activity during episodic memory retrieval statistically mediated the relationship between trauma severity and psychotic symptom severity in youth at clinical high risk for psychosis.

Methods: Data from 795 participants in the second phase of the North American Prodrome Longitudinal Study were analysed, including the Childhood Trauma and Abuse scale and neurocognitive measures (a paired-associate episodic memory task; fPAM, Hopkins Verbal Learning Task and Brief Visuospatial Memory task). In a subsample of 198 participants, functional activity from five regions of interest associated with memory processing (inferior parietal lobe, superior frontal gyrus, inferior frontal gyrus, superior temporal gyrus, medial temporal gyrus) and data from the Scale of Prodromal Symptoms were analysed. Linear regressions were conducted to measure whether 1) trauma severity predicted delusion and hallucination severity, 2) trauma severity predicted neurocognitive measures and 3) neurocognitive measures predicted hallucination or delusion severity. Statistical mediation analysis was conducted when all paths were significant. All findings controlled for age, sex, site, racial background, parental education, IQ, and antipsychotic medication.

Results: Trauma severity significantly predicted hallucination and delusion severity ($B=0.399$ and $B=0.368$, $p < .01$) and significantly predicted the number of correct true positives ('hits') in the fPAM task ($B=-0.006$, $p=.028$). Average functional activation in the five memory-associated regions mediated 8.74% of the association between DT and hallucination severity, and 7.02% between DT and delusion severity. Inferior parietal lobe activity specifically mediated 10.08% of the association between DT and hallucination severity, and 8.70% between DT and delusion severity.

Discussion: This is the first study to report memory-associated functional brain alterations to mediate the association between developmental trauma exposure and psychotic symptom severity. Average activity from the five regions of interest and from the inferior parietal lobe

specifically mediated this association for both delusion and hallucination severity. Regarding memory performance, increased trauma severity was associated with a significantly lower number of hits within the fPAM, and reduced visuospatial memory performance was significantly associated with increased delusion severity. These findings were significant after controlling for all covariates. This study suggests a role of episodic memory processing and inferior parietal lobe activation in the association between DT and psychosis. Focusing further on these measures could provide insight into the underlying mechanism of this association, and have clinical implications in trauma-exposed individuals with psychosis.

F137. RATES AND PREDICTORS OF SERVICE DISENGAGEMENT IN FIRST EPISODE PSYCHOSIS: RESULTS FROM A 2-YEAR FOLLOW-UP STUDY IN AN ITALIAN REAL-WORLD CARE SETTING.

Lorenzo Pelizza*¹, Enrico Plazzi¹, Emanuela Leuci², Emanuela Quattrone², Marco Menchetti¹
¹*Bologna University*, ²*AUSL di Parma*

Background: Service disengagement is a major concern for “Early Intervention in Psychosis” (EIP). Understanding predictors of engagement is also crucial to increase effectiveness of mental health treatments, especially in young individuals with First Episode Psychosis (FEP). The goal of this research was to assess service disengagement rate and predictors in an Italian sample of FEP subjects treated within an EIP program across a 2-year follow-up period, within a real-world clinical setting.

Methods: All patients were young FEP help-seekers, aged 12-35 years, recruited within the “Parma Early Psychosis” (Pr-EP) program in Northern Italy. At baseline, they completed the Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) scale. Univariate and multivariate Cox regression analyses were carried out.

Results: 489 FEP subjects were enrolled in this study. Across the 2-year follow-up period, a 26% prevalence rate of service disengagement was found. Particularly strong predictors of disengagement were living with parents, poor treatment adherence at presentation and a low baseline PANSS “Disorganization” factor score.

Discussion: More than a quarter of our FEP individuals disengaged the Pr-EP program during the first 2 years of intervention. The findings of this investigation showed that a low baseline acceptance of psychosocial interventions was one of the most robust predictors of service disengagement for FEP patients entered the Pr-EP program. This result supports the meta-analytic evidence on poor treatment adherence as consistent predictive factor related to leaving EIP services, and may reflect low trust in the specialized care that EIP protocols offer to the patient and/or family members, or misconceptions about the therapeutic models provided by some service providers. Another robust predictor of service disengagement from the Pr-EP program was living with parents. This showed that family may not necessarily represent a supportive environment and that a family supportively involved with treatment might not lead to a service-user internally driven motivation to engage. Finally, an additional robust predictor of service disengagement was the presence of lower severity levels in disorganization at entry. A possible solution to reduce disengagement and to facilitate re-engagement of these young patients might be to offer the option of low-intensity monitoring and support, also via remote technology and tele-mental health care.

F138. GOING FURTHER PROCESSING SPEED IN SCHIZOPHRENIA: IMPACT OF GENETIC SUSCEPTIBILITY AND CANNABIS CONSUMPTION IN PATIENTS, CONTROLS, AND SIBLINGS

Ángel Yorca-Ruiz*¹, Nancy Murillo-García², Rosa Ayesa-Arriola³

¹Valdecilla Research Institute, ²Valdecilla Biomedical Research Institute. Research Group on Mental Illnesses, ³Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria

Background: Processing speed (PS) deficit observed in individuals with schizophrenia spectrum disorders is recognised as central aspects of the illness. Cannabis consumption in first-episode of psychosis (FEP) has been linked to PS deficit, however, this association remains under discussion as certain studies report no significant correlation between these two variables. Furthermore, the interplay that cannabis use and genetic factors may exert an influence on PS in individuals affected by schizophrenia is underexplored. This study aimed to investigate, in a family design study, whether genetic (polygenic score for schizophrenia) and environmental (cannabis use) factors influence PS.

Methods: The sample were a total of 388 participants from PAFIP-FAMILIAS project in Santander, Spain, consisting of 122 First Episode Psychosis (FEP) patients, 93 siblings, and 175 controls. Each participant provided a DNA sample, and information on cannabis use at the study's outset, and completed a neuropsychological assessment that included a PS measure: Digit Symbol Coding Test from WAIS-III. Standard quality control measures were implemented before Polygenic Risk Scores (PRS) calculation. The PRS for schizophrenia was determined using the PRS continuous shrinkage method (1). Two linear mixed models were applied, both with Digit symbol coding test scores as the outcome for PS. The first model incorporated variables such as group, intelligence, sex, and age, potentially linked to PS as fixed effects for PS, and family code as a random factor. The second model integrated polygenic scores and cannabis use as additional fixed effects.

Results: The first model explained 63% of the variance on PS ($R^2 = 0.63$), with group, intelligence, sex, age, and years of education, contributing significantly ($p < 0.05$) to the prediction of the outcome. The second model, including PRS for schizophrenia and cannabis use as predictors, significantly improved the predictive power up to 64% ($\chi^2 = 13.073$, $p < 0.001$). In this model, sex, intelligence, age, and years of education maintained significance as predictors of PS ($p < 0.010$) and cannabis was significant values as well.

Discussion: The results indicate that genetic susceptibility to schizophrenia and irregular cannabis use have significant associations with PS. Overall, more research is needed to fully understand the complex relationship between cannabis use and PS in schizophrenia, including the role of genetic factors and the timing and pattern of cannabis use.

F139. REMARKABLE COGNITIVE RESERVE IN WOMEN: A FAMILIAL MODEL ON FIRST-EPISODE PSYCHOSIS PATIENTS

Rebeca Magdaleno Herrero*¹, Nancy Murillo-García¹, Ángel Yorca-Ruiz¹, Rosa Ayesa-Arriola²

¹Marqués de Valdecilla University Hospital, IDIVAL, ²Marqués de Valdecilla University Hospital, Network Centre for Biomedical Research in Mental Health (CIBERSAM), Marqués de Valdecilla Research Institute (IDIVAL), University of Cantabria. Spain

Background: The constant need for adaptation to social, technological, and cultural changes is undeniable. In this dynamic context, Cognitive Reserve (CR) plays a crucial role in counteracting brain damage, providing greater resilience. This is especially evident in schizophrenia spectrum disorders (SSD), where higher CR was associated with a later onset and increased ability to compensate for psychotic damage. Research highlights that women showed a higher estimation of CR, influencing their approach to environmental and mental health challenges. CR, influenced by factors such as the environment and genetics, and is linked to contemporary challenges like education and healthy habits. Although a genetic influence is suggested, this relationship is imprecise. Familial aggregation, a result of genetic or environmental similarities, emerges as a crucial element by indicating familial phenotypic similarities. This study seeks to analyze CR variability by sex in patients with first-episode psychotic disorders (FEP) and their first-degree relatives, providing a comprehensive insight into how men and women experience CR and face challenges associated with the disease.

Methods: A total of 133 FEP patients and their 244 first-degree relatives (parents and siblings). The sample was divided by sex, being 170 males (82 FEP patients, 55 fathers, and 33 brothers) and 207 females (51 FEP patients, 91 mothers, and 65 sisters). CR was estimated for the entire sample by considering years of education and high-density lipoprotein (HDL) levels as proxies. Linear mixed-effects models, accounting for family identity and considering intelligence quotient (IQ) and age as random factors. Finally, the familiarity of CR was assessed through the Intraclass Correlation Coefficient (ICC).

Results: The participants who obtained the highest estimate of CR were the sisters (mean= 55.12), followed by the female FEP patients (mean= 51.50), brothers (mean= 49.61), mothers (mean= 49.37), fathers (mean= 46.68), and finally male FEP patients (mean= 45.35). Male FEP patients exhibit a significantly lower mean CR than the rest of the participants, except for their fathers. Additionally, females show a higher mean CR than males, especially female FEP patients and sisters. Specifically, female FEP patients and sisters display a significantly higher mean than male FEP patients and fathers. The levels of CR familiarity are moderate, with an ICC of 0.319. When dividing the sample by sex, we obtain a CR familiarity ICC of 0.322 for males (FEP patients, fathers, and brothers) and 0.442 for females (FEP patients, mothers, and sisters).

Discussion: Women, especially FEP patients and their sisters, exhibit higher CR and greater familial aggregation compared to men, suggesting superior adaptive capacity in the face of cognitive challenges, even during a FEP. Sex-based CR variability raises questions about the influence of familial aggregation, potentially linked to family dynamics. In Spain's social context, daughters' active participation and shared family moments are usually greater than in sons. It is plausible that they are exposed to more shared family time, thus strengthening their CR. This pattern could be more pronounced in the rural environment of Cantabria, where community cohesion and stress reduction act as protective factors. Complex family dynamics, coupled with biological and hormonal differences, could contribute to sex disparities in CR. This finding underscores the need to explore pattern transmission within families for targeted interventions addressing individual and familial factors influencing CR variability.

F140. THE IMPACT OF GENETIC BACKGROUND ON INFLAMMATORY RESPONSE IN SCHIZOPHRENIA

Philomena Hallford^{*1}, Antonia Pritchard¹, Ryan McLean¹

¹*University of the Highlands and Islands*

Background: Schizophrenia is a debilitating neurological condition with a prevalence of about 1% in the general population and with a heritability of between 64-81%. Familial high penetrance copy number variants (CNVs) have been identified that confer increased heritable risk to schizophrenia. Environmental and lifestyle are also important factors and several studies have suggested a role for the immune system in the development of schizophrenia.

Maternal immune activation during foetal development has been linked to the risk of developing schizophrenia: maternal circulating cytokines, TNF α , IL-1 β and IL-6, were elevated in the mothers of offspring who later developed psychosis. Previous studies have shown differences in response to IFN γ and cell type specific effects of IL-6 but not to IL-1 β between schizophrenia patients and controls. Human induced pluripotent stem cells (hiPSCs) have provided vital insights in the study of neurodevelopmental disorders in the past decade. A recent study showed that IFN γ -treatment of hiPSC- neural progenitor cells (NPCs) from healthy controls increased neurite outgrowth, a cellular phenotype associated with neurodevelopmental disorders. Examination of how CNVs associated with schizophrenia development are influenced by immune factors have not been undertaken.

Methods: The hiPSCs used in this study were cell lines from patients diagnosed with schizophrenia and (a) family members carrying the established schizophrenia associated 16p13.11 microduplication CNV; (b) siblings with defined CNVs without known association with schizophrenia; and control cell lines, with no known neurodevelopmental disorders and defined population CNVs. The hiPSCs were developed into embryoid bodies, and then further differentiated to NPCs by culturing with SMAD inhibitors and neural differentiation factors. Pro-inflammatory cytokines were used to treat hiPSC-derived NPCs, to mimic a maternal environmental change that may influence neurodevelopment. Phenotypes and parameters being examined included neurosphere migration assay; scratch migration assay; RNAseq; NPC cell toxicity and death assays.

Results: The hiPSC lines have been successfully differentiated to give neural progenitor cells and these have been characterised using immunohistochemistry and flow cytometry with antibodies against the NPC markers nestin and Pax-6: with the differentiated cells show high levels of expression of both. While experiments are currently still on-going, to date, the neurosphere migration assay, scratch migration assay and proliferation assays, have been carried out in cases and controls in response to IFN γ stimulation have been completed. Work is continuing to increase the numbers of both schizophrenia with defined CNVs and control hiPSC derived NPCs that will be examined for further parameters, including RNAseq and more assays.

Discussion: This study aims to address several hypotheses: There are differences in the cellular phenotypes and parameters between hiPSC-derived NPCs from patients with schizophrenia and control subjects; hiPSC-derived NPCs from schizophrenia patients show different response to inflammatory triggers and cytokines compared with those from control subjects; and there are differences in the response of hiPSC-derived NPCs to pro-inflammatory challenges between schizophrenia samples with different genetic backgrounds. While analyses are on-going, our early data currently suggests that differences reported in the literature of gene expression after treatment with IFN γ might be influenced by the CNVs present in schizophrenia patients. Future work will be to establish the precise gene(s) present in regions of CNV deletion/duplication that influence these responses.

F141. ASSOCIATION OF SCHIZOPHRENIA POLYGENIC RISK SCORES WITH TREATMENT-RESISTANCE

Clement Zai*¹, Kosar Teymouri², Mahbod Ebrahimi³, Ayesah Mohuiddin⁴, Pratyusha Attaluri⁴, Maria Tampakeras⁴, Natalie Freeman⁵, Gwyneth Zai⁶, Daniel Mueller⁴, James Kennedy⁴, Arun Tiwari⁴

¹University of Toronto and CAMH, ²Center for Addiction and Mental Health, ³Centre for Addiction and Mental Health, University of Toronto, ⁴Centre for Addiction and Mental Health, ⁵Centre for Addiction and Mental Health (CAMH), ⁶Centre for Addiction and Mental Health; University of Toronto

Background: Psychotic symptoms persist in a significant proportion of patients after at least two antipsychotic medication treatment trials. These patients are considered to be treatment resistant and clozapine is often prescribed for this patient population. Studies have attempted to examine the genetic factors underlying treatment resistant schizophrenia, with most recent studies reporting associations with polygenic risk score (SCZ-PRS) for schizophrenia based on summary statistics from earlier genome-wide association studies (GWAS).

Methods: We conducted a polygenic risk score analysis of treatment resistance using the latest (Phase 3) schizophrenia GWAS summary statistics in our sample of 156 schizophrenia or schizoaffective disorder patients of European ancestry. We used PRS-CS-auto to calculate standardized SCZ-PRS from summary statistics of the latest schizophrenia GWAS (leave-one-out; Trubetskoy et al, 2022). We ran logistic regression to test the effect of SCZ-PRS on the risk of treatment resistance based on clozapine use status, with sex, age, and the first two population principal components as covariates.

Results: We found higher SCZ-PRS to be associated with being treatment resistant (beta=0.54, SE=0.21, p=0.012). Patients in the top 10% of SCZ-PRS were at 4.76 folds the likelihood of being treatment resistant compared to the other patients (p=0.006), after adjusting for covariates.

Discussion: Our findings support the potential use of genetic risk scores for schizophrenia in predicting treatment outcomes. We will replicate these results in additional in-house samples and present a summary of the latest evidence in a meta-analysis.

F142. THE SPECIFICITY OF ENDOPHENOTYPES

Michael Herzog*¹, Simona Garobbio², Dario Gordillo³, Maya Roinishvili⁴, Eka Chkonia⁵, Andreas Brand²

¹EPFL, ²Brain Mind Institute, EPFL, ³École Polytechnique Fédérale de Lausanne (EPFL), ⁴Free University of Tbilisi, Beritashvili Centre of Experimental Biomedicine, ⁵Tbilisi State Medical University, Free University of Tbilisi

Background: Schizophrenia has a high heritability, still, single genetic mutations contribute very little to the disease. For this reason, endophenotypes, i.e., tests targeting aspects between the genotype and the phenotype, are of crucial interest.

Methods: We tested a visual backward masking procedure in ? patients, ? siblings, first-episode patient, ? depressive patients, and ?? controls. EEG was recorded during the task and blood taken for genetic analyses. In backward masking a target stimulus is presented for a few milliseconds and followed by a masking stimulus, which strongly impedes the visibility of the target. We also tested performance in the Wisconsin-Card sorting test and a body ownership task.

Results: Visual backward masking was strongly deteriorated in the patients compared to controls and their relatives. Effect sizes are large with a Cohen's d of ??. Relatives performed

significantly worse than controls, indicating that masking is, indeed, targeting trait rather state markers, which is crucial for an endophenotype. First episode patients were also deteriorated compared to controls further supporting the notion that masking deficits are present before disease onset. Depressive patients showed no differences to controls indicating that masking is specifically sensitive to schizophrenia. The N1 amplitudes of the EEG were strongly diminished in the patients compared to controls. Genetically, we found that a mutation in the nicotinic alpha 7 receptor explained the masking deficits in the patients. Based on these results, we conclude that patients are impaired in enhancing weak neural signals, e.g., related to the shortly presented target, which usually goes unnoticed if there is no special need to attend to it. Importantly, performance in the masking endophenotype did not correlate with performance in the two other endophenotypes, i.e., the WCST and the body ownership task

Discussion: Visual backward masking is a promising endophenotype of schizophrenia, which relates genetic insights to the phenotypes of the disease. Cholinergic dysfunctions may explain a wide range of deficits in schizophrenia, in particular, abnormalities wherever information needs to be stabilized. Backward masking performance does not correlate with performance in other tests indicating that there are many trait deficits at work. Combining endophenotypes may, hence, be a promising tool to understand the heterogeneity of the disease in a high dimensional space spanned by a battery of tests.

F143. ASSOCIATION BETWEEN SLEEP-RELATED POLYGENIC SCORES AND LITHIUM RESPONSE IN BIPOLAR DISORDER

Marina Zafrilla-López^{*1}, Miriam Acosta-Díez¹, Daniel Herrera-Escartín¹, Maria Guardiola-Ripoll², Anna Giménez-Palomo³, Pilar Alejandra Saiz⁴, Carme Barrot¹, Esther Jiménez⁵, Sergi Papiol⁶, Victoria Ruiz⁷, Patricia Gavín⁸, Leticia González-Blanco⁹, Thomas G Schulze¹⁰, Mar Fatjó-Vilas¹¹, Antoni Benabarre¹², Marina Mitjans¹³, Barbara Arias¹⁴

¹University of Barcelona, ²FIDMAG Research Foundation; CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III., ³Hospital Clínic de Barcelona; Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ⁴CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III; University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto de Neurociencias del Principado de Asturias (INEUROPA), Servicio de Salud del Principado de Asturias (SESPA), ⁵CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III; Hospital Clínic de Barcelona; Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ⁶CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich. Max Plank Institute of Psychiatry, ⁷Hospital Clínic de Barcelona., ⁸Hospital Clínic de Barcelona, ⁹CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III; University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto de Neurociencias del Principado de Asturias (INEUROPA)., ¹⁰Institute University Hospital, LMU Munich; Johns Hopkins University School of Medicine; University of Barcelona, ¹¹FIDMAG Research Foundation; University of Barcelona; CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, ¹²CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III; Hospital Clínic de Barcelona; Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS); University of Barcelona, ¹³University of Barcelona; Biomedicine Institute of the University of Barcelona (IBUB); CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III; Institut de Recerca Sant

Marina Zafrilla-López

Background: Bipolar disorder (BD) has disrupted circadian rhythms, affecting sleep, arousal, and inducing evening chronotype. Moreover, genetic risk factors for BD susceptibility overlap with risk for sleep disorders and determinants of chronotype (Rohr and McCarthy., 2022). Lithium (Li) treatment is the first-line choice of long-term mood-stabilizing therapy in BD although only between 24%-45% of the patients are excellent responders (ExRp) (Riedinger et al., 2023). Li also seems to stabilize sleep and activity rhythms in ExRp by affecting cellular circadian rhythms, increasing morningness and having beneficial effects in sleep (Rohr and McCarthy., 2022). This study aimed to evaluate the polygenic burden of seven sleep-related traits in a group of BD patients excellent responders (ExRp) to Li compared to non-responders (non-Rp).

Methods: We estimated the polygenic burden of morningness, sleep duration, ease of getting up, napping, daytime dozing, insomnia, and snoring in a sample of 96 European BD patients (DSM-IV-TR) recruited from the Bipolar Disorder Program of the Hospital Clinic of Barcelona and Mental Health Services in Oviedo, that were categorized as Ex-Rp (N=58; 50% females) and non-Rp (N=38; 44.74% females) based on the reduction of 50% of the episodes. Whole-genome profiles were obtained using Infinium Global Screening Array-24 v3.0 BeadChip (Illumina) in peripheral blood. Polygenic Scores (PGS) were calculated with PLINK based on the results of the Genome-wide analysis of Jansen et al., (2019) with the clumping-and-thresholding approach. Logistic regression models were calculated with R Studio 4.1.2. To estimate the risk increase, the sample was divided into quartiles of increasing polygenic load, and the extreme quartiles were compared using SPSS 27.0.

Results: Morningness, insomnia, daytime dozing, and napping are associated with Li response in our sample, and they explain, respectively 6.28% (p-value= 0.032), 1% (p-value= 0.008), 5.15% (p-value= 0.049), and 1.01% (p-value= 0.007). No association was found when using the PGS for sleep duration, ease of getting up, or snoring (p-value GREATER THAN 0.05). In addition, a higher genetic load of morningness and napping increased the probabilities of being an ExRp (OR= 3.40; 95% CI (1.027-11.257); χ^2 p-value= 0.042, and OR= 6.86; 95% CI (1.448-17.271); χ^2 p-value= 0.009, respectively), and insomnia of being an non-Rp (OR= 0.22; 95% CI (0.062-0.794); χ^2 p-value= 0.017), but there was not significative tendency for daytime dozing.

Discussion: Our results align with previous studies indicating that ExRp to Li have more polygenic burden for morningness (Rohr and McCarthy., 2022). As this is a genetic risk, it could indicate that the mechanisms by which Li exerts responsiveness overlap with those that cause the chronotype shift. Also, BD has a higher prevalence of sleepiness than controls (Walz et al., 2022), and Li is used to treat some sleep-related disorders for its beneficial effects on sleep (Miller and McCall., 2022), being consistent with our dozing and insomnia results. Also, short naps improved cognitive performance (Dutheil et al., 2021).

F144. THE DIFFERENTIAL ASSOCIATIONS OF NEGATIVE SYMPTOM DIMENSIONS AND CORTICAL THICKNESS IN FIRST EPISODE PSYCHOSIS

Arsime Demjaha*¹, Silvana Galderisi², Birthe Glenthøj³, Celso Arango⁴, Armida Mucci², Andrew Lawrence¹, Owen O'Daly⁵, Matthew J. Kempton¹, Simone Ciufolini¹, Lone Baandrup⁶, Bjørn H. Ebdrup⁷, Roberto Rodriguez-Jimenez⁸, Maria Diaz-Marsa⁹, Covadonga Diaz-Caneja¹⁰, Inge Winter-van Rossum¹¹, Rene Kahn¹², Paola Dazzan¹, Philip McGuire¹

¹IOPPN, KCL, ²University of Campania Luigi Vanvitelli, ³Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Center Glostrup, University of Copenhagen, Glostrup Denmark – and University of Copenhagen, ⁴Hospital General Universitario Gregorio Marañón, ⁵King's College London, ⁶Center for Neuropsychiatric Schizophrenia Research, Mental Health Center Glostrup and Mental Health Center Copenhagen, ⁷Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, ⁸Instituto de Investigacion Sanitaria Hospital 12 de Octubre, ⁹Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, CIBERSAM, School of Medicine, Universidad Complutense de Madrid., ¹⁰Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense, ¹¹UMC Utrecht, ¹²University Medical Centre Utrecht, Brain Centre Rudolf Magnus,

Background: Recent work has linked negative symptoms to cortical thickness (CTh) alterations in several brain areas, particularly in frontal and temporal regions. To our knowledge, no studies to date, have investigated how these may relate to underlying negative symptom dimensions: Expressive Deficit (ED) and Social-Amotivation (SA). We examined the associations between these dimensions and cortical thickness in a large sample of antipsychotic-naïve or minimally treated patients with First-Episode Psychosis (FEP).

Methods: T1-weighted structural MRI brain scans were acquired from 178 antipsychotic - naïve or minimally treated patients recruited as part of the multi-center OPTiMiSE study. CTh was examined using FreeSurfer version 6.00, QDEC (Query, Design, Estimate Contrast) tool, using the General Linear Model (GLM). Site, age and Total Intracranial Volume were used as covariates and, multiple comparisons were corrected via Monte Carlo z-field simulation at p LESS THAN 0.05 (2-tailed).

Results: The SA dimension was associated with reduced CTh in the left superior frontal gyrus ($p = 0.005$), the left precentral gyrus ($p = 0.003$), the left rostral middle frontal gyrus ($p = 0.01$), the left medial orbitofrontal gyrus ($p = 0.02$), and the right cuneus ($p = 0.002$). The DE was associated with only one region, the right postcentral gyrus ($p = 0.001$).

Discussion: Our findings indicate that negative symptom dimensions are differentially associated with cortical thickness. The results are unlikely to be affected by treatment or illness chronicity since they are evident in predominantly untreated FEP patients.

F145. THE SHARED GENETIC ETIOLOGY OF ANTISOCIAL BEHAVIOUR, SCHIZOPHRENIA, SUBSTANCE USE AND RELATED BRAIN MORPHOLOGY

Megan Campbell^{*1}, Alexey Shadrin², Olivia Wootton¹, Dennis van der Meer³, Markos Tesfaye³, Natalia Tesli⁴, Ole Andreassen³, Dan Stein¹, Unn Haukvik³, Jaroslav Rokicki⁵

¹University of Cape Town, ²NORMENT, Institute of Clinical Medicine, University of Oslo and NORMENT, Oslo University Hospital, ³University of Oslo, ⁴University of Oslo and Oslo University Hospital, ⁵SIFER Centre of Research and Education in Forensic Psychiatry, and NORMENT Norwegian Centre for Mental Disorders Research, Oslo University Hospital

Background: Individuals with antisocial behaviour (ASB) exhibit increased risk of substance use disorders, likely linked to shared genetic vulnerabilities and overlapping neural pathways involved in reward processing and impulse control. This susceptibility is further accentuated by the comorbidity of ASB with a number of psychiatric disorders, a finding that again points

to the potentially important role of shared genetic underpinnings. Despite this there remains a paucity of work examining the shared genetic etiology of ASB, related neuropsychiatric traits and relevant brain regions.

Methods: Using GWAS of ASB ($n=50,252$), surface area and thickness of cortical frontal regions, volumes of the amygdala nuclei, and psychiatric and substance use phenotypes, we utilized Linkage Disequilibrium Score Regression (LDSC) to assess the genetic correlation between these phenotypes. We then leveraged genetic overlap to boost discovery of genomic loci associated with ASB, and to identify specific variants associated with both ASB and each phenotype, using the conditional/conjunctional false discovery rate (cond/conjFDR) approach. FUMA was used for functional analyses.

Results: Using LDSC, we identified significant genetic correlations between ASPD and drinks per week ($r_g=0.28$; $p=1.33 \times 10^{-9}$), cannabis ($r_g=0.37$; $p=1.91 \times 10^{-8}$), bipolar disorder (BD, $r_g=0.20$; $p=1.95 \times 10^{-5}$), major depressive disorder (MDD, $r_g=0.53$; $p=1.09 \times 10^{-15}$) and marginally significant correlations with caudal anterior cingulate surface area ($r_g=-0.17$; $p=0.04$), superior frontal surface area ($r_g=0.18$; $p=0.03$), and global measures of cortical surface area ($r_g=-0.15$; $p=0.02$) and thickness ($r_g=-0.13$; $p=0.04$) and ICV ($r_g=-0.2$; $p=0.01$). A total of 54 loci, representing 127 independent variants, became significant after conditioning on related psychiatric disorders (8 SCZ, 7 BD, 11 MDD), substance use traits (18, drinks per week; 10, cannabis use) and the corpus callosum (11 anterior, 7 mid anterior, 8 central, 6 mid posterior, 9 total CC). These variants have been associated with schizophrenia, disruptive behaviour, risk taking behaviours, substance use disorders and cortical surface area in prior GWAS. Two biological processes were implicated: ethanol oxidation and metabolism.

Discussion: Our results reveal a complex genetic relationship between substance use, psychiatric traits, and ASB. We provide strong evidence for existence of distinct genetic loci exhibiting pleiotropic effects in both ASB and related traits. Our findings provide convergent evidence to suggest that substance use traits and psychiatric disorders have shared genetic underpinnings with ASB.

F146. THE ROLE OF ANXIETY AND DEPRESSIVE SYMPTOMS IN THE RELATIONSHIP BETWEEN COVID-19 PERSEVERATIVE COGNITION AND SUBCLINICAL PSYCHOTIC SYMPTOMS: A SERIAL MEDIATION ANALYSIS

Natalie Wing Tung Chu¹, Ryan Sai Ting Chu¹, Joe Kwun Nam Chan¹, Corine Sau Man Wong¹, Gabbie Hou Sem Wong¹, Janet Hiu Ching Lei¹, Yuen Kiu So¹, Vivian Shi Cheng Fung¹, Albert Kar Kin Chung¹, Calvin Pak Wing Cheng¹, Krystal Chi Kei Lee¹, Heidi Ka Ying Lo¹, Wai Chi Chan¹, Wing Chung Chang^{*1}

¹*The University of Hong Kong*

Background: The COVID-19 pandemic has affected almost every aspect of human lives. Widespread fear of disease infection and social-distancing policies may lead to perseverative cognition, a repetitive and uncontrollable thought on negative content. Psychotic-like experiences are subclinical delusional ideas and perceptual disturbances that serve as a risk factor for the development of mental health disorders like psychosis, depressive disorders and anxiety disorders. Prior studies suggested that perseverative cognition is associated with a higher risk of experiencing these subclinical psychotic symptoms (PS), but the potential roles of mediators were understudied. This study aimed to investigate the mediating role of anxiety and depressive symptoms on the relationship between perseverative cognition with COVID-19 and subclinical PS among the public during the fifth wave of the pandemic in Hong Kong.

Methods: 13,964 community-dwelling adults aged 18 or above completed a survey between March 15 to April 3, 2022 to understand their mental wellbeing and adaptation to the fifth wave of the COVID-19 pandemic. The fifth wave of the pandemic was the most disastrous wave and peak of the COVID-19 pandemic in Hong Kong. Serial-mediation models were adopted to investigate the role of potential mediators, anxiety and depressive symptoms, on the relationship between COVID-19 perseverative cognition and subclinical PS with socio-demographics as covariates. Perseverative cognition with COVID-19 was assessed by The Obsession with COVID-19 Scale (OCS) while psychotic-like experiences were assessed by items from The Community Assessment of Psychic Experiences-Positive scale (CAPE-P15) questionnaire. A weighted score of subclinical PS for each participant was derived by multiplying frequency and distress scores from 4 CAPE positive symptom items that measured persecutory ideation, bizarre experiences, and auditory and visual perceptual abnormalities. Depressive and anxiety symptoms were assessed by the Patient-Health-Questionnaire-9 (PHQ-9) and the Generalised-Anxiety-Disorder-7 scale (GAD-7) respectively.

Results: COVID-19 perseverative cognition, anxiety and depressive symptoms were all positively correlated with one another. The serial mediation model revealed a partial mediation effect of anxiety ($\beta=0.047$ [0.031–0.063]), depressive symptoms ($\beta=0.007$ [0.004–0.011]), and anxiety-depressive symptoms ($\beta=0.087$ [0.071–0.105]) on the relationship between COVID-19 perseverative cognition and subclinical PS. Among the three mediation paths, the majority of mediation effects can be attributed to the anxiety-depressive symptoms pathway (62%), followed by the anxiety (33%) and depressive symptoms (5%) pathway.

Discussion: The current study affirms the importance of anxiety and depressive symptoms in mediating the relationship between perseverative cognition and subclinical PS. It is essential to develop strategies targeting anxiety and depressive symptoms to reduce the occurrence of subclinical PS in view of stressors such as a pandemic. Our current findings imply that such strategies may be applicable in preparation for future pandemics.

F147. LONG-TERM PATIENT FUNCTIONING AND ILLNESS BURDEN ASSOCIATED WITH COGNITIVE IMPAIRMENT AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Kira Griffiths¹, Min Min Chan¹, Theresa Cassidy^{*2}, Mayowa Oyesanya¹, Rifqi Alkhatib¹, Suzanne St. Rose², Rashmi Patel³

¹Holmusk Technologies Inc, ²Boehringer Ingelheim Pharmaceuticals, Inc., ³King's College London

Background: Cognitive impairment (CI) and negative symptoms (NS) are core features of schizophrenia, but the evidence base for specific treatments is limited. Research typically uses standardized psychometric scales to measure these symptom domains, and studies have reported significant associations with long-term outcomes such as treatment resistance, hospitalization, unemployment, and increased risk of poor treatment adherence. The current study analysed real-world data from electronic health records (EHR) to identify clinician-reported CI and negative symptoms in a large and representative sample of patients with schizophrenia and to investigate associations with real-world clinical outcomes.

Methods: This is a retrospective study using de-identified electronic health record data from patients receiving mental healthcare across 25 mental health providers in 15 US states between 1999-2021. NeuroBlu v22r3 was used to assemble a cohort of adult (GREATER THAN 18years) patients with schizophrenia (ICD-9: 295*; ICD-10: F20*). Index date (baseline) was

defined as the first recorded schizophrenia diagnosis and baseline variables were extracted at index ± 14 days. Presence of cognitive impairment, negative symptoms or positive symptoms was defined as having one or more clinician-documented symptom within these symptom domains derived from free-text documented during mental status examination (MSE) using natural language processing (NLP) models. Cox and negative binomial regression were used to investigate associations between baseline symptom presentation and 1) time to first psychiatric hospitalization 2) number of unique inpatient visits and 3) total duration of inpatient days. For time to psychiatric hospitalization, data were censored at 18-months. For frequency of inpatient visits, patients with follow-up LESS THAN 3 months were excluded and an offset term was included in each model whereby the follow-up duration for a patient was defined as time from index to last recorded visit date. For descriptive statistics, the duration of inpatient visits was defined as the total duration of days spent in an inpatient setting calculated from the mean length of inpatient hospitalization by averaging the annualized cumulated length of day across all patients. Covariates included age, gender, race, year of index, clinic type, plus baseline psychotherapy exposure, illness severity (CGI-S), functioning (GAF) pharmacological prescriptions, psychiatric comorbidities, and social features.

Results: Patients with CI at baseline were at increased risk of psychiatric hospitalization (total $n = 4,469$ patients, Hazard Ratio (HR) = 1.19, 95% CI = 1.04-1.37, $p = 0.01$), and had a significantly higher total length of inpatient stay ((total $n=3,799$ patients, Incidence Rate Ratio (IRR) = 1.23, 95% CI = 1.06-1.43, p LESS THAN 0.01) compared to patients without documented cognitive symptoms. The mean (SD) annualized total number of inpatient days for those with CI was 30.7 (53.2) days, compared to 29.0 (49.4) days for those without documented CI. Presence of both positive symptoms and negative symptoms were also associated with increased risk of hospitalization (positive: HR= 1.65, 95% CI = 1.39-1.96, p LESS THAN 0.01; negative: HR=1.61, 95% CI=1.37-1.89, p LESS THAN 0.01) and increased frequency and length of inpatient stays across follow-up (positive: visits: HR=1.57, 95% CI=1.32-1.88; duration: IRR = 1.60, 95% CI = 1.34-1.92, all p LESS THAN 0.0000001; negative: visits: IRR = 1.55, 95% CI = 1.32-1.89; duration: HR = 1.59, 95% CI = 1.35-1.89, all p LESS THAN 0.0000001). Other covariates associated with increased risk of hospitalization included higher baseline illness severity (CGI-s) and lower baseline functioning (GAF). Prescription of a mood stabilizer, negative housing features and negative financial features also increased hospitalization risk. Similar associations were found between these clinical features and number of days of inpatient hospitalization. Exposure to psychotherapy at baseline was associated with substantially reduced risk of psychiatric hospitalization (HR=0.35, 95% CI = 0.28-0.43, p LESS THAN 0.01) across follow-up, plus a reduced number and duration of inpatient visits.

Discussion: Results demonstrate that patients with clinician-documented negative and cognitive symptoms are at increased risk of poor outcomes and higher inpatient resource utilization and that this effect is in part independent of positive symptoms. These findings support the growing body of evidence that implicates cognitive impairment in the long-term illness burden of schizophrenia. Additionally, cognitive and negative symptoms in schizophrenia are likely underreported in RWD sources. The potential overlapping relationship between cognitive and negative symptoms in schizophrenia highlights the need to measure each of these symptom domains to better identify patient sub-groups for treatment. Treatments which target these symptom domains hold potential to reduce personal and economic burden associated with the disorder. Associations between psychotherapy and better outcomes may reflect a cohort who are relatively more well and less likely to experience an exacerbation in illness across follow-up.

Funding: Funding for the studies presented was provided by Boehringer Ingelheim.

F148. MULTIPLE EXPOSOME-WIDE ASSOCIATION STUDIES OF PSYCHIATRIC DISORDERS IN THE UK BIOBANK

Angelo Arias-Magnasco^{*1}, Lotta-Katrin Pries¹, Bochao D. Lin², Sinan Guloksuz³

¹*School for Mental Health and Neuroscience, Maastricht University Medical Centre*, ²*School for Mental Health and Neuroscience, Maastricht University Medical Centre, Brainclinics Foundation, Institute of Biomedical Informatics, Bioinformatics Center, School of Basic Medical Sciences, Henan University*, ³*Maastricht University Medical Centre, Yale School of Medicine*

Background: Investigating non-genetic factors in mental health has traditionally followed a hypothesis-driven approach targeting selected exposures. By conducting multiple Exposome-Wide Association Studies (ExWAS) using the UK Biobank data, this study aims to systematically explore the complex network of nongenetic factors associated with psychiatric disorders including psychotic disorders.

Methods: In this study, we analyzed the Mental Health Survey data from the UK Biobank (UKB project number: 55392). The outcomes were self-reported presence of psychotic disorders, anxiety disorders, bipolar manic episode, depressive disorders, eating disorders, personality disorders (PD), and neurodevelopmental disorders. After quality control, 315 predictors were included in the analyses. First, an ExWAS of each psychiatric disorder was conducted in two equally split discovery and replication datasets, applying stringent Bonferroni correction to adjust for multiple testing ($P \text{ LESS THAN } 1.59 \times 10^{-4}$). Subsequently, variables associated with each psychiatric disorder were tested in a multivariable model per outcome.

Results: The study included 155,247 participants (57% females; mean age 55.94 years). In the discovery dataset, significant associations were identified across psychiatric disorders: 72 variables (23%) for psychosis, 61 variables (19%) for mania, 186 (59%) for depression, 170 variables (54%) for anxiety, 77 variables (24%) for personality disorders, and 45 variables (14%) for neurodevelopmental disorders. The replication dataset confirmed these associations with high replication rates: 78% for psychosis, 92% for anxiety, 74% for bipolar mania, 94% for depression, 81% for eating disorders, 85% for personality disorders, and 67% for neurodevelopmental disorders. Subsequent multivariable analyses revealed significant associations for 26 variables in psychosis, 65 in anxiety, 21 in bipolar mania, 80 in depression, 35 in eating disorders, 23 in personality disorders, and 16 in neurodevelopmental disorders. Strikingly, these analyses consistently showed associations of both childhood and adulthood traumatic experiences, as well as sleep issues, with each of the psychiatric disorder category. Cannabis use was also significantly associated with psychosis, bipolar mania, anxiety, and depression but not with personality disorders, eating disorders, and neurodevelopmental disorders. Uniquely, eating disorders showed specific associations with dietary patterns, such as reduced meat consumption, and gastrointestinal issues. For the neurodevelopmental disorders, a particular association observed was increased time spent on the computer.

Discussion: Our systematic investigation revealed unique and shared associations of mental health outcomes with both well-studied and unexplored variables. Our findings particularly highlight the importance of traumatic experiences for all mental health disorder categories. Our study offers a systematically constructed map of nongenetic factors associated with psychiatric disorders to guide the future work.

F149. VALIDATION OF THE KOREAN VERSION OF THE MALTREATMENT AND ABUSE CHRONOLOGY OF EXPOSURE (MACE) SCALE

Hyejin Sim^{*1}, Hyeyoon Kim¹, Seoyoung Kim², Euitae Kim²

¹Seoul National University, ²Seoul National University Bundang Hospital

Background: Adverse childhood experiences (ACE) during critical stages of brain development can result in a lifelong susceptibility to a broad spectrum of adverse health outcomes. In contrast to existing tools designed for the retrospectively assessment of early adversity in adults, the Maltreatment and Abuse Chronology of Exposure (MACE) scale investigates exposure to various adverse childhood experiences. It also explores the timing and duration of this exposure, which is useful for identifying developmental periods, particularly sensitive to childhood adversity. The present study aims to provide a Korean version of the MACE and to evaluate its psychometric properties.

Methods: The 52-item MACE was translated from English to Korean and administered as a self-report measure through an online survey. Participants also completed the Childhood Trauma Questionnaire (CTQ) and other psychiatric symptom-related scales to investigate convergent and predictive validity. To investigate test-retest reliability, participants completed MACE a few weeks later.

Results: The results from Rasch analysis and Anderson likelihood ratio tests showed that a 52-item version reliably captures exposure to the 10 types of ACEs. The MACE severity and multiplicity scores exhibited excellent convergent validity with the CTQ scores. Also, as compared to CTQ total scores, the MACE scores were more strongly associated with psychiatric symptoms.

Discussion: Overall, the Korean version of the MACE-52 comprehensively assessed past exposure to early childhood adversity in adults, had acceptable psychometric properties, and is a reliable tool for addressing sensitive periods for childhood adversities and associations with other mental health problems.

F150. BIOPSYCHOSOCIAL EXPOSURE TO THE COVID-19 PANDEMIC AND THE RELATIVE RISK OF SCHIZOPHRENIA: INTERRUPTED TIME-SERIES ANALYSIS ON A NATIONALLY REPRESENTATIVE

Stephen Levine^{*1}, Arad Kodesh¹, Yael Travis-Lumer², Yair Goldberg², Sophia Frangou³, Avi Reichenberg⁴

¹University of Haifa, ²Israel Institute of Technology, ³Icahn Medical School, Mt. Sinai Hospital, University of British Columbia, ⁴Icahn School of Medicine at Mount Sinai

Background: Studies of the association between biopsychosocial exposure to the COVID-19 pandemic and the risk of schizophrenia have yielded conflicting results. These studies were conducted early in the pandemic and did not take into account factors such as lockdowns or actual COVID-19 infection. Consequently, we investigated the link between COVID-19 biopsychosocial exposure and the onset of schizophrenia.

Methods: Interrupted time-series study design (that is quasi-experimental) was conducted based on Israeli electronic health records from 2013 to 2021 with national coverage. The interval of the COVID-19 pandemic biopsychosocial exposures from March 2020 to February 2021 was classified as exposed, otherwise unexposed. The effect of the COVID-19 pandemic on incident schizophrenia was quantified by fitting a Poisson regression and modeling the

relative risk (RR) and 95% confidence intervals (CI). Projections were made for three scenarios spanning from the third lockdown to a 10-month period, aiming to forecast incident schizophrenia rates and establish their corresponding 95% prediction intervals (PI).

Results: The population (N = 736,356) yielded 4,310 cases of incident schizophrenia over time. In the primary analysis the period exposed to the COVID-19 pandemic compared to unexposed was associated with a reduced RR (RR = 0.81, 95% CI = 0.73, 0.91, p LESS THAN 0.001). This conclusion was not attenuated in 12 sensitivity analyses, including scrutinizing lockdowns and COVID-19 infection status. Two of three forecast scenarios projected an incident increase post-pandemic over 10 months (6.74, 95% PI = 5.80, 7.84; 7.40, 95% PI = 6.36, 8.60).

Discussion: The decreased risk of schizophrenia observed during the pandemic implies that there was no immediate triggering of new onsets, either by the virus itself or the psychosocial challenges induced by the pandemic. However, the anticipated increase in presentations following the relaxation of restrictions holds significance for clinicians and healthcare policy.

F151. PERCEPTUAL JUDGMENTS AND METACOGNITIVE EFFICIENCY IN SCHIZOPHRENIA

Alexandra Straková*¹, Vladimír Ivančík¹, Natália Čavojská¹, Hana Hollá Kutlíková¹, Ján Pečeňák¹, Anton Heretik¹, Michal Hajdúk¹

¹*Comenius University,*

Background: Previous findings have underscored the multidimensional nature of impairments in individuals with schizophrenia (SCZ), encompassing perceptual, metacognitive, and neurocognitive deficits. Moreover, visual perceptual abnormalities contribute to distressing experiences associated with psychosis. Metacognitive deficits are increasingly recognized as a key aspect explaining real-world functioning in SCZ, yet with mixed evidence on the nature of the impairment. This study aims to compare the performance of individuals with SCZ and healthy controls (HC) on a perceptual judgment task including a metacognitive assessment of one's performance. A secondary aim was to analyze associations among task performance, symptoms, and neurocognition.

Methods: Sample consists of 38 individuals with schizophrenia spectrum disorders (age M = 36.66; SD = 8.86; 55% female) and 38 age- and sex-matched HC (age M=36.40; SD=8.82; 55% female). Psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) and Community Assessment of Psychic Experiences (CAPE-42). Snowy Picture Task was used to assess perceptual judgments (total score, d-prime, response bias). Metacognitive parameters were computed using meta-d (sensitivity) and M-ratio (efficiency). Neurocognition was assessed using Symbol Coding, Trail Making Test, and Verbal Fluency Test and was administered only to a part of the sample (N=25). Group differences were analyzed using t-test and Mann-Whitney U test. Associations between variables were analyzed using Spearman's rank correlation.

Results: SCZ group had a significantly lower total score in perceptual task (U=942.5; p=0.021, r=0.305). There was no significant group difference in d-prime, response bias, meta-d, and M-ratio. In SCZ group, agitation and mania (BPRS) were associated with poorer perceptual judgments (rs=-0.338; p=0.038), lower perceptual sensitivity (rs=-.342; p=0.036), and lower M-ratio (rs=-.411; p=0.024). M-ratio was further negatively correlated with positive symptoms (BPRS) (rs=-0.435; p=0.016). Self-reported psychotic symptoms (CAPE-42) were not associated with perceptual and metacognitive judgments in SCZ. However, meta-d was negatively correlated with subjective reports of positive (rs=-0.652; p LESS THAN 0.001),

negative ($r_s=-0.683$; $p < 0.001$), and depressive symptoms ($r_s=-0.608$; $p < 0.001$) in HC. In SCZ group, aberrant perceptual discriminability and d-prime were negatively associated with neurocognitive deficits (r_s from -0.42 to -0.51). There was no significant association between neurocognitive and metacognitive deficits in SCZ group.

Discussion: Individuals with SCZ showed deficits in visual discrimination. Altered visual perception was associated with symptoms of agitation, mania and neurocognitive deficits. We found no significant differences in metacognitive performance between groups. However, M-ratio was linked to objectively assessed positive symptoms, agitation and mania in SCZ but not to self-reported psychotic symptoms. Lower meta-d was accompanied by more frequent self-reported psychotic experiences in HC but not in SCZ, suggesting that this mechanism may be affected by other factors in SCZ.

F152. PATIENTS WITH SEVERE MENTAL ILLNESS IN THE GENERAL EMERGENCY DEPARTMENT: CLINICAL CHARACTERISTICS, QUALITY OF CARE AND CHALLENGES

Sharon Taub^{*1}, Noa Menkes-Caspi², Shiri Kamhi- Neshet³, Amir Krivoy³

¹Geha Mental Health Center, ²Geha Data Research Center, ³Geha Mental Health Center, Tel-Aviv University

Background: Morbidity and mortality rates are notably higher in individuals with schizophrenia and other severe mental illnesses (SMI) compared to the general population. The causes to this excess morbidity include increased risk of cardio-vascular disease, metabolic syndrome and other causes, such as infectious diseases and malignancy. People with SMI often have a lower access to health care services and the medical care they receive is known to be suboptimal due to various reasons, including psychosocial stressors and negative stigma of care providers. Consequently, treatment in the acute care setting, rather than community setting, is relatively more common among people with SMI. Yet, data on the characteristics of the treatment given in the general emergency department (ED) for this population is prominently lacking. This study aims to explore the medical care in the ED for people with SMI compared to control population. We hypothesize that patients diagnosed with SMI will differ in their complaints, course of ED workout and length of stay in comparison to control population.

Methods: In this nested case- control study data was retrieved from the largest health maintenance organization in Israel – Clalit Health Services (CHS). We extracted data on all adult patients (age 18-65 years) CHS members who referred to general ED in CHS hospitals during the years 2018-2022. Patients diagnosed with SMI (ICD-10 codes for schizophrenia, schizoaffective disorder and bipolar disorder) were randomly matched with a control group of ED patients without SMI, based on age, sex, socioeconomic status, Charlson comorbidity index and ED facility, in a 1:3 ratio. The two groups were compared regarding parameters of ED management and outcomes, including workout (lab tests and imaging), specialist consultations, length of ED stay, hospitalization and mortality. Main complaints at ED arrival were clustered into seven categories: traumatic injury, pain, weakness, fever, cardiac symptoms, gastrointestinal symptoms and respiratory symptoms. The comparisons were further conducted for each cluster separately. Significance was set at $p < 0.05$ for all statistical tests and computer software used for data analyses were R and SPSS.

Results: The total sample ($n=92,848$) included ED patients with SMI ($n= 23,212$) and without ($n= 69,636$). Most common ED admission reasons in both groups were pain (29.2% of all ED

visits, and 26.5% among people with SMI), traumatic injury (20.5% and 17.2%) and cardiac symptoms (8.4% of all ED visits and 7.8% among people with SMI). Patients in the SMI group had higher rates of diagnosed diabetes mellitus and chronic obstructive pulmonary disease compared to the control group (14.2% vs. 12.3% and 4.4% vs. 2.3%, respectively, $p < 0.001$). ED workout for patients with SMI lasted longer with mean length of stay of 4.1 hours compared to 3.6 hours ($p < 0.001$) in the control group and significant time differences were observed for most ED admission reasons. No significant differences were observed between groups regarding rate of imaging in respiratory cases and troponin blood level measurement when presented with cardiac complaints. ED management in the SMI group included more specialist consultations for trauma cases (12.8% vs. 8.1%), cardiac (9% vs. 6.7%) and weakness complaints (33.2% vs. 29.5%) compared to controls. Additionally, Individuals with SMI presented with respiratory symptoms and fever needed hospitalization in higher rates. Mortality over time was almost twice as high among SMI group (5.7% vs. 2.7%). **Discussion:** ED workout was similar between patients with and without SMI for most main complaints. Yet, people with SMI needed more specialist consultations, their ED visits were more prolonged and they were hospitalized more often. All of which is linked with higher rates of morbidity and complexity in treatment. As expected, mortality rates during follow-up period were higher among this group. We conclude that, on average, individuals with SMI treated in the ED received treatment as good as people without SMI in most of the study parameters, despite possible stigma. Nevertheless, special awareness and more integrated resources are required in order to improve the management and the physical health care of people with SMI.

F153. VALIDATING ICD-CODE-BASED CASE DEFINITIONS FOR PSYCHOTIC ILLNESS ACROSS THREE HEALTH SYSTEMS

Anthony Deo^{*1}, Victor M. Castro², Ashley Baker³, Devon Carroll⁴, Joseph Gonzalez-Heydrich⁵, David C. Henderson⁶, Daphne J. Holt⁷, Kimberly Hook⁸, Rakesh Karmacharya⁹, Joshua L. Roffman¹⁰, Emily M. Madsen¹¹, Eugene Song¹², William G. Adams¹³, Luisa Camacho³, Sarah Gasman³, Jada S. Gibbs¹⁴, Rebecca G. Fortgang¹⁵, Chris J. Kennedy¹⁶, Galina Lozinski³, Daisy C. Perez¹⁷, Marina Wilson¹⁸, Ben Y. Reis¹⁹, Jordan W. Smoller²⁰

¹Rutgers University, ²Research Information Science and Computing, Mass General Brigham, ³Boston Medical Center, ⁴Boston Children's Hospital, University of Rhode Island, ⁵Boston Children's Hospital, Harvard Medical School, Tommy Fuss Center for Neuropsychiatric Disease Research, Early Psychosis Investigation Center, ⁶Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, ⁷Massachusetts General Hospital, Harvard Medical School, ⁸Harvard T.H. Chan School of Public Health, ⁹Harvard Medical School, Center for Genomic Medicine, Massachusetts General Hospital, Chemical Biology and Therapeutic Science Program, Broad Institute of MIT and Harvard, Schizophrenia and Bipolar Disorder Program, McLean Hospital, ¹⁰Massachusetts General Hospital and Harvard Medical School, ¹¹Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, Center for Precision Psychiatry, Massachusetts General Hospital, ¹²Massachusetts General Hospital, ¹³Boston Medical Center, University Chobanian and Avedisian School of Medicine, ¹⁴Rutgers New Jersey Medical School, ¹⁵Massachusetts General Hospital, Harvard University, ¹⁶Center for Precision Psychiatry, Massachusetts General Hospital, Boston, ¹⁷Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, ¹⁸Center for Precision Psychiatry, Massachusetts General Hospital, Boston, Psychiatric and Neurodevelopmental Genetics Unit,

Center for Genomic Medicine, Massachusetts General Hospital, ¹⁹Predictive Medicine Group, Harvard Medical School, Computational Health Informatics Program, Boston Children's Hospital, ²⁰Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Center for Precision Psychiatry, Massachusetts General Hospital, Stanley Center for Psychiatric Research, Broad Institute

Background: Early detection of psychosis is critical to improve outcomes. Increasingly, algorithms derived from electronic health record (EHR) data are being developed to predict or detect untreated mental health outcomes such as psychosis. The performance of such algorithms depends on the validity of the case definitions they use, which are typically based on diagnostic codes. To date, data on the validity of psychosis-related diagnostic codes has been limited. In this study, as part of an effort to develop algorithms to detect undiagnosed psychosis, we evaluated the positive predictive value of ICD codes for psychotic illness across three independent healthcare systems.

Methods: Using EHRs at three large health systems in the Boston area, ICD codes comprising primary psychotic disorders and mood disorders with psychosis were grouped into five higher-order groups: schizophrenia - unspecified state, schizoaffective disorder, other unspecified psychosis and/or psychotic disorders, major depressive disorder with psychosis, and bipolar disorder with psychosis. For each of the five code groups, the first instance of a psychosis diagnostic code was selected for evaluation. Up to 100 patient records from each group at each health system (total records = 1,133) were sampled for chart review and clinical confirmation by experienced clinicians using the full EHR and a structured chart review tool. Positive predictive values (PPVs, the probability of chart-confirmed psychosis given ICD psychosis codes from each diagnostic code group) were calculated across multiple treatment settings at the three participating health systems.

Results: Overall, PPVs across all diagnostic groups exceeded 70% and were comparable across the three hospital systems including Massachusetts General Brigham (MGB) 0.72 [95% CI 0.68-0.77], Boston Children's Hospital (BCH) 0.80 [0.75-0.84], and Boston Medical Center (BMC) 0.83 [0.79-0.86]. Of the five diagnostic code groups, schizoaffective disorder PPVs were consistently the highest across sites: 0.80 [0.69-0.90] at MGB, 0.90 [0.80-1.01] at BCH, and 0.92 [0.87-0.97] at BMC. PPVs for major depressive disorder with psychosis showed the greatest variation across sites: MGB 0.57 [0.45 – 0.69], BCH 0.73 [0.64 – 0.83], BMC 0.79 [0.71 – 0.87]. To increase the likelihood that the first documented code indeed captured first-episode psychosis (FEP), we further excluded cases with any prior chart evidence of a previously diagnosed psychotic disorder or treatment for psychosis. PPVs for FEP were substantially lower (0.08 – 0.62) when these restrictions were applied.

Discussion: Using EHRs from three health systems, we found that the first documented diagnostic (ICD) code for psychotic illness accurately captures true episodes of psychosis but was a poor index of FEP. These data have important implications for the development of risk prediction models designed to predict or detect undiagnosed psychosis.

F154. PREMATURE MORTALITY IN INDIVIDUALS WITH NON-AFFECTIVE PSYCHOSIS: A 20-YEAR RETROSPECTIVE EVALUATION OF A FIRST EPISODE PSYCHOSIS COHORT

Paloma Fuentes Pérez¹, Claudia Ovejas Catalán¹, Jorge Romay González², Marcos Gómez-Revuelta², María Luz Ramírez Bonilla³, Rocio Perez-Iglesias³, Paula Suárez Pinilla², Benedicto Crespo-Facorro⁴, Javier Vázquez-Bourgon*⁵

¹*Instituto de Investigación Marqués de Valdecilla (IDIVAL), Universidad de Cantabria,*
²*University Hospital Marqués de Valdecilla - Instituto de Investigación Marqués de Valdecilla (IDIVAL), Universidad de Cantabria,* ³*University Hospital Marqués de Valdecilla - Instituto de Investigación Marqués de Valdecilla (IDIVAL),* ⁴*School of Medicine, University Hospital Virgen del Rocío-IBiS, Centro de Investigación Biomédica en Red en Salud Mental (CIBERSAM),* ⁵*University Hospital Marques de Valdecilla -IDIVAL; University of Cantabria; CIBERSAM*

Background: People with schizophrenia and other psychoses have a 2-3 times higher risk of premature mortality (Gronholm et al., 2021), with a life expectancy that is 10 to 15 years shorter compared to the general population (Liu et al., 2017). Despite the overall increase in life expectancy in recent decades, the mortality gap between individuals diagnosed with schizophrenia and the general population has persisted or even increased in recent years, according to the most recent studies (Yung et al., 2021). The primary causes of premature death in psychotic disorders are attributed to natural causes, primarily related to cardiovascular diseases, respiratory diseases, and cancer (Correll et al., 2022). Additionally, there has been evidence of an association between premature mortality and non-natural causes, especially suicide or accidents (Dua et al., 2017). Premature mortality in psychosis has received limited research attention in Europe, necessitating studies that provide data to determine the factors associated with premature mortality (Kiejna et al., 2023). The aim of this study was to analyze the characteristics of premature mortality in a cohort of patients with a first episode of psychosis.

Methods: A retrospective study was conducted on a cohort of non-affective psychosis patients from the PAFIP Program. The cohort data was obtained through retrospective analyses of the clinical records of those treated, between 2001 and 2018, in the longitudinal intervention program for first-episode psychosis called PAFIP (Early Intervention in Psychosis Program), at the Marqués de Valdecilla University Hospital in Cantabria (Spain). Patients who met the inclusion criteria and their families provided written informed consent before their inclusion in the program. Information on deaths was obtained by reviewing the patients' medical records in February 2023. The medical records of 677 patients (374 males and 294 females) with a first episode of psychosis that occurred 5-22 years ago were reviewed.

Results: The results revealed a premature mortality rate in the PAFIP cohort of 4.3% (N=29). The average age at the time of death was 41.8 years (range: 19-67 years). The average time to premature death in these patients was 6.6 years from the onset of their psychotic condition (range: 1-192 months). The cause of death was traumatic (non-natural) in 11 (37.9%) cases, including 9 suicides (31%) and 2 accidents (6.9%). In 11 (37.8%) cases, the death was due to natural causes, including 5 due to cancer (17.2%), 2 due to cardiovascular pathology (6.9%), 2 due to digestive pathology (6.9%), 1 due to renal pathology (3.4%), and 1 due to neurological pathology (3.4%). In 7 (24.1%) cases, the cause of death was not recorded in the medical records.

Discussion: We observed an excess of premature mortality in patients with psychosis, although lower than that described in previous studies. The lack of information about the causative event in medical records is noteworthy, which hinders the conduct of studies that could improve this outcome. Improving access to and follow-up in healthcare, as well as early prevention and intervention, may help to reduce the mortality rate among individuals with psychosis.

F155. EVALUATION OF THE CLINICAL EFFECTIVENESS OF AN INTENSIVE HOME PROGRAM FOR THE ACUTE TREATMENT OF PATIENTS WITH PSYCHOSIS IN THE COMMUNITY

Leila Palé^{*1}, Ana María Besoain², Jara López³, Lucía Alonso³, Sonia Sáez³, Sofia Torrejón³, Saray Palma³, Inmaculada Ruiz³, Ignacio Aznar²

¹*Equipo de Atención Domiciliaria Intensiva Llobregat Centre*, ²*Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Teaching, Research and Innovation Unit, Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu*, ³*Intensive Home Care Service of the Baix Llobregat Center area, Parc Sanitari Sant Joan de Déu*,

Background: Home mental health hospitalization has begun to be widely developed in recent years. Despite the lack of studies providing objective data, there is a general consensus on the potential benefits of home treatment. Experiences in the United Kingdom and the Netherlands confirm that these programs allow an increase in the portfolio of services, reduces the trauma frequently experienced in hospital care and allows the development of coping strategies for patients in their own environment. The bulk of these teams' activity is on patients with severe mental health problems and many of them are suffering from psychotic symptoms. The aim of our study is to assess clinical changes in patients with psychosis who are admitted to a mental health intensive home program.

Methods: A single cohort observational study was conducted on patients who received care from the Intensive home treatment team (IHTT) of the Parc Sanitari Sant Joan de Déu in Barcelona. The sample included patients suffering from an acute disorder with psychotic comorbid symptoms and that met criteria for admission in the program for one year. The diagnosis of the psychotic symptoms was made by clinicians of the team. The patients were evaluated using the PANSS scale and the GAF clinical scale on admission and at discharge. The SUMD scale was evaluated at discharge. Sociodemographic characteristics were also reported. The outcome variables were analyzed by intention-to-treat (ITT) as well as per protocol (PP).

Results: From January 2021 to December 2021, 108 patients with psychotic symptoms were referred to the IHTT and included in the sample. Only 98 of them completed the whole program and were included in the PP analysis. Mean age was 40 and 54,6% were men. The PANSS total mean was reduced by 16 points (from 72,4; 22,0% reduction) in the ITT analysis and by 18 points (from 71,0; 25,4% reduction) in the PP analysis. Both results, were statistically significant (P LESS THAN 0,001). In the ITT analysis the mean of the GAF scale was 44,1 at admission (44,7 in PP analysis) and 59,1 at discharge (61,3 in PP analysis) with a total increase of 33,9% (37,1% in PP analysis). The total mean of the SUMD scale was 9.

Discussion: The profile of patients attended by the IHTT had serious acute disorders with severe psychotic symptoms at admission (PANSS GREATER THAN 70) and very low functioning (GAF LESS THAN 50). The intensive home treatment proved clinical efficacy with GAF levels improving 34%-37% after the treatment and a 22%-25% reduction in the PANSS scale. The level of insight in psychotic patients after being admitted to the IHTT is slightly above the median value. It represents quite low insight levels even with the intensive psychotherapeutic approach. Despite the positive results, there are some limitations that should be considered for future investigations. Although SUMD values at admission were disregarded, it would be interesting to collect these data as well as other follow-up measures. Moreover, the comparison between samples of psychotic patients treated by IHTT and those receiving usual treatment within the hospital would provide much more evidence to the literature regarding this area of knowledge.

F156. THE REAL-WORLD UTILISATION OF MOOD STABILISERS AS AN AUGMENTATION STRATEGY IN PSYCHOSIS: A MIRROR IMAGE DESIGN

Emma Butler*¹, Daisy Kornblum², Rashmi Patel³, Oliver Howes⁴, Alice Egerton⁵

¹South London and Maudsley, ²BRC Nucleus, South London and Maudsley NHS Foundation Trust, UK, ³Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ⁴MRC LMS and KCL, ⁵King's College London

Background: Across the globe, 5-24% of people on an antipsychotic will be prescribed an anticonvulsant / mood stabiliser, and this may be increasing (1–3). There is most evidence for Carbamazepine, Sodium Valproate, Lamotrigine and Topiramate as augmentation agents in Schizophrenia(3). Meta-analysis of RCTs showed an improvement in symptoms for those given an anticonvulsant augmentation of Clozapine(4). However, evidence is still limited with little literature on the longitudinal impact of this practice (5). To assess the real-world impact of mood stabiliser augmentation strategies in the management of psychotic disorders

Methods: Using electronic health records of South London and Maudsley NHS Trust to conduct a naturalistic mirror comparison of service use and clinical outcomes, for the 2 years before and after the combination of antipsychotic and mood stabiliser.

Results: 1224 patients were identified from electronic health records of South London and Maudsley NHS Trust who had taken a combination of antipsychotic and mood stabiliser for a minimum of 6 months. Overall, service use outcomes and symptoms were significantly worse in the 2 years after the start of this combination compared to the 2 years before. Admissions (+0.146), Bed days (+53.787), Attended medical events (+7.086) and Home treatment team (HTT) involvement (episodes +0.079, Days +2.022) showed a mean increase in two years after compared to before augmentation ($p=0.005$ - LESS THAN 0.0001). The mean change for Positive (+0.358) and Negative symptoms (+0.414) of psychosis also showed a worsening of symptoms in the two years after augmentation (p LESS THAN 0.0001). Sodium Valproate had significant increase in admissions (+0.194), bed days (+55.052), attended medical events (+7.168), positive symptoms (+0.365), negative symptoms (+0.396), yet some improvement in agitated behaviours (- 0.288) ($p=0.035$ - LESS THAN 0.0001). Lithium and Lamotrigine showed similar increases in service use and symptoms ($p = 0.042$ - LESS THAN 0.0001). Of note, those with high number of treatment episodes (GREATER THAN 9) showed improvement in symptoms; HoNOS Total (-1.972), Agitation (-0.428) and Hallucination (-0.302) in two years following augmentation, while showing no significant change in admission numbers, number of attended medical events or HTT involvement. However, number of bed days (+100.673) did still show a significant increase (p LESS THAN 0.001), along with NLP Positive (+0.385) and Negative Symptoms (+0.554), ($p=0.035$ -0.007). Those with low number of treatment episodes (LESS THAN 4) showed no significant change in HoNOS total or individual items, but did show significant increases in admissions (+0.353), bed days (+76.601), attended medical events (+19.098) and HTT episodes (+0.216), alongside increases in positive (+0.798) and negative (+0.915) symptoms ($p=0.028$ - LESS THAN 0.0001).

The longer a patient was on mood stabilisers the larger the improvement from the 2 years before augmentation on Admissions ($rs(1222)=0.063, p=0.027, CI: 0.007-0.119$), Bed days ($rs(1222)=0.091, p=0.001, CI: 0.040-0.145$), and negative symptoms ($rs(1222)=0.062, p=0.028, CI: 0.011-0.119$), with a small but significant positive correlation for improvement in these outcomes.

Discussion: Conclusions: The polypharmacy approach of a combination of antipsychotic and mood stabilisers to treat psychotic symptoms may only be appropriate of specific subsets of patients, in particular those who have trialled multiple antipsychotics previously.

F157. RISK FACTORS OF LATE-ONSET PSYCHOSIS

Joseph Skinner*¹, Lauren Moran²

¹Brigham and Women's Hospital, ²Harvard Medical School/ McLean Hospital

Background: Previous studies suggest that the onset of schizophrenia occurs after the age of forty in up to twenty percent of cases. Despite being well established as clinically distinct from Early-Onset Schizophrenia (EOS), risk factors for Late-Onset Schizophrenia (LOS) remains an understudied area. Specifically, studies often neglect utilizing an appropriate age matched comparison group when investigating risk factors for LOS.

Methods: In a case control study using electronic health records (EHR), individuals over the age of 40 years with an encounter at Mass General Brigham for a first episode of psychosis were initially defined by an encounter with an ICD code for psychotic disorders between the years 2013 and 2021. All patients were required to have at least 3 outpatient visits to a primary care physician or psychiatrist prior to the date of the first ICD diagnosis code for psychosis, with one encounter in the previous year, to capture patients with high EHR continuity. Chart review was conducted to ensure patients had a true episode of LOS. After review of charts for 575 patients with an initial psychosis code, 142 were included as true LOS cases. The 142 cases of LOS were matched 1:4 to 568 patients without psychosis receiving outpatient care at MGB on age, sex, race, and year of encounter.

Covariates for the primary analysis included age at encounter, sex, year of encounter, race/ethnicity, insurance type, alcohol use disorder, cannabis use, and polysubstance use. Binary covariates for the presence or absence of past psychiatric diagnoses and medications preceding the encounter were included. Additionally, binary covariates for the presence or absence of psychosocial factors preceding initial onset of symptoms were also included. Conditional logistic regression models were used to assess the odds of late onset psychosis with the potential risk factors. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) are presented.

Results: Compared with matched controls, the odds of late-life onset psychosis were increased by immigration (aOR 3.30, 95% CI 1.56-6.98), depression (aOR 3.58, 95% CI 2.01-6.38), anxiety (aOR 2.12, 95% CI 1.20-3.75), cannabis use (aOR 3.00, 95% CI 1.36-6.61), alcohol use disorder (aOR 5.46, 95% CI 2.41-12.36), polysubstance use (aOR 4.22, 95% CI 1.30-13.7), history of severe trauma (aOR 2.29, 95% CI 1.08-4.48) and caregiver burden (aOR 15.26, 95% CI 3.85- 60.48).

Discussion: These risk factors can help clarify potential points of intervention for LOS. More research is needed with appropriate comparator groups for these patients to parse out in which ways the etiology of LOS is distinct from other conditions.

F158. INFLAMMATION IN SCHIZOPHRENIA IS ASSOCIATED WITH VASCULAR REMODELLING AND EXTRACELLULAR MATRIX INCREASES ALONGSIDE REDUCED NEUROGENESIS

Hayley North*¹, Cynthia Shannon Weickert²

¹Neuroscience Research Australia/ University of New South Wales, ²Neuroscience Research Australia: Schizophrenia Research Laboratory

Background: Schizophrenia is a heterogeneous disorder and while the pathogenesis is unclear, elevated inflammation is implicated in the aetiology and the neuropathology of a subgroup of schizophrenia cases. Inflammation regulates neurogenesis, and markers for stem cells and neuronal progenitors are reduced in the high inflammation subgroup of schizophrenia in the subependymal zone (SEZ) – the brain’s largest region of neurogenesis. Neurogenesis in the SEZ is highly dependent on the niche microenvironment whereby neural stem and progenitor cells receive signals from the vasculature and extracellular matrix (ECM) that influence their proliferation and differentiation. This research employed RNA sequencing to discover differences in the SEZ between high and low inflammation subgroups of schizophrenia.

Methods: We performed total RNA sequencing in the SEZ of 27 post-mortem schizophrenia brains previously designated into low inflammation (n=13) and high inflammation (n=14) subgroups, based on cluster analysis of inflammation gene expression (IL6, IL6R, IL1B, IL1R1, CXCL8 and SERPINA3). An average sequencing depth of 109 million unique paired-end reads was attained per sample and the average read depth did not differ between comparison groups [t(25)=0.02, p=0.49]. We have also performed single nuclei RNA sequencing (snRNAseq) from the young and adult human brain SEZ to determine the cellular origin of transcripts of interest.

Results: 718 genes were differentially expressed (DE) in high compared to low inflammation schizophrenia (FDR p LESS THAN 0.05). DE genes with increased expression in high inflammation schizophrenia were most significantly over-represented in the pathway ‘Hepatic Fibrosis/Hepatic Stellate-Cell Activation’. Genes in this pathway encompass those important for ECM stability [(including ten collagens, FN1 and TIMP1) (all FDR p LESS THAN 0.04)] and for vascular remodelling [(VEGFA, VEGFR1, VEGFR3, END1, MYH11) (all FDR p LESS THAN 0.02)]. Upregulation of these mRNA factors suggests ECM stiffening and increased angiogenesis with inflammation in the SEZ in schizophrenia. snRNAseq data suggests that the majority of DE ECM and angiogenesis related transcripts are produced by ependymal and endothelial cells. In contrast, VEGFA mRNA is expressed in a variety of neurogenic cell types of the SEZ including neural stem cells, neuroblasts and oligodendrocyte progenitor cells.

Discussion: This discovery-driven comparison of inflammatory subgroups elucidates how inflammation in schizophrenia most significantly contributes to changes in the SEZ microenvironment. We find a potentially pre-fibrotic ECM along with higher levels of angiogenesis in high inflammation schizophrenia. Further, our findings suggest that neural stem cells and neuroblasts may be upregulating angiogenesis promoting factor VEGFA. Considering other angiogenesis genes are also upregulated in endothelial cells, increased angiogenesis may be linked to the reduced neurogenesis we found in people with schizophrenia in an inflammatory state. These findings suggest that anti-inflammatory treatment could lead to restoration of a normal neurogenic subependymal zone microenvironment for this subgroup.

F159. FIRST EPISODE PSYCHOSIS: ALTERED ENERGY PATHWAYS IN THE IMMUNE SYSTEM

Jaana Suvisaari^{*1}, Martina Jonsson², Linnea Hartwall², Kirsi Sepponen², Heikki Laurikainen³, Maija Lindgren¹, Jarmo Hietala³, Jarno Honkanen²

¹*Finnish Institute for Health and Welfare*, ²*University of Helsinki*, ³*University of Turku*

Background: Psychotic disorders are associated with immunological changes, including elevations of inflammatory cytokines and chemokines in blood and cerebrospinal fluid (CSF),

alterations in monocyte and T-cell activation, and increased expression of pro-inflammatory genes in peripheral blood cells, CSF as well as in post-mortem brain tissue. However, there is still limited understanding on the immune system dysfunction at a cellular level in patients with first psychotic episode.

Methods: In two Finnish first-episode psychosis studies from Helsinki and Turku area, we collected peripheral blood mononuclear cells (PBMCs) from first episode psychosis (FEP) patients (n=29) and matched healthy controls recruited from the general population (n=31). From the PBMCs we analyzed the frequencies of monocytes, CD141(-) and CD141(+) myeloid dendritic cells (mDC1 and mDC2, respectively) and plasmacytoid dendritic cells (pDCs), regulatory T helper cells (Tregs) and effector T helper cells (Teffs) and purified the cell populations with flow cytometry. The purified cell populations were analyzed with RNAseq.

Results: Analysis of the FACS data showed that patients had elevated monocyte levels and decreased T helper cell frequencies in peripheral blood. When the global RNA expression of the purified cell populations was analyzed and the list of differentially expressed genes (DEGs) was subjected to an Ingenuity Pathway Analysis (IPA, Qiagen), monocytes from FEP patients showed inhibition of pathways associated with mitochondrial electron transport chain and oxidative phosphorylation (for e.g., ATP5F1A, COX6C, COX7B, NDUFA3 and NDUFV5). In the IPA analysis of Tregs and Teffs, FEP patients showed alterations in TCR-mediated activation pathways of T cells. When dendritic cells were analyzed we observed aberrancies in co-stimulatory pathways of dendritic cells regulating T cell activation, OX40-OX40L pathway being the most affected pathway. RNAseq analysis of dendritic cell populations also revealed highly activated antigen-presentation pathways (HLA class I and II) in FEP patients.

To further study the functioning of the mitochondria in the monocytes we collected another set of blood samples from FEP patients (n=11) and matched controls (n=11) recruited from the Turku area who were scanned with positron emission tomography and the translocator protein radiotracer (TSPO)[¹¹C]PBR28 at the time of collecting the blood samples. Regional distribution volume (DV) of [¹¹C]PBR28 was used as a proxy for TSPO expression in the outer membrane of mitochondria. From the PBMCs we analyzed the mitochondrial mass and mitochondrial reactive oxygen species production in the untreated and LPS-stimulated monocytes with FACS using MitoSox superoxide indicator (Thermo Fisher). We also purified monocytes, mDC1s, mDC2s, pDCs, Tregs and Teffs for transcriptomics analysis. IPA of the differentially expressed genes revealed mitochondrial pathways to be affected, thus replicating the observation of mitochondrial dysfunction made in the first phase of the study. FEP patients showed comparable level of superoxide positivity in untreated monocytes, whereas FEP patients showed similar mitochondrial mass compared to healthy controls. Patients had equal levels of superoxide-positive monocytes compared to healthy controls in unstimulated monocytes. When the monocytes were stimulated with LPS, patients showed lower level of superoxide-positive monocytes compared to the healthy controls. Interestingly, the frequencies of superoxide positive monocytes correlated with TSPO-PET DV whereas no such correlations could be observed in the FEP patients.

Discussion: Our data suggest that FEP patients have aberrant immune activation in the peripheral immune system at cellular level and that aberrancies in the energy production in innate immune cells may contribute to abnormal immune responses in FEP patients. Mitochondrial dysfunction and poor energy production could lead to weak immune responses against invading pathogens, thus making FEP patients susceptible to reoccurring and elongated infections causing low-grade inflammation. Our findings are also consistent with previous post-mortem brain studies and suggest that mitochondrial dysfunction may have a role in the etiology of psychotic disorders.

F160. HYPERACTIVATION OF GQ SIGNALING IN PREFRONTAL ASTROCYTES IMPAIRS COGNITION VIA ACTING ON THE KYNURENINE PATHWAY

Tina Notter*¹, Sina Schalbetter¹, Kim Ferrari¹, Johanna Furrer¹, Viktor Beilmann¹, Bruno Weber¹, Urs Meyer¹

¹*University of Zurich, Institute of Pharmacology and Toxicology,*

Background: Astrocytes are an integral part of the tripartite synapse and regulate behavior and cognition by modulating neuronal signaling. Abnormalities in prefrontal astrocytes appear to be involved in the pathophysiology of psychosis-related disorders. It remains elusive; however, how aberrant activity of prefrontal astrocytes contribute to behavioral and cognitive dysfunctions implicated in these disorders.

Methods: We used the designer-receptor-exclusively-activated-by-designer-drugs (DREADDs) system to selectively manipulate astrocyte activity in the prefrontal cortex of mice and explored its consequences on behavior, cognition and brain metabolites of the kynurenine (KYN) pathway.

Results: Chemogenetically induced hyperactivation of Gq signaling in prefrontal astrocytes impaired sensorimotor gating, working memory and temporal order memory in both male and female mice without affecting basal locomotor behavior and anxiety-like behavior. Furthermore, overstimulation of prefrontal astrocytes resulted in elevated levels of kynurenic acid (KYNA), a key metabolite of the KYN pathway acting as endogenous antagonist of N-methyl-D-aspartate (NMDA) receptors. Finally, pharmacological inhibition of kynurenine aminotransferase II, which is the key enzyme mediating the transamination of KYN into KYNA, reinstated the deficits in sensorimotor gating, working memory and temporal order memory after chemogenetically induced hyperactivation of Gq signaling in prefrontal astrocytes.

Discussion: Our study suggests that overstimulation of astrocytic Gq signaling in the prefrontal cortex impairs cognitive functions via acting on the KYN pathway. By identifying a causal link between hyperactivation of prefrontal astrocytes, increased production of KYNA, and disruption of cognitive functions, our study provides preclinical evidence supporting a pathophysiological role of aberrant astrocyte functions in psychotic disorders and beyond.

F161. THE ROLE OF ASTROCYTES IN POSTNATAL SYNAPTIC REFINEMENT OF THE MEDIAL PREFRONTAL CORTEX

Johanna Furrer*¹, Sina Schalbetter¹, Sarai Fischer¹, Viktor Beilmann¹, Urs Meyer¹, Bruno Weber¹, Tina Notter¹

¹*University of Zurich*

Background: Functional and structural abnormalities of the prefrontal cortex (PFC), a brain region providing executive top-down control of a variety of cognitive processes and sociability, have been implicated in major psychiatric disorders, including schizophrenia (SZ). During its protracted maturation throughout adolescence, the PFC undergoes substantial synaptic rearrangement where superfluous synapses are eliminated to optimize neuronal circuits underlying adult cognitive functions. According to a prevailing hypothesis, the etiopathology of SZ involves excessive synaptic pruning resulting in miswiring of the brain. In support of

this are the observed decreases in synaptic densities in prefrontal regions of SZ patients. The exact underlying mechanisms of prefrontal synaptic pruning remain, however, unknown. Recent findings in mice have shown that microglia can shape medial PFC (mPFC) maturation during adolescence and thereby alter the trajectory of cognitive development. Alike microglia, astrocytes have been shown to actively contribute to postnatal synaptic refinement of the visual and somatosensory system. However, the extent to which astrocytes actively contribute to the functional maturation of the mPFC remains currently unknown. In this study, we aim to elucidate the dynamics of prefrontal synaptic density and composition during adolescence to define the sensitive period of synaptic refinement in this brain region. Further, we explore how prefrontal astrocytes contribute to synaptic refinement along adolescence and thereby modulate cognitive development.

Methods: Using immunohistochemistry and confocal microscopy synaptic density and composition were extensively studied in postmortem tissue of C57BL6 mice collected along adolescence (postnatal day (PND) 21 – PND 56) and adulthood (PND 91). The role of astrocytes in prefrontal synaptic maturation was explored by selectively manipulating the Gq-protein-coupled receptor (GPCR) signaling pathway during the sensitive period by either enhancing (hM3DGq-DREADD) or attenuating (iβARK) this pathway in prefrontal astrocytes of C57BL6 male and female mice. Upon reaching adulthood, the animals were subjected to a battery of behavioral and cognitive tests, followed by measuring synaptic composition and density in postmortem tissue using immunohistochemistry and confocal microscopy.

Results: Overall synapse density in the prefrontal cortex most prominently decreased between PND 28 – PND 49 in females and PND 35 – PND 56 in males. This decrease was driven by the loss of excitatory synapses. Transient manipulation of astrocytes during this sensitive window of synaptic refinement resulted in persistent and sex-specific behavioral deficits in adulthood, including deficits in pre-attentive filtering and sociability.

Discussion: While previous studies have documented protracted synaptic pruning in the prefrontal cortex, our research contributes unique insights through detailed synapse analyses, enhancing the comprehension of synaptic refinement in male and female wildtype C57BL6 mice. Furthermore, our findings are the first to suggest an active involvement of astrocytes in the functional maturation of the mPFC, suggesting that astrocytes could be involved in the pathophysiological mechanisms underlying major psychiatric disorders such as schizophrenia.

F162. PREDICTING TREATMENT RESPONSE USING MRI MEASURES OF DOPAMINE AND GLUTAMATE

Cecelia Shvetz^{*1}, Rami Hamati², Reggie Taylor³, Nour Kanaa⁴, Greg Dance⁴, Clifford Cassidy³, Lauri Tuominen³

¹Carleton University, ²Department of Cellular and Molecular Medicine, University of Ottawa, ³University of Ottawa Institute of Mental Health Research, ⁴Department of Neuroscience, Carleton University

Background: One in three schizophrenia patients do not respond adequately to first-line antipsychotic treatment such as olanzapine¹. Currently, there is no tool to identify patients who respond favorably to first-line treatments from those who will need clozapine. Such a tool could reduce delay to start clozapine. Here, we propose a combined testing and development of the most promising biomarkers for treatment response: dopamine and glutamate⁴ using quick and non-invasive MRI methods. We predict that individuals responding to olanzapine will have higher dopamine turnover, and lower glutamate concentration relative to clozapine users. We

also hypothesize that these measures carry independent information so that in combination, they can be used to more reliably differentiate the two groups.

Methods: Thus far, 3 participants taking olanzapine treatment (first-line treatment respondent), and 4 participants taking clozapine treatment (first-line treatment-resistant) have completed a clinical interview to characterize symptom severity using the Positive and Negative Syndrome Scale⁶ and an MRI scan. Dopamine signal in the substantia nigra was measured using neuromelanin-MRI and glutamate concentration in the dorsal anterior cingulate cortex was measured with magnetic resonance spectroscopy.

Results: No significant differences were found between groups in terms of age, sex, or symptom severity (all p GREATER THAN 0.05). Preliminary results show no significant differences between individuals on olanzapine ($M = 13.22$, $SD = 1.78$) and individuals on clozapine ($M = 15.01$, $SD = 2.14$) in neuromelanin signal in the SN ($t(4.87) = 1.21$, $p = 0.28$), nor between olanzapine ($M = 0.68$, $SD = 0.07$) and clozapine groups ($M = 0.67$, $SD = 0.01$) in glutamate concentration in the dACC ($t(3.21) = 0.30$, $p = 0.79$). Logistic regression showed moderate power at predicting treatment group membership ($AUC = 0.75$).

Discussion: Our preliminary results show promise in predicting response to antipsychotic treatment. No significant differences were found in dopamine signal in the substantia nigra, nor glutamate concentration in the dorsal anterior cingulate cortex between treatment groups. Further data collection is ongoing.

References:

1. Suzuki, T., et al. (2011). Treatment resistant schizophrenia and response to antipsychotics: A review. *Schizophrenia Research*, 133(1-3), 54-62.
2. Williams, R., et al. (2017). What Is the Place of Clozapine in the Treatment of Early Psychosis in Canada? *Canadian Journal of Psychiatry*, 62(2), 109-114.
3. Siskind, D., et al. (2017). Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. *Canadian Journal of Psychiatry*, 62(11), 772-777.
4. Howes, O., et al. (2015). Glutamate and dopamine in schizophrenia: An update for the 21st century. *Journal of Psychopharmacology*, 29(2), 97-115.
5. Cassidy, C.M., et al. (2019). Neuromelanin-sensitive MRI as a noninvasive proxy measure of dopamine function in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 116(11), 5108-5117.
6. Kay, S. R., et al. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*, 13(2), 261-276.

F163. ASSOCIATIONS BETWEEN RELATIVE THETA POWER, PSYCHOTIC DISORDERS AND THEIR POLYGENIC LIABILITY

Melissa Zandstra¹, Hannah Meijs², Bochao Lin¹, Bieke de Wilde³, Jan van Hecke³, Peter Niemegeers³, Erwin Bekema¹, Kristel van Eijck¹, Willem Otte¹, Cornelis Stam⁴, Dirk Smit⁵, Sinan Guloksuz⁶, Edwin van Dellen¹, Jurjen Luyckx¹

¹UMC Utrecht, ²UMC Utrecht, Maastricht University, ³Ziekenhuis Netwerk Antwerpen,

⁴VUmc, Amsterdam, ⁵UMC AMC, Amsterdam, ⁶Maastricht University Medical Centre

Background: Psychotic disorders (PD) are highly heritable and have long been linked with aberrant neural oscillations, particularly heightened theta power. Relative theta power, in turn, also might be influenced by genetics. This study aims to explore the association between polygenic risk scores for schizophrenia (PRS-SCZ) and relative theta power, while also examining potential mediation effects.

Methods: Resting-state EEG (rsEEG) was recorded in 1041 participants (459 females) admitted to a psychiatric hospital: patients with a mood disorder (MD), psychotic disorder (PD), and substance use disorder (SUD). SCZ-PRS of 666 participants was generated with PRSice-2 and was based on published genome-wide association data. General linear models (GLM) were performed to assess the difference in relative theta power between PD and non-PD patients, and the relationship between SCZ-PRS and relative theta power. Finally, mediation regression analysis was conducted to examine the relative associations between SCZ-PRS, theta power, and PD.

Results: rsEEG relative theta power was higher in PD compared to non-PD ($F(1, 1036) = 17.28$, $p < .001$, $\eta^2 = 0.16$). A positive association was found between SCZ-PRS and relative theta power ($p\text{-threshold} = 5.0E3$; standardized regression coefficient, $\beta = 0.10$, $p = .012$). Importantly, relative theta power significantly mediated the relationship between SCZ-PRS and PD.

Discussion: Findings reveal that polygenic risk for schizophrenia is associated with increased relative theta power in a psychiatric population. Moreover, the mediation analysis highlights the role of relative theta power as a mediator in the association between polygenic risk score for schizophrenia and the manifestation of psychotic disorders.

F164. ALTERED WHITE MATTER MICROSTRUCTURE OF WHITE MATTER LANGUAGE PATHWAYS AND SEMANTIC COGNITION DEFICIENCIES IN EARLY PSYCHOSIS

Werner Surbeck^{*1}, Noemi Dannecker¹, Anna Steiner¹, Robin Samuel², Allegra Gasser¹, Dominic Fabian¹, Niklaus Denier³, Tobias Bracht³, Peter Brugger¹, Philipp Homan¹

¹*Psychiatric Hospital of the University of Zurich*, ²*University of Luxembourg, Esch-sur-Alzette, Luxembourg*, ³*Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern*

Background: Semantic processing anomalies, clinically manifested by disorganized speech, constitute a core symptom of schizophrenia-spectrum disorders. Semantic cognition relies on two principal interacting neural systems: one for representation and another for control. Recent evidence pointing to a selective impairment of semantic control, rather than semantic representation, in individuals with early psychosis suggests the potential presence of an anatomical substrate associated with this characteristic feature of schizophrenia. Tract specific abnormal maturation and accelerated aging of the inferior fronto-occipital fasciculus (IFOF), a component of the ventral language stream, have been recently reported in comparison to control subjects. Notably, the IFOF is considered a potential candidate for executive and semantic control over conceptual knowledge, thereby offering a plausible anatomical correlate for this specific deficit within a subsystem of semantic cognition in schizophrenia-spectrum disorders.

Methods: Semantic representation was examined using the multiple-choice word test. Control of semantic cognition was tested using a semantic verbal fluency task as well as by the Camel

and Cactus Test. DTI combined with manual fiber tractography were applied in 40 early psychosis patients and 80 healthy controls. The latter were divided into individuals with high schizotypy (40) and low schizotypy (40) based on the Oxford-Liverpool Inventory of Feelings and Experiences. For the ventral language stream, we assessed the left IFOF, while the left arcuate fasciculus (AF) was used as representative of the dorsal language stream. Since not associated to language, the left corticospinal tract was used as control tract.

Results: Using Poisson regression models adjusted for attention and executive function, age, gender, and education, diffusion measures FA and MD of the three tracts examined showed no significant ($p < 0.05$) association with semantic representation either within the patient group or within the control groups. In contrast, some FA and MD measures were mostly negatively associated with verbal fluency as measured with naming items within one minute (IRR .903 to 1.080, $p < 0.05$) within all groups, except for early psychosis patients, using Poisson regression models and random-effects multinomial logit models, as appropriate and as adjusted as above. However, this was not specific to the IFOF but also found for the AF. No significant correlations were found with regard to the CST.

Discussion: For both patients and healthy controls, no significant association of semantic representation was found regarding white matter microstructure as measured by DTI. In contrast, a correlation between microstructural alteration and semantic control ability, assessed through the semantic verbal fluency task, was observed in healthy individuals with low and high schizotypy, respectively. Remarkably, this correlation was not evident in early psychosis patients. Furthermore, these findings related to semantic control were not specific to the IFOF but were observed with a similar pattern in relation to the AF. While these results suggest that the control of semantic information in healthy individuals is not exclusively mediated by the ventral language pathways but involves the entire perisylvian white matter language connectivity, this does not hold true for individuals with early psychosis. For the latter, there was no corresponding evidence for either the ventral or dorsal language stream. A detailed analysis of the ventral language stream, encompassing indirect pathways (inferior longitudinal and uncinate fasciculi), and the inclusion of homologous contralateral pathways (for the analysis of the relative anatomical changes in the left language pathways compared to the opposite side) could potentially offer more clarity regarding this unexpected finding. The corresponding results will be available by the congress date and will be presented.

F165. INTRA- AND INTER-NETWORK DYSCONNECTIVITY AMONG RESTING STATE GLOBAL FUNCTIONAL NETWORKS IN INDIVIDUALS AT ULTRA-HIGH-RISK FOR PSYCHOSIS: COMPARISON WITH ULTRA-HIGH-RISK FOR BIPOLAR DISORDER AND HEALTHY CONTROLS

Burcu Verim^{*1}, Cemal Demirlek¹, Nabi Zorlu², Muhammed Demir¹, Berna Yalincetin¹, Merve Gurbuz¹, Ezgi Cesim¹, Simge Uzman Ozbek¹, Tevhide Ekin Sut¹, Emre Bora¹

¹Dokuz Eylul University, ²Katip Celebi University

Background: Schizophrenia and bipolar disorder are chronic psychiatric illnesses associated with aberrations in functional connectivity during rest. Compared to chronic and first episode phases, information about the prodromal stages of these illnesses is scarce. The aim of this study was to investigate how functional connectivity patterns change in individuals at ultra-high-risk for psychosis (UHR-P) in comparison to individuals at ultra-high-risk for bipolar disorder (UHR-BD) and healthy controls (HC).

Methods: Thirty two individuals with UHR-P who meet the criteria of the Turkish version of Structured Interview for Prodromal Syndromes (SIPS), 26 individuals with UHR-BD who meet the criteria of the Turkish version of the Bipolar Prodrome Symptom Interview and Scale-Full Prospective (BPSS-P) from the Early Diagnosis and Intervention Service at Dokuz Eylul University Hospital/Department of Psychiatry and 19 HC were included in this study. All participants underwent clinical interviews and 3 Tesla resting state functional MRI scanning sessions. Network-based statistics (NBS) toolbox was used to analyze global network properties. For multiple comparisons, corrections were applied (10000 permutations, $p < 0.05$). Additionally, gender and age were included as covariates in the analyses.

Results: NBS analyses revealed hypoconnectivity between default mode and salience networks, between default mode and frontoparietal networks along with decreased connectivity within the default mode network in the UHR-P group compared to HC. Moreover, the most prominent findings regarding hyperconnectivity in the UHR-P group compared to HC are between the default mode and the visual networks, between the salience and the visual networks, and lastly, between the cingulo-opercular and the visual networks. There was no statistically significant difference between UHR-P and UHR-BD as well as UHR-BD and HC groups.

Discussion: This study demonstrated distinctive neural signatures associated with the prodromal stage of psychosis but it didn't find any significant difference between clinical risk groups and also between individuals at clinical high risk for bipolar disorder and healthy controls. Given the heterogeneity of these groups, longitudinal studies with larger samples are needed in order to shed light onto their neurobiology and inform the development of more targeted diagnostic and therapeutic strategies.

F166. FUNCTIONAL CONNECTIVITY CORRELATES OF GAMMA-AMINOBUTYRIC ACID IN ANTIPSYCHOTIC MEDICATION-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

Genelle Samson^{*1}, Jose Maximo¹, Eric Nelson¹, Seyedeh Adnani², Adil Bashir², Adrienne Lahti¹

¹The University of Alabama at Birmingham, ²Auburn University

Background: Functional connectivity, the temporal correlation between neurophysiological events in different brain regions, is significantly altered in patients with psychosis spectrum disorders. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system, and its role in psychosis spectrum disorders is under-investigated, as is its relationship to functional connectivity in these patients. Data from animal and postmortem studies suggest GABAergic dysfunction in psychosis spectrum disorders, but little is known about GABA pathology at the early stages of illness, especially prior to treatment. The relationship between GABA levels within the anterior cingulate cortex (ACC), a region implicated in a number of complex cognitive functions frequently impaired in psychosis spectrum disorders, and functional connectivity among different key brain networks may play a pivotal role in the pathophysiology of psychosis spectrum disorders. We hypothesize that GABA's relationship with functional connectivity will differ between patients and healthy controls.

Methods: We used magnetic resonance spectroscopy (MRS) with a MEGA-PRESS sequence to quantify GABA in the ACC of 67 antipsychotic medication-naïve first-episode psychosis patients (FEP) and 110 healthy controls (HC). Whole brain functional connectivity (FC) analyses were performed in CONN (version 20b) within the default mode (DMN, posterior

cingulate cortex seed), salience (SN, ACC seed), dorsal attention (DAN, right intraparietal sulcus seed), and executive control (ECN, right posterior parietal lobule seed) networks. We then assessed ACC GABA-FC correlations in each sample and tested these between HC and FEP.

Results: We performed a one-way ANCOVA controlling for age, gender, and smoking (as measured by packs per day) to compare ACC GABA levels between groups, and did not find a significant difference in GABA levels between FEP and HC ($p = 0.125$). However, when examining ACC GABA-FC, significant clusters showed group interactions in the SN and ECN where GABA concentration positively correlated with FC for HC, but this relationship was inverse in FEP.

Discussion: Our findings support that GABA concentration in the ACC plays a significant and differential role in FC in key brain networks. Our data add to the growing body of evidence suggesting GABA's significant role in psychosis spectrum disorders, especially as it relates to FC. Further investigation of how GABA's role in FC within and between these networks differs between FEP and HC is merited. Examination of longitudinal trajectories of GABA over the course of treatment can also further elucidate this model. Our data support that GABA and FC work differently in FEP as compared to HC, which calls for further exploration of the mechanisms underlying altered activation and connectivity in psychosis spectrum disorders.

F167. BRAIN ACTIVATION AND ABERRANT EFFECTIVE CONNECTIVITY IN THE MENTALIZING NETWORK OF PREADOLESCENT CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

Lotte Veddem*¹, Vibeke Bliksted², Yuan Zhou³, Anna Krogh Andreassen⁴, Christina Bruun Knudsen⁵, Aja Neergaard Greve⁶, Nanna Lawaetz Steffensen⁶, Merete Birk², Nicoline Hemager⁷, Julie Marie Brandt⁸, Maja Gregersen⁹, Line Johnsen¹⁰, Kit Melissa Larsen¹¹, William Frans Christiaan Baaré¹², Kathrine Skak Madsen¹², Hartwig Roman Siebner¹³, Kerstin Jessica Plessen¹⁴, Anne Amalie Thorup¹⁵, Leif Østergaard¹⁶, Merete Nordentoft¹⁷, Ole Mors¹⁸, Torben Ellegaard Lund¹⁶, Martin Dietz¹⁹

¹The Psychosis Research Unit, Aarhus University Hospital; Aarhus University; iPSYCH - The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ²Psychosis Research Unit, Aarhus University Hospital, ³Institute of Psychology, Chinese Academy of Sciences, ⁴The Psychosis Research Unit, Aarhus University Hospital Psychiatry The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ⁵Psychosis Research Unit, Aarhus University Hospital, The Lundbeck Foundation Initiative for Integrative Psychiatric Research - iPSYCH; Aarhus University, ⁶Psychosis Research Unit, Aarhus University Hospital Psychiatry, ⁷Research Unit of Mental Health Centre Copenhagen at Gentofte University Hospital; Mental Health Services in the Capital Region of Denmark, ⁸CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, ⁹CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, ¹⁰Danish Research Center for Magnetic Resonance, University Hospital Hvidovre, ¹¹Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, ¹²Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital - Amager and Hvidovre, ¹³Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, Copenhagen University

Hospital Bispebjerg, Institute for Clinical Medicine, University of Copenhagen, ¹⁴ University Hospital of Lausanne, Switzerland, ¹⁵ Child and Adolescent Mental Health Center Capital Region of Denmark, ¹⁶ Center of Functionally Integrative Neuroscience, Institute of Clinical Medicine, Aarhus University, ¹⁷ Mental Health Centre Copenhagen, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), ¹⁸ Psychosis Research Unit, Aarhus University Hospital, ¹⁹ Center of Functionally Integrative Neuroscience, Aarhus University

Background: Schizophrenia and bipolar disorder are associated with impairments in social cognition and recent research has identified alterations of the social brain in both disorders. However, it is unknown whether familial high-risk of these mental disorders is associated with neurobiological alterations already present in childhood.

Methods: As part of The Danish High Risk and Resilience Study – VIA 11, we examined a cohort of same-aged children at familial high-risk of schizophrenia (FHR-SZ, n = 121) or bipolar disorder (FHR-BP, n = 75) and population-based controls (PBC, n = 128). Using functional magnetic resonance imaging (fMRI) and dynamic causal modeling (DCM), we investigated brain activation and effective connectivity during the social cognition paradigm from the Human Connectome Project.

Results: We found similar activation of the mentalizing network across the three groups, including visual area V5, dorsomedial prefrontal cortex (dmPFC), and posterior superior temporal sulcus (pSTS). Nonetheless, both familial high-risk groups showed aberrant brain connectivity compared with PBC. Both groups had increased feedforward connectivity from left V5 to pSTS. Children at FHR-SZ had reduced intrinsic connectivity in bilateral V5, whereas children at FHR-BP showed reduced intrinsic connectivity in right pSTS and reduced reciprocal connectivity between right dmPFC and pSTS.

Discussion: Our results provide first-time evidence of aberrant brain connectivity in the mentalizing network of preadolescent children at FHR-SZ or FHR-BP compared with PBC. We identified both shared and unique profiles of aberrant brain connectivity in children at FHR-SZ or FHR-BP relative to PBC. This suggests that abnormal synaptic mechanisms may be present before alterations in regional brain activation or marked behavioral deficits, indicating that mentalizing deficits may have a neurodevelopmental origin. Longitudinal research is warranted to clarify whether aberrant brain connectivity during mentalizing constitutes an endophenotype associated with the development of a severe mental disorder later in life. To this end, our cohort follow-up study at age 15 (VIA 15) is currently under way.

F168. LONGITUDINAL CHANGES IN HIPPOCAMPAL SUBFIELD VOLUMES ARE NOT RELATED TO GLUTAMATE LEVELS IN ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

Eric Nelson*¹, Nina Kraguljac², Adil Bashir³, Jose Maximo¹, William Armstrong¹, Adrienne Lahti¹

¹University of Alabama at Birmingham, ²The Ohio State University, ³Auburn University,

Background: Postmortem and neuroimaging studies have implicated hippocampal abnormalities in the neuropathology of psychosis spectrum disorders. Reduced hippocampal volume has been reported across all illness stages, and this atrophy has been hypothesized to be the result of glutamatergic excess. To test this hypothesis, we measured hippocampal subfield volumes and hippocampal glutamate levels in antipsychotic naïve first episode patients (FEP) and the progression of volume decline and changes in glutamate levels over a 16-week antipsychotic drug (APD) trial. We aimed to determine if subfield volumes at baseline

linked with glutamate levels, and if baseline glutamate levels were predictive of change in subfield volumes over time.

Methods: We enrolled ninety-three medication-naïve FEP patients and eighty matched healthy controls (HC). T1 and T2 weighted images and magnetic resonance spectroscopy (MRS) data from a voxel prescribed in the left hippocampus were collected from participants at baseline and after 6 and 16 weeks of APD treatment. Hippocampal subfield volumes were assessed using FreeSurfer 7.1.1., while glutamate levels were quantified using jMRUI version 6.0. Data were analyzed using linear mixed models.

Results: We found regional subfield volume deficits in the CA1 ($p = 0.008$), and PR subiculum ($p < 0.001$) in FEP at baseline, that further expanded to include the molecular and granule cell layer of the dentate gyrus (GC/ML/DG) ($p = 0.026$) and CA4 ($p = 0.004$) by weeks 6 and 16, respectively. Baseline hippocampal glutamate levels in FEP were not significantly different than those of HC ($p = 0.117$), and there was no effect of treatment on glutamate ($p = 1.000$). Glutamate levels were not related to initial subfield volumes or volume changes over 16 weeks.

Discussion: We report a progressive loss of hippocampal subfield volumes over a period of 16 weeks after initiation of treatment, suggestive of early progression in neuropathology. Our results do not suggest a role for glutamate as a driving factor. This study underscores the need to further research the mechanism(s) underlying this phenomenon as it has implications for early intervention to preserve cognitive decline in FEP patients.

F169. NEUROMELANIN ON SALIENCE NETWORK EFFECTIVE CONNECTIVITY IN FIRST EPISODE SCHIZOPHRENIA

Jessica Ahrens^{*1}, Sabrina Ford², Betsy Schaefer³, David Reese⁴, Ali Khan⁴, Philip Tibbo⁵, Clifford Cassidy⁶, Lena Palaniyappan⁷

¹Douglas Research Centre, ²University of Western Ontario, ³Western University, Robarts Research Institute, ⁴Robarts Research Institute, ⁵Dalhousie University, Halifax, NS Canada, ⁶University of Ottawa, ⁷Douglas Mental Health University Institute

Background: Basic cognitive processes, such as working memory and attention, are notably impaired in those with schizophrenia. There is a strong association between cognitive impairment and a reduction in quality of life; however, available interventions for schizophrenia are not effective in reversing this impaired cognition. Emerging evidence points to two mechanisms for explaining these cognitive deficits within this population: (1) disruptions of a brain network called the salience network, which includes the anterior insula and the anterior cingulate cortex; and (2) increased dopamine turnover, which has been found to be implicated in the positive symptoms of schizophrenia, such as hallucinations and delusions. I propose to use measures of effective connectivity to examine the relationship between these two mechanisms and test if they lie on the same causal pathway of impaired cognition in schizophrenia. Generating this knowledge will provide the in vivo markers of target engagement for many emerging pro-cognitive treatments. Recent work suggests neuromelanin sensitive MRI (NM-MRI) may provide a proxy measure of dopamine system function, based on the tendency of neuromelanin, which is a breakdown product of dopamine, to accumulate in the substantia nigra. NM-MRI is both practical and non-invasive, providing a highly feasible and acceptable approach to study patients living with schizophrenia. Therefore, this study aims to: (1) investigate if prior research results on excess neuromelanin in established schizophrenia extends to a sample of those with first episode schizophrenia; and (2) determine

the effect of dopaminergic turnover on the connectivity of the salience network. I hypothesize that: (1) first episode patients will have higher NM-MRI signal than healthy controls; and (2) patients with higher NM-MRI signal will have reduced effective connectivity between areas of the salience network.

Methods: N=30 first episode schizophrenia patients and N=30 healthy controls were recruited from the Prevention and Early Intervention Program for Psychosis in London, Ontario and the community surrounding. Groups were matched on sex, gender, age, education, and parental socioeconomic factors. Participants underwent a resting state functional MRI scan and a NM-MRI scan. A Bayesian statistical approach that allows for the direction and strength of the connectivity between brain areas, Dynamic Causal Modeling, will be used to quantify the effect that any individual neuromelanin differences may have on the salience network.

Results: Second-level (group; group-with-neuromelanin) dynamic causal modelling results to be determined. Neuromelanin of each voxel and mean of the substantia nigra has been quantified and first-level dynamic causal models have been specified for each participant.

Discussion: To date, no studies have addressed the modulatory effect(s) of neuromelanin on the salience network. This work is essential to understand how dopamine may influence the salience network and thus clarify a promising mechanism for the cognitive deficits in schizophrenia. Additionally, current global efforts focused on neuromelanin in schizophrenia have highlighted the value of using this as a marker in upcoming clinical trials, which can significantly enhance therapeutic options for patients.

F170. THE RELATIONSHIP BETWEEN CAT OWNERSHIP, TOXOPLASMA, AND PSYCHOTIC EXPERIENCES IN YOUNG PEOPLE

Jehanita Jesuthasan^{*1}, Kate Merritt¹, Sarah Ashley¹, Pedro Luque Laguna², Anthony David¹

¹*Institute of Mental Health, UCL*, ²*CUBRIC*

Background: Schizophrenia and related disorders have been associated with cat ownership, a relationship hypothesised to be mediated by *Toxoplasma gondii*, a parasite transmitted to humans by cats. This study therefore examined the associations between cat ownership, toxoplasma serology, and psychotic experiences, as well as structural brain changes associated with *T. gondii*.

Methods: Using the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we studied 6,716 individuals for whom data on psychotic experiences at age 18, cat ownership in early life (8 weeks gestation to 33 months), and toxoplasma serology was available. Associations were examined using univariate ANOVA, t-tests, and chi-square. Voxel-based morphometry examined whether MRI measures of grey matter volume were associated with *T. gondii* among 87 individuals aged 20 years with psychotic experiences (n = 30 suspected, n = 34 definite, n = 23 psychotic disorder) and 201 controls.

Results: Cat ownership was not associated with positive toxoplasma serology sampled in adolescence (age 11: $t = -1.38$, $p = 0.167$; age 15: $F = -1.44$, $p = 0.151$) or with psychotic experiences ($\chi^2 = 0.84$, $p = 0.840$). Toxoplasma serology was not associated with psychotic experiences when samples were taken at age 11 ($F \text{ LESS THAN } 0.001$, $p = 0.997$); or age 15 ($F = 0.40$, $p = 0.526$). In the neuroimaging sample, neither toxoplasma at age 11 ($p\text{FWEs} \geq 0.876$, $Z_s \leq 4.38$) nor toxoplasma at age 15 ($p\text{FWEs} = 1.000$, $Z_s \leq 3.18$) were associated with volumetric changes.

Discussion: Overall, our results suggest that exposure to *T. gondii* is not associated with an increased risk of developing psychotic experiences. Future work examining the relationship between toxoplasma and schizophrenia should focus on serology rather than cat ownership as

a proxy measure of *T. gondii* exposure, as there was no association between cat ownership and toxoplasma.

F171. REDUCED INTER-SUBJECT SYNCHRONIZATION IN PATIENTS WITH SCHIZOPHRENIA DURING EMPATHIC ACCURACY TASK ARE ASSOCIATED WITH NEGATIVE SYMPTOMS

Yi Wang^{*1}, Ding-ding Hu², Xiao-dong Guo², Cheng-cheng Pu³, Raymond C.K. Chan¹

¹*Institute of Psychology Chinese Academy of Sciences*, ²*Institute of Psychology Chinese Academy of Sciences; University of Chinese Academy of Sciences*, ³*Peking University Sixth Hospital, Peking University, Institute of Mental Health, NHC Key Laboratory of Mental Health, National Clinical Research Center for Mental Disorders*

Background: The Empathic Accuracy Task (EAT) captures how accurately an individual understands emotions of others while watching naturalistic video stimuli. Previous studies suggested that schizophrenia (SCZ) patients exhibiting altered brain activations in the precuneus, middle frontal gyrus and thalamus during EAT. Our study aimed to adopt inter-subject correlation (ISC) analysis, a method measuring the consistent neural activity among individuals engaging in naturalistic stimuli, to examine neural synchronization during the EAT in SCZ patients compared to healthy controls.

Methods: Forty-three patients with SCZ and forty-one matched healthy controls (HC) were recruited to undergo the Chinese version of EAT in a 3T GE MR750 scanner. During EAT, all participants watched four videos (two positive, two negative) of a target telling his/her autobiographical stories in the scanner while continuously rate the emotional valence of the target. Empathic accuracy (EA) was calculated using the Spearman's correlation between the ratings of target and each participant. Clinical symptoms of SCZ patients were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS). Preprocessing of the functional MRI data were performed using the SPM12. ISC analyses were conducted by correlating the blood oxygen level dependent (BOLD) time-series of one participant and the average time-series of remaining participants in the same group at each voxel of whole brain. The correlation coefficients were fisher-z transformed for further analyses. Group comparisons of the ISC in HC and SCZ group were performed using independent sample t-tests. Threshold for significance were set at peak-level uncorrected $p < 0.001$ and cluster-level FWE corrected $p < 0.05$. Clusters with significant group differences were defined as regions of interests and we calculated the corresponding ISC values of all SCZ patients with HC group mean to examine clinical correlations with the PANSS and CAINS. Bonferroni corrections were used to control for multiple comparisons.

Results: Significant group differences of ISC in brain activations while performing EAT were found, with SCZ group showing weaker ISC than HC group in bilateral inferior frontal gyrus (IFG, right: $t = 6.84$, $p < 0.001$; left: $t = 5.25$, $p = 0.013$), right dorsomedial prefrontal cortex (dmPFC, $t = 5.92$, $p < 0.001$), caudate head ($t = 5.50$, $p < 0.001$), precentral gyrus ($t = 4.67$, $p = 0.039$), middle temporal gyrus (MTG, $t = 4.38$, $p = 0.005$), as well as in left fusiform gyrus ($t = 5.83$, $p = 0.032$), precuneus ($t = 5.20$, $p < 0.001$), middle occipital gyrus (MOG, $t = 5.10$, $p = 0.010$) and cerebellum Crus I ($t = 4.72$, $p = 0.024$). The ISC of SCZ patients with HC group mean in left cerebellum Crus I were negatively correlated with negative ($r = -0.53$, $p < 0.001$) and general ($r = -0.48$, $p = 0.001$) symptom dimensions of the PANSS, as well as CAINS expression dimension ($r = -0.54$, $p < 0.001$).

Discussion: These findings revealed reduced ISC in brain activations of SCZ patients in social brain network (e.g., dmPFC, precuneus), sensory processing regions (e.g., MTG, fusiform gyrus), and cerebellum, suggesting altered neural synchronization of SCZ patients when performing EAT. Moreover, the ISC of SCZ patients exhibited negative associations with negative symptoms. These findings highlight the underlying neural mechanisms of social cognition deficits in SCZ patients, and provide new perspectives on understanding negative symptoms and social cognition in schizophrenia.

F172. THE LONGITUDINAL EFFECT OF ANTIPSYCHOTIC DRUGS ON STRIATAL DOPAMINE SYNTHESIS CAPACITY IN DRUG-NAIVE FIRST-EPIISODE PSYCHOSIS

Seoyoung Kim¹, Euitae Kim^{*1}

¹*Seoul National University Bundang Hospital*

Background: Antipsychotic drugs are known to be effective treatment for majority of first episode psychosis (FEP), yet its longitudinal effect is less investigated where previous studies have shown inconsistent results. While dopamine hypothesis is suggested as leading neurobiological mechanism underlying psychotic disorders, and all antipsychotic drug is dopamine antagonist, an effect of specific antipsychotic drug on dopamine synthesis capacity is unclear. Predicting treatment response to antipsychotic drugs is important in improving the prognosis of psychosis and monitoring presynaptic dopamine synthesis capacity in FEP after antipsychotic treatment might give some clue regarding treatment responsiveness. The aim of this study was to prospectively observe the change in striatal dopamine capacity during 1-year treatment with amisulpride and three months after switching to aripiprazole.

Methods: Twenty-seven antipsychotic-naive FEP patients, aged 19 or more and less than 45, were enrolled, along with 31 age- and sex-matched healthy controls. Striatal dopamine activity was assessed as k_{ic} value using [18F]DOPA PET, before initiating treatment (baseline) and after 6 weeks and 1 year of amisulpride treatment and 3 months after switching to aripiprazole. Healthy controls also underwent [18F]DOPA PET scans according to the corresponding schedule of the patients. Patients were clinically assessed regularly with Positive and Negative Symptom scale (PANSS) and Clinical Global Impression-severity scale (CGI-S) at baseline and after 2, 4, 6, 12, 24 weeks and 1 year of amisulpride treatment. Information regarding pharmacological treatment were obtained on every study visit.

Results: There were no significant difference in demographic characteristics between FEP patients and healthy controls. Mean PANSS total score of FEP patients at baseline, 6-week and 1-year follow-up were 67.8, 47.8, and 40.0, respectively. All patients showed treatment response after 6-week treatment of amisulpride, while 2 patients had worsening of psychotic symptom and 1 patient had switched to another antipsychotic drug due to adverse effect, afterwards. The mean dose of amisulpride at 1-year follow-up was 198mg. The change in k_{ic} value over time significantly differed between FEP patients and healthy controls.

Discussion: Significant change in dopamine synthesis capacity were found after 1-year amisulpride treatment but not after 6-week treatment in FEP patients. These results suggest that the effect of antipsychotics treatment on dopamine neurotransmission might be related to a delayed change of striatal dopamine synthesis capacity. Longer prospective study is needed to confirm the antipsychotic effect on the dopamine synthesis capacity in FEP.

F173. CHANGES IN RESTING CEREBRAL BLOOD FLOW IN PEOPLE WITH CHRONIC SCHIZOPHRENIA: STRIATAL HYPERPERFUSION ACCOMPANYING WIDESPREAD CORTICAL HYPOPERFUSION

Stephanie Hare^{*1}, Bhim M. Adhikari², Hwiyoung Lee¹, Shuo Chen¹, Deanna L. Kelly¹, Laura M. Rowland³, Robert W. Buchanan¹

¹Maryland Psychiatric Research Center, ²UTHealth Houston, McGovern Medical School,

³National Institute of Mental Health

Background: Magnetic resonance imaging (MRI) has been an important tool to improve understanding of the brain pathophysiology of schizophrenia. Yet, the copious amount of functional MRI studies that have been performed have yielded mixed results supporting a hypothesis of widespread brain dysconnectivity in people with schizophrenia (PSz), wherein changes in functional connectivity are reported across the entire brain (rather than a localized set of brain regions). This leaves open the questions of (1) whether blood oxygen level dependent (BOLD) fMRI signal(s) are predominately increased or decreased in PSz and (2) whether consistent, replicable patterns of activity in PSz can be mapped to specific circuits. Arterial spin labeling (ASL) imaging is a less utilized MRI measure that can be used to quantify resting brain cerebral blood flow (rCBF) and is sensitive to pharmacological manipulation and related to metabolic demand and cognitive function. In this data-driven analysis, we identify significant differences in rCBF in PSz vs. healthy control (HC) participants.

Methods: This study included 37 participants that met DSM-IV-TR/DSM 5 criteria for either schizophrenia, schizoaffective, or schizophreniform disorder and 32 HC participants. CBF data was obtained by performing a pseudo-continuous ASL scan. Eight participants' ASL data was did not pass quality control assessment (Final N = 61; 31 HC and 30 PSz). Data preprocessing included normalization, smoothing (5 mm FWHM), motion and partial volume corrections. The average CBF signals (in ml/100 g/min) for 246 brain regions of interest were extracted using the Brainnetome atlas. During the study, the MR scanner was upgraded from a Siemens Trio 3T MR system to a Siemens PRISMA 3T MR system. The scanner upgrade resulted in different scales of measured CBF intensity for values obtained from the Trio vs. PRISMA scanner. To harmonize these values, we applied the NeuroCombat harmonization procedure. To account for the patterns of co-dependence of CBF in nearby regions, we applied the innovative Fase autoregressive model to examine PSz vs. HC differences in rCBF; P-values were FDR-corrected for multiple tests.

Results: In PSz (relative to HC), rCBF was significantly decreased across 115 cortical brain areas and significantly increased in two subcortical striatal regions in PSz: left ventromedial putamen and right dorsolateral putamen. Exploratory linear regression analyses in the PSz revealed that rCBF in these two striatal regions was not significantly associated with overall symptom severity (total score on the Brief Psychiatric Rating Scale) nor an estimate of current antipsychotic medication dose (chlorpromazine equivalent dose).

Discussion: Our findings fall in line with a recent meta-analysis of rCBF studies of PSz reporting that the strongest effects were decreased rCBF in frontal and other cortical areas, and increased rCBF in the putamen relative to controls (du Sert et al. 2023). Intriguingly, a single dose of antipsychotic medication in healthy individuals was shown to boost CBF in the putamen (Selvaggi et al. 2019). Future research is needed to learn how the observed patterns of resting CBF in PSz are influenced by chronic administration of antipsychotic medications and how changes in rCBF may relate to severity of different symptoms.

F174. RESTING-STATE FUNCTIONAL CONNECTIVITY WITHIN SOCIAL BRAIN NETWORKS SHOW DIFFERENTIAL ASSOCIATIONS WITH NEGATIVE SYMPTOM DOMAINS IN SCHIZOPHRENIA

Anna Knippenberg*¹, Lauren Luther¹, Gregory P Strauss¹, Lawrence Sweet¹

¹*University of Georgia*

Background: Negative symptoms of schizophrenia (SZ) are currently defined as two broad dimensions within the DSM-5 (i.e., Volition and Diminished Expression). However, recent factor analyses support a 5-domain conceptualization of negative symptoms (i.e., asociality, anhedonia, avolition, alogia, blunted affect). Although each negative symptom domain is likely driven by unique neural mechanisms, it is currently unclear which specific neural processes drive abnormalities in each domain. The current study examined the validity of the 5-domain conceptualization by evaluating the selectivity of the association with resting-state functional connectivity (RS-FC) within five large-scale brain networks previously shown to be important for social functioning.

Methods: 39 outpatients with schizophrenia completed clinical symptom ratings and resting-state magnetic resonance imaging (rsMRI). RS-FC analyses were employed to evaluate the synchrony between regions of interest (ROIs) in five social brain networks – aversion, affiliative, perception, mentalizing, and mirror networks.

Results: Results indicated a selective association between asociality and increased synchrony within the aversion, affiliative, perception, and mirror networks that was not observed with other negative symptom domains. Worse social cognition was uniquely associated with increased network synchrony.

Discussion: Findings suggested that resting state social brain networks governing social behavior in healthy individuals have a unique association with the negative symptom domain of asociality in SZ. Findings support the 5-domain conceptualization and that they're associated with distinct mechanisms. Domains may require different mechanistic approaches to treatment and the DSM-5 conceptualization of negative symptoms may need to be reconsidered to account for recent evidence supporting a more granular structure.

F175. EFFECTS OF DIAZEPAM ON HIPPOCAMPAL BLOOD FLOW IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS

Nicholas Livingston*¹, Amanda Kiemes¹, Gabriel A. Devenyi², Samuel Knight¹, Paulina Lukow³, Luke Jelen¹, Thomas Reilly⁴, Aikaterini Dima¹, Maria Antonietta Nettis¹, Cecilia Casetta¹, Tyler Agyekum², Fernando Zelaya¹, Thomas Spencer¹, Andrea De Micheli¹, Paolo Fusar-poli¹, Anthony A. Grace⁵, Steven C.R. Williams¹, Philip McGuire⁴, Alice Egerton¹, M. Mallar Chakravarty², Gemma Modinos¹

¹*Institute of Psychiatry, Psychology, and Neuroscience, King's College London*, ²*Cerebral Imaging Center, Douglas Mental Health University Institute, McGill University*, ³*Institute of Cognitive Neuroscience, University College London*, ⁴*University of Oxford*, ⁵*University of Pittsburgh*,

Background: Elevated regional cerebral blood flow (rCBF) of the hippocampus has been robustly observed in individuals at clinical high-risk for psychosis (CHR-P), which may be a novel target for intervention. Preclinical studies demonstrated that administration of a GABA-enhancing compound such as diazepam could downregulate hippocampal hyperactivity and

prevent the emergence of psychosis-like phenotypes. Mechanistic evidence of the effects of diazepam on hippocampal hyperactivity in CHR-P is lacking. The aim of this study was to determine whether an acute dose of diazepam compared to placebo can reduce and normalise rCBF in the hippocampus and its subfields in CHR-P individuals.

Methods: We conducted a within-subject, double-blind, placebo-controlled, randomised, cross-over design study in 24 CHR-P individuals. Participants underwent two MRI sessions, three weeks apart; once under a single dose of diazepam (5 mg) and once under placebo (50 mg ascorbic acid). rCBF was measured using a pseudocontinuous arterial spin labelling sequence and a previously collected dataset of 21 healthy controls (HC) was used for comparison. Subject-specific hippocampus and subfield masks were generated using the MAGeT Brain toolbox. Using the minc-toolkit-v2/1.9.18, these masks were registered and resampled to the individual's respective rCBF map, and the mean rCBF value was extracted per hemisphere in native space from the following regions: whole hippocampus, CA1, subiculum, CA4/dentate gyrus, and total brain grey matter. Mixed ANCOVAs (covarying for global rCBF, age, and sex) and linear mixed-effects models (participant ID as random effect) investigated the effect of group (HC vs. CHR-P placebo and HC vs. CHR-P diazepam) and condition (CHR-P placebo vs. CHR-P diazepam), respectively, on hippocampal/subfield rCBF per ROI. Significance was set at pFDR LESS THAN 0.05. Exploratory analyses assessed broader diazepam effects on voxel-wise grey matter rCBF (linear mixed-effects model), and whether baseline clinical characteristics were associated with diazepam-induced changes in hippocampal rCBF (Pearson's correlations).

Results: Under the placebo condition, CHR-P individuals (mean[$\pm$ SD] age: 24.1[$\pm$ 4.8] years, 15F) showed significantly elevated rCBF compared to HC (mean[$\pm$ SD] age: 26.5[$\pm$ 5.1] years, 11F) in the hippocampus ($F(1,36)=8.2$, pFDR=0.004) and across its subfields (all pFDR LESS THAN 0.01). Following diazepam, rCBF in the hippocampus (and subfields, all pFDR LESS THAN 0.001) was significantly reduced ($t(69)=-5.1$, pFDR LESS THAN 0.001) and normalised to HC levels ($F(1,41)=0.3$, pFDR=0.225). Exploratory analyses revealed additional widespread reductions in rCBF by diazepam across several cortical and subcortical regions (e.g., medial/dorsolateral prefrontal cortex, nucleus accumbens, amygdala), and suggested that CHR-P individuals with highest attenuated psychotic symptom severity ($r=0.598$, $p=0.003$) and poorest social functioning ($r=-0.538$, $p=0.008$) at baseline had the smallest changes in diazepam-induced hippocampal rCBF.

Discussion: Our study shows that diazepam can normalise hippocampal hyperperfusion in CHR-P individuals, consistent with evidence implicating medial temporal GABAergic dysfunction in the pathophysiology of psychosis. Our results suggest the development of more hippocampal-selective GABAergic pharmacological agents as a promising strategy for preventing psychosis development.

F176. BRAIN METABOLITES IN THE PREFRONTAL AND MEDIAL TEMPORAL CORTICES IN CHILD AND ADOLESCENT OFFSPRING OF PATIENTS WITH BIPOLAR DISORDER

María Ortuño^{*1}, Adriana Fortea¹, Irene Martínez¹, María Muriel¹, Patricia Camprodon¹, Elena De la Serna², Roger Borràs³, Isabel Valli¹, Daniel Ilzarbe¹, Mireia Masias⁴, Inmaculada Baeza³, Josefina Castro-Fornieles³, Gisela Sugranyes¹

¹Fundació Clinic Recerca Biomèdica - Institut d'Investigacions Biomèdiques August Pi i Sunyer, Clinical and Experimental Neuroscience, ²Centro de Investigación Biomédica En Red

de Salud Mental CIBERSAM, Child and Adolescent Psychiatry, ³Institute of Neurosciences, University of Barcelona, ⁴BCN-MedTech, Universitat Pompeu Fabra

Background: The offspring of patients with bipolar disorders are at an increased risk of developing both their parental disorder and any other mental disorder during their lifetime [1]. Meta-analytical findings have described anomalous levels of metabolite concentrations in several brain areas in bipolar disorders. Examining the neurometabolic profile in child and adolescent offspring of patients with the disorder allows us to understand the neural correlates of familial risk for the disease and identify changes associated with the early stages of the illness. The aim of this study was to assess differences in measures of neurometabolites in two brain regions relevant to the disease between offspring of patients with bipolar disorder (BpO) and controls, and their relationship with age and psychosocial functioning.

Methods: 43 BpO (mean age 16.7 ± 4.7 , 58% females) and 139 healthy subjects (mean age 16.5 ± 3.4), all aged between 6 to 25 years old were recruited in the Hospital Clinic of Barcelona. No BpO met criteria for bipolar disorder. Every subject underwent the acquisition of two magnetic resonance imaging (MRI) sequences on a 3T scanner: a T1-weighted sequence and a magnetic resonance spectroscopy sequence (MRS) in two volumes of interest (VOIs) located in the lateral prefrontal cortex (PFC) ($2 \times 2 \times 2 \text{ cm}^3$) and the medial temporal lobe (mTL, $3 \times 2 \times 2 \text{ cm}^3$). MRS data was processed employing LCModel in order to obtain the creatine-corrected ratios of glutamate, glutamate + glutamine (Glx), N-acetylaspartate (NAA+NAAG), choline (GPC+PCh) and inositol (mIns). Moreover, all participants underwent an evaluation of functioning employing the Global Assessment of Functioning (GAF) scale. Linear models were conducted in R with metabolite as the dependent variable and group, GAF, sex and age and the interaction between them as fixed effects.

Results: A significant main effect of group by age was observed in NAA+NAAG levels in the PFC ($\beta = 0.01$, SE LESS THAN 0.01, $t = 2.30$ $p = 0.02$), whereby NAA+NAAG levels increased significantly with age in BpO compared to controls. In addition, there was a significant negative effect of levels of mIns in the PFC on GAF scores ($\beta = -0.002$, SE LESS THAN 0.01, $t = -2.03$ $p = 0.04$) in BpO. Moreover, a significant interaction between group and age was found in mIns levels in the mTL ($\beta = 0.01$, SE=0.01, $t = 2.186$, $p = 0.03$), whereby mIns levels increased more pronouncedly with age in BpO compared to controls.

Discussion: Our results show abnormal NAA+NAAG and mIns level increases with age in BpO relative to controls. Further, these findings indicate a negative relationship between mIns and psychosocial functioning in non-bipolar BpO. NAA+NAAG is a marker of neuronal density and function, hence increased levels of this metabolite in BpO could be due to protective mechanisms in healthy BpO. Likewise, mIns is implicated in intracellular second messenger systems and is related to glial proliferation and therefore higher levels could reflect variations in signaling pathways in the BpO population. Nevertheless, although studying the neurometabolic profile of BpO holds promise to gain a better knowledge of the biological alterations associated with risk and resilience in this population, future research needs to further disentangle the phenotypic correlates of these neurometabolic changes.

This study was funded by Instituto de Salud Carlos III co-funded by the EU (PI1800976, PI2100330, PI2100519), and by the EU grant (101057529), TV3_SalutMental_21 (202232-30), Alicia Koplowitz Foundation, CIBERSAM and 2021 SGR 01319.

F177. EXPLORING NEURAL CORRELATES OF NMDA RECEPTOR HYPOFUNCTION THROUGH MULTIMODAL IMAGING POST-KETAMINE

ADMINISTRATION: INVESTIGATING MARKERS OF GLUTAMATERGIC NEUROTRANSMISSION MODULATION

Moritz Haaf^{*1}, Jonas Rauh¹, Michael Jacob², Saskia Steinmann¹, Dhurba Poudel¹, Claudius Wellen¹, Twishi Puri³, Anastasia Haidar³, Nora Penzel⁴, Lipeng Ning³, Amanda Lyall³, Tashrif Billah³, Kang Ik Kevin Cho³, Johanna Seitz-Holland³, Ofer Pasternak³, Yogesh Rathi³, Marek Kubicki³, Daniel Mathalon², Christoph Mulert⁵, Martha E. Shenton³, Gregor Leicht¹

¹University Medical Center Hamburg-Eppendorf, ²University of California, San Francisco, ³Brigham and Women's Hospital, Harvard Medical School, ⁴Massachusetts General Hospital, Harvard Medical School, ⁵Justus-Liebig University

Background: Schizophrenia is characterized by a complex interplay of neurobiological alterations, comprising glutamatergic dysfunction and consequently excitatory-to-inhibitory (E/I) imbalance. A key component is the hypofunction of the N-Methyl-D-Aspartate Receptor (NMDAR), which can be effectively modeled by administering ketamine to healthy volunteers. However, the field lacks robust methods for assessing the individual extent of this hypofunction and evaluating responses to targeted therapies such as glycine, a co-agonist of the NMDAR. Our research builds on recent advances that highlight low gamma activity (30-50 Hz), evoked via an attention-demanding auditory choice reaction task in electroencephalography (EEG), as a promising biomarker indicative of NMDAR functionality. Incorporating a multimodal imaging strategy, we combine diffusion magnetic resonance imaging (dMRI) with simultaneous EEG/functional MRI (fMRI), to explore the neural correlates of NMDAR hypofunction and their potential as a biomarker for individualized therapy in schizophrenia.

Methods: In this longitudinal, placebo-controlled study, 32 healthy volunteers were administered ketamine to simulate NMDAR hypofunction. Each participant experienced three imaging sessions: a baseline with placebo, followed by two sessions involving either intravenous glycine or placebo pretreatment before ketamine infusion. Sessions were spaced at least a week apart, with the order of pretreatments counterbalanced. We focused on low gamma activity changes using simultaneous EEG/fMRI during an auditory choice reaction task and subsequently conducted dMRI to assess white-matter properties. Our statistical analysis employed linear mixed models (LMM) and incorporated covariates such as age and cannabis use. For the analysis of our fMRI data, we employed Generalized Linear Models (GLM).

Results: Ketamine administration resulted in an increase in schizophrenia-like symptoms, reflected in elevated Positive and Negative Syndrome Scale (PANSS) scores, and task-related error rates. This was paralleled by reduced activity in attention-related brain regions in fMRI and diminished gamma activity in EEG, coupled with an increase in whole-brain fractional anisotropy (FA). Glycine did not affect these MRI changes; however, it notably impacted task-related error rates, specifically mitigating the ketamine-induced increases which were otherwise apparent in the placebo condition. Additionally, glycine attenuated the effects on gamma activity, resulting in a neurophysiological state distinct from the placebo and ketamine conditions.

Discussion: Our results align with the conjecture that reductions in task-associated activity in fMRI and EEG reflect NMDAR hypofunction. The increase in FA post-ketamine, although surprising, mirrors trends seen in major depressive disorder, and may be linked to astrocyte plasticity. Importantly, the modulation of EEG-monitored gamma activity by glycine offers a nuanced perspective on the E/I balance. This suggests that such EEG markers could potentially provide a deeper understanding of individual response to glutamatergic therapies in schizophrenia.

F178. THE ASSOCIATION OF TOBACCO SMOKING AND METABOLITE LEVELS IN THE ANTERIOR CINGULATE CORTEX OF FIRST-EPISODE PSYCHOSIS PATIENTS: A CASE-CONTROL AND 6-MONTH FOLLOW-UP 1H-MRS STUDY

Merel Koster*¹, Marieke van der Pluijm¹, Elsmarieke van de Giessen¹, Anouk Schrantee¹, Carmen F. M. van Hooijdonk², Jean-Paul Selten², Jan Booij¹, Lieuwe de Haan¹, Tim Ziermans³, Jentien Vermeulen¹

¹Amsterdam UMC, ²University of Maastricht, ³Universiteit van Amsterdam

Background: Tobacco smoking amongst patients with schizophrenia is 2-3 times higher compared to the general population [1], and it is associated with worse clinical outcomes such as relapse and readmission [2]. Remarkably, few neuroimaging studies have explored the effect of tobacco on the brain in psychosis. In particular limited studies have assessed the effect of tobacco on the levels of different neurometabolites, whilst neurometabolites such as glutamate and choline have been implicated in psychosis and tobacco smoking separately. The current study therefore aimed to investigate the influence of chronic smoking on neurometabolite levels in the anterior cingulate cortex (ACC) of first-episode psychosis (FEP) patients and controls, as shared ACC abnormalities may contribute to the development or maintenance of smoking in schizophrenia.

Methods: 59 FEP patients and 36 controls were included in the study. Proton magnetic resonance spectroscopy (1H-MRS) was acquired using a Point Resolved Spectroscopy (PRESS) pulse sequence on a 3 Tesla Philips MRI scanner. Associations between smoking status (i.e. smoker yes/no) or average number of cigarettes smoked per day in the past year and Glx (glutamate + glutamine, as proxy for glutamate) and total choline (tCh) levels were assessed at baseline in both groups separately using analysis of covariance (ANCOVA) and linear regressions. For 37 patients, six months follow-up data were acquired to assess longitudinal changes in neurometabolite levels using linear mixed models. We controlled for the use of cannabis in all analyses, considering the strong correlation of cannabis use with tobacco smoking.

Results: No significant differences in Glx or tCh levels in the ACC were found between smoking (n=28) and non-smoking (n=31) FEP patients, at baseline nor in longitudinal analyses. Negative associations were observed between cigarettes smoked per day, and Glx (pFDR=0.025) and tCh levels (pFDR=0.019) in controls but not in FEP patients.

Discussion: We found that tobacco smoking is associated with differences in neurometabolite levels in controls but not in FEP patients. Schizophrenia patients already appear to have an aberrant glutamate system and show dysregulated nicotine acetylcholine receptor (nAChR) expression. Nicotine, the primary addictive substance in tobacco, exerts its effects on the brain through the activation of nAChRs, and chronic tobacco exposure results in desensitization, inactivation, and upregulation of these receptors [3]. In addition, it has been hypothesized that abnormalities in neurometabolite signalling in schizophrenia are due to divergent nAChR signalling [4]. Thus, possibly, pre-existing disease-related neurometabolite deficits or alterations at nAChR level in FEP patients underlie the differences in tobacco-related effects on glutamate and choline levels. However, MRS does not allow for observation of neurometabolite function at receptor level. Future research for example through PET-imaging, could focus on investigating nAChR dysfunctioning to elucidate underlying reasons for the absence of differences in neurometabolites between smoking and non-smoking FEP patients.

F179. GLUTAMATE AND GABA LEVELS IN THE ANTERIOR CINGULATE CORTEX IN TREATMENT RESISTANT FIRST EPISODE PSYCHOSIS PATIENTS

Marieke Van der Pluijm^{*1}, Maartje Alting¹, Anouk Schrantee¹, Richard Edden², Jan Booij¹, Lieuwe De Haan¹, Elsmarieke Van de Giessen¹

¹*Amsterdam UMC, University of Amsterdam*, ²*Johns Hopkins University*,,

\

Background: Around 30% of schizophrenia patients do not respond sufficiently to conventional antipsychotic treatment. Glutamate and γ -aminobutyric acid (GABA) may be implicated in treatment resistant (TR) patients. Previous research indicates that TR patients show increased glutamate levels compared to responders, but findings are inconclusive and limited in the early disease stage. Furthermore, the two neurotransmitters have rarely been assessed in conjunction. We therefore aimed to investigate the role of glutamate and GABA in first episode TR patients and explore whether these neurometabolites could be potential predictive markers for treatment resistance in schizophrenia.

Methods: We used proton magnetic resonance spectroscopy (MRS) to assess Glx (glutamate + glutamine) and GABA+ (GABA including macromolecules) in the anterior cingulate cortex (ACC) of 58 first episode psychosis patients. A short-TE Point Resolved Spectroscopy (PRESS) pulse sequence was used to acquire the metabolite spectra for Glx measurements and GABA-edited proton J-difference spectra were acquired using a Mescher-Garwood Point Resolved Spectroscopy (MEGA-PRESS). At six months follow-up treatment response was determined. Patients were considered TR when, despite adequate treatment with a minimum of two trials of different antipsychotics, at least one of the following items of the Positive and Negative Syndrome Scale was scored moderate or higher: delusions (P1), conceptual disorganization (P2), hallucinatory behaviour (P3), mannerisms and posturing (G5) and unusual thought content (G9). In a subgroup of 33 patients a follow-up MRS scan was acquired to assess changes in neurometabolite levels over six months.

Results: At six months follow-up 12 patients were classified as TR and 46 patients as responders. The two groups did not significantly differ on gender, IQ, use of medication, and substance use. The TR patients had longer duration of antipsychotic use and higher symptom severity scores. Glx and GABA+ levels were not significantly different between TR patients and responders at baseline and the levels did not change at six months follow-up. The groups differed in voxel fractions of white matter (WM) and cerebral spinal fluid (CSF), with TR patients showing lower WM and higher CSF fractions.

Discussion: Our findings do not provide evidence that glutamate or GABA levels in the ACC differ between TR patients and responders in the early disease stage of schizophrenia. However, differences in WM and CSF voxel fractions may have influenced our results. Previous studies and our results also suggest that MRS measurements of glutamate and GABA are susceptible to multiple confounders including tissue fractions, illness duration, medication dose, and clozapine responsiveness. This complicates disentangling the role of glutamate and GABA in treatment resistance schizophrenia. Future research should take these confounders into account and particularly focus on clozapine responsiveness, inclusion of medication-naïve patients and longitudinal follow up/medication effects to better understand the complex interplay of glutamate and GABA in treatment resistant schizophrenia.

F180. ASSOCIATION BETWEEN INCREASED ANTERIOR CINGULATE GLUTAMATE AND PSYCHOTIC-LIKE EXPERIENCES, BUT NOT AUTISTIC TRAITS IN HEALTHY VOLUNTEERS

Verena Demler*¹, Elisabeth F. Sterner¹, Martin Wilson², Claus Zimmer¹, Franziska Knolle¹

¹*Technische Universität München*, ²*Centre for Human Brain Health and School of Psychology, University of Birmingham*

Background: Despite many differences, autism spectrum disorder and schizophrenia spectrum disorder share environmental risk factors, genetic predispositions as well as neuronal abnormalities, and show similar cognitive deficits in working memory, perspective-taking, or response inhibition. These shared abnormalities are already present in subclinical traits of these disorders. The literature proposes that changes in the inhibitory GABAergic and the excitatory glutamatergic system could explain underlying neuronal commonalities and differences, but only few studies explored changes of neurotransmitter concentrations associated to psychotic-like experiences and autistic traits.

Methods: Using magnetic resonance spectroscopy (1H-MRS), we therefore investigated the associations between glutamate concentrations in the anterior cingulate cortex (ACC), the left/right putamen, and left/right dorsolateral prefrontal cortex and psychotic-like experiences (Schizotypal Personality Questionnaire) and autistic traits (Autism Spectrum Quotient) in 53 healthy individuals (26 women, aged 18-35 years). To investigate the contributions of glutamate concentrations in different cortical regions to symptom expression and their interactions, we first performed two linear regression models, using psychotic-like experiences and autistic traits as outcome variables, with glutamate levels from the ACC, left DLPFC, and right DLPFC as predictor variables, while accounting for age and sex. Levels of glutamate could not be reliably estimated in the putamen. To investigate non-linear relationships between clinical traits and glutamate concentrations, we dichotomised the clinical scores by a median split (psychotic-like experiences, median=75; autistic traits, median=22) and performed logistic regression analyses corrected for age and sex.

Results: We found that levels of glutamate in the ACC significantly predicted psychotic-like experiences, but not autistic traits. Whereas glutamate concentrations in the DLPFC did not yield any significant results. Supporting this finding, a binomial logistic regression predicting median-split high and low risk groups for psychotic-like experiences (PLE-group ~ Glu DLPFC_R + Glu DLPFC_L + Glu ACC + age + sex) revealed ACC glutamate levels as a significant predictor for group membership. There was a 33.1% increase in the odds of an individual being in the high psychotic-like experiences group for every one-unit rise in ACC glutamate, with all other predictor variables held constant. The effects of the linear and logistic regressions both survived Bonferroni multiple comparison correction (level of significance, $p < 0.025$, correcting for two tests each).

Discussion: This study provides evidence for both a dimensional and a non-linear relationship, highlighting a positive linear correlation between the intensity of psychotic-like experiences and ACC glutamate levels across the entire sample. ACC glutamate also serves as a predictor for an individual's classification as a high-risk or low-risk individual, suggesting qualitative distinctions in the neuropathology of various disease stages. However, further exploration of this phenomenon is necessary in future research. Taken together, these results suggest that glutamate levels may be a potential candidate for identifying early-risk individuals prone to developing psychotic-like experiences.

F181. REPEATED TESTING INDUCES A DIFFERENTIAL STRIATAL RESPONSE DURING REWARD ANTICIPATION AND REWARD RECEPTION IN A LARGE GROUP OF PATIENTS WITH SCHIZOPHRENIA

Mariia Kaliuzhna*¹, Fabien Carruzzo¹, Noémie Kuenzi¹, Philippe N. Tobler², Matthias Kirschner³, Tal Geffen⁴, Teresa Katthagen⁴, Kerem Böge⁴, Marco M. Zierhut⁴, Florian Schlagenhauf⁴, Stefan Kaiser³

¹University of Geneva, ²Laboratory for Social and Neural Systems Research, University of Zurich, ³University Hospitals of Geneva, ⁴Charite University Medical Center Berlin, ,

Background: Improving treatment options in schizophrenia relies on the identification of biomarkers, i.e. characteristics robustly associated with a given dysfunction. Such biomarkers are of particular importance for negative symptoms of schizophrenia where treatment options are especially limited. Deficits in reward processing have been shown to be promising candidates as such biomarkers. Indeed, motivation relies on the ability to successfully integrate reward-related information. One important process is reward anticipation. In order to engage in goal-directed behaviours one needs to represent the potential reward it could bring. Another aspect is the ability to adequately represent the rewarding value of a stimulus once the reward is obtained. Adaptive coding of reward is the mechanism underlying this ability. Our work has assessed these processes in patients with schizophrenia.

Methods: We used the Monetary Incentive Delay (MID) task during functional magnetic resonance imaging (fMRI), in a large sample of patients (N=86) and healthy controls (N=66), recruited in two centres in Switzerland and Germany. Participants were tested twice, 3 months apart, to evaluate the stability of the effects in time. Our analyses focused on the phase of the task before the reception of reward, to evaluate reward anticipation, and on the feedback phase to evaluate adaptive coding of reward.

Results: During reward anticipation, in patients with schizophrenia as compared to healthy controls we found reduced activity in the ventral and dorsal striatum as well as the posterior putamen, bilaterally. In addition, patients also had reduced activation in the thalamus, amygdala, right anterior cingulate cortex and left calcarine gyrus. Similarly reduced activity was also found upon re-test. We found no correlations between striatal activity and motivational negative symptoms (apathy), positive and depressive symptoms or cognition, at either the first or second testing sessions. In patients, higher striatal activity correlated with higher amounts won on the task. During the outcome phase of the task, we also found reduced adaptive coding in patients in striatal regions. Specifically, patients' BOLD response increase to increasing rewards was less steep than that of controls in the reward context where fewer items needed to be represented and thus a steeper BOLD increase slope was to be expected. Interestingly, upon re-test, patients improved, showing adaptive coding to the same extent as controls. At re-test adaptive coding in patients correlated with negative symptoms, due to some patients showing overadaptation – BOLD response slopes that are too steep.

Discussion: Our findings are consistent with the hypothesis that ventral striatal activity reflects modulation of motivational saliency during reward anticipation and that these processes are impaired in patients with schizophrenia. Similarly, reward adaptation is impaired in schizophrenia and, in a subgroup of patients, might reflect faster saturation and an inability to adequately represent the full range of rewards. Interestingly, while the striatal response during reward anticipation remained consistent between sessions, there was an apparent improvement in striatal reward adaptation upon re-test, suggesting potential distinct mechanisms within the same brain regions. We provide additional evidence for the use of ventral striatal hypoactivity as a biomarker candidate for schizophrenia, but also raise critical issues that would need to be

resolved before this measure can be considered as a biomarker, in particular with respect to negative symptoms.

F182. DORSOLATERAL PREFRONTAL CORTEX ACTIVATION AND CONNECTIVITY IN PSYCHOSIS AND THE RELATION TO TREATMENT RESPONSE

Lara Wallenwein^{*1}, Alexander Sahm¹, Daniela Mier¹

¹*University of Konstanz*

Background: Cognitive impairments are a common symptom in psychotic disorders. They are often present before the onset of illness and constitute a predictor of poor functional outcomes. Aberrant activation and connectivity related to working memory performance has been found in psychosis. While neurocognitive abilities have been linked to treatment response, few studies investigated the predictive value of accompanying neural activation and connectivity.

Methods: In this ongoing study, 17 patients with psychotic disorders participated in functional magnetic resonance imaging during an in-patient stay in a psychotherapy ward. Fifteen healthy control participants served as comparison. During fMRI scanning, participants performed the Callicott n-back working memory task. Group differences in the 2-back GREATER THAN 0-back contrast in activation and gPPI connectivity with left and right dorsolateral prefrontal cortex (dlPFC) as seed regions were assessed on a whole-brain level. Moreover, activation within left and right dlPFC and connectivity with inferior and superior parietal lobule were correlated with changes in psychopathology and level of functioning. For the latter, difference scores in Positive and Negative Syndrome Scale and Global Assessment of Functioning were calculated between admittance and discharge from psychiatric care. FMRI data were acquired on a 3T Siemens Magnetom Skyra and analysed with SPM12. General task activation is reported FWE corrected p LESS THAN .05, connectivity results and group comparisons with an exploratory threshold of p LESS THAN .001 uncorrected, cluster size threshold 20 voxels.

Results: The preliminary results show strong task-based activation in the fronto-parietal network, insula, thalamus, and cerebellum over both groups, but no group differences. Also, no differences in performance were found. Task-based connectivity of dlPFC with frontal regions, superior parietal lobule, occipital cortex, cerebellum, and amygdala was found over both groups in gPPI analyses. On a whole-brain level, patients showed reduced connectivity between left dlPFC and left orbitofrontal cortex as well as between right dlPFC and right superior frontal cortex compared to the control group. Activation in bilateral dlPFC was able to predict improvements in general functioning over the course of in-patient treatment but was not related to changes in positive or negative pathology. Functional connectivity of dlPFC with inferior and superior parietal lobule could neither predict changes in level of functioning nor psychopathology.

Discussion: The activation and connectivity within the fronto-parietal network during performance of a working memory task is in line with pertinent literature. While differences in connectivity were present, we found no differences in performance and activation between groups. However, our analyses indicate that activation but not connectivity of dlPFC during working memory performance is predictive for treatment response in psychosis. Although our results warrant validation in a larger sample, they point towards complementary information of activation and connectivity and the importance of neurocognitive functions for therapeutic success in psychosis.

F183. EXAMINING AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS USING FUNCTIONAL CONNECTIVITY MRI FOLLOWING TREATMENT IN FIRST EPISODE PSYCHOSIS PATIENTS

Jose Maximo*¹, Adrienne Lahti¹

¹*University of Alabama at Birmingham*

Background: The clinical phenotype of first episode psychosis (FEP) is rather heterogeneous and current diagnostic criteria suggest a clear boundary between affective (major depressive and bipolar disorders) and non-affective psychotic disorders (schizophrenia and schizophrenia-related disorders). Furthermore, the impact that antipsychotic treatment may have on these subgroups may differ from one another. The present study measured resting state functional connectivity (rsFC) from brain networks deemed crucial for higher-order cognition: default mode (DMN), salience (SN), dorsal attention (DAN), and executive control network (ECN). Patients were dichotomized into affective and non-affective psychosis groups. Participants were scanned prior to treatment (baseline), 6 weeks, and 16 weeks following antipsychotic treatment. A group of healthy controls (HC) was also scanned. We hypothesized that affective and non-affective groups would show differential rsFC compared to HC throughout the trial.

Methods: Data from 87 antipsychotic medication-naïve FEP patients (non-affective = 65; affective = 22) and 87 HC were used. Medication-naïve patients received antipsychotic treatment for sixteen weeks. rsFC of the default mode (DMN), salience (SN), dorsal attention (DAN), and executive control network (ECN) was assessed prior to treatment, 6, and 16 weeks after treatment. We used linear mixed models to test group by time interactions within each network.

Results: Significant changes in rsFC (p LESS THAN 0.05, corrected) were found within the SN where affective patients showed reduced rsFC compared to HC and non-affective patients at baseline; at week 6 both affective and non-affective patients showed rsFC increases, but then at week 16 affective patients showed rsFC decrease whereas non-affective patients showed increases in rsFC. Interestingly, within the ECN both affective and non-affective groups showed decreased rsFC at baseline compared to HC and then a steady increase in rsFC throughout the antipsychotic trial.

Discussion: Here, we found that changes in intrinsic brain network rsFC were impacted by affective traits in medication-naïve FEP patients. Together, our data suggests modulation of affective traits should be taken into consideration when attempting to associate intrinsic brain network connectivity as a mechanism underlying FEP.

F184. CORTICAL AND SUBCORTICAL STRUCTURAL DIFFERENCES BETWEEN FIRST-EPISODE PSYCHOSIS AND FIRST-EPISODE BIPOLAR DISORDER

Cemal Demirlek*¹, Muhammed Demir², Berna Yalincetin¹, Burcu Verim¹, Ezgi Cesim¹, Merve S. Gurbuz¹, Nabi Zorlu³, Emre Bora⁴

¹*Institute of Health Sciences, Dokuz Eylul University*, ²*Dokuz Eylul University*, ³*Katip Celebi University, Ataturk Education and Research Hospital*, ⁴*Dokuz Eylul University, School of Medicine*,

Background: This study aims to explore the differences in cortical and subcortical structures between healthy controls (HC), patients with first-episode psychosis (FEP), and first-episode

bipolar disorder (FEM). The study's focus on these specific patient groups provides insights into the neurobiological underpinnings of these psychiatric conditions.

Methods: The study included 19 HCs, 23 patients with FEM, and 32 patients with FEP. Participants underwent interviews using the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Brain imaging was performed using a 3 T MR scanner with an 8-channel head matrix coil. T1 images were analyzed using FreeSurfer software. Data from each participant was processed through the standard FreeSurfer workflow using the 'recon-all' script. Structural brain differences between groups were determined using the General Linear Model (GLM). Cortical thickness maps were smoothed with a 10 mm full-width half-maximum Gaussian kernel. Group differences were examined using GLM with Monte Carlo z-field simulation, correcting for multiple comparisons at a threshold of $p < 0.05$.

Results: There were statistically significant increases in various brain regions in FEM patients compared to HCs, including left hemisphere inferior parietal surface area ($p = 0.005$), left paracentral surface area ($p = 0.01$), left inferior parietal volume ($p = 0.01$), right hemisphere frontal pole surface area ($p < 0.001$), right precuneus surface area ($p = 0.008$), right precentral surface area ($p = 0.005$), right inferior parietal surface area ($p = 0.01$), right lateral orbitofrontal volume ($p < 0.001$). A significant decrease was observed in the volume of the right hemisphere's lingual region in FEP patients compared to HCs ($p = 0.005$). A significant increase was found in the volume of the right hemisphere's parahippocampal region in FEM patients compared to FEP patients ($p = 0.02$). Comparisons between groups revealed significant differences in subcortical structures, particularly in the thalamus and amygdala. Left thalamus volume was decreased in FEP patients compared to HC ($p = 0.04$). Left Thalamus ($p = 0.01$) and right thalamus ($p = 0.03$) were increased in FEM patients compared to FEP. Right amygdala volume was increased in FEM patients compared to FEP ($p = 0.01$).

Discussion: The findings indicate distinct structural differences in both cortical and subcortical regions among patients with FEM or FEP. These differences might contribute to the understanding of the pathophysiology underlying these psychiatric disorders. The increased volumes in specific brain regions in FEM patients as compared to FEP patients and HCs suggest potential biomarkers for bipolar disorder. The study underscores the importance of neuroimaging in psychiatry and highlights the need for further research in this area to better understand these complex disorders.

F185. BRAIN STRUCTURE IN FAMILIAL HIGH RISK FOR PSYCHOSIS, ULTRA-HIGH RISK FOR PSYCHOSIS AND FIRST-EPISODE PSYCHOSIS

Cemal Demirlek^{*1}, Muhammed Demir², Berna Yalincetin², Merve S. Gurbuz¹, Ezgi Cesim², Burcu Verim², Nabi Zorlu³, Emre Bora⁴

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Dokuz Eylul University,* ³*Katip Celebi University, Ataturk Education and Research Hospital,* ⁴*Dokuz Eylul University, School of Medicine,*

Background: The study aimed to compare brain structures among individuals at familial high risk (FHR-P), ultra-high risk for psychosis (UHR-P), and those experiencing first-episode psychosis (FEP) using T1-weighted brain magnetic resonance imaging (MRI).

Methods: Participants underwent interviews using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). The Turkish version of the Structured Interview for Prodromal Syndromes (SIPS) was used to identify UHR-P. The study included individuals with FHR-P, defined as those with a first-degree relative diagnosed with schizophrenia but not meeting

UHR-P or FEP criteria. Brain MRI was conducted using a 3T MR scanner with an 8-channel head matrix coil. T1-weighted images were analyzed using the FreeSurfer's 'recon-all' command. General Linear Model (GLM) was utilized to identify structural brain differences between groups. Cortical thickness maps were smoothed using a 10 mm full-width half-maximum Gaussian kernel. Group differences were examined using a Monte Carlo Z-field simulation with a threshold of $p \text{ LESS THAN } 0.05$ for multiple comparisons, adjusted for age and gender as covariates. Volumes of subcortical structures were extracted using FreeSurfer's automated procedure ('aseg.vol').

Results: This study included 19 healthy controls, 19 individuals at FHR-P, 20 individuals at UHR-P, and 32 patients with FEP. A statistically significant difference in the thickness of the left hemisphere cuneus between individuals at FHR-P, UHR-P, and those with FEP ($p = 0.01$). Patients with FEP showed a statistically significant reduction in the volume of the right hemisphere lingual region compared to healthy controls ($p = 0.005$). In FEP patients, compared to UHR-P individuals, there was a significant reduction in the thickness of the left hemisphere rostral middle frontal region ($p = 0.01$) and the volume of the left hemisphere superior temporal region ($p = 0.01$). UHR-P individuals showed a significant increase in the thickness of the left hemisphere cuneus ($p = 0.007$) and the right hemisphere pericalcarine thickness ($p = 0.04$) compared to those at FHR-P. The left thalamus volume was significantly reduced in FEP patients compared to healthy controls ($p = 0.04$). A similar reduction in the left pallidum volume was noted in individuals at familial risk compared to healthy controls ($p = 0.03$) and in UHR-P compared to FHR-P individuals ($p = 0.01$).

Discussion: The study highlights distinct structural brain differences in individuals at different stages of psychosis risk and manifestation. The findings suggest that specific brain regions undergo changes not only in FEP but also in stages leading up to full-blown psychosis. This has implications for early detection and intervention strategies in psychosis. Further research is needed to understand the causal relationships and the potential for these brain structure changes to serve as biomarkers for psychosis risk.

F186. NEUROANATOMICAL CORRELATES OF MENTAL STATE REASONING IN SCHIZOPHRENIA: A MULTIMODAL IMAGING STUDY

Cemal Demirlek^{*1}, Burcu Verim², Merve Karakilic³, Ecenaz Sarikaya³, Berna Yalincetin², Adem Bayrakci³, Funda Gulyuksel³, Elif Oral³, Fazil Gelal², Nabi Zorlu³, Emre Bora⁵

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Katip Celebi University, Ataturk Education and Research Hospital,* ⁵*Department of Psychiatry, Dokuz Eylul University Medical School, Izmir, Turkey*

Background: Schizophrenia is characterized by established deficits in theory of mind. The ability to reason about mental states involves integrating contextual and past knowledge through representational systems. This study, employing multimodal neuroimaging, seeks to explore the neuroanatomical underpinnings of theory of mind's mental state reasoning component in both individuals with schizophrenia and healthy controls (HCs), utilizing T1-weighted and diffusion-weighted (DTI) magnetic resonance imaging (MRI).

Methods: The study comprised 62 individuals diagnosed with schizophrenia and 34 HCs. Mental state reasoning was assessed using Hinting tests. T1-weighted structural MRI scans were analyzed using FreeSurfer, while diffusion-weighted MRI scans were analyzed using FSL. Correlations between theory of mind's mental state reasoning components and cortical

parameters (thickness, volume, surface area) or DTI scalars (fractional anisotropy, axial diffusivity, radial diffusivity) underwent cluster-based correction for multiple comparisons.

Results: Within the schizophrenia group, the Hinting test scores exhibited favorable associations with cortical volumes in two distinct clusters. These clusters encompassed the left superior temporal sulcus volume extending to the inferior frontal region ($p = 0.014$, $r = 0.506$) and the left pars orbitalis volume ($p = 0.032$, $r = 0.525$). Furthermore, there was a positive correlation between hinting scores and surface area in a cluster within the left superior temporal sulcus surface area, extending to supra-marginal, middle, and inferior temporal regions ($p = 0.014$, $r = 0.473$). However, in the T1-weighted MRI analysis, no significant correlations were observed in HCs or in subcortical structures. Similarly, the DTI analysis did not reveal any significant correlations in mental state reasoning for both the schizophrenia group and HCs.

Discussion: In conclusion, this multimodal brain imaging study revealed significant differences in theory of mind and neuroimaging measures between patients with schizophrenia and HCs. This research also presented findings supporting the role of cortical volume and surface areas in distinct brain regions concerning the mental state reasoning components of theory of mind in individuals with schizophrenia.

F187. ALTERATION OF GRAY MATTER MICROSTRUCTURES IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA AFTER COMMENCING CLOZAPINE TREATMENT

Wonik Jo^{*1}, HyeJin Sim¹, Min Jeong Kwon¹, Seoyeong Kim², Ki Woong Kim², Euitae Kim²

¹Seoul National University College of Brain and Cognitive Science, ²Seoul National University Hospital

Background: To elucidate neurobiological mechanisms behind clozapine and treatment-resistant schizophrenia (TRS), neuroimaging studies have found structural alterations in different regions of the brain. However, these conventional imaging techniques lack the capability to detect microstructural alterations. This study aimed to investigate microstructural alteration in the brains of TRS patients after commencing clozapine treatment via texture analysis using a three-dimensional gray-level co-occurrence matrix (GLCM).

Methods: 30 patients with TRS and 18 with treatment response (NTRS) were recruited. T-1 weighted magnetic resonance imaging (MRI) was obtained twice within eighteen weeks of the interval. Texture features were calculated using GLCM from sixteen regions of interest (ROIs). A paired sample T-test and Wilcoxon signed-rank test were performed to figure out texture features that have changed significantly after adjusting the significance with the Bonferroni method. Features were eliminated via correlation analysis to reduce the dimension and intercorrelation between features from each ROIs. Differences in texture features between groups from each time point and the alteration of texture features were tested using the T-test and Mann-Whitney U-test. The association of these significant features and the symptom scores were evaluated with partial correlation while controlling the effect of antipsychotic equivalent dose, duration of illness, and age.

Results: Patients with TRS showed significant alterations in the texture features from the posterior corpus callosum, frontal cortex, and thalamus (p -Bonferroni LESS THAN 0.05). Patients with NTRS showed no significant alterations among features from ROIs. When comparing the significant texture features of TRS and NTRS patients from each time point, only uniformity from the frontal cortex after treatment ($t = -2.18$, $p = 0.036$) but none showed a difference between groups. However, there was a significant difference in the correlation

changes in the posterior corpus callosum (p LESS THAN 0.05). While there was a significant volume decrease in the thalamus and frontal cortex of TRS patients, there was no alteration in the volume of the corpus callosum besides the mid-posterior region. The alteration of correlation (T6), which has increased significantly after treatment with clozapine, had a positive correlation with the improvement of visual learning amongst TRS patients ($r = 0.59$, p -Bonferroni LESS THAN 0.05).

Discussion: Our finding suggests that there exists a microstructural alteration in the corpus callosum which has an association with improvement of cognitive function among patients with TRS. It is important to note that there was no significant change in the corpus callosum volume, while the texture feature has altered significantly after treatment. This may suggest that there could be a different mechanism of clozapine that induces subtle changes in the brain region and drives a positive outcome for patients.

F188. FACIAL AFFECT PROCESSING IN PERSONS WITH VARIED LEVELS OF SCHIZOTYPY: AN ERP STUDY

Jaime Morales*¹, Brooke Bonta¹, Mason Richards¹, Brian F. O'Donnell¹, William P. Hetrick¹

¹*Indiana University*

Background: Persons with schizophrenia present with facial affect recognition deficits early in the development and throughout the course of the disorder. Efforts have been made to pinpoint when, how, and where facial affect recognition deficits go awry before the onset of the disorder to help alleviate the impact of deficits as psychosis develops. Assessment of persons with elevated levels of schizotypy has been used to probe if facial affect recognition is a trait-like vulnerability for schizophrenia. Indeed, behavioral facial affect recognition is an area of deficit in persons with elevated schizotypy. Persons with higher schizotypy present with similar, yet attenuated levels of deficit as persons with schizophrenia. It is not well known whether there are underlying neuronal correlates of facial processing that can help determine if, when, and how facial affect recognition is impacted in schizotypy. We used event-related potentials (ERPs) to determine if facial affect recognition deficits arise from early visual processing and/or the encoding of facial features.

Methods: The present study examined the P1 early visual processing and N170 facial recognition ERPs during an emotion recognition task in young adults without a history of serious mental illness ($N=50$) within the Bloomington, Indiana community. Schizotypy was assessed utilizing the Schizotypal Personality Questionnaire Brief-Revised (SPQ-BR). During the EEG recordings, participants viewed pictures of faces expressing happy, angry, and neutral emotions. Participants were asked to assess which emotion was being presented. Amplitudes for both the P1 and N170 were examined from electrodes O1/O2 and P7/P8, respectively. Analyses focused on ERPs elicited to each emotion individually and then with all emotions combined.

Results: Correlation analyses revealed that participants with higher SPQ total scores associated with reduced N170 amplitudes to angry faces. No correlations between SPQ-total scores and other ERP amplitudes were found.

Discussion: This study shows that although persons with schizotypy typically have reduced behavioral emotion recognition, their neuronal responses (as measured by the P1 and N170) do not show similar abnormalities of both visual processing and facial recognition as observed in persons with schizophrenia for neutral and happy emotions. Yet, those with higher schizotypy tend to allocate fewer resources to facial recognition as indicated by reduced N170 amplitudes when viewing and assessing angry facial expressions; an avenue of exploration that

should be further examined to better understand if negatively valenced emotions are of importance when emotion recognition is impacted in schizotypy.

F189. BRAIN STRUCTURE AND FUNCTION IN ADULT SURVIVORS OF DEVELOPMENTAL TRAUMA WITH PSYCHOSIS: A SYSTEMATIC REVIEW

Alexander Noar*¹, Michael Bloomfield², Mustapha Modaffar¹, Camilla Walker³, Ting-Yun Chang¹

¹University College London, ²University College London and MRC Clinical Sciences Centre,

³Camden and Islington Foundation Trust

Background: Developmental trauma increases psychosis risk in adulthood, and is associated with poor prognosis and treatment response. It has been proposed that developmental trauma may give rise to a distinct alterations in brain structure and function. Our aim was to test this hypothesis by systematically reviewing neuroimaging studies of brain structure and function in adults with psychosis diagnoses, according to whether or not they had survived developmental trauma. We registered our search protocol in PROSPERO (CRD42018105021).

Methods: We systematically searched literature databases for relevant studies published before June 2023. We identified thirty-one imaging studies (n = 1,761 psychosis patients, n = 1,775 healthy controls or healthy siblings).

Results: Developmental trauma was associated with global and regional differences in grey matter; corticolimbic structural dysconnectivity; a potentiated threat detection system; dysfunction in regions associated with mentalization; and elevated striatal dopamine synthesis capacity.

Discussion: Trauma-induced changes in brain structure and function may induce vulnerability to psychosis. This would be consistent with findings from other studies that developmental trauma exposure is associated with changes in structure and function in circuits that are implicated in psychosis. Accumulated trauma-induced changes may have an additive effect on brain volume reductions that are known to occur in schizophrenia. Whilst the majority of studies were cross-sectional, there was high-quality prospective evidence of putative trauma-related effects alongside dose-effects of trauma severity on changes in brain structure which would support causation. These findings warrant further research to elucidate vulnerability and resilience mechanisms for psychosis in developmental trauma survivors.

F190. ALTERED TOPOLOGY OF THE FUNCTIONAL CONNECTOME IN PSYCHOSIS RISK AND MODULATION BY OXYTOCIN

Cathy Davies*¹, Daniel Martins¹, Ottavia Dipasquale¹, Rob McCutcheon², Andrea De Micheli³, Valentina Ramella-Cravaro³, Umberto Provenzano³, Grazia Rutigliano³, Marco Cappucciati³, Dominic Oliver², Steven CR Williams¹, Paul Allen¹, David Taylor⁴, Sukhi Shergill¹, Paul Morrison¹, Philip McGuire², Yannis Paloyelis¹, Paolo Fusar-Poli³

¹Institute of Psychiatry, Psychology and Neuroscience, King's College London, ²University of Oxford, ³EPIC Lab, , Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, ⁴Maudsley Hospital and Institute of Pharmaceutical Science, King's College London

Background: Functional brain network abnormalities are increasingly implicated in psychotic disorders. Aberrant connectome organisation is also present prior to the onset of psychosis in patients at Clinical High Risk (CHR) and is associated with disease onset and symptomatology. Previous research suggests that the neuropeptide oxytocin, a potential novel treatment, modulates network dynamics in healthy individuals but its effects in CHR patients remain unknown.

Methods: In two parallel randomised, double-blind, 40IU intranasal oxytocin vs placebo challenge studies with a crossover design, 47 males (30 CHR and 17 healthy controls) each participated in two resting-state fMRI scans: once following oxytocin and once following placebo. Using a graph theoretical approach, topological differences in the functional connectome were examined for group effects (CHR vs healthy control), treatment effects (oxytocin vs placebo) and group x treatment interactions.

Results: Group effects were observed predominantly in frontoparietal network regions and treatment effects in ventral attention network regions (all pFDR LESS THAN .05). Moreover, we found that many effects of oxytocin on network topology differ across CHR and healthy individuals, with significant interactions observed in numerous regions strongly implicated in psychosis onset, such as the thalamus, pallidum, entorhinal cortex and nucleus accumbens, and cortical regions localising primarily to the default mode network (all pFDR LESS THAN .05).

Discussion: Our findings provide novel evidence of functional brain network disorganisation associated with psychosis risk and demonstrate that oxytocin modulates network topology in regions implicated in the pathophysiology of psychosis in a clinical status/psychosis risk-specific manner. Given the current lack of effective pharmacotherapies for CHR patients, a deeper understanding of how connectomic alterations contribute to psychosis risk, and the potential ameliorative effects of experimental treatments such as oxytocin, remain important avenues for future research.

F191. TOPOLOGICAL ABNORMALITIES OF THE MORPHOMETRIC SIMILARITY NETWORK OF THE CEREBRAL CORTEX IN SCHIZOPHRENIA

Sung Woo Joo^{*1}, Young Tak Jo², Sun Min Kim¹, Daegeun Kim¹, Jinah Kim¹, So Young Yoo³, Soohyun Joe⁴, Jungsun Lee¹

¹Asan Medical Center, ²Kangdong Sacred Heart Hospital, ³SMG-SNU Boramae Medical Center, ⁴University of California San Diego

Background: The morphometric similarity (MS) network is constructed using multiple MRI parameters of each cortical region and similarity between cortical regions. Although the MS network can detect microstructural alterations of cortical regions and capture the connections between histologically similar cortical areas, it is uncertain how topological characteristics of the MS network are affected by schizophrenia.

Methods: We obtained T1- and diffusion-weighted images of 239 healthy controls and 190 patients with schizophrenia to construct the MS network. Group comparisons of the mean MS of the cortical regions and subnetworks were performed. The strengths of the connections between the cortical regions and the global and nodal network indices were compared between the groups. Clinical associations with the network indices were tested using Spearman's rho.

Results: Compared with healthy controls, patients with schizophrenia had significant group differences in the mean MS of several cortical regions and subnetworks. Patients with schizophrenia had both superior and inferior strength of connections between the cortical regions compared with healthy controls. We observed regional abnormalities of the MS

network in patients with schizophrenia in terms of lower centrality values of the pars opercularis, superior frontal, and superior temporal areas. Certain nodal network measures of the right pars opercularis and left superior temporal areas were associated with illness duration in patients with schizophrenia.

Discussion: We identified regional abnormalities of the MS network in schizophrenia and observed that the left superior temporal area may be a key region in the topological organization and connections between cortical regions.

F192. A LIVING SYNTHESIS AND TRIANGULATION OF THE EVIDENCE FROM CLINICAL TRIALS AND PRECLINICAL ANIMAL EXPERIMENTS INVESTIGATING TRACE AMINE-ASSOCIATED RECEPTOR 1 (TAAR1) AGONISTS FOR PSYCHOSIS

Spyridon Sifakis^{*1}, Robert R. McCutcheon², Virginia Chiochia³, Edoardo G. Ostinelli⁴, Charlotte Austin⁴, Claire Friedrich⁴, Jaycee Kennett⁴, Francesca Tinsdeall⁵, Fiona Ramage⁵, Nobuyuki Nomura¹, Grazia Rutigliano⁶, Luke Vano⁷, Simonne Wright⁸, Claire Stansfield⁹, Damian Omari Juma¹⁰, Ioannis Mantas¹¹, Oliver D. Howes¹², Lea Milligan¹³, Carmen Moreno¹⁴, Julian H. Elliott¹⁵, James Thomas⁹, Malcolm R. MacLeod⁵, Emily Sena⁵, Soraya Seedat¹⁶, Georgia Salanti¹⁷, Jennifer Potts⁴, Andrea Cipriani¹⁸, Stefan Leucht¹, for the GALENOS project¹⁹

¹Technical University of Munich, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London, University of Oxford, ³Institute of Social and Preventive Medicine, University of Bern, ⁴University of Oxford, ⁵Centre for Clinical Brain Sciences, The University of Edinburgh, ⁶King's College London, Institute of Psychiatry Psychology and Neuroscience (IoPPN), ⁷King's College London, Institute of Psychiatry, ⁸Stellenbosch University, Stellenbosch, ⁹EPPI Centre, Social Research Institute, University College London, ¹⁰My Mind Our Humanity, ¹¹Karolinska Institutet, ¹²King's College London, Institute of Psychiatry; Medical Research Council Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, ¹³MQ Mental Health Research, ¹⁴Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM. CIBERSAM. ¹⁵Cochrane Australia, School of Public Health and Preventive Medicine, Monash University, ¹⁶Stellenbosch University, ¹⁷Institute of Social and Preventive Medicine (ISPM), University of Bern, ¹⁸University of Oxford, ¹⁹<https://galenos.org.uk>

Background: Trace amine-associated receptor 1 (TAAR1) agonism offers a potentially emerging novel approach for treating psychosis, proposed to be efficacious and associated with a more favorable side-effect profile compared to current antipsychotics acting as dopamine D2 receptor antagonists. However, recent clinical trials have shown inconsistent findings regarding the efficacy of the TAAR1 agonists under clinical development (i.e., ulotaront and ralmitaront). Nonetheless, the volume of data is increasing, and additional compounds are undergoing preclinical development. Therefore, our aim was to facilitate bridging preclinical and clinical research through a living systematic review by synthesizing and triangulating evidence from human and non-human data.

Methods: The living systematic and meta-analysis is co-produced by multiple stakeholders within the GALENOS project (Cipriani et al., 2023), and its protocol was published (Sifakis et al., 2023) and registered with PROSPERO (ID: CRD42023451628). For the first iteration of the review, we searched in multiple electronic databases (last search in November 2023) for

randomized controlled trials (RCTs) and preclinical in vivo studies comparing TAAR1 agonists with antipsychotics, placebo or other control conditions in individuals with psychosis or animal models for psychosis, respectively. At least two independent reviewers screened the records found in the search, extracted data, and evaluated the risk of bias using appropriate tools. Our primary outcomes were overall symptoms measured by validated rating scales in RCTs and relevant behavioral proxies in animal studies, such as model-induced hyperlocomotion. We synthesized data from clinical and animal studies separately using random-effects meta-analyses and examined potential sources of heterogeneity. We evaluated the confidence in the evidence using the GRADE approach and organized a triangulation interdisciplinary meeting with independent experts to draw an overall conclusion from the evidence from human and non-human data.

Results: We found that TAAR1 agonists may have on average little to no effect compared to placebo on overall symptoms in adults with acute schizophrenia (k=4 studies, 3 examining ulotaront and 1 examining ralmitaront; n=1296 participants; SMD=0.14, 95%CI: -0.17, 0.46); however, the evidence is very uncertain. Conversely, TAAR1 agonists appeared to reduce model-induced hyperlocomotion in animal models of psychosis with a large effect size based on data from over 100 experiments but with notable heterogeneity (potential sources of heterogeneity under examination). The analyses and the triangulation meeting are ongoing, and the final results of the initial review iteration will be presented at the congress.

Discussion: We identified a discrepancy between the findings of preclinical animal experiments and RCTs examining TAAR1 agonists for psychosis. This living systematic review aims to understand this discrepancy and facilitate the bridging of the translational gap, potentially providing insights for the future development of novel antipsychotics.

Grant Information: We are funded by Wellcome, a global charitable foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

F193. ARIPIPRAZOLE 2-MONTH READY-TO-USE: A NOVEL LONG-ACTING INJECTABLE ANTIPSYCHOTIC FORMULATION FOR ADMINISTRATION ONCE EVERY 2 MONTHS

Matthew Harlin¹, Daiki Kaneko¹, Murat Yildirim ^{*2}, Pedro Such², Jessica Madera-McDonough¹, Frank Larsen²

¹*Otsuka Pharmaceutical Development and Commercialization, Inc.*, ²*H. Lundbeck A/S*

Background: Schizophrenia and bipolar I disorder (BP-I) are chronic mental health conditions that require maintenance pharmacological treatment to ensure symptom control. Despite this, suboptimal adherence with daily oral antipsychotic treatment is common. Long-acting injectable (LAI) antipsychotics have been developed to increase adherence versus oral medication; currently available LAIs offer dosing intervals that range from 2 weeks to 6 months. Data have shown a beneficial effect of LAIs versus oral antipsychotics in terms of reducing the risk of hospitalization and relapse. Aripiprazole exhibits partial agonist activity at dopamine D2 receptors and serotonin 5-HT1A receptors, full agonist activity at dopamine D3 receptors, and antagonist activity at serotonin 5-HT2A receptors. Until recently, aripiprazole has been available in a daily oral formulation and as an extended-release, once-monthly formulation for intramuscular (IM) injection (aripiprazole once-monthly 400 mg [AOM 400]).

Methods: Aripiprazole 2-month ready-to-use (Ari 2MRTU) has been developed as a novel LAI formulation of aripiprazole monohydrate for gluteal IM administration once every 2 months, for the treatment of schizophrenia or BP-I. Ari 2MRTU offers extended exposure to aripiprazole concentrations within the therapeutic window to 2 months.

Results: Ari 2MRTU has been shown to be generally well tolerated; investigators' assessments of the injection site reflected minimal reactions in adults with schizophrenia or BP-I. Ari 2MRTU is a prolonged-release suspension for injection in a single-use pre-filled syringe; it is provided in its final container, with no dilution or reconstitution required prior to administration. Each Ari 2MRTU pre-filled syringe contains 960 mg of aripiprazole monohydrate (total volume 3.2 mL) for administration once every 2 months, providing a dose of aripiprazole that is comparable with a monthly dose of AOM 400. In case of any tolerability issues, a 720-mg dose of Ari 2MRTU (total volume 2.4 mL) for administration once every 2 months is available, providing a dose of aripiprazole that is comparable with a monthly dose of AOM 300 mg. The suspension is a white to off-white color, with a neutral pH (approximately 7.0); Ari 2MRTU should be stored at controlled room temperature. Ari 2MRTU should be injected slowly as a single IM injection in the gluteal muscle. For patients who have never taken aripiprazole, tolerability to aripiprazole must be established prior to initiating treatment with Ari 2MRTU. Overlapping treatment with oral aripiprazole is required for patients initiating Ari 2MRTU, unless they have been stabilized on AOM. The recommended maintenance dose of Ari 2MRTU is 960 mg. A maintenance dose of 720 mg should be considered in the event of adverse reactions with the 960 mg dose and is recommended in patients who are poor metabolizers of CYP2D6 or who are taking strong inhibitors of CYP2D6 or CYP3A4. Following an initial dose, Ari 2MRTU should be administered once every 2 months (56 days after the previous injection).

Discussion: Ari 2MRTU is a novel LAI formulation of aripiprazole monohydrate for gluteal IM administration that comes in a ready-to-use syringe and does not require reconstitution. Increasing the dosing interval to 2 months has the potential to reduce the treatment burden for patients and clinicians.

F194. PREDICTIVE VALIDITY OF BEHAVIORAL ASSAYS RELEVANT TO SCHIZOPHRENIA IN ZEBRAFISH

Leonardo Bastos¹, Sofia Z. Becker¹, Matheus Gallas-Lopes¹, Carlos G. Reis¹, Thailana Stahlhofer-Buss¹, Elaine Elisabetsky¹, Angelo Piatto¹, Ana P. Herrmann¹, Ana Herrmann*¹

¹*Universidade Federal do Rio Grande do Sul*

Background: While the precise mechanisms that underlie schizophrenia remain elusive, there is mounting evidence that it is associated with abnormalities in glutamate receptor signaling and hyperactivity in mesolimbic dopaminergic pathways. MK-801 is a noncompetitive NMDA receptor antagonist used as a pharmacological strategy to mimic behavioral phenotypes related to schizophrenia symptoms in laboratory animals. In rodents, the administration of MK-801 leads to hyperlocomotion (relevant to positive symptoms), and social withdrawal (relevant to negative symptoms). However, there are few studies evaluating the effect of antipsychotics on behavioral changes induced by MK-801 in zebrafish. The aim of this study was to evaluate whether the antipsychotics olanzapine (atypical) and sulpiride (typical) counteract the effects induced by acute exposure to MK-801 on the social preference and open tank tests in adult zebrafish. Results are expected to inform on the predictive validity of these behavioral assays.

Methods: We used 240 male and female adult zebrafish (3-4 months old, 300-500 mg). The animals were randomly allocated to the experimental groups (n=15), and individually exposed

for 20 minutes to control solution or three different concentrations of olanzapine (experiment 1: 7.5, 15, and 30 mg/L) or sulpiride (experiment 2: 42.5, 85, 170 mg/L), followed by 5 μ M MK-801 or control solution for another 20 minutes. After exposure, the animals were subjected to the social preference test (5 minutes, after 2-minute habituation) to analyze time spent in the interaction zone, distance traveled, immobility time, and crossings, which was immediately followed by the open tank test (5 minutes) to analyze distance traveled, absolute turn angle, clockwise rotations, and immobility time. The videos were analyzed by blinded researchers using the ANY-Maze® software. Data were analyzed by two-way ANOVA/Bonferroni.

Results: In the social preference test, the only parameters consistently altered by MK-801 in experiments 1 and 2 was the number of crossings. MK-801 also reduced the time in the interaction zone (experiment 1) and increased the distance traveled (experiment 1) and the immobility time (experiment 2). In the open tank test, MK-801 decreased distance traveled, absolute turn angle, and clockwise rotations, while increased immobility time; these results were observed in both experiments. Olanzapine nonspecifically reduced the time in the interaction zone at the highest concentration, increased the distance traveled at the lowest concentration, and potentiated MK-801 effect on the number of crossings at the lowest and intermediate concentrations. In the open tank test, all olanzapine concentrations prevented the increase in immobility time induced by MK-801 and nonspecifically increased the distance traveled and the number of clockwise rotations (opposite effects to MK-801). Sulpiride had no significant effects on any of the parameters analyzed.

Discussion: MK-801 effects in the open tank test were more robust than in the social preference test, which may be more sensitive to unknown environmental variations and/or interindividual variability. Although olanzapine demonstrated opposite effects to those of MK-801 in the open tank test, the contrary was observed in the social preference test. More studies are needed to establish the predictive validity of these behavioral assays in zebrafish. The prospects of this work are to test other antipsychotics, expand the range of concentrations, change the order and duration of treatments, and evaluate the outcomes of interest in behavioral phenotypes more robustly altered by MK-801 (e.g., shoal cohesion test).

Jaguar Health Inc. provided financial support for this work.

F195. PSYCHIATRIST CONCERNS REGARDING POTENCIAL SIDE EFFECTS OF CLOZAPINE: AN ARGENTINEAN STUDY

Alejo Corrales*¹, Pedron Damian Gargoloff², Manuel Vilapriño³, Federico Rebok⁴

¹Argentine National University UNT, ²Hospital Alejandro Korn, Psychiatric department, La Plata, Argentina., ³Universidad Nacional de Cuyo, Departamento de Neurociencias de la Facultad de Ciencias Médicas, Mendoza, Argentina., ⁴Hospital "Dr. Braulio A. Moyano", Servicio de Emergencia, Buenos Aires, Argentina.

Background: Clozapine, the first atypical antipsychotic developed, is uniquely effective in its ability to improve clinical outcomes in patients with treatment-resistant schizophrenia (TRS). The clinical indications of clozapine are not limited to the two FDA indications (TRS and suicidality in patients with psychosis), patients who are sensitive to extrapyramidal symptoms are an important third group of patients who may benefit from clozapine. Accurate clozapine information is crucial for the clinician because adverse effects impose balancing its risk/benefits. Even though clozapine-induced agranulocytosis is the most well-known side effect, the use of clozapine is associated with several side effects such as myocarditis,

gastrointestinal hypomotility, seizures, substantial weight gain, and sedation so, for these reasons, clozapine is not considered as a first-line antipsychotic. However, there have been only a few studies shedding light on the clinician concerns regarding the potential side effects of clozapine, in Argentina. The aims of this study are: 1- To explore clinician concerns on clozapine-induced side effects, before starting clozapine treatment 2- to identify variables associated with these concerns.

Methods: This was an Argentinean study using an online survey that was carried out between May to August 2021. The online questionnaire was administrated through the google drive platform, and more than 3000 Argentinean psychiatrists were invited to participate in this study. The questionnaire included items concerning professional practice characteristics (such as years practicing as a psychiatrist, the modal work setting -inpatient/outpatient/partial hospitalisation, context in which the psychiatrists provide their service -public/private-, number of patients they are currently prescribing clozapine), and 8 common side effects related to clozapine (such as neutropenia, hypersalivation, gastrointestinal hypomotility, myocarditis, pulmonary embolism, seizures, metabolic syndrome). The concerns about side effects were evaluated on a five-point Liker scale (1= not at all concerned, 2 = sightly concerned, 3 = somewhat concerned, 4 = moderately concerned, 5 = extremely concerned). Statistical analysis was performed using the Chi-Square test.

Results: A total of 304 clinicians answered the survey. According to the data stemming from the drug company, our sample represents 35% of clozapine prescribers in Argentina. Conforming to the Liker scale rating, the level of concern was rated as follow; Neutropenia as moderately concerned (26%, n = 79), hypersalivation as moderately concerned (28%, n=85), gastrointestinal hypomotility/ileus as somewhat concerned (33%, n=99), myocarditis as moderately concerned (30%, n=85), pulmonary embolism as somewhat concerned (31%, n=95), seizures as moderately concerned (30%, n=91), metabolic syndrome as moderately concerned (34%, n=104). Statistical associations between the variables were not found (Chi Square=1.2, df=1, p GREATER THAN .05).

Discussion: This study shows that psychiatry concerns about clozapine-induced side effects are an important issue within the clinical setting, regardless of frequency and type of clozapine-induced side effects. The clinicians are aware of potential side effects before prescribing clozapine. Despite gastrointestinal hypomotility is a potentially dangerous side effect, the level of concern is similar among the side effects including agranulocytosis. The concerns on clozapine side effects could influence the decision-making in treatment-resistant schizophrenia.

F196. BEYOND DOPAMINE D2 RECEPTOR ANTAGONISM FOR THE TREATMENT OF POSITIVE SYMPTOMATOLOGY OF SCHIZOPHRENIA – MYTH OR REALITY?

Idil Mitsadali*¹, Haneul Choi², Ines Jimenez-Pulido³, Patricia Radu⁴, Jennifer Fletcher¹, Ben Grayson¹, John Gigg¹, Michael Harte¹

¹University of Manchester, ²University of Bath, ³University of Edinburgh, ⁴University of Nottingham

Background: Sub-chronic administration of phencyclidine (scPCP) has been shown to be a well-validated rodent model for schizophrenia, which induces relevant cognitive deficits and negative symptoms. Positive symptoms are usually studied by acute amphetamine injection followed by measuring locomotor activity (LMA) in otherwise healthy rodents. Utilisation of the scPCP model for positive symptomatology is uncommon thus striatal neurotransmission is

not well-studied in this model. This study investigated the relevance of scPCP rat model for the positive symptoms of schizophrenia, looking at 1) sensitisation to repeated amphetamine, 2) the effects of haloperidol, clozapine on amphetamine induced LMA and 3) the effect of xanomeline on acute amphetamine- or PCP-induced hyperlocomotion in scPCP and scVehicle (scVeh) treated rats.

Methods: 200 adult female Lister-Hooded rats either received scVeh (saline solution) or scPCP (2 mg/kg, bidaily i.p. injections for 7 days), followed by a 7-day washout. In experiment one, rats (n=20, 10 per group) received an acute amphetamine injection (0.75 mg/kg, i.p.) once a week for 3 weeks, and LMA was measured for 90 mins. In experiment two, rats (n=60, 30 per group) received haloperidol (0.05 mg/kg, s.c.), clozapine (5mg/kg, s.c.) or saline 30 mins prior to acute amphetamine (0.75 mg/kg, i.p.) or saline, and LMA was measured for 90 mins. In experiment 3, rats (n=120, 60 per group) received either saline or xanomeline (1, 3 or 10 mg/kg) prior to acute amphetamine (0.75 mg/kg, i.p.), PCP (2 mg/kg, i.p.) or saline, and LMA was measured for 90 mins. A haloperidol dose response (0.025, 0.05 and 0.075 mg/kg, s.c.) was also conducted in 60 scPCP rats using the same LMA test regimen as described above. Area under the curve was calculated from the ambulatory counts recorded in 5-min bins. Data was analysed using a two- or one-way ANOVA followed by Tukey's or Šídák's test.

Results: Both scVeh- and scPCP-treated rats showed sensitisation to amphetamine, measured as an augmented hyperlocomotion from week 1 to 2 (p LESS THAN 0.001; p LESS THAN 0.05 respectively). Only scPCP-treated rats showed further sensitisation from week 2 to week 3 (p LESS THAN 0.05). Both haloperidol (0.05 mg/kg) and clozapine (5 mg/kg) prevented amphetamine-induced hyperlocomotion in the scVeh group. Haloperidol at 0.025 and 0.05 mg/kg did not prevent amphetamine-induced hyperlocomotion in the scPCP group. Haloperidol at 0.075mg/kg and clozapine (5 mg/kg) prevented amphetamine-induced hyperlocomotion in the scPCP group. Xanomeline at 10 mg/kg prevented the amphetamine-induced hyperlocomotion in scVeh rats, but it did not prevent neither the amphetamine- nor acute PCP-induced hyperlocomotion in scPCP rats.

Discussion: These findings indicate the presence of a pathophysiology in the scPCP model that renders the model very relevant to the positive symptomatology in schizophrenia. The differential response following haloperidol and xanomeline highlight the importance of assessing symptomatology in relevant preclinical models and may hold importance for clinical translation. Future studies are underway to investigate striatal neurotransmission in the scPCP rat model and its relationship to clinical studies.

F197. THE INFLUENCE OF SEX AND MENOPAUSE ON ANTIPSYCHOTIC SERUM CONCENTRATIONS

Franciska de Beer*¹, Bodyl Brand¹, Iris Sommer¹, Marieke Begemann¹, Clementine Stuijt¹, Daan Touw¹

¹*University Medical Center Groningen*

Background: Most antipsychotics used today are prescribed using a one-size-fits-all approach, based on male-dominated clinical trials. At the same time, women are more likely to report antipsychotic side effects, and side effects in women are predicted by sex differences in drug pharmacokinetics. On average, sex differences in pharmacokinetics, with estrogen playing a significant role, cause the drug to stay longer in the female body. This is hypothesized to lead to higher serum concentrations in women when a one-size-fits-all approach is used. After menopause, estrogen levels remain low, which is hypothesized to affect antipsychotic serum

concentrations. We sought to explore sex differences in serum concentrations of 8 commonly used antipsychotics and examined how these sex differences change after the age of 45.

Methods: Antipsychotic concentrations of 14227 plasma samples were analyzed, which were drawn between January 2017 and December 2022 in the Netherlands in 5477 unique adult men and women, with a median of 2 samples per person (IQR=3). The dataset consisted of concentrations of olanzapine (n=1910, 41% female), clozapine (n=6410, 32% female), aripiprazole (n=1967, 41% female), and quetiapine (n=764, 62% female). To investigate the effect of sex on antipsychotic serum concentrations, we employed linear mixed-effects models (LMEMs) using R v4.0.3, accounting for age (fixed effect), time, measured as the number of months since the first measurement as fixed effect and a random intercept for participants. Next, we examined the effect of reaching the age of 45 (i.e., mean age of menopause in women), by dividing the samples according to sex and age (LESS THAN 45 vs. ≥ 45 years), using LMEMs with a random effect for patient and a fixed effect for time. When applicable, FDR-corrected post hoc comparisons were employed to compare men LESS THAN 45 with the other groups and to compare women LESS THAN 45 with women ≥ 45 .

Results: Preliminary analyses indicated a significant effect of sex on serum concentrations for 4 antipsychotics, with women having on average higher levels of serum concentrations of olanzapine, clozapine, and aripiprazole. Sex/age-group analyses revealed significant effects for clozapine, aripiprazole, and quetiapine. Pairwise post hoc comparisons revealed that that serum concentrations of clozapine were highest in women LESS THAN 45 compared to men, and compared to women ≥ 45 . Serum concentrations of aripiprazole were highest in women ≥ 45 , as compared to men LESS THAN 45. Conversely, serum concentrations of quetiapine were lower in women LESS THAN 45, women ≥ 45 , and men ≥ 45 .

Discussion: In sum, we found pronounced sex differences in serum concentrations, which differ per antipsychotic and may evolve with advancing age. Our findings suggest that the one-size-fits-all approach for prescribing antipsychotics may not serve both sexes equally, and stresses the need for further research into the sex and hormone-dependent pharmacokinetic mechanisms of antipsychotics.

F198. LIVING SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACOKINETIC DRUG-GENE INTERACTIONS IN SCHIZOPHRENIA PHARMACOTHERAPY: THE IMPORTANCE OF CYP450 GENETIC POLYMORPHISM

Filip Milosavljevic*¹, Stefan Leucht¹

¹*Klinikum Rechts der Isar, Technical University of Munich*

Background: While there is a great need for effective schizophrenia treatment options, pharmacotherapy in schizophrenia is often very challenging. Reasons include treatment resistance, frequent need for treatment adjustments and the risk of serious adverse reactions; while the development of new, superior drugs remains slow. In such a landscape, approaches such as pharmacogenomics hold a great potential to maximise the effectiveness of currently available psychiatric drugs by predicting and mitigating harmful pharmacokinetic drug-gene interactions. Our recent meta-analysis contributed to this research by precisely quantifying several such drug-gene interactions: +51% and +47% increase in aripiprazole plasma levels in CYP2D6 intermediate and poor metabolizers, respectively; and +40% and +31% increase in risperidone plasma levels in CYP2D6 intermediate and poor metabolizers, respectively; all compared to CYP2D6 normal metabolizers. Nevertheless, it is a major challenge to implement pharmacogenomics into everyday clinical practice, as clinical guidelines are unclear and often

have to rely on limited evidence and individual clinical trials with low statistical power. Here, we propose the protocol for the living systematic review and meta-analysis aimed to build on our previous work and overcome these shortcomings of pharmacogenomic clinical data in schizophrenia.

Methods: Living meta-analysis is an innovative, emerging type of scientific reporting that is continuously updated, which is especially important for the rapidly evolving research topics such as pharmacogenomics. Living meta-analysis can potentially accelerate the implementation of pharmacogenomics for antipsychotic drugs by summarizing, and subsequently increasing the statistical power of available evidence; and by rapidly implementing new data as it emerges. This project will start by transforming the data on Aripiprazole-CYP2D6, Risperidone-CYP2D6, Clozapine-CYP2C19, Haloperidol-CYP2D6 and Quetiapine-CYP2D6 drug-gene interactions into a format suitable for the continuous update and live online display. Next, the data on drug-gene interactions not encompassed in our previous work due to pragmatic reasons, will be systematically searched, extracted and analysed. This will include interactions of: Aripiprazole with CYP3A4/5; Asenapine with CYP1A2 and UGT1A4; Clozapine with CYP2D6, CYP1A2 and CYP3A4/5; Iloperidone with CYP3A4/5 and CYP2D6; Olanzapine with UGT1A4 and CYP1A2; Quetiapine with CYP3A4/5; Risperidone with CYP3A4/5; Zotepine with CYP3A4/5 and CYP1A2; Haloperidol with CYP3A4/5, UGT2B7 and CYP1A2; Chlorpromazine with CYP1A2, CYP3A4 or CYP2D6; and Zuclopenthixol with CYP3A4/5 and CYP2D6. For each drug-gene pair of interest, drug plasma concentration data and genomic data will be extracted regardless of the study design. Based on the CYP450 or UGT genotypes, patients will be classified into metabolizer groups (phenotypes) according to the current consensus guidelines (Clinical Pharmacogenetic Implementation Consortium - CPIC), or pragmatically analysed separately for every mutation of interest where such consensus is not achieved. Then, dose-corrected plasma concentration for the given drug will be compared between the reference phenotype and variant phenotypes with ratio-of-means meta-analysis method. If new genotype-phenotype classification consensus is to emerge during the life of this living systematic review, data will be reclassified accordingly. After the baseline for all of the mentioned data is established; automatic systematic search re-runs will be established and the team for the selection and extraction of those data will be designated, ensuring at least one monthly update. At the same time, openly available website will be assigned for the reporting of current magnitude of pharmacokinetic drug-gene interactions, as well as the strength of this evidence.

Results: As this abstract describes the proposed protocol for the living systematic review and meta-analysis, no results are available at the time.

Discussion: This living systematic review and meta-analysis will aim to encompass all clinically relevant antipsychotic drugs that are metabolized by at least one liver enzyme that is coded by the polymorphic gene. This way, the comprehensive database of pharmacokinetic drug-gene interactions relevant for the schizophrenia therapy will be created. Even though the importance of CYP450 and UGT polymorphism is often speculated to influence the efficacy, tolerability and the drug switching in antipsychotics, interventional clinical trials attempting to mitigate these effects have to rely on in-vitro data or on assumptions that are not evidence-based. This living meta-analysis will provide evidence-based and precisely estimated data on the extent of these pharmacokinetic drug-gene interactions that may inform future interventional pharmacogenomic clinical trials. Also, for the antipsychotic drugs where therapeutic drug monitoring is indicated, results of this living meta-analysis will be immediately useful to the clinicians by informing the expected drug plasma level changes based on a patient's genotype without the need to wait for the steady-state drug plasma concentrations to be achieved.

F199. EVIDENCE ON ANTIPSYCHOTIC DRUG TREATMENT FOR SCHIZOPHRENIA FROM WESTERN AND CHINESE TRIALS – IDENTIFYING TRIALS USING APPROPRIATE METHODS AND CONDUCTING JOINT NETWORK-META-ANALYSES

Johannes Schneider-Thoma*¹, Yikang Zhu², Mengchang Qin¹, Yu Dong², Shiwei Guan², Spyridon Sifakis¹, Chunbo Li², Stefan Leucht¹

¹*School of Medicine, Technical University of Munich*, ²*Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine*

Background: About one third of all conducted trials in schizophrenia in the past years comes from China. The majority of them are published in local Chinese journals only indexed in Chinese literature databases. Unfortunately, there are concerns about the methodological quality of these trials particularly in terms of methods of randomisation and allocation concealment. We aim to identify studies on antipsychotic drugs, request details about study methods from authors and include appropriately-conducted studies in joint meta-analyses together with studies identified in international databases (called “Western trials” because the majority comes from the USA and Europe).

Methods: This systematic review is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation – Project number 468853597) and the National Natural Science Foundation of China (NSFC – Project number 8211101161) and conducted in collaboration of the department of psychiatry of the Technical University of Munich, German and the Shanghai Mental Health Center, China. We search multiple international and Chinese electronic literature databases for randomized-controlled trials (RCTs) comparing antipsychotics (all second-generation antipsychotics; selected first generation antipsychotics) with each other or placebo for efficacy in schizophrenia. We contact authors of trials by telephone, email and letters to request additional information about the study methods used to allocate participants to treatment groups, to conceal allocation before participants’ inclusion and to blind treatment during the trial. Therefore, to facilitate answering and evaluation, we also created an online survey.

Of trials with appropriate methods we will extract multiple outcomes and conduct network meta-analyses to synthesize the evidence on comparative efficacy and tolerability between different antipsychotics.

Results: Concerning Chinese-trials, we screened more than 10 000 references in Chinese databases and found ca. 4500 studies described as using “randomisation” for group allocation. Ca. 200 of them mentioned that treatment was blinded, ca. 100 stated that treatment was open-label, the remaining more than 4000 studies did not mention blinding. In general, details about trial methods were often only briefly reported. Currently, the contacting of study authors to request additional information about study methods is ongoing.

Concerning Western-trials, we updated our database of studies based on previous systematic reviews. It comprises ca. 730 studies, of which the majority (ca. 630) are described as double-blind. Currently, we prepare for contacting the study authors. Results of the contacting, including the number of authors contacted and reached, reasons for unavailability as well as the received information about study methods and their evaluation will be presented on the poster at the congress.

Discussion: On the poster, we will discuss our experiences with contacting study authors and the challenges and limitations involved. Moreover, we will discuss the results of how many studies were identified as using appropriate or suboptimal/inappropriate methods and how this

information can guide other systematic reviewers who are faced with the question of whether to include studies from China.

F200. DYSGLYCEMIA ASSOCIATED WITH ANTIPSYCHOTIC USE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Emily Smith^{*1}, Kristoffer Panganiban¹, Kateryna Maksyutynska¹, Jiwon Lee², Femim Prasad², Sandra Pereira¹, Jonathan Monteiro³, Vedansh Kaushik², Kaitlin Fuller⁴, Michael McCarthy⁵, Jacob Ballon⁶, Tyler Prestwood⁶, Christoph Correll⁷, Sri Mahavir Agarwal⁸, Zachary Freyberg⁹, Margaret Hahn⁸

¹Centre for Addiction and Mental Health, University of Toronto, ²University of Toronto, ³McMaster University, ⁴St. Francis Xavier University, ⁵University of California San Diego, ⁶Stanford University, ⁷Zucker School of Medicine, ⁸Centre for Addiction and Mental Health, Banting and Best Diabetes Centre, University of Toronto, ⁹University of Pittsburgh

Background: Antipsychotics (APs) are the cornerstone of treatment for schizophrenia spectrum disorders (SSDs) and are approved for the treatment of affective disorders including bipolar disorder (BD). However, AP use is associated with severe metabolic consequences including weight gain, dyslipidemia, and dysglycemia. Although studies indicate that glucose dysfunction can occur independently of weight gain, AP-induced glycemic changes are usually considered to be a consequence of AP-induced weight gain. Therefore, the aims of this review are to: 1) specifically clarify the effect of APs on glucose homeostasis independently of weight gain and 2) determine whether APs similarly impact glycemic control independently of drug class and treatment duration.

Methods: We searched MEDLINE, EMBASE, PsychINFO, CENTRAL, CINAHL, and Web of Science from inception to August 2023 to identify all randomized controlled trials (RCTs) that compared the effect of APs on glucose metabolism to placebo (PBO), with no restriction on psychiatric diagnosis. Random effects meta-analyses examined glucose dysfunction as both continuous and dichotomous outcomes, with subgroup analyses conducted for study length, AP type, and age (child/adolescent vs. adult). Where possible, meta-regression analyses were conducted to explore the effects of weight gain, study length, and AP dose on change in glucose.

Results: Of 20954 references identified in our search, 70 RCTs in patients with SSDs (N=40 studies) and BD (N=30 studies) met our inclusion criteria. In both populations, AP use was associated with a significantly greater increase in blood glucose compared to placebo (mean difference (MD) SSD = 0.05 mmol/L [0.01, 0.09], p=0.01, I²=0%, n=8535 AP vs. n=3389 PBO; MD BD = 0.10 mmol/L [0.05, 0.15], p LESS THAN 0.0001, I²=46%, n=6018 AP vs. n=4137 PBO). Sub-group analyses revealed that neither study length nor AP type altered this finding. Nevertheless, in patients with BD, age significantly impacted AP-induced alterations in blood glucose, with adults showing a greater increase (p=0.03, I²=79%). Plasma insulin was also significantly increased by AP exposure (MD SSD = 13.97 pmol/L [6.42, 21.51], p=0.0003, I²=0%, n=3678 AP vs. n=1169 PBO; MD BD = 12.85 pmol/L [1.14, 24.56], p=0.03, I²=55%, n=2111 AP vs. n=1676 PBO), with a significant subgroup difference according to AP type in both groups (SCZ: p=0.02, I²=62.1%; BD p=0.0001, I²=85.6%). There was an additional effect of study length on plasma insulin in individuals with SSDs (p=0.03, I²=79.8%). Importantly, the strength of the effect of different APs on blood glucose did not appear to follow the established hierarchy of weight gain liabilities outlined in the literature. Specifically,

so-called ‘weight neutral APs’ such as ziprasidone and lurasidone produced comparable dysglycemia to APs traditionally associated with significant weight gain like olanzapine (SSD: $p=0.45$, $I^2=0\%$; BD: $p=0.46$, $I^2=0\%$). Subsequent meta-regression analyses found that AP-associated hyperglycemia may be independent of study length and AP dose in patients with SCZ (p GREATER THAN 0.05) and independent of study length and baseline-to-endpoint weight gain in patients with BD (p GREATER THAN 0.05). AP use did not appear to have a significant effect on HOMA-IR or treatment-emergent hyperglycemia (dichotomous outcome) in either patient group.

Discussion: Our review demonstrates that both short- and long-term exposure to APs are associated with a significant increase in dysglycemia risk as indicated by AP-induced elevations in glucose and insulin. Furthermore, all APs cause some degree of glucose dysregulation regardless of exposure time and established propensities for AP-induced weight gain. Further studies are required to better understand how AP use contributes to dysglycemia, including temporal changes throughout the treatment course, and how these effects could potentially be mitigated using metabolic interventions.

F201. COMPARATIVE EFFECTIVENESS OF LONG-ACTING INJECTABLE PALIPERIDONE WITH OTHER LONG-ACTING INJECTABLE AND ORAL ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA

Dae Geun Kim^{*1}, Sun Min Kim¹, Jinah Kim¹, Sung Woo Joo¹, Jungsun Lee¹

¹*University of Ulsan College of Medicine, Asan Medical Center*

Background: Even after several years since the introduction of long-acting injectable (LAI) antipsychotics, there is scarce evidence on the comparative effectiveness of LAI antipsychotics on clinical outcomes in schizophrenia. A low utilization rate of LAI antipsychotics in clinical practice limits the investigation of this issue through the traditional randomized clinical trial design. A nationwide health insurance database in South Korea has a notable strength of including information on the utilization of medical services by the entire population in South Korea. Here, we used the nationwide population database to investigate the comparative effectiveness of two LAI antipsychotics (paliperidone and aripiprazole), which are mostly used in South Korea, on the risk of treatment discontinuation and psychiatric admission.

Methods: We used the Health Insurance Review Agency database between July 2009 and July 2021 in South Korea. The prevalent cohort of schizophrenia patients was obtained based on operational conditions following our previous studies, which resulted in a total of 288,547 patients with schizophrenia. Treatment discontinuation was defined as a lapse of 28 days from the expected date of the next antipsychotic prescription. We compared the risk of treatment discontinuation and psychiatric admission among LAI paliperidone, LAI aripiprazole, and oral antipsychotics using a within-individual Cox regression model.

Results: For the risk of psychiatric admission, the LAI aripiprazole and oral antipsychotics had lower (0.90, 0.85-0.95) and higher (1.34, 1.31-1.38) risks compared with the LAI paliperidone, respectively. With a reference of the LAI paliperidone, oral antipsychotics were associated with a higher risk of treatment discontinuation (1.68, 1.61-1.74). The LAI aripiprazole had no significant difference in the risk of treatment discontinuation compared with the LAI paliperidone (0.99, 0.92-1.08).

Discussion: Our results show that the LAI paliperidone was inferior in lowering the risk of psychiatric admission than the LAI aripiprazole. However, no significant differences were observed in the risk of treatment discontinuation between the LAI paliperidone and LAI aripiprazole.

F202. CLOZAPINE-INDUCED RETROGRADE EJACULATION TREATED WITH IMIPRAMINE: A CASE REPORT AND LITERATURE REVIEW

Alexandra Cerulli-Kanellopoulos*¹, Alexandra Arruda¹

¹*Hôpital Sacré-Coeur de Montréal*

Background: Sexual adverse effects are commonly reported with antipsychotics, especially those with strong dopaminergic antagonism, and this can impair quality of life and lead to medication non-compliance. Retrograde ejaculation is a rare sexual side effect found with the use of typical and atypical antipsychotics, including clozapine. Management of this condition is largely based on observational data. Imipramine, a tricyclic antidepressant, has been suggested as a potential treatment strategy for antipsychotic-induced retrograde ejaculation. This could prove particularly useful for patients on clozapine, where reducing the dose or switching antipsychotics is not always feasible as it is considered the only effective medication for treatment-resistant schizophrenia. This study aims to present a case of improved retrograde ejaculation induced by clozapine with the use of imipramine.

Methods: We present a case of a 27-year-old Guinean man with resistant schizophrenia, hospitalized on a psychiatric unit, who developed retrograde ejaculation after recently being initiated on clozapine. A review of the literature was conducted in the MEDLINE, EMBASE and Pubmed databases to identify studies of retrograde ejaculation secondary to antipsychotic use and its management. After achieving a dose of clozapine 425 mg daily, the patient expressed concerns of producing little to no semen after ejaculation. Specific laboratory tests were ordered to rule out any physiological causes. A post-ejaculation urinary analysis was performed to objectively identify the presence of spermatozoa in the urine.

Results: Seventeen studies were retained for the literature review. Conference abstracts and research titles without any abstracts or full articles were excluded. Many of the included studies were case reports, with relatively few reports on clozapine. Treatment strategies used to reverse the retrograde ejaculation mostly included either reducing the antipsychotic dose or changing the antipsychotic agent. Imipramine was the only pharmacological agent used in four different studies of retrograde ejaculation secondary to thioridazine, iloperidone, risperidone and quetiapine. Physiological tests, including glycated hemoglobin, prolactin, luteinizing and follicle-stimulating hormones, total testosterone and thyroid-stimulating hormone returned normal. A post-ejaculation midstream urinary analysis identified very low levels of spermatozoa. As such, it was concluded that the retrograde ejaculation was secondary to clozapine use. As the dose of clozapine could not be reduced or the agent changed for another antipsychotic agent due to the severity of the patients' symptoms, imipramine was initiated and gradually increased to a dose of 75 mg daily. At follow-up eight months later, the patient reported a notable decrease in retrograde ejaculation.

Discussion: To our knowledge, this is the first case report of improved clozapine-induced retrograde ejaculation with imipramine. This is also the first study to assess the long-term efficacy of imipramine to treat this sexual side effect. It highlights the importance of identifying and addressing sexual dysfunction secondary to antipsychotic use, particularly with a drug like clozapine, the only effective medication for treatment-resistant schizophrenia. The onset of sexual dysfunction following the initiation of clozapine, and the exclusion of alternative causes, suggests a probable link to clozapine-induced retrograde ejaculation, as indicated by a Naranjo score of 7. While sexual side effects induced by certain antipsychotics, such as risperidone, typically result from dopaminergic antagonism in the tuberoinfundibular pathway, retrograde ejaculation seems to occur through antagonism at the $\alpha 1$ -adrenoreceptors in the bladder neck.

Other treatments have demonstrated effectiveness in alleviating retrograde ejaculation, but their use has not been documented in cases of antipsychotic-induced retrograde ejaculation. However, while limited data exists on its use, imipramine may show promise as a treatment strategy through its actions as an $\alpha 1$ -adrenergic receptor agonist. As clozapine is associated with fewer sexual adverse effects owing to minimal dopaminergic blockade, it is essential to address potential sexual side effects with clozapine to improve quality of life and to ensure medication adherence.

F203. THE EFFECTS OF CLOZAPINE ON BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A RETROSPECTIVE CHART REVIEW

Kateryna Maksyutynska*¹, Abdul Ahad², Zaineb Hamza³, Ashnie Sukhu¹, Sanjeev Kumar¹, Sri Mahavir Agarwal¹

¹*Centre for Addiction and Mental Health, University of Toronto*, ²*Centre for Addiction and Mental Health, University of Waterloo*, ³*Centre for Addiction and Mental Health, McMaster University*

Background: Behavioural and psychological symptoms of dementia (BPSD) are prevalent in individuals with neurocognitive disorders. Antipsychotic medications are frequently prescribed for severe BPSD, but have only modest benefit with significant treatment resistance. Limited research has been conducted on the effectiveness of clozapine (CLZ) in this population. Therefore, this study aims to explore the effectiveness of CLZ treatment for BPSD.

Methods: A retrospective chart review was conducted for inpatients diagnosed with neurocognitive disorder and initiated on CLZ. PRN medication administration was collected daily from 2 weeks prior to 12 weeks post CLZ initiation. Clinical assessments were drawn from the quarterly Resident Assessment Instrument-Mental Health (RAI-MH) conducted a minimum of 4 weeks pre and 4 weeks post CLZ initiation (on average, at the 9-week pre- and post-CLZ time points). Weight and complete blood count were recorded from baseline, every 4 weeks (+/- 2 weeks), to 12 weeks post CLZ initiation. Wilcoxon test was used to compare paired outcomes across time points.

Results: Nine patients (mean age 66.2 years, 66.7% males) were included; 7 had a comorbid diagnosis of a mood (n=1) or schizophrenia spectrum disorder (n=6). The highest stable mean CLZ dose attained was 206.9 mg. There was a significant decrease in the number of psychotropic PRN medications administered for BPSD at the 2-4 (M:5 [IQR:10.5]; p=0.035), 4-6 (M:0 [IQR:9]; p=0.017), and 8-10 (M:0 [IQR:12.5]; p=0.027) week time points post CLZ initiation, as compared to pre CLZ initiation (M:11 [IQR:10]). The total number of PRNs (psychotropic and non-psychotropic) also showed a similar pattern across time. Furthermore, patients were required to be observed by staff for fewer days (M:3 [IQR:6.5]; p=0.042) post CLZ initiation (M:2 [IQR:3]) as compared to before CLZ. No significant changes in other clinical assessments were noted post CLZ initiation. There were no significant changes in the use of PRNs administered for constipation, neutrophil count, or weight, up to 12 weeks post CLZ initiation.

Discussion: A significant decrease in PRN use and requirement for observations by staff was observed among inpatients with BPSD after CLZ initiation, without any significant increase in rates of adverse events. These findings highlight the need for further research to explore the effectiveness of CLZ in this population.

F204. DIFFERENTIAL EFFECTS OF D2/D3 ANTAGONISM AND D2/D3 PARTIAL AGONISM ON NEGATIVE SYMPTOMS AND REWARD PROCESSING IN HEALTHY HUMANS: A PLACEBO-CONTROLLED, DOUBLE-BLIND CROSSOVER STUDY

Martin Osugo^{*1}, Pierluigi Selvaggi¹, Uzma Zahid¹, Matthew Wall², Valeria Finelli¹, George Chapman³, Thomas Whitehurst³, Ellis Chika Onwordi³, Ben Statton⁴, Rob McCutcheon⁵, Tiago Reis Marques⁶, Mitul Mehta⁷, Robin Murray¹, Oliver Howes⁸

¹King's College London, Institute of Psychiatry, ²Imanova Ltd, Hammersmith Hospital, ³Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, London, UK, ⁴Imperial College London, ⁵University of Oxford, ⁶Imperial College School of Medicine, ⁷Center for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁸King's College London, Institute of Psychiatry; Medical Research Council Clinical Sciences Centre, Hammersmith Hospital, Imperial College London

Background: Negative symptoms are core features of schizophrenia. There are no licenced treatments as the underlying neurobiology is unclear, however dopaminergic dysfunction is implicated. A putative mechanism for antipsychotic (AP) induced negative symptoms is that antagonism of dopamine receptors leads to the blunted striatal reward response seen in AP treated schizophrenia patients. These reward deficits correlate with negative symptom severity, however drawing clear inferences on causation is challenging as the effects of the disease and AP use are difficult to disentangle. To address this, several studies in healthy volunteers have demonstrated reductions in striatal reward response following AP administration. However, all studies so far have used single doses and none have assessed the relationship between AP induced reward dysfunction and AP induced negative symptoms. We aimed to demonstrate a causal relationship between dopaminergic antagonism, reward dysfunction and negative symptoms by administering amisulpride (AMI; selective D2/D3 antagonist) and aripiprazole (ARI; D2/D3 partial agonist) to healthy humans.

Methods: A randomised, double-blind, placebo-controlled crossover study design was used. Two independent samples of healthy volunteers received AMI and placebo, or ARI and placebo, for seven days each. A washout period of at least 5 half-lives (drug and active metabolites) was used in between. AMI doses were: Day 1:200mg, Day 2:300mg, Days 3-7: 400mg. ARI doses were Days 1-2:5mg, Days 3-7:10mg. fMRI and negative symptoms were assessed at baseline and following administration of AP and placebo. Negative symptoms were assessed using validated scales (CAINS, BNSS, PANSS negative) and analysed using a mixed model, with pairwise comparisons corrected for multiple comparisons. Neural reward was assessed using the monetary incentive delay task. fMRI data were analysed in FSL, utilising standard pre-processing procedures, a whole brain paired t-test (cluster-based correction for multiple comparisons, Z GREATER THAN 2.3, p LESS THAN 0.05) comparing the AP and placebo conditions, and prespecified ROI analysis.

Results: 86 healthy volunteers were enrolled in total (39 AMI, 37 ARI). 50 completed the study (25 AMI, 25 ARI). Mean age was 26.6 ± 8.2 , 59% were female. There were no significant demographic differences between the AMI and ARI groups. For AMI (all three scales), the overall mixed effects models were significant (BNSS: $n=29$, $p=0.0004^*$) and corrected pairwise comparisons revealed significantly greater negative symptoms following

AMI administration compared to both placebo (BNSS: $n=29$, $p=0.028^*$), and baseline assessment (BNSS: $n=29$, $p=0.0003^*$). There were no significant differences between baseline assessment and placebo (BNSS: $n=29$, $p=0.32$). On AMI, we also found reduced BOLD activation during reward outcome in the prefrontal cortex, anterior cingulate, paracingulate, caudate and insula compared to placebo in both whole brain and ROI analyses, with medium-large effect sizes (-0.47 to -0.81). The reduction in caudate activation on AMI during reward outcome was correlated with AMI induced negative symptoms ($n=21$, $\rho = -0.492$, $p=0.024^*$). Compared to placebo, ARI had no effect on negative symptoms or reward processing.

Discussion: Subchronic D2/D3 antagonism induces negative symptoms in healthy volunteers, and this is correlated with drug induced reductions of reward response in the caudate. These findings provide causal evidence linking striatal dopaminergic dysfunction to negative symptoms. However, subchronic D2/D3 partial agonism has no effect on reward function or negative symptoms. Our findings confirm dopamine's central role in reward processing and have implications for the treatment of negative symptoms in schizophrenia.

F205. EFFECTS OF THE EARLY TREATMENT WITH THE POSITIVE ALLOSTERIC MODULATOR OF THE MGLU2 RECEPTOR JNJ-46356479 ON THE BCL-2 LEVELS IN A POSTNATAL KETAMINE MOUSE MODEL

David Olivares Berjaga^{*1}, Albert Martínez-Pinteño¹, Natalia Rodríguez¹, Santiago Madero², Alex González-Segura¹, Lluçia Prohens¹, Irene Martínez-Serrano², Sergi Mas¹, Constanza Morén¹, Eduard Parellada², Patricia Gassó¹

¹University of Barcelona, ²Hospital Clínic Barcelona

Background: Schizophrenia (SZ) glutamatergic dysfunction hypothesis proposes the presence of excessive Glutamate (Glu) levels, known as the Glu storm, leading to excitotoxicity during the disorder development. Evidence demonstrates excitotoxic events during the early stages of the disease could lead to excessive synaptic pruning due to increased apoptosis of the dendritic spines in critical brain areas (Parellada et al., 2021). Accordingly, dysregulation of the apoptotic protein levels has been observed in SZ patients and in SZ-like animal models. Consequently, it has been proposed that targeting the Glu-induced excitotoxicity and high apoptotic levels it would be possible to ameliorate patient's deterioration. New therapies targeting the glutamatergic system has been proposed. Positive allosteric modulators (PAM) of the metabotropic GLU receptor 2 (mGluR2), such as JNJ-46356479 (JNJ), inhibit the presynaptic release of GLU. In animal models, JNJ has previously shown the capacity of ameliorating the cognitive and negative deficits present in a postnatal ketamine (KET) mice model (Martínez-Pinteño et al., 2020) and partially attenuate the dysregulation of the apoptotic protein levels induced by KET (Olivares-Berjaga et al., under review). Additionally, early JNJ treatment during adolescence also improved cognitive and negative symptoms in the same model (Martínez-Pinteño et al., 2023). At cellular level, JNJ attenuated apoptosis, particularly the Caspase-3 activation, induced by dopamine and GLU in human neuroblastoma cell cultures (Gassó et al., 2023). We aimed to evaluate the effects of the early treatment with JNJ on the antiapoptotic protein Bcl-2 levels in prefrontal cortex (PFC) and hippocampus (HPC) tissues, studied in a SZ-like mice model postnatally exposed to KET. Also, we aimed to assess if treatment with the current antipsychotic drug clozapine (CLZ) promote the same effects.

Methods: SZ-like mice model was generated by the administration of KET (30mg/Kg) to the pups on postnatal days (PND) 7, 9 and 11. From PND 35 to 60, animals were treated with JNJ (10mg/Kg), CLZ (10 mg/Kg) or vehicle (VEH). Six experimental groups were generated

(VEH, VEH+JNJ, VEH+CLZ, KET+VEH, KET+JNJ, KET+CLZ). At adulthood (PND 120), mice were euthanized and perfused with PBS 1X followed by 4% paraformaldehyde. 30- μ m coronal sections of PFC and HPC tissues were obtained and prepared for immunofluorescent labelling with antibodies for Bcl2. Confocal images were automatically analysed using ImageJ software to quantify the fluorescence intensity of the protein. Significant differences between the groups were studied through Two-Way ANOVA, setting as factors the experimental group and the animal sex.

Results: Bcl-2 protein levels showed significant differences between the study groups in HPC. Protein expression was measured in CA1, CA2, CA3 and DG separately. Significant differences between the treatment groups were observed on CA1, CA3 and DG. After Bonferroni post hoc comparisons the three areas of the HPC demonstrated reduced Bcl-2 levels in the KET+VEH and KET+CLZ groups compared to the VEH+JNJ group. No significant reduction in Bcl-2 levels were seen in those animals exposed to KET treated with JNJ. No significant differences were observed in PFC or CA2.

Discussion: These evidenced early pharmacological treatment with JNJ could be able to attenuate brain apoptosis in the adult animal, as previously described in cell cultures (Gassó et al., 2023) and after treating the animals during the animal adulthood (Olivares-Berjaga et al., under review). Consequently, modulation of the glutamatergic system could be a useful target to alleviate the exacerbated apoptotic brain state observed in SZ patient or during the early stages of the disorder.

F206. SEXUAL SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS: A SYSTEMATIC REVIEW WITH SINGLE-ARM, PAIRWISE AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS AND NON-RANDOMIZED STUDIES

Shimeng Dong^{*1}, Johannes Schneider-Thoma¹, Spyridon Sifakis¹, Orestis Efthimiou², Stefan Leucht¹

¹*Technical University of Munich*, ²*Institute of Social and Preventive Medicine, University of Bern*

Background: Schizophrenia is a frequent, severe, and mostly chronic mental disorder, which typically starts in early adulthood. Antipsychotic drugs are the mainstay of acute treatment of schizophrenic psychosis and of recurrence prophylaxis. However, antipsychotics can disrupt normal sexual functioning by causing disorders of sexual desire, erection and ejaculation, vaginal lubrication, orgasm, as well as disorders of the breasts (growth, milk production) and the menstrual cycle. Such sexual side effects are very important for afflicted individuals, as they strongly reduce their quality of life. Subsequently, these side effects are a frequent cause for stopping antipsychotic treatment, which may lead to increased risk of persistent symptoms and relapses, with dire consequences for patients, relatives, and society in general. As the various licensed antipsychotics differ in their pharmacological mechanisms (receptor binding profiles), it is likely that they cause different sexual side effects, and to varying degrees. However, and despite the high clinical relevance, there has been no systematic comparison of the different antipsychotics in terms of sexual side effects. This systematic review aims to address this gap and provide evidence-based information, to facilitate the individual choice of medication.

Methods: To identify eligible studies, we will search the register of the Cochrane Schizophrenia group for randomized controlled trials (RCTs) and multiple electronic databases for non-randomised studies (NRSs) on antipsychotic drugs in schizophrenia. Both searches have no date/time, language, document type, and publication status restrictions. Patients with

schizophrenia or related disorders will be included. We will include all second-generation; first-generation antipsychotics as well as placebo will also be included when they were used as comparators. We will extract all adverse events related to sexual functioning. The primary outcome will be “any sexual side effect”: the number of patients with at least one event, as reported by the original authors. Secondary outcomes will be any sexual adverse event in men and women separately, and any adverse events related to the three phases of sexual response cycle i) “desire” (related terms are, e.g., libido, sexual thoughts), ii) “arousal” (e.g. erection, lubrication) and iii) “orgasm (e.g. ejaculation, anorgasmia)”, as well as any adverse related to iv) breast dysfunction (e.g. gynecomastia, galactorrhea) and v) menstruation irregularities (e.g. amenorrhea, dysmenorrhea). We are conducting separate single-arm and pairwise meta-analyses of RCTs and NRSs, and proceed to network meta-analysis of RCTs. Subsequently, we proceed with combined network meta-analysis of RCTs and NRSs if requirements in heterogeneity, transitivity, and consistency within and across designs are met.

Results: We will present the aims of the project and our methods in detail on the poster together with preliminary results of the systematic search.

Discussion: Potential strength and limitations of the review will be present and discussed on the poster.

F207. CASE REPORT: CLOZAPINE INDUCED AGRANULOCYTOSIS IN A PATIENT WITH TREATMENT-RESISTANT SCHIZOPHRENIA PREVIOUSLY STABLE ON CLOZAPINE

Sangeetha Elango¹, Nicholas Abraham*¹, Arvind Rajagopalan¹, Enquan Cheow¹

¹*Institute of Mental Health*

Background: Clozapine is an effective antipsychotic medication commonly used for treatment-resistant schizophrenia. Those who respond to Clozapine experience a significant increase in quality of life [1]. Approximately 1% of patients on Clozapine experience the potentially life-threatening side effect of Clozapine-induced agranulocytosis (CIA) [1], which is characterized by an absolute neutrophil count (ANC) less than 100 neutrophils per microlitre of blood. Peak incidence and mortality are noted to occur within the first 3 months of treatment [2]. Notably, CIA is an idiosyncratic adverse drug reaction, that occurs independent of dosing and at any time during treatment, with the majority of dyscrasias occurring within the first 18 weeks of treatment [2].

Methods: This is a case report of a 46-year-old Chinese male, a non-smoker with treatment resistant Schizophrenia, stable on Clozapine 150 mg every morning and 250 mg every night, for more than 20 years. He had previously experienced neutropenia (ANC 1.3x10⁹/L) whilst on Clozapine in August 2013 and Clozapine was stopped. The decision was made to rechallenge with Clozapine in February 2014 due to lack of treatment response. He again developed neutropenia over 9 days in March-April 2016 (lowest ANC 1.15 x10⁹/L), however Clozapine was not stopped during this time. He was on frequent full blood count (FBC) monitoring and his ANC eventually normalized.

Results: In October 2023 he had an unrelated medical issue that required transfer of care to another institution, following which Clozapine was stopped for 3 days. His ANC prior to stopping Clozapine was 4.01x10⁹/L. Upon readmission, Clozapine was restarted at 12.5mg twice daily and slowly titrated, as per our local guidelines. He underwent weekly FBC monitoring during titration, which was stable. Clozapine was titrated up to 75mg every morning

and 150mg every night by the 18th day post re-initiation. On the 19th day, he developed neutropenia (ANC $1.28 \times 10^9/L$) and agranulocytosis (ANC $0.47 \times 10^9/L$) on the 20th day. He was referred for specialist review, and the cause of the agranulocytosis was determined to be Clozapine, with no other medical causes established. Clozapine was stopped and he was switched onto Olanzapine. His ANC levels subsequently improved, and normalized 2 days later.

Discussion: When Clozapine treatment is started in an inpatient setting, it is recommended to start at 12.5mg once or twice daily on day one, followed by daily incrementations by 25–50mg [3]. A large study found that the risk of CIA in Asian individuals is 2.4-fold higher than in Caucasians [4]. It is reported that Caucasians, who are average Clozapine metabolisers, may need doses ranging from 300-600 mg per day to hit therapeutic concentrations (350 ng/ml). However, in Asian populations, average therapeutic Clozapine doses are below 300mg/day [5]. Additionally, approximately 10% of Asians are genetically poor metabolisers requiring even lower doses of 50-150mg per day for therapeutic effect. Some known risk factors of CIA include advanced age and CYP1A2 inhibiting medications such as Fluvoxamine and Sodium Valproate [6]. A possible factor to consider is that our patient was also on Sodium Valproate long-term, which could have contributed to the initial neutropenia. This is an unusual case of agranulocytosis noted on stopping and restarting Clozapine after 3 days, in a patient previously stable on Clozapine for more than 10 years. This case demonstrates the importance of close monitoring and slow titration of Clozapine when re-introducing it even in patients who had previously tolerated it well, reinforcing what is advised in most guidelines. It also underscores the fact that CIA is an idiosyncratic reaction [7], which is still poorly understood.

F208. SHORT-TERM WEIGHT AND METABOLIC OUTCOMES AFTER SWITCHING TO ARIPIPRAZOLE LAI IN SCHIZOPHRENIA

Seoyoung Kim^{*1}, Euitae Kim², Sung-Wan Kim³, Beomwoo Nam⁴, Kyoung-Uk Lee⁵, Bong Ju Lee⁶, Seung-Hee Won⁷, Chang Hwa Lee⁸, JUN SOO KWON⁹, the MAESTRO study group¹⁰

¹Seoul National University Bundang Hospital, ²Seoul National University College of Medicine, ³Chonnam National University Medical School, Gwangju Bukgu Community Mental Health Center, ⁴School of Medicine, Konkuk University, ⁵Uijeongbu St. Mary's Hospital, The Catholic University of Korea, College of Medicine, ⁶Lee Bong Ju Psychiatric Clinic, ⁷Kyungpook National University School of Medicine, ⁸Eulji University School of Medicine, Eulji University Hospital, Seoul National University College of Medicine, ¹⁰the MAESTRO study group

Background: Weight gain and metabolic disturbance is a major concern regarding antipsychotic treatment, associated with excess mortality in patients with schizophrenia compared to general population. It is well-known that the risk for weight gain differs among various antipsychotic drugs and aripiprazole has been demonstrated to have lower risk for weight gain and metabolic disturbance. While the mechanism underlying weight gain and metabolic disturbance is largely unknown, it has been suggested that both central satiety system and peripheral metabolic process is affected from antipsychotic drugs. Aripiprazole has a receptor profile as a dopamine partial agonist, and this unique feature might have a role in less weight gain and metabolic side effects. In this study, we aimed to monitor the change in weight and metabolic profile short-term after switching to LAI aripiprazole and to compare the outcomes based on previously prescribed antipsychotic drugs.

Methods: The study was based on an open-label, parallel-group study design. Patients diagnosed with schizophrenia who were clinically stable under oral antipsychotic drugs were enrolled. PANSS and CGI-S were used for clinical assessments. Weight and fasting blood metabolic profile were monitored before and after 4, 8, 12 and 16 weeks after switching to LAI aripiprazole. Patients who were previously treated with oral aripiprazole (Group I) and patients who were previously treated with oral antipsychotic drugs other than aripiprazole (Group II) were compared.

Results: At 16 weeks after switching to LAI aripiprazole, Group II resulted in weight loss and decreased waist circumference, while Group I showed almost no change. Significant decrease in serum LDL cholesterol level were observed in both Group II.

Discussion: Switching to LAI aripiprazole resulted in weight decrease and improved metabolic profile in patients treated with antipsychotics other than oral aripiprazole. This suggest that LAI aripiprazole can be an option for patients having weight gain side effects under antipsychotic drugs other than aripiprazole, but further research with longer follow-up is needed.

F209. OPTIMIZING PHARMACOLOGICAL TREATMENT FOR ADHD IN INDIVIDUALS WITH COMORBID PSYCHOTIC DISORDERS: CHALLENGES AND STRATEGIES

Olivier Corbeil^{*1}, Sébastien Brodeur², Laurent Béchar³, Maxime Huot-Lavoie², Charles Desmeules⁴, Elizabeth Anderson⁴, Josiane Courteau⁵, Marco Solmi⁶, Ridha Joobar⁷, Marc-André Roy², Marie-France Demers³

¹Laval University, ²Faculty of Medicine, Université Laval, ³Faculty of Pharmacy, Université Laval, ⁴School of Psychology, Université Laval, ⁵Sherbrooke University, PRIMUS Research Group, ⁶Department of Psychiatry, University of Ottawa, ⁷McGill University, Douglas Mental Health University Institute

Background: Attention-deficit hyperactivity disorder (ADHD) frequently coexists with schizophrenia spectrum and other psychotic disorders (SZSPD), contributing to poorer overall outcomes. The treatment of ADHD using psychostimulants, the first-line medications for managing ADHD, has been constrained due to concerns regarding an elevated risk of psychotic events. Existing evidence on this matter remains limited and inconclusive. Further data are crucial to gain a comprehensive understanding of this potential risk and to advance strategies promoting recovery in individuals facing these complex comorbidities.

Methods: A retrospective cohort study utilizing administrative health registries to assess the risk of hospitalization for psychosis subsequent to the initiation of psychostimulants among individuals diagnosed with SZSPD was conducted. Additionally, a narrative review of existing data will facilitate the proposal of optimized pharmacological approaches for managing ADHD within this specific population. The aim is to address prevailing challenges and provide potential strategies to enhance treatment efficacy in individuals facing these two comorbidities.

Results: Among 2219 individuals diagnosed with SZSPD and receiving combined treatment with antipsychotics, the initiation of psychostimulants did not show an increased risk of hospitalization for psychosis (adjusted HR = 0.36, 95% CI 0.24 - 0.54, p LESS THAN 0.0001). These outcomes corroborate an earlier observational study, albeit conducted with a smaller sample size. While general population data indicate a potential elevated risk of psychotic events with amphetamine use compared to methylphenidate, such evidence is yet to be established for

individuals with SZSPD. Concerns regarding psychotic events linked to psychostimulants primarily stem from experimental symptom provocation studies.

Discussion: Although recent observational studies suggest that using psychostimulants in individuals with SZSPD might be safer than traditionally perceived, several caveats remain regarding patient selection for this strategy, determining optimal psychostimulant doses, and defining the minimum duration of SZSPD remission for safe administration. Arguments can be presented to support favoring methylphenidate over amphetamines, restricting their use to individuals in remission adhering to adequate antipsychotic treatment, prioritizing long-acting formulations, and employing minimal effective doses. However, more robust evidence from randomized controlled trials is crucial to comprehensively evaluate the efficacy and safety of this approach. Meanwhile, judiciously selecting patients may allow for beneficial ADHD treatment alongside SZSPD, contributing to enhanced recovery.

F210. REPRODUCIBILITY OF BEHAVIORAL PHENOTYPES WITH RELEVANCE TO SCHIZOPHRENIA: A SINGLE-LABORATORY MULTI-BATCH STUDY ON THE EFFECTS OF MK-801 IN ZEBRAFISH

Matheus Gallas Lopes^{*1}, Elaine Elisabetsky¹, Angelo Piatto¹, Ana Paula Herrmann¹

¹*Universidade Federal do Rio Grande do Sul*

Background: Pharmacological blockade of NMDA receptors with antagonists such as MK-801 is the underpinning of popular animal models of schizophrenia that attempt to recapitulate the hypofunction of GABAergic interneurons. Most of these models also present face validity since they induce behavioral phenotypes relevant to the positive, negative, and cognitive symptoms of schizophrenia. Considering the recent failures in translating preclinical findings into new antipsychotic drugs, investigating the reliability of animal models is of great relevance to avoid research waste and further setbacks. The aim of this study was to employ a single-laboratory multi-batch design, followed by a random-effects meta-analysis, to evaluate the reproducibility of MK-801-induced behavioral phenotypes in the Social Preference (SPT) and Open Tank (OTT) tests in zebrafish.

Methods: We used 360 4-month-old wild-type zebrafish (*Danio rerio*), with an equal distribution of males and females (ethics committee 43858/2023). Following block randomization procedures, animals were allocated to one of two experimental groups: control or 5 μ M MK-801 ($n = 15$). Subjects were individually exposed to water or MK-801 for 20 min, and sequentially subjected to the SPT and OTT tests for 7 and 5 minutes, respectively. This experiment was repeated 12 times by the same research team at the same laboratory under consistent conditions, varying only the batch of animals. Social preference (as measured by the time spent near a stimulus shoal) and locomotor parameters were automatically scored using the software ANY-Maze. Data were analyzed by a random-effects meta-analysis to assess the combined effect of the intervention on each behavioral outcome across the experiments.

Results: In the SPT, significant effects of MK-801 in reducing social preference were observed in only 2 out of the 12 experiments. However, the meta-analysis yielded a significant overall effect of MK-801 in reducing social preference, with a pooled effect size of -0.45 [95%-CI -0.69; -0.21] and individual effect sizes ranging from 0.22 to -1.27 across experiments. This pattern was observed across most of the outcomes in the SPT. Conversely, in the OTT, a robust and significant effect of MK-801 was observed for its outcomes. For instance, reduction of the absolute turn angle was observed in all experiments, with a pooled effect size of -1.55 [95%-CI -1.97; -1.12] and individual effect sizes ranging from -3.01 to -0.86. This pattern was consistent for the other outcomes in the OTT.

Discussion: Two different behavioral assays were conducted to evaluate a range of phenotypes induced by the same intervention following the same protocol. Surprisingly, two distinct sets of results were obtained depending on the assay: while in the OTT we observed robust and significant effects across all experiments, in the SPT individual effect sizes were less consistent. Such intriguing divergence suggests that, apart from internal and external validity problems, reproducibility issues may also be correlated with factors intrinsically tied to the nature of the behavioral assays or the outcomes under examination. Further studies are needed to investigate which aspects of the behavioral assays may explain this phenomenon. Our findings also provide indirect evidence supporting within-study heterogenization as a method to improve the reproducibility of preclinical research, and underscore the importance of establishing sound foundational principles for experimental trials before continuing to replicate protocols that have consigned numerous drug candidates to the depths of the "valley of death" of translational science.

Funding: Jaguar Health Inc. provided financial support for this work.

F211. MAKING MEANING OF MULTIMORBIDITY FOR PEOPLE WITH SCHIZOPHRENIA

Sean Halstead¹, Dan Siskind², Nicola Warren¹, Dan Siskind*³

¹*The University of Queensland*, ²*School of Medicine, The University of Queensland, MIRT, Woolloongabba Community Health Centre, Addiction and Mental Health Services and MIRT*, ³*Metro South Addiction and Mental Health Service*

Background: People living with schizophrenia and other severe mental illness (SMI), experience a multitude of poorer health outcomes compared to those without mental illness, such as shortened life expectancy of 10-20 years. This is thought to be largely driven by the accumulation of multiple chronic diseases. The notion of additional disease outside of the SMI of interest has primarily been studied through the lens of comorbidity, a framework which emphasises the presence of a 'secondary' condition in relation to an index condition: (e.g., diabetes mellitus is a recognised comorbidity of schizophrenia). Conversely, multimorbidity, defined as the coexistence of two or more chronic conditions, has been proposed as a more useful framework for characterising the chronic disease burden faced by those with SMI, with respect the number and types of other physical and psychiatric conditions that people with SMI experience. Our aim was to describe the utility of applying a multimorbidity framework to assess and measure the chronic health burden of those with schizophrenia and other SMI, and understand how the combination of poor physical and mental health interact as a risk factor for adverse health outcomes.

Methods: The research presented here is a synthesis of a narrative literature review we undertook to contextualise how multimorbidity has been studied to date amongst those with SMI. We will present our synthesis of the literature for the following questions:

- 1) How is multimorbidity defined, both in- and outside of psychiatric contexts?
- 2) How does multimorbidity manifest in people with SMI with respect to the number and types of chronic conditions they experience?
- 3) How does multimorbidity mediate poor health outcomes as a risk factor?

4) How can multimorbidity be measured and applied in a clinically meaningful framework for those with severe mental illness?

Results: Multimorbidity is a term that has emerged in the literature relatively recently, particularly within psychiatric research. Narrative review highlighted that those with and without SMI experience similar clusters of physical multimorbidity with respect to the types of co-occurring conditions, however, those with SMI appear to experience a greater burden of multimorbidity at comparatively younger ages. Multimorbidity has been demonstrated to be a mediator of a variety of adverse health outcomes, specifically premature mortality, increased disability, and increased health-economic resource utilisation. We have also sought to summarise the existing models of how multimorbidity is measured, with respect to disease counts and existing indices such as the Charlson Comorbidity Index.

Discussion: Upon synthesising the existing literature, we proposed the utility in framing multimorbidity as a cumulative risk exposure variable that takes into account both quantity and duration of chronic illnesses. With this approach, we hypothesise that (i) people with SMI experience a greater cumulative exposure to chronic illness as part of multimorbidity during their lifetime, and (ii) this greater exposure is a significant mediator of adverse health outcomes such as premature mortality. For those with SMI, it is speculated that this exposure to chronic disease is exacerbated by diagnostic overshadowing, marked by increased under-diagnosis and under-treatment of physical health conditions in those with SMI. Ultimately, multimorbidity appears to be an emerging epidemiological concept that is integral to understanding the chronic disease burden faced by those living with SMI. We envision that a multimorbidity model of care that comprises a multidisciplinary team of various health disciplines will enable more holistic and integrated treatment of physical and mental health. This will be critical in mitigating the health inequities faced by those with schizophrenia and other SMI.

This research has previously been published as a Viewpoint in the Australian and New Zealand Journal of Psychiatry.

Halstead, S., Siskind, D., and Warren, N. (2023). Making meaning of multimorbidity and severe mental illness: A viewpoint. Australian and New Zealand Journal of Psychiatry, (Published Online First). <https://doi.org/10.1177/00048674231195560>

F212. EVALUATING THE EPIDEMIOLOGY OF CLOZAPINE-ASSOCIATED NEUTROPENIA AMONG PEOPLE ON CLOZAPINE ACROSS AUSTRALIA AND AOTEAROA NEW ZEALAND: A RETROSPECTIVE COHORT STUDY

Korinne Northwood¹, Nicholas Myles², Scott Clark³, Susanna Every-Palmer⁴, Hannah Myles⁵, Steve Kisely¹, Nicola Warren¹, Dan Siskind^{*6}

¹*The University of Queensland*, ²*Royal Adelaide Hospital*, ³*The University of Adelaide*, ⁴*University of Otago, Wellington*, ⁵*Northern Adelaide Health Network*, ⁶*Metro South Addiction and Mental Health Service*

Background: Clozapine is associated with the risk of serious neutropenia. However, this may decrease over time, meaning that indefinite absolute neutrophil count (ANC) monitoring may be unnecessary. This study aims to determine the epidemiology and timing of clozapine-associated neutropenia outcomes, investigate variables that may contribute to the odds of neutropenia, and determine risk of competing neutropenic events during clozapine treatment.

Methods: We performed retrospective analysis of the Australian and New Zealand Viatrix Pharmacovigilance system, one of two monitoring databases for these two countries, between

06 June 1990 and 25 October 2022. Patients were excluded from further analysis if they commenced clozapine prior to 1990 (when data recording reliably commenced), did not have a haematology test within two weeks of commencement date, or had zero-week follow-up. All other patients were included. Rates of minor ($\text{ANC} \geq 1.0 \times 10^9/\text{L}$) and severe ($\text{ANC} \text{ LESS THAN } 1.0 \times 10^9/\text{L}$) neutropenia, were determined, with time to event used to calculate rolling weekly average, and to perform competing risk analysis of outcomes using Cox proportional and Fine-Gray sub-distribution hazard calculation.

Results: 26,630 patients, with 2.6 million absolute neutrophil count (ANC) values were included. The total cohort was predominantly male ($n = 17585$, 66%) and young (mean age 36.1 years, $\text{SD}=13.7$). Rates for minor neutropenia ($\text{ANC} \geq 1.0 \times 10^9/\text{L}$), serious neutropenia ($\text{ANC} \text{ LESS THAN } 1.0 \times 10^9/\text{L}$) leading to cessation and serious neutropenia, unrelated to clozapine without cessation were 4.3%, 1.2% and 0.84% respectively. In clozapine naïve patients ($n=15,973$), serious neutropenia leading to cessation peaked in the first 18-weeks with a rolling averaged weekly incidence of 0.05%, stabilising at 0.001% weekly by 2-years. Minor neutropenia and serious neutropenia unrelated to clozapine rates remained constant at 0.02% and 0.002% per-week, respectively. The median time to a serious neutropenic event leading to cessation was 17-weeks (IQR 9.96–102). Prior clozapine exposure reduced the risk of serious neutropenia leading to cessation (OR 0.19, 95% CI 0.12 – 0.31, $p \text{ LESS THAN } 0.0001$).

Discussion: The majority of serious neutropenia leading to clozapine cessation occurs within 18 weeks of treatment and becomes negligible after two years. Weekly haematological monitoring for the first 18 weeks, may be safely reduced to four-weekly and ceased after two years unless clinically indicated. Clozapine retreatment after interruption with 2 cumulative years of unremarkable testing may not require further haematological monitoring. A serious neutropenia ANC threshold of $\leq 1.0 \times 10^9/\text{L}$ could be used in more jurisdictions.

F213. NO IMMEDIATE STRUCTURAL CHANGES INCURRED BY TMS TREATMENT IN SCHIZOPHRENIA

Peter Van Dyken^{*1}, Nadia Zeramdini², Hani Abdelhafiz², Jessica Ahrens², Farida Zaher², Marcelo Berlim², David Bloom², Ridha Joobar², Alkomiet Hassan³, Frank Padberg³, Nikolas Koutsouleris³, Emmanuel Schwarz³, Lena Palaniyappan²

¹University of Western Ontario, ²Douglas Mental Health University Institute, ³Ludwig-Maximilians-University

Background: Transcranial Magnetic Stimulation (TMS) is a promising treatment approach for patients with intractable symptoms of schizophrenia, with its noninvasive administration and minimal side-effect profile. Recent reviews (Patel et al., 2023; Poorganji et al., 2023; Soltani et al., 2022) have reported low-grade evidence of treatment efficacy for negative symptoms. The exact mechanism of TMS remain unclear, but it appears to modulate functional and structural plasticity (Jannati et al., 2023) and brain connectivity (Hernandez-Pavon et al., 2023). Schizophrenia is a malady of synaptic plasticity and dysconnectivity, accompanied by widespread cortical thinning (Banaj et al., 2023) and increases in white matter diffusivity. Long-term, stable improvement in persistent features such as negative symptoms after TMS may require the reversal of these structural changes (Hasan et al., 2017; Kozel et al., 2011). We investigated the extent to which a 3-week course of high frequency left DLPFC TMS affects brain structure in patients with high negative symptom burden in schizophrenia.

Methods: $N=11$ schizophrenia patients were recruited from a cohort in Montreal, Quebec, Canada. Participants were scanned before and after treatment with TMS following the RESIS

study protocol (10-Hz rTMS, 15 sessions, 1000 stimuli per session) (Hasan et al., 2016). Data was acquired with 3T MRI using diffusion-weighted (b=0,1000,2000; 95 directions; 1.6mm res) and T1-weighted (MPRAGE; 1mm res) protocols. Diffusion data was preprocessed with and FSL pipeline (degibbs, susceptibility distortion correction with topup, motion and eddy current correction with eddy). Anatomical surface meshes and cortical thickness was calculated with fastsurfer and ciftfy. Fractional anisotropy (FA) and mean, radial, and axial diffusivity (MD, RD, AD) were fit to the diffusion data in the grey matter and projected onto the cortical midsurface. Changes in cortical thickness and diffusivity between scans, as well as the interaction between thickness and PANSS30, using a mixed linear model, with subjects as random effects. Multiple comparisons were corrected using random field theory.

Results: No significant differences were found across scanning sessions for structural thickness, FA, MD, RD, or AD. There was no interaction between thickness and PANSS30 or any of the PANSS subscores. We are currently expanding our analysis across a larger sample size and exploring if region-specific changes restricted to the site of stimulation alone is more likely in this context.

Discussion: Detectable, global structural changes in the cortical grey matter are not found in the immediate wake of 10-Hz, 15-session, left DLPFC TMS in schizophrenia. Although this does not prove TMS is structurally inert, it does demonstrate a lack of immediate, easily visible, distributed change. Importantly, the cortex has a complex microenvironment not easily characterized by the simple diffusion tensor metrics reported above. More sophisticated diffusion models, such as NODDI, may provide a more subtle picture of structural change.

F214. HOW CAN WE BETTER MANAGE ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN PEOPLE LIVING WITH SEVERE MENTAL ILLNESS: A REALIST SYNTHESIS

Ian Maidment¹, Sheri Oduola*²

¹Aston University, ²University of East Anglia

Background: People with severe mental illnesses (SMI) such as schizophrenia, bipolar disorder die on average 15 to 20 years earlier than everyone else. Two thirds of these deaths are from preventable physical illnesses such as hypertension, cardiovascular disease, and diabetes, which are worsened by weight gain. Antipsychotics are associated with significant weight gain. The aim of the study was to use develop a framework and guidance for non-pharmacological approaches to manage antipsychotic-induced weight gain in people with severe mental illness (SMI). We present preliminary findings from the RESOLVE study.

Methods: We are conducting a realist review and realist evaluation. Two stakeholder groups, a lived experience group and a practitioner group input into the trajectory of the research. We developed initial programme theories currently being tested and refined. Our literature search identified 773 documents across seven bibliographic databases, of which 60 full text documents are included. The realist evaluation will incorporate up to 60 qualitative interviews with healthcare professionals, carers, and service users.

Results: the realist review indicate there are a range of service-level and individual-level approaches/interventions for managing antipsychotic-induced weight gain in mental healthcare. Our review shows that interventions need to be tailored to the individual, multimodal, flexible and commence as quickly as possible after prescription. Further, continuous support from various sources (e.g., family, peer, digital) is key to the success of the interventions, as this facilitates motivation and engagement.

Preliminary results from the realist evaluation (38 interviews) stress the importance of locating interventions within mental health services. However, the current configuration and dichotomous split between physical and mental health services results in unmet physical health needs for SMI patients. SMI and obesity are both long term conditions, mental health staff do not have the appropriate skills, knowledge, confidence, or experience to provide care for SMI patients with physical health needs such as weight gain. Small pockets of good practice exist in mental health services e.g., early intervention services but access to weight management support in mental healthcare is poor.

Discussion: An innovative systems wide approach to the management of antipsychotic medication related weight gain is required to improve the lives of people living with SMI. However, current mental healthcare systems in the UK are not effectively configured to manage antipsychotic weight gain.

F215. THE EFFECT OF METACOGNITIVE EDUCATION TREATMENT ON THOUGHT DISORDER AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA PATIENTS

Selis Koyuncuoglu¹, Emine Ilgın Hosgelen*¹, Bilge Targıtay Öztürk¹, Tolga Binbay¹, Berna Binnur Akdede¹, Köksal Alptekin¹

¹*Dokuz Eylül University,*

Background: Schizophrenia impairs psychosocial functionality, accompanied by delusions, hallucinations and disorganized behaviors, and impairments in language, thought and affect. Thought disorder includes disorders in the production and organization of thoughts. In recent years, in addition to antipsychotic treatment, various psychotherapies have been applied in schizophrenia to improve these clinical symptoms. Metacognitive treatment program aims to change the cognitive substructure of erroneous and distorted thoughts in patients and make them aware of their own mental processes. The aim of this study was to investigate the effect of Metacognitive Training on thought disorder and cognitive impairment in schizophrenia patients.

Methods: In this study, 61 patients diagnosed with schizophrenia according to DSM-V criteria who applied to Dokuz Eylül University school of Medicine, Department of Psychiatry, Schizophrenia and Other Psychotic Disorders Outpatient Unit were included. Twenty-one patients were included into the Metacognitive Training Group (MCT) and 40 patients were in the control group. Metacognitive Training Program was applied for 8 weeks, 1 day a week by face-to-face sessions with the MCT group patients. Thought disorders were evaluated by the Formal Thought Disorder Scale (FTD) and cognitive tests included the Dokuz Eylül Theory of Mind Scale (DEZİKÖ), Reading the Mind from the Eyes (RMET) test, Digit Span and Category Fluency (CFT) test. Severity of schizophrenia symptoms were evaluated by using PANSS (Positive and Negative Syndrome Scale). Depression level of the patients was measured by the Calgary Schizophrenia Depression Scale. All tests were applied to MCT group and control group at the beginning and at the end of 8 weeks.

Results: We found no statistically significant difference between the pre-test and post-test FTD scores of the MCT group and the control group. However, there was a statistically significant difference pre-test and post-test DEZİKÖ scores of MCT group and control group. DEZİKÖ scores of the MCT group significantly increased after the metacognitive therapy compared to control group ($z = -2.317$; $p=.021$). Also, depression scores of the MCT group significantly decreased after metacognitive therapy compared to control group ($t(1,20) = 2.496$; $p=.021$).

There were no statistically significant differences between MCT and control groups regarding PANSS positive, PANSS negative, PANSS psychopathology, PANSS total and RMET scores, and the neuropsychological tests Digit Span and CFT scores.

Discussion: In this study, we found metacognitive training program could be an effective program to increase social cognition skills in schizophrenia patients. In addition, there was a decrease in the severity of depression in schizophrenia patients who received MCT. First of all, it is thought that not being able to reach the targeted sample in the experimental group in this study had a detrimental effect on the meaningfulness of the data evaluation. Theory of mind skills occupy a large place in MCT. In the MCT program, it was observed that the skills were improved in patients in a manner consistent with the literature due to the fact that the skills were worked with modules in a repetitive manner. Considering this curative effect, it is seen that the skills targeted to be given to patients with MCT overlap with ToM skills.

F216. TREATMENT OF SMOKING CESSATION BY VIRTUAL REALITY IN SCHIZOPHRENIA

Köksal Alptekin¹, Emine Ilgın Hosgelen^{*2}, Faik Kartelli¹, Markus Berger¹, Oğuz Kılınc³, Gonca Ercegil⁴, Berna Yalınçetin², Özge Akgül⁵, Görsev Yener⁵, Berna Binnur Akdede¹

¹*Dokuz Eylul University*, ²*Dokuz Eylul University, Institute of Health Science*, ³*Dokuz Eylul University School of Medicine*, ⁴*Psychotherapist in Private Practice*, ⁵*Izmir Democracy University*,

Background: Patients with schizophrenia live twenty years less than normal people. Smoking cigarettes is one of the leading causes of early death and 60-80 % of patients with schizophrenia smoke. Their daily number of smoking cigarettes is high. Moreover, different from healthy people, patients with schizophrenia are consecutive smokers and they inhale cigarettes more deeply. There are Both behavioral and drug treatments aim to decrease smoking or achieve smoking cessation in schizophrenia patients; however, they are not successful. Virtual reality (VR) is composed of imitated real environments on computers. VR in the treatment of schizophrenia is new to science and offers promising VR application on normal people is effective in smoke addiction. Therefore, VR therapy may be an effective way of quitting smoking in patients with schizophrenia. However, there has not been any VR treatment of smoking cessation for schizophrenia patients. This research will be the first study in the world investigating the effect of Virtual Reality Treatment on smoking cessation in schizophrenia patients.

Methods: The participants who were smoking and diagnosed as Schizophrenia according to DSM-IV criteria were categorized into four groups: two experimental groups undergoing VR sessions, namely VR-Sch (n=26) for patients with schizophrenia, and VR-Healthy Controls (VR-HC, n=22). Additionally, two control groups were established, with one being the Sch group (non-VR-Sch, n=23) and the other the HC group (non-VR-HC, n=21), both without receiving VR interventions. VR sessions included ten individual virtual reality (VR) sessions, administered on a weekly basis, focused on smoking cessation. In order to evaluate smoking addiction level, we assessed the Fagerstrom Test for Nicotine Dependence (FTND). Also, participants were assessed in terms of quality of life by using the WHOQOL-Bref (WHO Quality of Life Scale), neuropsychological performance by using a neuropsychological test battery, theory of mind by using the Dokuz Eylul Theory of Mind Index (DEZİKÖ), psychosocial functioning by using Personal and Social Performance Scale (PSP). These tests were applied as pre (T0) and post-tests (T1) at the beginning of the intervention and 10 weeks

later, at the end of the intervention. Multi-factorial repeated measures ANOVA was performed to test the difference within and between groups in SPSS.

Results: Age and total education years were not significantly different between VR-Sch (43.20 ± 1.74 ; 10.52 ± 5.37), VR-HC (39.1 ± 1.9 ; 12.14 ± 3.18), non-VR-Sch (40.65 ± 1.85 ; 11.83 ± 3.07) and non-VR-HC (42.1 ± 1.9 ; 13.52 ± 4.52) ($p=0.42$, $p=0.19$, respectively). The main effect of time was significant [$F(1,88)=19.74$, p LESS THAN .001]. The main effect of time x group interaction was significant [$F(1,88)=4.26$, $p=.042$] indicating that the FTND score of VR groups showed a significant decrease compared to non-VR groups. The main effect of time x group interaction was not significant for VR-Sch and Non-VR-Sch groups [$F(1,88)=67.53$, $p=.007$]. The mean scores of FTND decreased over time in VR-Sch (T0: 6.31 ± 1.91 , T1: 4.27 ± 2.34) and VR-HC (T0: 4.68 ± 2.1 , T1: 2.86 ± 2.36) groups. However, the main effect of time was not significantly different between VR-Sch and VR-HC [$F(1,88)=.47$, $p=.49$].

Discussion: This study indicates that VR intervention programs designed for smoking cessation effectively reduce dependence levels in individuals who smoke. The findings suggest that the “VR Smoking Cessation Program” might be beneficial not only for those with schizophrenia but also for the general smoking population. It may also serve as a supplementary therapeutic approach, alongside pharmacotherapy, for individuals who are motivated to quit smoking.

F217. NETWORK META-ANALYSIS ABOUT THE EFFECTS OF NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR TREATMENT RESISTANT SCHIZOPHRENIA

Stefan Leucht^{*1}, Carolin Lorenz², Shimeng Dong², Nobuyuki Nomura³, Spyridon Sifakis²

¹Technical University of Munich, ²Klinikum rechts der Isar, School of Medicine and Health, Technische Universität München, ³School of Medicine and Health, Technical University of Munich

Background: Antipsychotics are the cornerstone of treatment, but around 40% of patients do not respond adequately to antipsychotics, and up to a third do not respond to two adequate antipsychotic trials, meeting the criteria for 'treatment-resistant' schizophrenia according to international guidelines. Effective interventions for treatment-resistant schizophrenia are of great importance and a top priority for research, according to a consensus of patients and clinicians published in Nature. Clozapine is the only antipsychotic indicated for treatment-resistant schizophrenia as it has high efficacy, however the non-response rate is up to 60%. Among the limited treatment options for non-response to antipsychotics, adjunctive treatment with non-invasive brain stimulation (NIBS) may be promising. Several techniques have been investigated in clinical trials, and two of them, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), are currently recommended in international guidelines for treatment-resistant schizophrenia. However, these recommendations are based on mixed and outdated evidence, which is also reflected in inconsistencies between expert groups. In addition, all currently available reviews performed a pairwise meta-analysis, where studies comparing two interventions can be analyzed simultaneously. Most NIBS techniques have not been directly compared in single studies and therefore it is still unclear which are the most effective, acceptable and tolerable. To close this knowledge gap, a network meta-analysis (NMA) is required.

Methods: We plan to conduct a network meta-analysis (NMA) on the comparative efficacy and safety of NIBS. First, we will conduct a series of pairwise meta-analyses. If the conditions for an NMA are met (see below), we will perform the NMA in a frequentist framework using

netmeta in R. We will use a random-effects model as heterogeneity is likely, and a fixed-effects Mantel-Haenszel method in the case of rare dichotomous outcomes (96), such as mortality. The certainty of the evidence for the primary outcome (i.e. overall symptoms) and for discontinuations for any reason will be assessed using the Confidence in Network Meta-Analysis (CINeMA) approach, taking into account within-study bias, reporting bias, indirectness, impression, heterogeneity and incoherence. Alpha is set at two-sided 5%, except for heterogeneity/incoherence tests at 10%. We will examine inconsistency and publication bias with appropriate measures.

Results: Study selection and data extraction have been completed. Analysis is currently ongoing. First results will be ready and presented at the conference.

Discussion: Treatment-resistance remains an extremely important problem in the treatment of schizophrenia. With the current network meta-analysis we will identify the most effective non-invasive brain stimulation techniques for this condition. Moreover, substantial information for the design of studies in this area will be obtained.

F218. A SYSTEMATIC REVIEW ON THE IMPACT OF VIRTUAL REALITY INTERVENTIONS ON PSYCHOSOCIAL OUTCOMES IN PSYCHOSIS

Emine Ilgin Hosgelen¹, Sinem Güneri*¹, Burak Erdeniz², Berna Akdede¹, Köksal Alptekin¹

¹Dokuz Eylül University, ²İzmir University of Economics,

Background: Decrease in social and vocational skills is common in individuals with psychotic disorders, leading to an increased risk of social isolation (Dziwota et al., 2018), impacting roughly 80% of those with psychotic disorders (Suman et al., 2023). This heightened social isolation has

severe consequences, negatively impacting the overall quality of life, daily life functioning, functional outcome, and motivation levels, and increasing the risk of relapse. Virtual reality (VR) integrated intervention programs have a promising method for psychosocial intervention by providing a controlled environment for individuals to practice social skills under the supervision of mental health professionals. This study aims to conduct a systematic review in terms of the effectiveness of VR interventions that aim to improve social skills in psychotic disorders.

Methods: PRISMA guideline was followed in the current systematic review. Literature search was performed twice on 1 March 2023 and on 20 August 2023 in two academic databases, Web of Science (WoS) and PubMed by two independent researchers (EIH and SG). The reason for performing the literature search twice was to include the latest articles during the last six months. For the review, we included studies if they (1) included social situations in VR intervention programs, (2) focused on social functioning and/or social cognition, (3) evaluated patients before and after the VR intervention (4) included patients diagnosed with psychosis or schizophrenia according to DSM-IV-TR, DSM-5 or ICD-10 criteria, (5) were research article, (6) were in English. Quality assessment was conducted by using the manual of The Effective Public Health Practice Project (EPHPP, 2010).

Results: From two databases, a total of 331 articles were obtained. Duplicate records (n=89) and ineligible articles were removed after evaluation. In the final review, fifteen studies that met the inclusion criteria were included into the study. The studies primarily focused on three key areas: psychosocial functioning (n=5), social cognitive skills (n=7), and vocational training (n=3). Out of 8 studies, 7 were cohort studies with a single-group pre and post-treatment evaluation while only one study included a control group. In addition, 1 controlled trial and 6

randomized controlled trials were included in the review. In particular, 6 of these studies conducted follow-up evaluations. Session duration of the studies ranged from 10 hours to 16 weeks and intervention frequency ranged from twice a week to a weekly basis. Few studies (single-group n=2; with a control group n=4) reported significant improvements while others (single-group n=4; with a control group n=3) observed no change after the intervention.

Discussion: The use of VR in interventions for psychosocial functioning for individuals diagnosed with psychosis represents a significant advancement in therapeutic approaches. However, studies aiming to improve psychosocial functioning used different methodologies including session scenarios, duration, and frequency of the sessions. They enable researchers to create social and vocational environments that cannot be replicated in real-life settings during therapy sessions. However, not all studies indicated effective or sufficient results. There is a need for conducting additional research and developing new VR designs to comprehensively understand the effectiveness of VR in enhancing psychosocial functioning in individuals diagnosed with psychosis.

F219. EFFECTIVENESS OF ECT AMONG THE PATIENTS WITH SCHIZOPHRENIA, SCHIZOAFFECTIVE DISORDER, AND CATATONIC SYMPTOMS

Veonho Joo^{*1}, Imyel Kim², Jiyoung Kim¹, Jina Kim¹

¹Asan Medical Center, University of Ulsan College of Medicine, ²Maumchan Psychiatric Clinic

Background: Electroconvulsive therapy has long been used in the treatment of schizophrenia and its related disorders. Its relative effectiveness among schizophrenia and its related disorders has not been clarified yet. We were trying to investigate the relative effectiveness of ECT among schizophrenia, schizoaffective disorder, delusional disorder, and patients with psychotic and catatonic symptoms.

Methods: All the patients with schizophrenia, schizoaffective disorder, and delusional disorder at our department who were admitted and received ECT since 2003, and were included in the study. Among the 46 patients, 32 were patients with schizophrenia, 11 were patients with schizoaffective disorder, and 3 were patients with delusional disorder. Using retrospective chart review, two authors at our department independently assessed the effectiveness of ECT at the time of discharge of patients. The criteria for being improved were clinically significant reduction of psychotic symptoms including delusions and /or hallucinations and reduction of aggressive behaviors toward self or others. The consensus decisions for the improvement were made between the two authors.

Results: The proportion of patients that responded to ECT were 65.6% in schizophrenia, 72.7% in schizoaffective disorder, and 33.3% in delusional disorder. The 77.8% among patients with catatonic symptoms (7/9) responded to ECT. Our results showed that the patients with catatonic symptoms responded to ECT better than patients without catatonic symptoms. The patients with schizoaffective disorder responded relatively better than patients with schizophrenia.

Discussion: The reason for superior effectiveness of ECT among the patients with schizoaffective disorder compared to schizophrenia was speculated. It is well known that the effect of ECT on severe depression and bipolar disorder is more superior than on schizophrenia. In that sense, schizoaffective disorder which has mood symptoms could have better response to ECT than schizophrenia.

F220. PROMOTING INTIMATE RELATIONSHIPS IN MENTAL ILLNESS: A SYSTEMATIC REVIEW OF INTERVENTIONS

Meryl Caiada*¹, Simon Felix¹, Sarah Guionnet¹, Kevin-Marc Valery¹, Julien Bonilla-Guerrero², Jean-Marc Destailats², Antoinette Prouteau³

¹University of Bordeaux, ²Hospital of Jonzac, ³University of Bordeaux and Hospital of Jonzac

Background: The following abstract is based on the original article, published in the Community and Mental Health Journal (Caiada et al., 2023, DOI: 10.1007/s10597-023-01204-z). Persons with Serious Mental Illness (SMI) express unmet needs in the intimate relationship domain and suffer from a severe lack of social participation. Indeed, they are more single and less married than the general population (Thornicroft et al., 2004; White et al., 2021). However, these unmet needs have received little attention until recently. This study reviews interventions that aim to facilitate the development and the maintenance of intimate relationships (IR) of persons with schizophrenia, bipolar disorder and major depression.

Methods: A systematic review following PRISMA guidelines was conducted. Studies published in Scopus, PubMed, EBSCO (Psych INFO, Psych ARTICLES, Psychology and Behavioral Sciences Collection) from January 1, 2000, to December 2021, were screened. Interventions focusing on sexual health only were excluded.

Results: The search using terms referring to “schizophrenia”, “bipolar disorder”, “major depression”, “IR” and “interventions” revealed 11 studies. Among them, ten reported interventions for persons with depression and nine were couple therapy. Most interventions targeted satisfaction with couple relationships as the main therapeutic objective. Heterogeneity in study design precludes any firm conclusions about their efficacy. Interestingly, only one intervention focused on single persons interested in developing IR and only one were designed for persons with psychosis disorder.

Discussion: The results highlight the lack of interventions: (i) aimed at promoting IR, (ii) designed for single persons, and (iii) targeting persons with psychotic disorders. This result may reflect the persisting stigmatization of persons with psychotic disorders, and the taboo associated with the IR and sexuality of persons with mental illness. Further studies are needed to develop inclusive interventions promoting the development of IR in persons with mental illness.

F221. ENHANCING PATIENT-CENTERED CARE IN SCHIZOPHRENIA TREATMENT: DEVELOPMENT AND EVALUATION OF THE PROTECTS-SE APPLICATION

Alessandro Rodolico¹, Pierfelice Cutrufelli*², Antonio Di Francesco², Davide Conti², Irene Bighelli¹, Pasquale Caponnetto², Carmen Concerto², Rosaria Furnari², Gabriele Leotta³, Ludovico Mineo², Katharina Müller¹, Spyridon Sifas¹, Antonino Petralia², Stefan Leucht¹, Maria Salvina Signorelli²

¹Technical University of Munich, ²University of Catania, ³Darwin Technologies

Background: The importance of patient-centered care and shared decision-making in treating schizophrenia spectrum disorders is widely recognized, yet its effective implementation continues to be a significant challenge, particularly regarding the management of side effects. To address this issue, we developed the Patients Reported Outcomes Technological Evidence-Centered Tool for Schizophrenia - Side Effects (PROTECTS-SE), a novel tool with an

interactive user interface, designed for clinicians and patients. This tool provides access to evidence-validated information regarding side effects management and advanced decision-support algorithms, thereby streamlining the process of making and understanding medical decisions. The platform incorporates the GASS scale to systematically collect data on experienced side effects from the patient. Based on this data and following medical guidelines, the platform generates evidence-based solution proposals for subsequent psychiatrist-patient discussion. The application functions on a secure HIPAA-compliant platform to ensure the confidentiality and safety of patient information.

Methods: This study used a qualitative research design, analyzing semi-structured interviews with patients and healthcare providers. Themes were extracted, systematically analyzed, and organized in a framework to evaluate the impact of the PROTECTS-SE application on crucial usability issues: ease of use, clarity of data presentation, fulfillment of user needs, enhancement of patient-physician collaboration, improvement in adherence to treatment, patient sense of empowerment, and utility for the clinician.

Results: The preliminary findings indicate that PROTECTS-SE may facilitate shared decision-making process between clinicians and patients, effectively addressing multiple intrinsic barriers to patient empowerment. This includes perceived improvements in patient-clinician communication, trust, and overall patient engagement in their healthcare. Efficiency in the clinical process decision for the physician and increasing patients' sense of participation in their care were highlighted as strengths during the interviews. However, some areas require further development, specifically regarding data representation, which is potentially overloaded and complex for some users.

Discussion: The results highlight the potential utility of PROTECTS-SE in enhancing patient-centered care in schizophrenia spectrum disorders. The application integrates real-time data analytics, evidence-based guidelines, and a user-friendly interface, offering a comprehensive solution to the difficulties involved in shared decision-making and helping to address the complexities of antipsychotics side-effects management. Integrating evidence-based medicine with a patient-focused approach, tools like PROTECTS-SE could improve patient empowerment and clinician proficiency. Future studies should focus on assessing this application's real-world performance and efficacy.

F222. ENHANCING EVERYDAY FUNCTIONING IN LONG-TERM PSYCHIATRIC CLINICAL CARE: A PRAGMATIC RANDOMIZED CONTROLLED PILOT TRIAL INTO THE ACCEPTABILITY AND FEASIBILITY OF COGNITIVE REMEDIATION AND TDCS FOR PEOPLE WITH SEVERE MENTAL ILLNESS

Anika Poppe¹, Leonie Bais², Nienke Buist^{*1}, Daniëlle van Duin³, Branislava Curčić-Blake⁴, Marieke (Gerdina) Pijnenborg¹, Lisette van der Meer¹

¹University of Groningen, ²Lentis Center for Mental Health Care, ³Phrenos Center of Expertise, ⁴BSCS Cognitive Neuroscience, University Medical Center Groningen,

Background: Cognitive impairments are commonly experienced by individuals with severe mental illness (SMI) and predict problems in everyday life. This pragmatic, randomized, controlled, pilot trial explored the acceptability, feasibility, and preliminary effects of cognitive remediation (CR) combined with transcranial direct current stimulation (tDCS) for cognitive and everyday functioning in individuals with SMI in long-term psychiatric clinical care.

Methods: Twenty-four individuals with SMI were randomized to either CR+active tDCS (n = 13) or CR+sham tDCS (n = 13) over 32 sessions (16 weeks). Acceptability was evaluated in

semi-structured interviews. Cognitive and everyday functioning were evaluated at baseline, post-16 week waiting period, post-intervention, and 6-months post-intervention.

Results: Overall, participants were positive about the training. Over 60% of participants completed at least 20 sessions, exceeding predefined feasibility criteria. CR appeared to yield personal benefits to participants, significant improvements in cognitive tests post-intervention and at follow-up and improved self-reported negative symptoms at follow-up. Observed everyday functioning and cognition, and subjective cognitive complaints did not change following CR.

Discussion: This study concludes that CR is an acceptable and feasible intervention for individuals with SMI in long-term psychiatric clinical care. The addition of tDCS requires further investigation to ascertain its potential benefits. Currently, a larger randomized controlled trial following this pilot trial is set up.

F223. DON'T STOP ME NOW: A SPORT-BASED INTERVENTION TO PROMOTE SOCIAL INTEGRATION IN EARLY PSYCHOSIS – A STUDY PROTOCOL

Akke-Marij Ariesen*¹, Laura Steenhuis², Susanne Spoelman³, Nynke Boonstra⁴, Claudia Emck⁵, Clement Waarheid³, Jooske van Busschbach⁶, Marieke Pijnenborg²

¹University of Groningen, ²University of Groningen /Mental Health Institution GGZ Drenthe, ³Mental Health Institution GGZ Drenthe, ⁴Mental Health Institution KieN-VIP / NHL Stenden University of Applied Sciences/University Medical Center Utrecht, ⁵Vrije Universiteit Amsterdam, ⁶Windesheim University of Applied Sciences /University of Groningen, University Medical Center Groningen

Background: Already in the early phase of psychosis, individuals often experience problems with participating in society. After having experienced a psychotic episode, people frequently stop working or studying, participate less in leisure activities, and lose contact with their peers. Several factors, including negative symptoms, (self)stigma, and social exclusion, may contribute to this reduced social participation. Additionally, physical health problems, such as metabolic risk factors, are often already present in the early phase of psychosis, and may increase due to inactive behaviour. In order to prevent a progressive worsening of social isolation it is essential to timely intervene. This study presents the protocol of a research project that aims to examine the effectiveness of a sport-based intervention developed to promote the social (re)integration of individuals in the early phase of psychosis.

Methods: 24 individuals, between 18-65 years of age, within the first five years of diagnosis of a psychotic disorder, and currently in care at one of four participating mental health facilities in the Netherlands will be included. In terms of content and design, the intervention was partly based on the outcomes of a qualitative needs and barriers study conducted in the target population, and was improved on the basis of a feasibility study. The intervention includes a minimum of 22 sessions, in a 24-26 week time-frame, and consists of three phases: phase 1 – individual psychomotor therapy (focused on goal setting and regaining trust in one's physical capabilities); phase 2 – group sessions combining psychomotor therapy and sports (focused on social connectedness); phase 3 – joining a self-selected sports club or activity in the local community, under guidance of a community sport coach (focused on social integration). The intervention is tailored to an individual's personal needs and goals. The effectiveness of the intervention will be tested by means of a multiple baseline single-case design (n = 1). Measurement instruments include interviews, questionnaires, accelerometers (ActiGraphs), and experience sampling.

Results: The primary outcome is the level of social integration as determined by 1) self-reported daily and overall changes in the social network, level of social functioning, and experienced social inclusion, and 2) whether participants have successfully commenced and continued sports activities in their local community. Additionally, changes in daily and overall levels of self-stigma, physical activity, self-esteem, and negative symptoms are assessed. Improvements in these outcome measures post-intervention and at 6-month follow-up mark the (expected) effectiveness of the intervention. At follow-up, the secondary outcome is to explore the lived experiences of social participation after partaking in the intervention in terms of employment, studies, leisure activities, and the fulfilment of social roles.

Discussion: By building a bridge between sport-related activities in a mental health care setting, and sport activities in the local community, the proposed intervention aims to contribute to the social participation and social (re)integration of individuals in the early phase of psychosis.

F224. INTEGRATING A MOBILE APP FOR SHARED DECISION-MAKING IN TREATMENT FOR PSYCHOTIC DISORDERS: PRELIMINARY FINDINGS AND IMPLICATIONS

Mari Skoge*¹, Sofie Ragnhild Aminoff¹, Gina Engen Bryhni², Elizabeth Ann Barrett¹, Erlend Mork¹, Kristine Kling¹, Kari Jorunn Kværner³, Ingrid Melle⁴, Carmen Elisabeth Simonsen¹, Linn Nathalie Støme³, Tor Gunnar Værnes¹, Kristin Lie Romm¹

¹Early Intervention in Psychosis Advisory Unit for South East Norway, Clinic of Mental Health and Addiction, Oslo University Hospital, ²Sanderud Hospital, Psychiatric Health Services Division, Innlandet Hospital Trust, Norway, ³Centre for Connected Care, Clinic of Mental Health and Addiction, Oslo University Hospital, ⁴Institute of Clinical Medicine, University of Oslo,

Background: Strengthening shared decision-making (SDM) in mental healthcare can improve the precision and quality of treatment. Patients with psychotic disorders may have problems expressing their needs, due to symptomatology and contextual factors. Digital tools, such as mobile applications (apps), may act as facilitators for SDM. While the literature is promising, there is a need for a deeper understanding about the integration of apps into treatment as usual for psychotic disorders, from both patient and clinician perspectives. The aim of this study is to investigate feasibility and acceptability of integrating an app for SDM, iTandem, in treatment for psychotic disorders. iTandem is designed to be flexible, with a personalized interface. It contains eight modules: sleep, medication, recovery, mood, psychosis, activity, substance use, and feedback on therapy. This paper comprises an iteration in the development and investigation of iTandem, and the preliminary findings guide the future work on clinical applications of digital tools.

Methods: Eight clinicians and nine patients from inpatient and outpatient units at Innlandet Hospital Trust, a mainly rural area of Norway, were recruited. Patients were recruited consecutively, were above 18 years old and currently undergoing treatment for psychotic disorders. Patients and clinicians jointly selected app modules to focus the treatment during a six-week pilot trial. Data from the app were securely transferred to a report accessed by clinicians, and discussed during sessions. The report was used to monitor symptoms and recovery process, and to guide interventions according to the input. A mixed methods approach was used for data analysis. Quantitative data was collected with pre- and post-intervention questionnaires, including items on patient demographics (age, gender, time in treatment,

distance to hospital), and the System Usability Scale (SUS). Data were analysed in SPSS Statistics 29. Qualitative data were collected from individual in-depth semi-structured post-intervention interviews and analysed in NVivo 14, using systematic text condensation.

Results: Preliminary findings suggest positive user experiences. Mean SUS scores for patients and clinicians were 75 and 82, respectively. Some of the preliminary themes emerging from the qualitative analysis were shared by both groups as iTandem: 1) enabled an overview of problem areas and their connections, 2) served as an aid for memory and structure, and 3) facilitated broader discussions of the patients' needs. Patients underlined the importance of clinician engagement, and some experienced the need of social support to be able to actively take part in the intervention. Clinicians found it challenging to introduce and implement a digital tool into treatment as usual, as it felt unfamiliar. Furthermore, they expressed concerns about patient vulnerability, as well as organisational factors, as barriers to implementation.

Discussion: Patients and clinicians recognize the potential of a digital tool for SDM, emphasizing how it increased involvement and personalization according to individual needs. However, clinicians seem to have concerns regarding this patient group's level of functioning, which might act as a barrier to offer such tools. The findings indicate that there are stronger predictors for successful integration than symptom severity. Variables such as tech-savviness, digital habits and motivation may be of great impact. In addition, clinicians experienced organisational factors as obstacles. Implementing digital tools in mental healthcare, needs to be followed by careful considerations to service design and integration into the routines of consultation.

F225. METACOGNITIVE TRAINING FOR AUDITORY HALLUCINATIONS: EFFICACY OF AN ONLINE-BASED SELF-HELP INTERVENTION

Laura Fässler*¹, Steffen Moritz², Malek Bajbouj³, Christine Knaevelsrud⁴, Kerem Boege³

¹Charité, University Medicine Berlin, ²University Medical Center Hamburg, ³Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin, ⁴Freie Universität Berlin, Institute for Psychology

Background: Auditory hallucinations (AH) are considered as a hallmark characteristic of schizophrenia spectrum disorders (SSD). However, AH can be assumed on a continuum from ordinary to pathological perceptions. A broad range of affected persons with mental disorders and SSD experience their AH as severely distressing and functionally restrictive. In recent years, psychotherapeutic approaches have been established as complementary to pharmacological interventions for SSD. Previous research highlights the empirical evidence for the effectiveness of metacognitive approaches for positive symptoms in SSD. However, there remains insufficient evidence for effective, cost-efficient, and accepted interventions for AH that needs to be investigated further. Moreover, there is still an incisive lack in the psychological care of SSD, primarily caused by several structural flaws and shortcomings in treatment accessibility. To minimize the research and care gap in the psychotherapeutic treatment of persons with SSD and AH, we aimed to investigate the efficacy of an online-based self-help intervention for AH that is primarily based on metacognitive training (MCT) according to Moritz and Woodward (2007).

Methods: For the first time worldwide, we intended to examine an adaptive and particularly low-threshold self-help manual for distressing AH based on MCT. The recruitment took place at the Department of Psychiatry and Psychotherapy of the University Medical Centre Hamburg-Eppendorf (UKE) in cooperation with the Department of Psychiatry and Psychotherapy at

Charité – University Medicine Berlin, Campus Benjamin Franklin, and various support groups and online platforms. The project is implemented as a randomized controlled trial (RCT) with self-reported assessments at baseline (T0) and post-intervention (T1) after six weeks. Participants were randomly allocated to the intervention or waitlist-control group. The intervention is carried out online (PDF file) with various worksheets and interactive elements that are primarily based on MCT. To date, we randomized N = 74 persons with AH. The data collection process will end in December 2023.

Results: As the primary outcome, we will analyze the frequency and distress of AH measured by the hallucination subscale of the Psychotic Symptom Rating Scale (PSYRATS). The primary analysis will be calculated using an analysis of covariance (ANCOVA) model with group differences from T0 to T1 as the dependent variable. We will include the baseline data of AH and the medication dosage as covariates to increase the power of the results. Furthermore, we will conduct an intention-to-treat (ITT) analysis with multiple imputation methods by chained equations to consider missing data. Additionally, we will only include complete cases with baseline and post data in a per-protocol (PP) analysis. To examine the subjective satisfaction with the intervention, we will report descriptive results to analyze satisfaction. Since the data collection will end in December 2023, we will present new and unpublished data. Preliminary analyses revealed no significant differences between the intervention and control group ($F(3, 39) = 4.67, p = .29, \eta^2_{\text{partial}} = .03$). However, the satisfaction with the intervention indicated high subjective reported rates that need to be further evaluated.

Discussion: Due to still existing and tremendous shortcomings in the psychotherapeutic supply of SSD, it is crucial to investigate low-threshold complementary interventions to conventional approaches further. The proposed study aims to examine a particular straightforward treatment for AH within a self-help manual based on MCT. Due to its low threshold and cost-effective implementation, the intervention is suitable for conduct in low- and middle-income countries, independent of language or residence. In this regard, we aspire to reveal relevant insights into a novel psychotherapeutic approach that addresses a clinical population that frequently experiences personal and structural marginalization and stigmatization.

F226. COMPARISON OF FEASIBILITY, SAFETY, AND EFFICACY OF TELEHEALTH-BASED VS. IN-PERSON AEROBIC EXERCISE TO IMPROVE NEUROCOGNITION AND DAILY FUNCTIONING IN INDIVIDUALS WITH SCHIZOPHRENIA

David Kimhy*¹, Luz H. Ospina¹, Melanie Wall², Dan Altshuler², L. Fredrik Jarskog³, Jacob Ballon⁴, Joseph McEvoy⁵, Matthew Bartels⁶, Marianne Goodman¹, Sloane Miller¹, T. Scott Stroup²

¹*Icahn School of Medicine at Mount Sinai*, ²*Vagelos College of Physicians and Surgeons, Columbia University*, ³*University of North Carolina, Chapel Hill*, ⁴*Stanford University*, ⁵*Augusta University Health*, ⁶*Albert Einstein College of Medicine*

Background: People with schizophrenia display significant deficits in neurocognition that have been identified as key predictors of poor daily functioning and disability. Previous reports have indicated that aerobic exercise (AE) training can enhance neurocognitive functioning in this population, with training traditionally having been administered via in-person AE sessions. However, following the advent of the COVID-19 pandemic and the subsequent shelter-in-place orders, many clinics transitioned their clinical services to telehealth-based delivery. Yet, there

is scarce information about the feasibility, safety, and efficacy of telehealth-based AE in people with schizophrenia.

Methods: Here we describe outcomes from a single-blind, randomized clinical trial examining the impact of 12-week AE vs. a stretching-and-toning control intervention on neurocognition and daily functioning in people with schizophrenia. Following the onset of the COVID-19 pandemic, the trial transitioned from in-person format to remote AE intervention via telehealth, with training frequency and duration, along with research procedures, remaining identical. The in-person AE involved trainer-led use of AE equipment (e.g., treadmill, elliptical machine, stationary bikes) and active-play video games (e.g., Xbox Kinect). Participants in the telehealth-based AE exercised at home (e.g., jumping jacks, jogging in place) via a 2-way video link with a trainer using iPads. We compared the feasibility, safety, and efficacy of trainer-led AE training among participants in the in-person (pre-COVID-19) vs. telehealth AE phases (post-COVID-19 onset).

Results: Compared to in-person AE, telehealth-based AE was associated with significantly lower drop-out rate (7/23 vs. 0/14, respectively), though also lower number of sessions attended, total time spent exercising, and proportion of session-time exercising at or above target intensity. There were no serious adverse events associated with either AE formats. Similarly, there were no significant group differences in the proportion of patients with any AE-related minor or moderate adverse events (e.g., joint pain, muscle strain, blisters, dyspnea). Employing longitudinal mixed-effect analyses, there were no significant differences between the in-person vs. telehealth groups regarding changes in aerobic fitness (VO₂max), neurocognition (MATRICS Consensus Cognitive Battery; MCCB), and functioning (Schizophrenia Cognition Rating Scale (SCoRS) and Specific Levels of Functioning Scale (SLOF)). However, the in-person AE group displayed significantly greater improvement in the SLOF Interpersonal domain (ES=.79, p=.03).

Discussion: Our preliminary findings suggest telehealth-based delivery of AE is feasible, safe, and results in comparable cognitive and functional benefits, except for aspects of social functioning. We discuss the implications of these findings, along with a review of the challenges associated with delivery of telehealth-based AE.

F227. NEURAL CORRELATES AND NEURAL STIMULATION OF SENSORIMOTOR TEMPORAL RECALIBRATION MECHANISMS IN SCHIZOPHRENIA SPECTRUM DISORDERS AND HEALTHY SUBJECTS

Christina Schmitter^{*1}, Konstantin Kufer¹, Olaf Steinsträter¹, Jens Sommer¹, Tilo Kircher¹, Benjamin Straube¹

¹Philipps-University

Christina Schmitter

Background: Core symptoms in patients with schizophrenia spectrum disorders (SSD), such as hallucinations or ego-disturbances, have been associated with a failure of internal forward models to adequately predict the sensory outcomes of self-generated actions. Importantly, due to dynamically changing environmental conditions, forward models must also be capable of flexibly recalibrating their predictions, for example, to account for additional delays between action and outcome. This mechanism is known as sensorimotor temporal recalibration.

Methods: In two studies with healthy subjects, we investigated (1) the neural correlates of sensorimotor temporal recalibration using fMRI (N = 25), and whether (2) transcranial direct current stimulation (tDCS) can be used to facilitate behavioral recalibration effects (N = 22).

In a third study, we assessed whether (3) sensorimotor temporal recalibration effects are reduced in patients with SSD (N = 22) compared to matched healthy controls (N = 20), and whether tDCS can facilitate recalibration in both groups. In all studies, subjects were repeatedly exposed to delays between actively elicited or passively performed button press movements and auditory or visual sensory outcomes. The effects of this procedure on temporal perception were assessed with a delay detection task.

Results: Results showed that (1) recalibration was related to clusters of activation in left hippocampus [$t = 4.28$, nr. voxels = 120, peak: $x = -36$, $y = -10$, $z = -18$] and in the bilateral cerebellum [$t = 4.35$, nr. voxels = 1716, peak: $x = -10$, $y = -46$, $z = -16$]. (3) Patients with SSD exhibited no difference in behavioral temporal recalibration effects compared to healthy controls [$F(1,40) = .267$, $p = .608$, $\eta^2 = .007$], and, compared to sham stimulation, anodal tDCS of the cerebellum facilitated temporal recalibration (2) in healthy subjects [$t(21) = 3.090$, $p = .006$, $d = .659$] and (3) across both patients and healthy controls [$t(41) = 2.472$, $p = .009$, $d = .381$].

Discussion: These findings show for the first time that the hippocampus plays an important role in temporal recalibration, presumably related to the updating and encoding of the newly learned temporal relationship between movements and their sensory outcomes. They further indicate that sensorimotor temporal recalibration mechanisms may be preserved in SSD and highlight the importance of the cerebellum in both patients and healthy subjects for this process. Additionally, the results suggest that cerebellar tDCS could be a promising tool for addressing deficits in action-outcome monitoring and related adaptive sensorimotor functions in SSD.

F228. EFFECTS OF VIRTUAL REALITY BASED SOCIAL SKILLS TRAINING ON SOCIAL COGNITION AND SELF-DISTURBANCES IN INDIVIDUALS WITH SCHIZOPHRENIA

Hyeon-Seung Lee^{*1}, Michael Sangimino¹, Catherine Chang¹, Nilanjan Sarkar¹, Sohee Park¹

¹*Vanderbilt University*

Background: Social impairment and self-disturbances are core features of schizophrenia that contribute to long-term disability and poor outcome. Although there is good evidence to link self-disturbance and social impairments, they are not typically targeted together for intervention. Importantly, the potential impact of social skills training on bodily self-disturbance has not been studied. We implemented a simulation-based social skills game, which focuses on rehearsing interpersonal interactions that might unfold under familiar scenarios in VR rather than explicitly teaching social cognitive skills. We expected to observe improvements in clinical symptoms, social impairments and self-disturbance in individuals with schizophrenia (SZ).

Methods: In a cross-over design, SZ participated in 8 sessions of novel social skills training program and 8 sessions of a control condition in which they played a non-social VR game. The order of the two conditions was counterbalanced across participants. The social skills training game in VR involved achieving interpersonal ‘missions’ with an avatar under multiple familiar scenarios (e.g. bus stop, shop). They worked through these social missions of varying difficulty levels while receiving feedback. The control condition consisted of 8 sessions of commercial, nonsocial games. Clinical symptoms assessment, social cognitive tests, computerized mapping of embodied emotion (self disturbance assessment) and resting state functional brain scans were conducted pre- and post- training and also at pre- and post - control condition.

Results: After VR training, there were significant improvements in positive and negative symptoms, social functioning and self-disturbance. Across a range of emotions, awareness and

localization of bodily sensations improved after training. Awareness of embodied emotions was associated with the integrity of the frontoparietal social brain networks. In addition, participants reported gaining confidence in social interactions.

Discussion: Simulating and rehearsing interpersonal interactions in VR improved clinical symptoms, social functioning, emotion embodiment and the integrity of the frontoparietal network of SZ. These results indicate the importance of targeting self-disturbance and social impairment in concert in the context of intervention. Note that there was no explicit training or teaching of specific social skills or rules. These results suggest that simulation and rehearsal of making small talk with a stranger in a low-stakes scenario may be an effective strategy for improving social functioning.

F229. MODERATING EFFECTS OF CLINICAL AND DEMOGRAPHIC CHARACTERISTICS ON VIRTUAL REALITY CBT FOR PARANOIA: FOR WHOM DOES IT WORK?

Maureen Berkhof¹, Elise van der Stouwe¹, Roos Pot-Kolder², Mark Van der Gaag³, Wim Veling¹, Chris Geraets*¹

¹University Medical Center Groningen, ²The University of Melbourne, ³VU University Amsterdam Clinical Psychology

Background: VR-CBT can be effective in treating paranoia and anxiety in people with a psychotic disorder. However, it is unknown who benefits most from VR-CBT. The aim of this study is to investigate moderating factors that may influence the effectiveness of VR-CBT.

Methods: In total, 95 patients with a psychotic disorder and paranoid ideations were included from a multicenter RCT. Participants were assigned to VR-CBT or treatment as usual (TAU). The VR-CBT group received 16 sessions of individual treatment. Moderator analyses were performed to explore the influence of demographic (age, gender, and education) and clinical characteristics (illness duration, paranoia, anxiety, depression, safety behaviour, self-esteem, and social functioning) on post-treatment effects of paranoia and anxiety as measured with questionnaires as well as the experience sampling method (ESM).

Results: Higher levels of safety behaviour before the treatment resulted in greater benefits of VR-CBT on paranoid ideation and ESM paranoia. Higher age was associated with greater benefits of VR-CBT on social anxiety, but not paranoia outcomes. There was no consistent evidence of moderation by any of the other sociodemographic or clinical variables for paranoid ideation and social anxiety.

Discussion: The findings suggest that a diverse spectrum of patients, with different backgrounds and symptom severity can benefit from VR-CBT. VR-CBT can be recommended to a broad spectrum of patients with a psychotic disorder, and particularly those with high levels of safety behaviors, including severe avoidance.

F230. METABOLIC SYNDROME IN PEOPLE TREATED WITH ANTIPSYCHOTICS (RISKMET): A MULTIMETHOD STUDY PROTOCOL INVESTIGATING GENETIC, BEHAVIOURAL, AND ENVIRONMENTAL RISK FACTORS

Giovanni de Girolamo*¹, RISKMET Consortium¹

¹IRCCS St. John of God Clinical Research Centre

Background: Many individuals who suffer from mental disorders in both childhood and adulthood (1) and are undergoing antipsychotic (AP) treatment are at significant risk of physical comorbidities. Second-generation antipsychotics (SGAs) are commonly prescribed to manage symptoms primarily linked with schizophrenia spectrum disorders (SSD), bipolar disorder (BD) and other mental health conditions in paediatric populations, such as disruptive behaviour disorders and irritability or aggression in the context of neurodevelopmental disorders. The rise in the number of associated medical conditions in these patients can be attributed to several factors: (a) pathogenetic and biological factors (e.g., metabolic or immune system disorders, genetic susceptibility); (b) unhealthy behaviours, including poor diet, smoking, sleep disturbances and low levels of physical activity; (c) low utilisation of healthcare services, often due to stigma; and (d) negative consequences of common medications (e.g., side effects). The most frequent medical comorbidities in psychiatric patients include type-2 diabetes, cardiovascular disease (CVD), and endocrine disorders, such as metabolic syndrome (MetS). MetS is indicative of a preclinical state characterised by a cluster of risk factors for CVD and type-2 diabetes mellitus, which tend to cooccur in individuals with MetS. To meet MetS diagnostic criteria individuals have to satisfy at least three of the following five diagnostic criteria: (1) waist circumference GREATER THAN 102 cm (M); GREATER THAN 88 cm (F); (2) fasting glucose GREATER THAN 100 mg/dL (or antidiabetic treatment); (3) blood pressure GREATER THAN 130/85 mmHg (or treatment with antihypertensive agents); (4) triglycerides GREATER THAN 150 mg/dL; and (5) HDL cholesterol LESS THAN 40 mg/dL (M); LESS THAN 50 mg/dL (F). The prevalence of MetS is markedly high among patients with SSD, BD and NDD: notably, many of those patients underwent prolonged treatment with APs, often in combination.

Methods: The RISKMet project has three objectives, each with distinct research phases.

1.The first objective is to ascertain risk factors for MetS in patients treated with APs, particularly SGAs. The study will utilize a case–control design, with two subject groups recruited from both adult and paediatric populations: patients diagnosed with MetS (cases, MetS+) and patients without MetS (controls, MetS-), who will be matched for sex, age group, disease severity, using Clinical Global Impression (CGI) (30), diagnosis and AP treatment. To identify risk factors for MetS, a thorough assessment of familiarity with MetS will be carried out, together with an assessment of psychological and functional risk factors (e.g., behavioural characteristics, disability, quality of life, diet, sleep quality).

2.The second objective is to thoroughly assess the present health status of patients who have been given SGAs and either have or do not have symptoms of MetS. A large set of biomarkers will be investigated, notably: Ab-Tg, Ab-TPO, Adiponectin, ALT, Apo A1, Apo B, AST, C-Peptide, Fetuin-A , Glycoprotein, Ft4, GGT, Glycemia, HbA1c, HDL, Insulin, LDL, Leptin, Lp (a), Oral Glucose Tolerance Test (OGTT), Protein Glycation Derangements, P-Selectin Glycoprotein, Total cholesterol, Triglycerides, TSH, Vitamin D, Zinc-Alpha2-Glycoprotein, Zonulin.

3.The third objective is to prospectively investigate behavioural patterns linked to MetS, including PA, sleep, and dietary habits. PA and sleep will be tracked with a wrist-worn accelerometer, while eating behaviours (such as daily caloric intake, binge eating episodes, night-time eating, cravings, fast food consumption, and satiety) will be monitored through a mobile-based ESM.

Results: The objectives of the RISKMet project are multipronged, aiming to explore MetS from clinical, biological, and behavioural perspectives. This multifaceted approach is crucial for comprehensively understanding the risk factors, characteristics, and behavioural patterns

associated with MetS in AP-treated patients. By focusing on high-risk populations, the project seeks not only to identify risk factors but also to intervene and prevent the progression of this condition, which is a significant contributor to morbidity and mortality in this population. The project is a two-year multicentre, multiphase study that will recruit diverse patient populations from different locations and age groups, including adults and children. This comprehensive approach will have 2 evaluation time points (T0 and T3) and will involve multiple study sites to enhance robustness and generalizability. The study will include individuals with MetS (MetS+), control groups of individuals without MetS (MetS-), and, in the paediatric population, their parents. This comprehensive approach will explore familial genetic susceptibility for MetS and consider potential confounding factors by recruiting healthy controls, thereby enabling investigation of horizontal familial liability for MetS.

Discussion: There is growing attention being paid to devising preventive measures that reduce the risk of comorbidities associated with SGA usage. This study will provide helpful information to improve the clinical use of SGA, modifying the risk/benefit ratio in the direction of more benefits and fewer risks.

F231. ECOLOGICAL MONITORING OF PHYSICAL ACTIVITY, EMOTIONS AND DAILY LIFE ACTIVITIES IN SCHIZOPHRENIA: THE DIAPASON STUDY

Giovanni de Girolamo*¹, DIAPASON Consortium²

¹*IRCCS St. John of God Clinical Research Centre*, ²*DIAPASON Consortium Italy*

Giovanni de Girolamo

Background: Patients with schizophrenia spectrum disorders (SSD) often show marked impairments in daily time functioning, with adverse consequences for prognosis, number of medical comorbidities and mortality rates. However, despite the importance assigned to the daily time use of patients with SSD, most studies have mainly collected self-reported retrospective data. The use of retrospective self-reports in patients with severe mental disorders is prone to errors related to recall bias and to potentially impaired cognitive capacities. The integration of innovative methodologies (eg, ecological momentary assessment (EMA)) and wearable devices like accelerometer-based biosensors in research and clinical practice with individuals with SSD is promising. These tools reduce biases, provide longitudinal, objective and time-resolved ecologically valid data (ie, a fine-grained picture of patients' experiences in their natural contexts) and capture the variability over time and the dynamic patterns of reactivity to the environment. We performed a cohort study aimed at investigating: (1) the differences in PA, daily activities and emotions between patients with SSD and healthy controls (HC); (2) the strength of the association between these variables and clinical features among patients with SSD.

Methods: Ninety-nine patients with SSD (53 residential patients, 46 outpatients) and 111 matched HC were assessed for several clinical variables, and levels of functioning by means of standardised clinical measures. Self-reported daily activities and emotions were assessed with a smartphone application for ecological momentary assessment (EMA), and PA levels were assessed with a wearable accelerometer for 7 consecutive days. Sociodemographic, physical and clinical assessments. The 24-item Brief Psychiatric Rating Scale (BPRS) was used to assess psychopathology. Negative symptoms severity was assessed with the Brief Negative Symptom Scale (BNSS). The 43-item Specific Levels of Functioning Scale (SLOF) was used for the assessment of levels of functioning. The WHO Disability Assessment Schedule 2.0

(WHODAS 2.0) was used for the assessment of disability level. Self-reported daily time use (i.e., daily activities) and emotions were prospectively assessed with a brief questionnaire on a smartphone-based application for EMA, developed ad hoc for the project. The mobile application included three sections: current activities, social contacts and emotions. Notifications occurred 8 times a day, from 08:00 a.m. to 12:00 p.m., for seven consecutive days. PA was monitored using the wearable accelerometer-based biosensor ActiGraph GT9X Link worn on the non-dominant wrist for seven consecutive days (the same days for the EMA monitoring). Data were summarised using mean and SD, median and IQR for quantitative variables, counts and percentages for qualitative ones. Comparisons of sociodemographic and clinical variables across residential patients, outpatients and control participants were carried out through the χ^2 test for categorical variables and the analysis of variance test for continuous variables.

Results: Patients with SSD, especially those living in residential facilities, spent more time being sedentary, and self-reported more sedentary and self-care activities, experiencing higher levels of negative emotions compared with HC. Moreover, higher functioning levels among patients were associated with more time spent in moderate-to-vigorous activity. The three groups significantly differed for all activity levels (both min/day and %), with healthy controls showing higher PA levels than the two patient groups, even controlling for daily % of wearing time, the number of cigarettes per day and season. Time spent in different PA levels are expressed in mean min/day. Sedentary time was significantly higher in residential patients compared with both outpatients and healthy controls (respectively RR 1.16 (95% CI 1.10 to 1.23); $p < 0.001$; RR 1.15 (95% CI 1.15 to 1.28); $p < 0.001$). Outpatients and healthy controls did not differ from each other for time spent sedentary (RR 1.04 (95% CI 0.99 to 1.10); $p=0.10$). When expressed in relative terms, the sedentary time represented 48% 51% of total wake time in patient groups, which was also a significantly larger fraction compared with healthy controls (i.e., 40%). MVPA was significantly higher in healthy controls (91.3 mean min/day) than in both outpatients (64.1 mean min/day) and residential patients (44.6 mean min/day). Outpatients spent a significantly larger fraction of time doing MVPA per day compared with residential patients (RR 0.70 (95% CI 0.53 to 0.92); $p=0.01$) and lower time when compared with healthy controls (RR 0.70 (95% CI 0.55 to 0.90); $p=0.004$).

Discussion: Sedentary behaviour and negative emotions are particularly critical among patients with SSD and are associated with more impaired clinical outcomes. Mobile-EMA and wearable sensors are useful for monitoring the daily life of patients with SSD and the level of PA. This population needs to be targeted with specific rehabilitative programmes aimed at improving their commitment to structured daily activities.

F232. SCHIZOTYPY EFFECTS ON (ANTERIOR) HIPPOCAMPUS VOLUME AND BLOOD FLOW IN HEALTHY SUBJECTS ARE MODULATED BY AUTISTIC TRAITS

Ahmad Abu-Akel^{*1}, Tina Meller², Ulrika Evermann³, Julia-Katharina Pfarr², Andrea Federspiel⁴, Sebastian Walther⁵, Sarah Grezellschak², Igor Nenadić²

¹University of Haifa, ²University of Marburg, ³Philipps-University Marburg, ⁴University Hospital of Psychiatry, ⁵University Hospital of Psychiatry and Psychotherapy Bern,

Background: Recent studies in schizotypy (a well-validated psychosis risk phenotype), clinical high-risk, and first episode schizophrenia have reported changes in anterior

hippocampus volumes, with putative progression to posterior hippocampus areas during disease progression. This has led to the hypothesis that the anterior hippocampus might be an “epicenter” in developing schizophrenia. However, there is also substantial overlap with other pathologies for this brain structure and accounting for this overlap or co-morbidities (e.g., autism spectrum disorders, affective disorders) is mostly lacking. Given the limitations of classical case-control designs, new approaches are needed to identify biological underpinnings of disease spectra and their interaction.

Methods: They study assessed autistic and schizotypal traits—as models of subclinical expressions of disease phenotypes—and examined their association with volumes and regional cerebral blood flow (rCBF) of bilateral anterior, mid- and posterior hippocampus segments from structural MRI scans in 318 and arterial spin labelling (ASL) in 346 nonclinical subjects, which overlapped with the structural imaging sample (N = 298). The association of hippocampal volume and rCBF with AQ, schizotypy and their interaction were performed using MANCOVA, while accounting for age, sex, IQ, depressive symptoms, and total intracranial volume. Response surface methodology was used to estimate the response surface pattern of the association of interacting autistic and schizotypal dimensions with level of hippocampal volume/rCBF.

Results: Analyses reveal that the association of positive schizotypy (a proxy of psychosis proneness) with hippocampal subfield volume variation is modulated by both AQ social skills (anterior, mid- and posterior bilaterally) as well as AQ imagination difficulties (anterior bilaterally). Moreover, results show that AQ attention switching (increased focus of attention) is associated with right hippocampal head (anterior) rCBF, and that the association of positive schizotypy with hippocampal tail (posterior) rCBF is associated with AQ attention to detail, bilaterally.

Discussion: The study’s findings provide empirical evidence for the modulation of hippocampal subfield structure and function through the interaction of subclinical schizotypal and autistic traits. Intriguingly, while positive schizotypy is associated with variation in both hippocampal volume and rCBF, its association with volume is modulated by autistic socio-cognitive traits, while its association with rCBF is with autistic attentional traits. Taken together, these results make the case for considering the synergistic impact of different (subclinical) disease spectra on transdiagnostic biological parameters in psychiatry.

F233. PSYCHOMETRIC PROPERTIES OF RADAR (RETROSPECTIVE ASSESSMENT FOR DEFINITIVE ANTIPSYCHOTIC RESPONSE) SCALE

Pavithra Jayasankar*¹, Vanteemar Sreeraj¹, Suhas Satish¹, Ranjitha R¹, Logesh K¹, Debanjan Bhattacharjee², Naren Rao³, Vijay Kumar¹, Shivarama Varambally¹, Ganesan Venkatasubramanian¹

¹National Institute of Mental Health and Neurosciences, ²Consultant Psychiatrist, ³Manoshanti Clinic,

Background: The anti-psychotic drugs are the main stay of treatment in psychotic disorders including schizophrenia. The response to anti-psychotics is heterogenous as is the symptom manifestation, course, and outcome of schizophrenia. Predicting the factors determining the response to an antipsychotic is an important step in ahead in personalizing the treatment. Most often, course of the illness is not considered while assessing the anti-psychotic response. There are no standard tools that can evaluate the long-term response to a given antipsychotic. Hence

a scale for assessment of definitive response to antipsychotic was developed. Development of the scale:

Based on literature review and expert group discussions RADAR was developed to assess response to antipsychotic over a longitudinal course of illness considering multiple factors that influence clinical improvement. It has two parts with a total of 15 items. Higher score represents the strength of definitive response to a given anti-psychotic.

Methods: This study aims to assess the concurrent validity, inter rater reliability and internal consistency of RADAR scale. Two out of three raters assessed the antipsychotic response using RADAR scale separately for 36 anti-psychotic trials. Spearman correlation was used to assess concurrent validity. Intra-class coefficient and Cronbach's alpha was calculated to measure inter-rater reliability and internal consistency respectively.

Results: There was a significant negative correlation between RADAR total score and Clinical Global Impression - Improvement (CGI – I) ($r = 0.68$, $p < 0.001$). Intra-class correlation coefficient among the two raters was 0.95 ($p < 0.001$). The Cronbach's alpha among items was 0.45.

Discussion: RADAR has good concurrent validity with CGI – I. A high inter-rater reliability is encouraging for its utility in clinical research. Future studies with higher sample would assist in standardising the tool.

F234. EXPERIENCING SCHIZOPHRENIA SYMPTOMS THROUGH AUGMENTED REALITY: FROM ASSESSING STUDENTS' NEEDS TO PROTOTYPING A SIMULATION

Emma Tison^{*1}, Solène Delsuc¹, Claudia Krogmeier², Arnaud Prouzeau², Martin Hachet², Antoinette Prouteau¹

¹University of Bordeaux, ²Centre Inria de l'université de Bordeaux

Background: The stigma of schizophrenia, in addition to being present among mental health professionals (for a review see Valery and Prouteau, 2020), is already present among students (Sideli et al., 2021) and even associated with the level of clinical experience (Fernandes, 2022). There are a whole host of technological interventions to train professionals: they have shown contradictory results, particularly in terms of impact on stigma (for a review see Rodriguez-Rivas et al., 2022 ; Tay et al., 2023). Some have actually proven counterproductive, increasing the desire of subjects for social distance from those with schizophrenia (Brown, 2020 ; Morgan et al., 2018 ; Rodriguez-Rivas et al., 2022 ; Silva et al., 2017). Rodriguez-Rivas et al. (2022) argue that these negative outcomes may be explained by the focus of the interventions on symptoms rather than the recovery process, which may increase stereotypes and prejudice. Moreover, it has been suggested that they should be used with caution and ideally in combination with educational or contact interventions (Ando et al., 2011). We aim at developing an augmented reality (AR) intervention for training mental health students. Nonetheless, there is no data on French mental health students' training needs. Our objectives were i) to explore the training needs of mental health students for an AR instrument and ii) to use this data to prototype a unique AR simulation of schizophrenia symptoms for training purposes.

Methods: A mixed participatory approach (qualitative and quantitative) was used to analyze students' needs and comprised two stages.

Following Traynor (2015) methodology, a focus group of N=6 psychology students was organized to identify i) the relevance of a survey on the training needs of health students and

ii) create the survey content. A thematic analysis of the transcript was then carried out using QDA Miner Lite. Finally, items for a survey were generated with the focus group on the basis of the thematic analysis results. The resulting questionnaire comprised 20 questions divided into 5 categories: "satisfaction with mental health training and the role of clinical practice", "legitimacy", "satisfaction with schizophrenia training", "AR tool" and "suggestions and information". It was distributed via LimeSurvey to health and social work students at University of Bordeaux. We received and analyzed 288 responses.

Results: Almost 70% (69.4%) of the sample were moderately or not at all satisfied with the information they received on schizophrenia during their initial training course. Almost 90% (88.5%) of the sample were interested in an AR simulation of the positive and negative symptoms of schizophrenia. Participants also described how they thought the simulation should be implemented: preferably in small groups (80.2%), preceded by theoretical course and a post-intervention debriefing (86.8%), with third- and first-person symptom's visualization (73.3%) and retracing different moments in the life of a person with schizophrenia (49.7%). This, with the basis of the scientific literature, enabled us to develop the AR prototype. It is a simulation of different symptoms of schizophrenia (auditory hallucinations, anhedonia, delusions, etc.) in different life contexts (schoolwork, telephone conversations, etc.). The poster will contain images and concrete examples of the content of the simulation.

Discussion: This study enabled us to obtain, create and design an AR prototype to simulate the symptoms of schizophrenia. This prototype was built not only on the basis of the scientific literature, i.e. what works best to educate and destigmatize, but also on the basis of the actual needs of the students who will be involved in this training. Future research will focus on testing the simulation in terms of training and destigmatizing efficacy.

F235. DEVELOPMENT AND VALIDITY OF LIFESTYLE SCALE FOR PSYCHIATRIC PATIENTS WITH METABOLIC SYNDROME

Bo-Hyun Yoon^{*1}, Won-Myong Bahk², Young-Joon Kwon³, Kwanghun Lee⁴, Moon-Doo Kim⁵, Haran Jeong¹, Kyungmin Kim¹

¹Naju National Hospital, ²Yeouido St. Mary's Hospital, The Catholic University of Korea, ³Soonchunhyang University, ⁴College of Medicine, Dongguk University, , ⁵Jeju National University Hospital

Background: This study examines the applicability of the 'Lifestyle Evaluation Tool for Patients with Metabolic Syndrome (LET-PMS) questionnaire' to psychiatric patients with metabolic syndrome which was originally developed for general population.

Methods: A cohort of 320 patients diagnosed with schizophrenia spectrum disorder (N=190), bipolar spectrum disorder (N=65), and depressive disorder (N=65) participated in this study. They underwent assessment using 36 items from the LET-PMS questionnaire and various established scales. The evaluation encompassed psychometric properties, including reliability analysis, exploratory factor analysis, and confirmatory factor analysis.

Results: We refined the LET-PMS questionnaire by eliminating six items through a reliability test. The resultant questionnaire exhibited 6 factors. The overall Cronbach's alpha value was 0.896, with factor-specific reliability coefficients ranging from 0.730 to 0.859. Confirmatory factor analysis of the adapted LET-PMS yielded a 0.069 (between 0.05 and 1.1) root mean square error of approximation, Goodness of fit and comparative fit indexes were 0.815 and 0.821, respectively. Consequently, all 30 items met the criteria for suitable configuration.

Discussion: 'Lifestyle Evaluation Tool for Psychiatric Patients with Metabolic Syndrome (LET-PPMS)' questionnaire demonstrated suitability for psychiatric patients with metabolic syndrome, exhibiting robust internal consistency and sound structural validity.

F236. THE ROLE OF HYPOESTROGENIC CONDITIONS IN WOMEN WITH PSYCHOSIS

Maria Antonietta Nettis^{*1}, Khalida Ismail², Robin Murray², Kathy Greenwood⁴, Zerrin Atakan², Shubulade Smith², Fiona Gaughran²

¹*South London and Maudsley NHS Foundation Trust*, ²*Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London*, ⁴*School of Psychology, University of Sussex and Sussex Partnership NHS Foundation Trust*,

Background: Increasing evidence suggests that oestrogen levels in women with psychosis may affect the severity and course of psychiatric symptoms, as well as response to medications. Indeed, oestrogens not only have shown neuroprotective effects, but also the ability to increase D2 receptor sensitivity to antipsychotic medications (González-Rodríguez et al. 2022) (Brand et al. 2021). However, such a protective factor in women may be lost in conditions associated with reduced circulating oestrogens, such as the menopause or iatrogenic hyperprolactinemia. In fact, antipsychotic-induced hyperprolactinaemia is associated with ovulatory dysfunction and gonadal suppression. However, the relationship between hyperprolactinemia, women's age (and related hormonal phase) and clinical symptoms of psychosis is still unclear. This work aimed at:

1. investigating how psychiatric symptoms presentation differs according to women's specific age ranges (corresponding to different oestrogenic status)
2. investigating the relationship between hyperprolactinemia and psychiatric symptoms in women with psychosis with both a cross sectional and longitudinal approach and according to different age ranges.

Methods: We analysed data on 176 women aged 18-65, from the IMPaCT study ("Improving physical health and reducing substance using in psychosis") (Gaughran et al., 2017).

We analyzed data on i) mental health status with the Positive And Negative Syndrome Scale (PANSS), and Montgomery Asberg Depression Rating Scale (MADRS); ii) current medications; iii) period frequency, with the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) and iv) prolactin levels, at baseline and 15-month follow-up.

We used tMann-Witney and Kruskal-Wallis tests to explore differences in clinical symptoms across different ages. We used Spearman rho correlations to investigate the association between prolactin changes and symptoms changes over time in the different age groups.

Results: We found that women aged above 40 (N=102) (when perimenopause usually starts) had higher PANSS total scores than their younger counterparts (N=63) (Mann-Whitney U=-2506.5, p=0.018). Similar results were found for PANSS General symptoms (Mann-Whitney U=2666.5, p=0.036). In women above 40, hyperprolactinemia seemed to be associated with worse positive symptoms. In particular, those with baseline hyperprolactinemia (above 510 ml/U, N=26), showed a trend towards higher baseline PANSS positive symptoms scores (Mann-Whitney U= 860.0, p=0.08) compared with women in the same age range but without hyperprolactinemia, N=47 (mean PANSS positive score= 13.23±5.83 vs 10.7±3.75, respectively). Moreover, longitudinal analyses showed a positive correlation between overtime

increases in prolactin levels and PANSS positive symptoms scores in the total sample (Spearman rho=0.332, p=0.004), and this association persisted in the group of women older than 40 (Spearman rho=0.36, p=0.012).

Discussion: Overall, hypoestrogenic conditions might affect the psychiatric presentation of women with pre-existing psychosis. Screening for and treating hormonal changes, as well as adjusting anti-psychotic medications accordingly, are crucial steps towards better care for women's mental and physical health.

F237. “AND GIVEN THAT OUR MEDICINES CAN CAUSE A PERSON TO DEVELOP DIABETES, I THINK IT COULD HAVE BEEN OUR OBLIGATION TO ACTUALLY FOLLOW UP ON IT” EXPERIENCES OF HEALTH PROMOTION WORK IN PSYCHOSIS CARE

Matilde Zerme Nilsson^{*1}, Carina Sparud Lundin¹, Katarina Eeg-Olofsson¹, Jarl Torgerson², Christopher Holmberg¹

¹*The Sahlgrenska Academy at University of Gothenburg*, ²*Sahlgrenska University Hospital*

Background: Severe mental illnesses, including schizophrenia, affect both mental and physical health, reducing life expectancy by 10-20 years attributed to several factors such as medication side effects, poor lifestyle habits, and limited healthcare access. It is therefore recommended to integrate physical health promotion into psychiatric care. However, a recent national evaluation in Sweden revealed varied adoption rates, and while there was a general increase of annually conducted health examinations, health promotion activities were not as common, and cardiometabolic mortality continued to rise. This study explores the experiences of healthcare professionals and unit leaders in Swedish psychosis outpatient units regarding health promotion efforts.

Methods: This study adopted an interview study design, using thematic analysis and abductive approach. Participants consisted of ten healthcare professionals (HCP) (e.g., physician, nurses, psychologist) and 3 heads of units from psychosis outpatient units. Self-determination theory was employed to explore motivation among HCPs and head of units regarding working with patients' physical health.

Results: The participants described their experiences of health promotive work with patients as complex and influenced by various factors. Theme 1, "Organizational prerequisites". Routines, working methods and HCPs perception of these means affects efficiency. Resources such as allocated time was a crucial, specialized HCPs and a supportive environment, e.g. nature access, enhanced health promotion.

“I know that we are very bad at doing annual follow-ups. We still try, and it is up to each HCP and the doctor to do it once a year. But I think only some people choose to do it.” Theme 2: "Health care professional's competences and attitudes". Attitudes and values held by HCPs impacted the execution of health initiatives and was crucial for motivation. HCPs varied in their strategies and approaches to promote physical health, including motivational work. Challenges lead to discontinuation, requiring recurring motivational approaches. “It is not only that we should increase physical health to reduce the risk of dying from cardiovascular diseases, but also to increase the mental well-being of the person.” Theme 3: "Patient related aspects". Participants detailed various patient-related factors influencing physical health and requiring interventions. Socio-demographic aspects and factors associated with schizophrenia, including lifestyle habits, symptoms and duration of illness perceived to have an impact. The negative

effect of antipsychotic medications on physical health is highlighted and pose a dilemma for HCPs. “You don’t seek help for your somatic problems very often. You wait and when you do seek help, you’re not received in the way another person would have been.”

Discussion: The study emphasizes the importance of organizational support, the competence of the HCP, and an understanding of patient-related aspects. The HCP's level of self-determined interest in physical health impacts engagement with health promotive measures. Having specialized staff with expertise in physical health within the psychiatric team promotes teamwork and reduces concerns about insufficient competence among HCP when addressing patients' physical health. The three tenets of Self-Determination theory (competence, relatedness, and autonomy) were evident across all themes, indicating a promising way forward to increase motivation for measurements focused on physical health within psychosis outpatient care.

F238. FACTORS ASSOCIATED WITH PHYSICAL ACTIVITY IN A BRAZILIAN SAMPLE OF PATIENTS WITH SCHIZOPHRENIA

Joao Salgado*¹, Breno Cruz¹, Edilene Silva¹, Vinícius Pietra², Lucas Mantovani²

¹*Federal University of Minas Gerais*, ²*Instituto Raul Soares*

Background: In individuals with schizophrenia, the average life expectancy is approximately 14.5 years less than that of the general population. Recent data indicate that physical illnesses account for 75% of deaths in this population, with cardiovascular diseases related to metabolic syndrome (MS) being the leading cause of death. Behavioral factors such as an unhealthy lifestyle, including low physical activity, substance abuse, smoking, and inadequate diet, contribute to the increased risk of cardiovascular diseases and MS among patients with schizophrenia. A meta-analysis by Stubbs et al. (2016) revealed significantly lower levels of physical activity, both moderate and vigorous, in patients compared to control individuals. Understanding the factors associated with this reduced physical activity, including their geographical and cultural nuances, is crucial. This study aims to assess the socioeconomic and clinical factors associated with physical activity in a Brazilian sample of patients with schizophrenia.

Methods: Sixty-three stabilized schizophrenia patients from three tertiary psychiatric centers were evaluated. Diagnosis confirmation was conducted using the SCID-5, and stability was determined by a score of less than 20 on the PANSS positive subscale. The Simple Physical Activity Questionnaire (SIMPAQ) was employed, with its subscales indicating bed rest, sedentary behavior, walking, physical exercise, and other physical activities. Patients also completed a sociodemographic-clinical questionnaire and the Simpson Angus scale for extrapyramidal symptoms. Due to non-normal distribution, correlations were assessed using the Spearman test.

Results: No significant correlations were found between positive and negative symptoms (evaluated by PANSS), age, gender, education, or family income with SIMPAQ variables. Negative symptoms showed a trend of correlation with subscale 3 (walking, $p = 0.06$) and 4 (physical activity, $p = 0.07$). Antipsychotic dosage, assessed by chlorpromazine equivalent, exhibited significant negative correlations with physical exercise (subscale 4) and overall physical activity (sum of subscales 3, 4, and 5). No significant correlation was observed between benzodiazepine or biperiden use and SIMPAQ variables. Extrapyramidal symptoms assessed by the Simpson-Angus Scale showed a significant positive correlation with time spent in bed (subscale 1, $p=0.01$) and sedentary behavior (subscale 2, $p=0.02$).

Discussion: The results suggest that antipsychotic dosage, assessed in chlorpromazine equivalent, and the presence of extrapyramidal effects, resulting from high doses of antipsychotics, are significant factors in the reduced physical activity of patients. These findings are preliminary, and the lack of a significant effect in some correlations (e.g., negative symptoms) may be due to the small sample size. Regression models to control intervening variables should be employed in future research.

F239. UNDERSTANDING THE DEMOGRAPHIC AND PSYCHOSOCIAL RISK FACTORS FOR PHYSICAL MULTIMORBIDITY IN PSYCHOSIS: A SYSTEMATIC REVIEW

Erin Lawrence^{*1}, Abigail Thomson¹, Kamaldeep Bhui², Mark Freestone¹, Georgina Hosang¹

¹*Queen Mary University of London*, ²*University of Oxford*

Background: People with psychotic disorders have a reduced life expectancy of up to 18 years relative to the general population. A key factor contributing to this premature mortality within this group is the high prevalence of physical multimorbidity (MM [co-existence of two or more physical long-term health conditions]). This includes the co-occurrence of cardiovascular, metabolic, and respiratory diseases, but little is known about the psychosocial factors, such as stress, that may elevate the risk of physical MM in this population. In view of this, we conducted a systematic review aiming to identify demographic and psychosocial risk factors for physical MM among individuals with psychotic disorders.

Methods: The systematic review protocol was registered with PROSPERO (CRD42022382661) and conducted in accordance with PRISMA guidelines. Three databases (Embase, PubMed, and PsychINFO) were searched from March 2023 with no limits for study design up to December 2023. Studies were eligible for inclusion if they assessed the impact of demographic and/or psychosocial factors on physical MM outcomes among people with psychotic disorders. Forwards and backwards citation searches were conducted on the study papers eligible for inclusion in the review. Grey literature such as preprints, PhD theses and public health research were also considered.

Results: Of 4361 articles, 11 met the inclusion criteria. Study quality was deemed reasonable for all included articles. Preliminary findings of this review identified the following demographic and psychosocial risk factors for physical MM in psychosis: gender, age, age of psychotic illness onset, ethnicity, material deprivation and childhood maltreatment. Groups at higher risk of physical MM include women, those with an earlier age of psychotic illness onset, Black African, Black Caribbean and Black British ethnic groups (compared to White British groups), Malay and Indian ethnic groups (compared to Chinese ethnic groups), those living in areas with high levels of material deprivation, and individuals who have experienced childhood abuse or neglect. The included studies reported mixed findings for age as a risk factor for physical MM.

Discussion: The findings provide insights into vulnerability factors that can inform strategies for preventing physical MM, aiming to improve the quality of life for individuals and mitigate premature mortality rates among individuals with psychotic disorders. However, risk factors for MM in psychosis remain understudied. Further research is needed to replicate and extend existing preliminary findings and identify additional potential psychosocial risk factors that are yet to be investigated, such as social isolation. Study limitations include varied definitions of MM. Future research should adopt a universal definition of physical MM to allow for valid comparisons across studies.

F240. PREDICTING METABOLIC RISK IN EARLY PSYCHOSIS - EXTERNAL VALIDATION OF THE PSYCHOSIS METABOLIC RISK CALCULATOR

Jaakko Keinänen*¹, Benjamin Perry², Saana Eskelinen³, Jaana Suvisaari⁴, Graham Murray²

¹*University of Helsinki*, ²*University of Cambridge*, ³*Helsinki University Hospital*, ⁴*Finnish Institute for Health and Welfare*

Background: The risk of cardiometabolic dysfunction, including metabolic syndrome, is high during the first years of early psychosis. We conducted an external validation of the psychosis metabolic risk calculator (PsyMetRiC), a cardiometabolic risk prediction tool tailored for young people with psychosis originally developed in the UK. PsyMetRiC has been validated in the UK and two Western European nations. We tested its predictive performance in a Finnish sample of individuals with first-episode psychosis (FEP) and high-risk for psychosis, with the aim of recognizing individuals with high risk for cardiometabolic dysfunction. Prediction of the metabolic risk is important to effectively target interventions to individuals with the highest risk of metabolic dysfunction, and testing in different populations is critical to confirm generalisability and likely clinical usefulness.

Methods: We conducted an external validation of PsyMetRiC in a sample of individuals over 18 years of age with early psychosis recruited to the Helsinki Early Psychosis Study and Turku Early Psychosis Study. After excluding those with baseline metabolic syndrome and individuals over 35 years, the sample consisted of 210 individuals. Of those, 146 were FEP patients from the Helsinki and Uusimaa Hospital District (n=97) and Turku and the Southwest Finland Hospital District (n=49). The cohort also included 104 individuals with high-risk for psychosis (n=60 fulfilled SIPS criteria; 47 clinically evaluated as high-risk). Discrimination (C-statistic), calibration (calibration plots), and decision curve analysis were used to assess the predictive performance and clinical utility of PsyMetRiC.

Results: We included 210 individuals with early psychosis (of them all were of White European ethnicity, 59% male, mean age 24.6 years, 39% smoking, mean BMI 23.7). Discrimination was better in the full model compared with partial model (full model C=0.73, 95% CI, 0.63–0.80, partial model C=0.68, 95% CI 0.60–0.75). For the high-risk for psychosis sample, discrimination C-statistics were 0.71 (95% CI 0.58-0.85) and 0.66 (95% CI 0.51-0.80) for the full and partial models, respectively. Calibration plots displayed evidence of minor miscalibration which corrected after recalibration. Decision curve analysis showed that PsyMetRiC offers clear evidence of likely clinical usefulness in improving cardiometabolic risk management in individuals both with psychosis, and those at high-risk for psychosis.

Discussion: This study showed that PsyMetRiC has utility in predicting cardiometabolic risk also in high-risk for psychosis population, as well as in individuals with FEP, in Finland. Predictive performance in this study was similar to external validations in other European nations, suggesting that PsyMetRiC is likely to be generalisable for use. Recalibration further improved the predictive accuracy of PsyMetRiC. Further studies with larger sample sizes and with samples from different geographical locations are needed to further improve the performance of the models. With adjustments to account for the differences in metabolic risk in different populations, PsyMetRiC can be used to target interventions effectively.

F241. EXPLORING SEX DIFFERENCES IN PHYSICAL ACTIVITY PATTERNS AMONG INDIVIDUALS WITH SCHIZOPHRENIA SPECTRUM DISORDER: INSIGHTS FROM THE DIAPASON PROJECT

Alessandra Martinelli*¹, Elena Toffol¹, Giulia Moncalieri¹, Silvia Leone¹, Jacopo Santambrogio², Matteo Rocchetti³, Manuel Zamparini¹, Martina Carnevale⁴, Stefano Calza⁴, Giovanni de Girolamo¹

¹*IRCCS St. John of God Clinical Research Centre*, ²*Adele Bonolis AS.FRA. Onlus Foundation, Vedano al Lambro (MB)*, ³*ASST of Pavia*, ⁴*University of Brescia*

Background: Schizophrenia Spectrum Disorders (SSD) affect females differently than males, yet there is limited research on Physical Activity (PA) levels and possible sex differences in patients with SSD. This is a prospective cohort study with the aim of comparing PA levels between patients with SSD and control participants, matched by sex and age, with a specific focus on sex differences.

Methods: As part of the DiAPAsen project, 132 patients with SSD, living either in a residential or outpatient setting (48 females and 84 males), and 113 healthy controls (46 females and 67 males) were assessed using standardised clinical tools. PA levels were monitored for seven consecutive days using a wearable actigraph; data on socio-demographics, clinical and anthropometric characteristics were collected along with assessments of symptom severity, cognition, and functioning. Descriptive and regression analyses were conducted.

Results: Levels and patterns of PA did not differ by sex among SSD patients, while female controls spent longer times in sedentary activity than male controls (787.3 vs 706.8 minutes, $p < 0.001$). Male patients spent more time in sedentary activity ($p < 0.001$) but less time in light PA (both $p < 0.001$) and MVPA (respectively, $p < 0.001$ and $p = 0.004$) compared to male controls. Outpatient and female residents spent longer time in Sedentary PA (respectively, $p = 0.006$ and $p = 0.020$) than female controls; female outpatients spent significantly less time in daily light PA ($p = 0.008$), and female residents in MVPA ($p = 0.002$) than female controls. Higher levels of psychosocial functioning were associated with higher moderate PA (*60 min/day: $B = 4.21$; 95%CI=0.70 to 8.33; percentage: $B = 0.57$; 95%CI=0.08 to 1.21) and MVPA bouts per weekday (*60 min/day) ($B = 5.34$; 95%CI=0.65; 11.40) in male patients only.

Discussion: Our findings suggest that male patients with SSD may benefit from MVPA-focused interventions across settings, while personalized PA interventions tailored to specific settings could be more beneficial for female patients.

F242. PSYCHOTHERAPY FOR PSYCHOSIS AS A SYNDROME: PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL FOR A SYMPTOM-BASED MANAGEMENT APPROACH FOR PSYCHOSIS

Edo Jaya*¹

¹*University of Indonesia*

Background: In light of recent shortcomings in treatment developments derived from decades of researching the causes and treatment of psychosis, there has been a reevaluation of the disorder, considering it as a syndrome (e.g., Carpenter, 2016, 2022; van Os and Guloksuz, 2022). This perspective views the condition not as a singular disease necessitating a uniform treatment but as a cluster of symptoms stemming from various causes that demand specialized interventions. Notably, randomized controlled trials (RCTs) focusing on psychotherapies tailored to specific comorbidities among individuals with psychosis have not only alleviated the targeted disorder but also subsequently reduced psychotic symptoms (e.g., insomnia (Freeman et al., 2015)). In accordance with the syndrome model of schizophrenia, psychotic symptoms could be construed as emerging from a combination of coexisting mental disorder

symptoms, and improvements may thus manifest upon identification and treatment of these comorbidities. Cognitive Behavioral Therapy for psychosis (CBTp) has amassed substantial evidence of its efficacy in treating schizophrenia as a discrete disorder. Our aim is to devise a CBTp tailored for schizophrenia as a syndrome.

Methods: We plan to carry out a two-arm (treatment vs. treatment-as-usual), assessor-blinded Randomized Controlled Trial (RCT) involving 150 outpatients aged 18-65 diagnosed with psychosis (specifically, schizophrenia or schizoaffective disorder) from two Indonesian cities (Jakarta and Padang). The aim is to evenly split the sample between the two groups to detect a moderate-to-large effect size with 80% power and a significance level of 0.05. Crucial participant inclusion criteria will be a Psychotic Symptoms Rating Scale (PSYRATS) score of 2 or higher for either hallucinations or delusions, persisting for at least three months.

Exclusion criteria will entail a primary diagnosis of substance use disorder, organic syndrome (including brain injury), language deficits hindering engagement in therapy, or ongoing enrollment in other individual psychotherapy. Participants experiencing significant changes in pharmacotherapy must wait at least one month for stabilization of the new dosage. Random allocation (1:1) will be based on participants' city of residence.

Primary outcome measures will assess psychotic symptoms using PSYRATS, Brief Psychiatric Rating Scales (BPRS), and Community Assessment of Psychic Experience (CAPE-42). Secondary outcomes will cover depression, general anxiety, somatoform symptoms (Patient Health Questionnaire), panic symptoms (Panic Disorder Severity Scale), insomnia (Insomnia Severity Index), obsessive-compulsive symptoms (Obsessive-Compulsive Inventory-Revised), mania (Young Mania Rating Scale), trauma (International Trauma Questionnaire), and social anxiety (Social Phobia Inventory). Additionally, emotional regulation skills (Emotional Regulation Skills Questionnaire) and loneliness (UCLA Loneliness Scale 6) will be evaluated. Follow-up assessments are planned at 8 and 24 weeks.

The CBT for psychosis as a syndrome will systematically address comorbidities by utilizing case formulation to direct the treatment sequence. For instance, priority will be given to addressing social anxiety if it is identified as a trigger for depression through social withdrawal. Additionally, it will follow combinability principles, such as integrating behavioral activation for depression with sleep hygiene techniques for managing insomnia. The treatment manual will encompass a range of CBT techniques tailored for common comorbidities associated with psychosis. These techniques include exposure-and-response-prevention for managing symptoms of obsessive-compulsive disorder, sleep hygiene strategies for insomnia, behavioral activation to address depression, behavioral experiments targeting social anxiety, and interoceptive exposure techniques for managing panic disorder.

Statistical analyses will adhere to an intention-to-treat basis. A planned mediation analysis will investigate whether the reduction in comorbidities mediates the decrease in psychotic symptoms.

Results: The expected outcomes will include a significant reduction in psychotic symptoms, as assessed with the PSYRATS, BPRS, and CAPE-42 compared to treatment as usual. Additionally, significant improvement will also be anticipated in the secondary outcome measures. These significant differences will be expected to be observable during the 8 and 24-week follow-up. Furthermore, the longitudinal mediation analyses will be expected to demonstrate that changes in the secondary outcome measures lead to changes in psychotic symptoms.

Discussion: The trial results will shed light on the effectiveness of symptom-based management in treating psychosis, a complex disorder characterized by numerous comorbidities. Hopefully, the evidence gleaned from this trial may contribute to the discussion on whether schizophrenia can be regarded as a syndrome.

F243. “NO TEARS OR BRAIN WORDS”: A CASE REPORT ON SINGLE-SESSION DANCE/MOVEMENT THERAPY FOR INDIVIDUALS WITH SCHIZOPHRENIA

Jacelyn Biondo*¹

¹N/A

Background: Individuals diagnosed with schizophrenia face a multitude of challenges in their lifetime including complex symptomatology, co-morbid health concerns, profound levels of stigmatization, diminished access to quality care, and an overall lack of healthcare equity. Systemically racist provisions and social determinants of health further stigmatize these individuals, calling for action against such human rights violations. Globally, over 21 million people are diagnosed with schizophrenia, many of whom are experiencing healthcare disparities posing a significant public health concern. Dance/movement therapy (DMT) is an equitable healthcare provision situated in a strengths-based and trauma-informed psychotherapeutic framework. Dance/movement can support the symptomatic needs of schizophrenia including alternate reality orientations, thought and behavioral disorganization, and diminished interpersonal engagement.

Methods: This intrinsic case report examines the experience of a 37-year-old African American cisgender male who engaged in a single-session DMT intervention. This report explores an under-researched phenomenon of the lived experience of a DMT intervention for an individual with high symptom acuity. It will review the quantitative data, reviewing the Brief Psychiatric Rating Scale (BPRS) scores individually and as compared with other members of the DMT cohort. Additionally, the report will highlight the participant's experience in the DMT session through qualitative data collected in a semi-structured individual interview following the single-session intervention.

Results: Results showed that following the intervention, the participant exhibited a decrease in symptomatology as evidenced by the BPRS in total scores as well as subscales of psychological distress, positive symptoms, negative symptoms, and resistance. Moreover, in his interview, the participant expressed having a transformative experience in the single-session DMT intervention, feeling like a contributing member of the group process, exhibiting a sense of pride, experiencing the ability to engage in healthy relationships, and noting shared and meaningful experiences in his group process.

Discussion: This case report highlights the impactful effects of a single-session DMT intervention for a participant experiencing acute positive symptomatology and affective dysregulation associated with a diagnosis of schizophrenia. Historically, research has listed positive or acute exacerbations of schizophrenia as exclusionary criteria. This is not only a human rights violation (Hall et al., 2019; WHO, 2023), but is also deeply rooted in stigmatization against individuals diagnosed with schizophrenia. Moreover, this disallows data collection, phenomenological experiences, and overall voices of individuals with schizophrenia when making decisions regarding treatment, research, and policy. The particular participant identified in this case report is one who may have otherwise been excluded from both psychosocial treatment and research opportunities due to the acuity of his presentation. Details of this case report suggest that individuals experiencing acute symptomatology and high levels of positive symptoms can not only participate in appropriately designed

interventions, but they can also experience changes towards health in a brief intervention. The disparities faced by individuals diagnosed with schizophrenia are a violation of human rights and dehumanize this population by diminishing their value through limited quality and accessibility of healthcare options. Dance/movement therapy is an inclusive, strengths-based, trauma informed psychotherapeutic treatment option that aims to reduce stigma, increase accessibility, and create spaces of inclusion and belonging. Its focus on non-verbal communication and processing of unconscious material through the arts and creative expression makes DMT an innovative and promising intervention for those who may not prioritize verbal language and may experience alternate reality bases as compared to the general population. Moreover, the trauma-informed approach of DMT provides consideration, awareness, and incorporation of social determinants of health as factors that contribute to diagnoses and symptomatology.

F244. ATHENS MULTIFAMILY GROUP THERAPY PROJECT (A- MFGT) AFTER A FIRST PSYCHOTIC EPISODE: PRELIMINARY CLINICAL RESULTS

Mirjana Selakovic*¹, Dimitris Galanis², Afrodite Zartaloudi³, Afrodite Feretzaki¹, Irine Ralli⁴, Vasiliki Efsthathiou⁵, Valeria Pomini⁴

¹*GH Sismanogleio*, ²*EPAPSY*, ³*Nursing University of West Attica*, ⁴*National and Kapodistrian University of Athens Medical School, Eginition Hospital*, ⁵*School of Medicine, National and Kapodistrian University of Athens*

Background: Family interventions have been shown to reduce the likelihood of relapse for individuals across the spectrum of psychosis and are recommended in practice guidelines for psychosis internationally (Mc Farlane, 2016). The Athens Multifamily Group Therapy Project (A- MFGT) aims to provide systemic multifamily therapy to youths who experienced a first psychotic episode and their families.

Methods: A group of 22 young adults who presented a first psychotic episode participated with their families to multi-family group systemic therapy, after discharged from in-patient treatment. Sessions were conducted by three therapists twice a month, for nine months and supervision meetings were provided once a month. Six groups of families have been conducted since 2017. Clinical outcome was assessed through PANSS at baseline, one month later after patient's discharge from in-patient treatment, and one year after, at the end of the multifamily group treatment. Time intervals till relapse were also assessed. Participants' clinical findings were compared with findings from a matched group of 40 patients who did not attend the multifamily therapy program and were treated as usual.

Results: Two-way mixed ANOVA was conducted to assess PANSS scores change over time (t1: at base line, t2: at one month and t3: one year), while differences were investigated between the two groups of patients and interactions were checked. Regarding PANSS-positive scale and PANSS-general scale, no differences were found between the two groups in neither of the three time points; Regarding PANSS-negative scale, patients attending MFGT presented statistically significantly lower scores in t3 than patients treated as usual, but not in t1 and in t2 (i.e., prior to therapy). Moreover, both patients' group showed improvement from t1 to t2, but only patients attending MFGT further improved from t2 to t3. Among patients attending MFGT 2 (9.1%) had a relapse compared to 9 (22.5%) of the patients treated as usual, however this comparison did not reach statistical significance ($p = 0.300$).

Discussion: MFGT seems to be a viable way to support the patient as well as the whole system facing psychosis, with the aim of preventing relapse and implementing quality of life for all the participants.

F245. FORMATION OF A WORKING ALLIANCE AND POTENTIAL EFFICACY OF A DIGITAL THERAPEUTIC TO TREAT EXPERIENTIAL NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Cornelia Dorner-Ciossek¹, Cassandra Snipes², Eehwa Ung³, Brendan D Hare^{*4}, Alankar Gupta⁵, Shaheen E Lakhan²

¹Boehringer Ingelheim International GmbH, ²Click Therapeutics, Inc., ³Click Therapeutics, Inc. (at time of study); University of California, San Francisco (USCF), ⁴Boehringer Ingelheim Pharmaceuticals, Inc.; Click Therapeutics Inc. (at time of study), ⁵Click Therapeutics, Inc. (at time of study)

Background: Experiential negative symptom (ENS) severity predicts real-world functioning in schizophrenia. However, currently there are no FDA-cleared pharmacological treatments for schizophrenia that satisfactorily address ENS. A digital therapeutic (DTx) designed to impact ENS could deliver evidence-based care while addressing access barriers given widespread smartphone ownership. The development, approval and use of DTx are steadily increasing, although there has been limited testing in schizophrenia. Here we report results from two exploratory studies to evaluate a beta version of CT-155 for the treatment of ENS in patients diagnosed with schizophrenia. These studies aimed to explore whether patients living with schizophrenia could form and maintain a digital working alliance (DWA) with a beta version of CT-155 (Part 1) and assess the impact of using a beta version of CT-155 on ENS (Part 2).

Methods: Part 1: Single arm, 3-week, multi-centre study of a beta version of CT-155 in adults with ENS of schizophrenia. Part 2: Single-arm, 7-week, multi-centre study of a second beta version of CT-155 in adults with ENS of schizophrenia. For both studies, patients were aged ≥ 18 years with schizophrenia, self-reported ENS (score of ≤ 30 on the Motivation and Pleasure-Self Report) and were on stable antipsychotic medication for ≥ 12 weeks. Patients had on-demand access to a beta version of CT-155 and engagement was measured throughout the studies. ENS were assessed at baseline using the Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP). DWA was assessed weekly via the mobile Agnew Relationship Measure (mARM) in Part 1, and at Week 3 in Part 2.

Results: In Part 1, 49 adult patients were enrolled of whom 46 (94%) completed the study. In Part 2, 50 adult patients enrolled of whom 43 (86%) completed the study. In both studies, the majority of patients were male (71% and 80%, respectively), non-white (57% and 70%), and never attended college (63% and 64%), with a median age of 46 and 54 years, respectively. In Part 1, total and subscale mARM scores indicated that a positive DWA was established with a beta version of CT-155 after one week (mean [standard deviation; SD]: 5.15 [0.7]) and was maintained over 3 weeks (5.16 [0.8]). As expected, mARM scores positively correlated with number of sessions completed ($r^2=0.4$, $p=0.01$). We did not observe a significant difference in mARM depending on ENS severity. In Part 2, a DWA was again established within 3 weeks (mean [SD] mARM score: 5.36 [1.1]). Patients opened a beta version of CT-155 on 77% of the 49 study days and engaged for ≥ 60 seconds in a mean (SD) of 42 (19.6) sessions. ENS (CAINS-MAP score) were significantly reduced ($p=0.004$) in the 7 weeks from baseline (mean [SD]: 20.2 [8.6]) to end of study (16.8 [7.8]; $n=43$). In both studies, no relationship between CAINS-

MAP and lesson completion was observed. There were 3 non-serious and non-treatment-related adverse events reported in Part 2.

Discussion: Patients formed and maintained a positive DWA with a beta version of CT-155 over the 3-week period and use of this DTx significantly improved ENS symptoms in patients diagnosed with schizophrenia. These highly favourable findings alongside the positive safety profile support advancing CT-155 into late-phase clinical development.

Clinical research was funded by Boehringer Ingelheim and Click Therapeutics.

F246. BRAIN (BETTER UNDERSTANDING AND PREVENTION OF NEUROPSYCHOLOGICAL DIFFICULTIES): A TOOLKIT OF KNOWLEDGE TRANSFER DEVELOPED WITH AND FOR PERSONS WITH LIVED EXPERIENCE

Caroline Cellard^{*1}, Caroline East-Richard¹, Élisabeth Thibaudeau², Geneviève Dufour³, Ariane Giguère-Rancourt¹, Éva Racine¹, Mélissa Turcotte¹, Andréanne Simard¹, Gabriel Demers¹, Jean-Jacques Tremblay¹

¹Université Laval, ²McGill University, Douglas Mental Health University Institute, ³CIUSSS de la Capitale Nationale

Background: “I might not be as smart as my friends” or “I forgot my books at home... again” are cognitive subjective complaints reported by people with cognitive impairments. Cognition is defined as the perception, learning, understanding, and use of information that involves domains such as attention, memory and executive functions. Cognitive impairments are highly prevalent in people with schizophrenia spectrum disorders and have detrimental effects on daily functioning and recovery. Despite the prevalence and consequences of these impairments, a gap remains in knowledge transfer, regarding cognitive impairments and their impacts, from research to the general population, including people with schizophrenia spectrum disorder. As such, providing an informational toolkit of evidence-based and accessible information regarding cognition and cognitive impairments could help individuals better understand their difficulties and receive timely and appropriate care. However, to increase the relevance of this information, it is essential to co-develop these tools in collaboration with health care professionals as well as people with lived experience of schizophrenia spectrum disorders.

Methods: The co-development of a toolkit called BRAIN (Better undeRstanding And prevention of Neuropsychological difficulties) will be presented. Open science principles on co-design and knowledge transfer were used to develop BRAIN. Both health care professionals and people with lived experience were involved in the iterative development of the toolkit from the discussions about their needs to comments about the different versions of the toolkit. This co-design methodology was used to ensure that the toolkit was both clinically relevant and responded to the needs of everyone involved.

Results: An initial theoretical booklet was developed to explain cognitive functioning, the impact of cognitive impairments on daily life, as well as the factors that can influence the development of cognitive impairments (e.g. mental disorders). This was followed by the development of several clinical booklets intended for various ages and groups, including adolescents, young adults, as well as family and friends. Additionally, a web platform comprised of 27 video capsules explaining different cognitive domains and strategies was recently developed.

Discussion: The co-design of the BRAIN toolkit led to engaging, flexible and service user-focused information about cognition to increase knowledge transfer from research to the daily lives of people with lived experience of schizophrenia spectrum disorders and the clinical practice of their health care professionals. The next step will be to evaluate the acceptability of the Brain toolkit in clinical settings.

F247. CO-STARS: A CO-PRODUCED, CULTURALLY APPROPRIATE MENTAL HEALTH LITERACY TRAINING PACKAGE TO REDUCE MENTAL HEALTH INEQUALITIES FOR BLACK MINORITY GROUPS FROM UNDERSERVED COMMUNITIES

Sian Lowri Griffiths*¹, Eliza Cherrington¹, Gerald Jordan², Luke Brown¹, Megan Pope¹

¹*University of Birmingham*, ²*Yale University*

Background: Psychotic disorders are among the most disabling illnesses worldwide and disproportionately affect minoritized ethnic groups and those in socioeconomic disadvantage. Within the UK, people from Black ethnic backgrounds (African, Caribbean, British) are 3-5 times more likely to experience a first episode of psychosis (FEP), five times more likely to be detained, and are more likely to be subjected to the Mental Health Act than White British people. Factors contributing to these disparities are complex and influenced by wider inequities within and beyond health systems, including bias, discrimination, cultural insensitivities, and racism towards Black individuals. This often perpetuates feelings of mistrust, disempowerment, and disengagement with services, which is further compounded by stigma and lack of recognition of the symptoms of mental illness within Black communities. There is a clear need for services to improve cultural awareness and understanding of the broader social needs of minoritized groups, as well as the eradication of racial bias and discrimination from mental health services. Improving mental health literacy within Black communities will empower individuals to advocate for their mental health, seek timely support, and identify gaps in service provision.

Methods: Co-STARS is a participatory social action research study which aims to co-produce a culturally appropriate mental health literacy training package delivered by young people with lived experience to underserved communities across Birmingham, UK, and via an e-learning package implemented within Early Intervention Services (EIS).

Results: Eight young people (18-30 years) from Black ethno-racial Background:s with lived experience of severe mental illness are participating in a series of co-produced workshops and 1:1 interviews to develop training outputs (completion February 2024). Clinical staff from EIS (N=8) will also be recruited along with carers (N=6). Interview transcripts and workshop observation notes will be subjected to thematic analysis by two researchers (e.g., research associate and peer researcher) to identify recurrent and important themes, using computer-assisted qualitative data analysis software (NVivo).

Discussion: The outputs from the co-production will provide a novel, culturally adapted mental health training package to tackle mental health inequalities in care access and outcomes for underserved groups. The second phase of this project will co-evaluate the implementation of the training resources within a feasibility study adopting participatory Methods: and novel epidemiological analyses to explore downstream effects of the training (i.e., improved care access and reductions in compulsory detentions for Black ethno-racial groups within a targeted intervention area in Birmingham, UK).

F248. SPEAKING ABOUT STIGMA: EXPERIENCES OF STIGMA AND SELF-STIGMA IN YOUNG PEOPLE AT-RISK OF PSYCHOSIS

Zoe Waters*¹, Yael Perry², Ashleigh Lin¹, Jeneva Ohan¹

¹University of Western Australia, ²Telethon Kids Institute, University of Western Australia

Background: The stigma associated with mental illness has a profound effect on those that experience it, and may give rise to self-stigma, which involves the internalisation of negative public stereotypes. Stigma and self-stigma are known to produce harmful outcomes such as reduced self-esteem, and increased hopelessness and suicidality. While psychotic disorders are widely recognised as the most stigmatising of all mental health disorders, there is currently a dearth of research investigating how stigma and self-stigma are experienced by young people at ultra-high risk for psychosis. Consequently, the current qualitative study sought to explore how young people at ultra-high risk of psychosis experience stigma and self-stigma.

Methods: 12 young people identified as being at ultra-high risk for psychosis aged 14-25 participated in this study. 6 participants were interviewed in a one-on-one meeting about their experiences with stigma and self-stigma, and 6 took part in an online workshop exploring stigma and self-stigma in the ultra-high risk of psychosis population. The interviews and focus group were transcribed and analysed using reflexive thematic analysis.

Results: Five themes were developed through reflexive thematic analysis, including: 1) Being UHR is an inherently difficult, uncertain experience; 2) Stigma is a pervasive force; 3) Stigma becomes internalised; 4) Stigma is painful; and 5) Defending against stigma, which contains three subthemes including 5i) Hiding one's UHR status; 5ii) Rebutting stigma; and 5iii) Educating self and others. All participants identified experiences with stigma and self-stigma, reflecting the widespread impact of stigmatising beliefs and attitudes upon these young people.

Discussion: Results indicated that although they are not necessarily diagnosed with a psychotic disorder, young people at UHR for psychosis experience pervasive stigma that has detrimental consequences for them and leads them to seek ways to protect themselves and others from stigma. Given the complexity of the ultra-high risk population, where co-occurring mental health conditions are the rule rather than the exception, there is a clear need to understand experiences of stigma and self-stigma from an intersectional lens that includes consideration of other mental health diagnoses. Additional research is required further explore the effects of stigmatising beliefs upon this vulnerable population.

F249. QUALITATIVE ANALYSIS OF MENTAL HEALTH CLINICIANS' EXPERIENCES OF TALKING WITH PEOPLE ABOUT HEARING VOICES

Kriti Sharma*¹, Jenny Barnes², Aikaterini Rammou³, Mark Hayward⁴, Neil Thomas¹

¹Swinburne University of Technology, ²Canterbury Christ Church University, ³University of Sussex, ⁴Sussex Partnership NHS Foundation Trust

Background: Hearing voices is a common symptom of schizophrenia that can often be distressing and disabling for many individuals. In contrast to the amount of research investigating formal therapies such as cognitive behavioural therapy for psychosis (CBTp), there has been very little examining practice models for the broader mental health workforce to incorporate into day-to-day work with clients who hear voices. The current study aimed to identify the types of questions asked and the range of strategies that frontline mental health practitioners currently use when talking with people who hear voices.

Methods: A sample of 148 UK National Health Service mental health staff completed an electronic survey regarding their experiences of speaking with clients about their experiences of hearing voices. Adopting an inductive approach, content analysis was used to analyze the survey responses and code subcategories relevant to the research questions. These were then grouped into categories and overarching themes.

Results: The themes which emerged were to: (1) help the person feel understood and safe to discuss voices; (2) explore the person's experience of voices; (3) discuss how the experience of voices affects the person; (4) discuss meaning associated with voices; (5) give information about the experience of hearing voices; and (6) help the person be less impacted by the voices. Themes 1 and 6 were the two most frequently endorsed themes, with both reported by more than half of practitioners surveyed (54.1% and 61.5% respectively).

Discussion: This study identified a range of strategies currently used by practitioners in their interactions about hearing voices. Many of these are common factors of general mental health practice and are not unique to conversations about hearing voices. The strategies which emerged also converged with common practices within noted approaches to support voice hearers such as CBTp and Hearing Voices Network (HVN) groups. The results indicate the utility of future research evaluating the usefulness of a combination of strategies from both modalities and increased synergy between professionals and HVN groups. However, by comparing the results of the current study with past research there were potential discrepancies highlighted between how various professional disciplines approach interactions about voices. This should be further investigated and may be remedied by the formulation of multidisciplinary practice guidelines. The results of the current study are being used to formulate a Delphi seeking consensus on which elements of practice are essential when supporting someone hearing voices.

F250. EXPERIENCES OF CHILDHOOD POVERTY AMONG COORDINATED SPECIALTY CARE SERVICE USERS AND ASSOCIATIONS WITH CLINICAL OUTCOMES: PRELIMINARY DATA FROM THE CALIFORNIA EPI-CAL PROJECT

Kathleen E. Nye^{*1}, Valerie L. Tryon¹, Stephania L. Hayes¹, Deanna M. Barch², Mark Savill¹, Sabrina Ereshefsky¹, Katherine Pierce¹, Chelyah Miller¹, Madison J. Miles¹, Amanda McNamara³, Merissa Kado-Walton³, Khanh Linh H. Nguyen¹, Nitasha Sharma¹, Christopher K. Hakusui¹, Viviana Padilla¹, Maliha Safdar³, Rachel Loewy⁴, Laura M. Tully¹, Andrew J. Padovani⁵, Leigh Smith¹, Adam B Wilcox², Lindsay M. Banks¹, Karina Muro¹, Daniel I. Shapiro¹, Khalima A. Bolden¹, Renata M. Botello¹, Rebecca E. Grattan¹, Yi Zhang⁵, Joy Melnikow⁵, Daniel J. Tancredi¹, Bonnie Hotz¹, Sonya Gabrielian⁶, Steven R. Lopez⁷, Lisa Dixon⁸, Cameron S. Carter¹, Tara A. Niendam¹

¹University of California, Davis, School of Medicine, ²Washington University in St. Louis, ³Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, ⁴Weill Institute for Neurosciences, University of California, San Francisco, ⁵Center for Healthcare Policy and Research, University of California, Davis,, ⁶David Geffen School of Medicine, University of California, Los Angeles, ⁷University of Southern California, ⁸NYSPI/Columbia University Medical Center

Background: Coordinated Specialty Care (CSC) is an evidenced-based practice for early psychosis (EP). The effectiveness of CSC outside of clinical trials continues to be evaluated, including by NIH's EPINET project (<https://nationalepinet.org/>) which has created a network

of EP program hubs across the country, including California's EPI-CAL project (<https://epical.ucdavis.edu>). Recent studies suggest that CSC is not as effective for individuals with less economic advantage. This is critical, as approximately 37 million, or 12%, Americans, lived in poverty each year between 2020 and 2022. In 2022, 15% of American children lived in poverty, noteworthy because childhood economic disadvantage is predictive of both development of psychosis-spectrum disorders as well as other health problems. To better understand early experiences of poverty of service users in community CSC programs, this analysis examined experiences of early childhood poverty of EPI-CAL service users and explored how these experiences are related to high-priority clinical outcomes.

Methods: CSC service users and their primary support persons (PSP) completed surveys at EPI-CAL enrollment and every 6 months throughout treatment. PSP who lived with the service user before they turned five reported subjective poverty indicators experienced in the household during that time. Participants also reported their demographics and clinical outcomes, including symptoms (Modified Colorado Symptom Index (MCSI)), recovery (Questionnaire about the Process of Recovery (QPR)), and quality of life (Personal Wellbeing Index (PWI)). Descriptive analyses summarized demographics and poverty indicators. Independent-samples t-tests were run to determine if there were differences in specific outcomes (MCSI, QPR, and PWI) between service users with and without a history of early poverty, and family-wise error rate was adjusted to correct for multiple comparisons. Chi-square tests were used to examine group differences between specific demographic factors and those with and without childhood poverty experiences.

Results: At enrollment, 165 PSPs (Ages 16-66, M=45.76, SD=9.17) reported on subjective experiences of poverty had by the service user (ages 12-32, M=17.78, SD=3.72; 66% FEP, 27% CHR, 11% Diagnosis Unconfirmed) prior to age five. We found 29 (18%) PSPs who endorsed that the service user had at least one subjective experience of poverty prior to age 5. When examining demographic factors, there was a significant association between race and experience of childhood poverty ($\chi^2(4) = 14.91$, $p < .01$) with African American/Black individuals reporting more childhood poverty experiences than expected. Individuals who had subjective experiences of poverty during childhood reported worse clinical outcomes on the recovery measure at baseline, with individuals without poverty experiences having higher scores on the QPR (M = 34.63, SD = 8.90) than those with poverty experiences (M = 27.94, SD = 11.00; $t(49) = 2.31$, $p = .01$, corrected $p = .038$).

Discussion: To date, the proportion of individuals with experiences of childhood poverty is higher than the general American population. These experiences of poverty disproportionately affect Black and African American service users. Individuals with these experiences were less likely to agree with statements indicating recovery at their first recorded assessment in CSC. This continues to support that socioeconomic experiences should be considered as a factor contributing to clinical outcomes. Future analyses will examine current socioeconomic status (SES) as a moderator of clinical outcomes at baseline and explore how childhood poverty and current SES may moderate change in clinical outcomes throughout CSC treatment.

F251. IMPLEMENTATION OF GUIDELINES ON FAMILY INVOLVEMENT FOR PERSONS WITH PSYCHOTIC DISORDERS (IFIP): IMPACT ON PATIENTS, RELATIVES, AND SUPPORT SERVICES

Irene Norheim^{*1}, Reidar Pedersen², Maria Lie Selle³, Jan Ivar Røssberg⁴, Lars Hestmark², Kristin Sverdvik Heiervang⁵, Torleif Ruud⁶, Vilde Maria Åsholt¹, Kristiane Hansson², Paul Møller¹, Roar Fosse¹, Maria Romøren²

¹Vestre Viken Hospital Trust, , ²Centre for Medical Ethics, Institute of Health and Society, University of Oslo, ³Health Services Research Unit, Akershus University Hospital, ⁴Institute of Clinical Medicine, University of Oslo, Oslo University Hospital, ⁵Division of Mental Health Services, Akershus University Hospital, ⁶Institute of Clinical Medicine, University of Oslo

Background: Psychotic disorders often lead to functional and social impairment, affecting the life and well-being of both patients and relatives. Relatives may provide a unique and long-lasting social support, while being a rehabilitation resource for the patients. At the same time, the nature of psychosis constitutes a great burden for relatives and may lead to depression, stress and burnout. Family involvement is therefore a decisive part of treatment, aiming to improve conditions for patients' and relatives' psychosocial health and well-being. Despite family interventions are recommended in treatment guidelines worldwide at all stages of psychotic disorders, it is scarcely provided in routine clinical practice. This sub-study is part of The Implementation of guidelines on Family Involvement for persons with Psychotic disorders (IFIP)' trial. The aim is to examine how much family involvement the patients and their relatives received in the intervention- and control arm, and the patients' and relatives' service satisfaction, perceived psychosocial health and quality of life.

Methods: A multicenter, parallel cluster randomized controlled trial randomly assigned 15 Norwegian Community Mental Health Center (CMHC) units to "The IFIP intervention" or treatment as usual (TAU). The intervention consisted of 1. Clinical interventions: Basic family involvement practices (BFIS) and family psychoeducation (FPE); 2. Implementation interventions: Implementation team, family coordinator, training etc.; 3. Implementation strategies: Leadership commitment, whole ward approach and responsive evaluation. The units recruited patients with psychotic disorders and their closest relative in pairs to answer a questionnaire at baseline, 6 and 12 months follow-up. The primary outcome for patients was the relationships subscale of The Behavior and symptom identification scale (Basis-24), and for the relatives the experienced support from the health services of Carer well-being and support questionnaire (CWS-B).

Results: Totally 231 patient-/relative pairs were analyzed (135 intervention; 96 TAU). Response rate for instrument completion at 6 and 12 months follow-up was 89 and 90 % for patients and 84 and 89 % for relatives. Except 25% of the 6 months questionnaires, the follow-up data were collected during the COVID-19 pandemic. The IFIP intervention significantly increased the amount of various types of family involvement and support services from the CMHC units, including FPE. Preliminary analyses of the patients and relatives' outcomes indicate differences in service satisfaction and psychosocial health between the intervention and the TAU group. The analyses will be finished this year.

Discussion: To our knowledge, this is the first study to investigate the direct impact of an intervention on family involvement and support services and indirectly on the patients and relatives during a comprehensive, system-wide implementation of family involvement in routine mental health services. The results indicate that the IFIP intervention, despite being substantially affected by the pandemic, did increase the amount of BFIS and FPE, and preliminary results shows some positive outcomes for patients and relatives in the intervention arm. Findings from this study confirms the importance of CMHC units ensuring routines, knowledge, and competence among clinicians to offer family involvement tailored to the needs of each patient and their families in everyday mental health practices.

F252. OCCUPATIONAL IMPACT OF TARDIVE DYSKINESIA: A CROSS-SECTIONAL, INTERNATIONAL SURVEY ASSESSING THE PERCEPTIONS AND EXPERIENCES OF PATIENTS WITH TD AND PHYSICIANS WHO TREAT TD

Rinat Ribalov¹, Ayelet Yaari^{*2}, Aviva Peyser Levin³, Amy Yang⁴, Dahbia Horchi⁵, Erwan Berjonneau⁵, Perrine Le Calvé⁵, Marc Tian⁶, Shoshana Reshef⁷, Suzanne Reed⁵

¹Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research,

²Teva Pharmaceutical Industries, Ltd., ³Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs, , ⁴Teva Branded Pharmaceutical Products R and D, Inc., Global Health Economics and Outcomes Research, ⁵Oracle, Paris, ⁶Teva Branded Pharmaceutical Products R and D, Inc., Real World Evidence Statistics, ⁷Teva Branded Pharmaceutical Products R and D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany,

Background: Tardive dyskinesia (TD) is an involuntary, hyperkinetic movement disorder that markedly affects the quality of life of involved patients. This study assessed patient and physician perceptions of the impact of tardive dyskinesia (TD) on occupational functionality.

Methods: Adults (aged ≥ 18 years) with self-reported physician diagnoses of TD and schizophrenia or schizoaffective disorder, bipolar disorder, or major depressive disorder and TD-related movements were invited to complete an online questionnaire (27 June–17 October 2022). Certified physicians (neurologists and psychiatrists) practicing for ≥ 3 years, with $\geq 60\%$ of their time in direct patient care and treating ≥ 3 patients with TD in the prior 2 years, were also invited to complete an online questionnaire (27 June–27 July 2022). Physicians' and patients' data and questionnaires were unlinked.

Results: Patients (n=435; mean age, 42.4 years, 52% female) from Australia, China, South Korea, and Brazil and physicians (n=340; 61% psychiatrists) from Australia, China, South Korea, Brazil, and Israel were included in the study. Across countries, 248 (57%) patients reported not currently working. Among the 248 patients not working, 124 (50%) stated that TD symptoms are behind the fact that they are not working. Among these 124 patients, 44% cited physical limitations because of TD symptoms as the primary reason, followed by not being able to find an employer that will employ them because of TD symptoms (23%), embarrassment about TD symptoms (19%), and having to take a step down or change industry (15%). 61% of physicians reported "often"/"always or almost always" assessing impact of TD on occupational functioning. 75% and 72% of physicians perceived a "moderate"/"very strong" impact of TD on obtaining/maintaining employment and on the inability or reduced ability of patients to perform job duties, respectively.

Discussion: In these surveys, patients and physicians agreed that TD considerably impacts occupational functionality. Among patients who were unable to work because of their TD, the most common reason for not working was because of TD-related physical limitations.

F253. ATTITUDES DRIVING REGIONAL DIFFERENCES IN LAI ANTIPSYCHOTIC UTILIZATION FOR SCHIZOPHRENIA AMONG HEALTHCARE PROFESSIONALS, PATIENTS, AND CAREGIVERS (ADVANCE): PATIENT AND CAREGIVER QUALITATIVE INTERVIEWS

Kelli R. Franzenburg^{*1}, Rolf T. Hansen², Mark Suett³, Ayelet Yaari⁴, Aviva Peyser Levin⁴, Martin Sergerie⁵, Alma Gonzalez⁶, Kameron Sedigh⁷, Stephan Heres⁸, Martha Sajatovic⁹

¹Teva Branded Pharmaceutical Products R and D, Inc., ²Teva Branded Pharmaceutical Products R and D, Inc., North America Medical Affairs, ³Teva UK Limited, Global Medical Affairs, ⁴Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs, , ⁵Teva

Canada, Medical Affairs, ⁶Teva Branded Pharmaceutical Products R and D, Inc., Global Medical Affairs, ⁷Syneos Health New York, ⁸kbo-Klinik für Psychiatrie und Psychotherapie Nord. ⁹University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine,

Background: Schizophrenia imparts a substantial burden on individuals and society and is increasing in prevalence. Long-acting injectable antipsychotics (LAIs) improve adherence and reduce relapse and hospitalization rates compared with oral treatments for schizophrenia, yet rates of LAI use are low and inconsistent across regions. The objective of the Attitudes DrIVING regional differences in LAI ANTipsychotic utilization for schizophrenia among healthcare professionals (HCPs), patients, and CaregivErS (ADVANCE) study is to observe attitudes towards LAI use across regions.

Methods: Patients with schizophrenia and caregivers of patients with schizophrenia were recruited from Australia, Canada, China, Germany, Israel, Spain, South Korea, and the United States. Patients were ≥ 18 years of age and were being treated with LAIs or recommended LAI treatment for schizophrenia. Caregivers were actively participating in the management and treatment of schizophrenia for the person for whom they cared. For this qualitative portion of the ADVANCE study, qualified patients and caregivers completed a 60-minute interview.

Results: Twenty patients and 19 caregivers participated. Depending on their initial experience, 2 distinct patient treatment/disease management pathways emerged: 1) treatment at diagnosis early in symptom development with strong support in the outpatient setting, and 2) severe, acute episodes that required hospitalization—each with contrasting downstream effects on patient perspectives on LAI treatment. Patients who received initial outpatient treatment tended to be motivated to treat their condition and return to their pre-diagnosis state of being. They also tended to trust in the healthcare system, and to feel involved and collaborative regarding their treatment. Some noted the important role that their families play in their treatment. Patients who received initial outpatient treatment were likely to prefer an LAI over an oral treatment or to accept a recommendation of an LAI. Patients who initially received inpatient treatment had fears associated with treatment, felt a lack of control, and felt social stigma regarding their condition; they appeared unlikely to accept an LAI for long-term care because of a desire for autonomy or control over their treatment and/or a negative experience with injectable antipsychotics during their hospitalization. In general, patients with positive perceptions of LAIs were more likely to have strong family support, early disease detection, LAI use early in the disease course, and strong trust in their HCPs. Those with negative perceptions of LAIs likely had multiple hospitalizations, inconsistent or no family support, a history of forced/coerced treatment, and a lack of continuity of care from inpatient to outpatient care. Caregivers played various roles in disease management for those for whom they care and tended to focus on elements of patient quality of life rather than treatment management. The key caregiver-reported advantage of LAIs was less frequent reminders of the disease for both the patient and the caregiver; cost was also noted as a barrier towards LAI adoption. Caregivers reported receiving little education about treatment options available for schizophrenia.

Discussion: Initial schizophrenia presentation, family support, hospitalizations, HCP trust, and logistical challenges may all play a role in patient outcomes and perceptions of LAIs. Unfavorable early experience, especially in an inpatient setting, can have detrimental impact on patient perception of and willingness to accept LAIs. Ongoing research aims to extricate these variables influencing LAI acceptability in schizophrenia.

F254. ATTITUDES DRIVING REGIONAL DIFFERENCES IN LAI ANTIPSYCHOTIC UTILIZATION FOR SCHIZOPHRENIA AMONG

HEALTHCARE PROFESSIONALS, PATIENTS, AND CAREGIVERS (ADVANCE): HEALTHCARE PROFESSIONAL QUALITATIVE INTERVIEWS

Kelli R. Franzenburg*¹, Rolf T. Hansen², Mark Suett³, Ayelet Yaari⁴, Martin Sergerie⁵, Sigal Kaplan⁶, Alma Gonzalez⁷, Kameron Sedigh⁸, Stephan Heres⁹, Martha Sajatovic¹⁰

¹*Teva Branded Pharmaceutical Products R and D, Inc.*, ²*Teva Branded Pharmaceutical Products R and D, Inc., North America Medical Affairs*, ³*Teva UK Limited, Global Medical Affairs*, ⁴*Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs*, ⁵*Teva Canada, Medical Affairs*, ⁶*Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcome Research*, ⁷*Teva Branded Pharmaceutical Products R and D, Inc., Global Medical Affairs*, ⁸*Syneos Health New York*, ⁹*kbo-Klinik für Psychiatrie und Psychotherapie Nord*. ¹⁰*University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine*,

Background: Healthcare professional (HCP) views on and use of long-acting injectable antipsychotics (LAIs) in schizophrenia treatment vary widely despite known benefits. Here, a subset of data generated in a novel, multi-national survey study, Attitudes DriVing regional differences in LAI ANTipsychotic utilization for schizophrenia among HCPs, patients, and CaregivErs (ADVANCE), was leveraged to elucidate qualitative data on HCP attitudes on LAI use.

Methods: HCPs from Australia, Canada, China, Germany, Israel, Spain, South Korea, and the United States (US) were screened via questionnaire and included if they specialized in psychiatry, spent ≥65% of their time providing direct patient care, managed ≥10 adult patients with schizophrenia monthly, and reported treating patients with second-generation LAIs. HCPs who met inclusion criteria were interviewed regarding their experience managing and treating patients with schizophrenia, including the role of LAIs.

Results: Ten psychiatrists (spending an average of 45% of their time at hospital-based outpatient clinics) and 7 psychiatric nurses (averaging 47% of time at community mental health centers) were interviewed. HCPs reported that patients often follow a treatment and relapse cycle leading to encounters with inpatient and outpatient systems and providers. Systemic factors, including lack of community psychiatrists (Australia, Canada, China, Germany, and Israel) and low cost of inpatient care for the patient (Australia, Canada, and Germany), may drive patients toward inpatient care. Inpatient treatment focuses on acute symptom management and crisis stabilization, while outpatient treatment is more likely to incorporate patient perspectives and prioritize long-term quality-of-life considerations. Treatment objectives of psychiatrists were particularly focused on managing positive symptoms, especially in the inpatient setting, whereas psychiatric nurses were more focused on patient quality of life. Psychiatrists and psychiatric nurses reported mean (range) LAI use of 27% (10%–50%) and 30% (5%–60%), respectively. Overall, HCPs conveyed positive perspectives of LAIs and noted that side effects were a key consideration when choosing an LAI. There was a lack of consensus about the ideal patient profile for LAIs; however, most HCPs were aligned that use in younger patients or those with less severe disease should be limited. The most common barriers to LAI use were patient aversion to injections, logistical challenges (lack of staff and training), patient trauma from prior forced injection, and lack of product availability/cost; HCPs from Israel and the US also noted private insurance coverage issues, and HCPs from China reported cost to the patient as the key barrier towards LAI adoption. In the inpatient setting, costs and logistical considerations for LAIs were deemed less of a barrier. Community treatment orders or involuntary treatment with LAIs (Australia, Canada, and Israel) may lead to negative patient perceptions of LAIs.

Discussion: HCPs reported that patients with schizophrenia had cyclical encounters with HCPs in inpatient and outpatient settings as well as barriers to care, which may influence treatment planning, including LAI recommendations and patient acceptance. In some countries, HCPs report that systemic factors drive patients to inpatient care settings where the focus on positive symptom control may lead to negative patient experiences with LAIs. Regional differences in LAI utilization rates are likely influenced by a combination of factors, including systemic, HCP, and patient factors. Ongoing research aims to disentangle these factors and understand the impact on regional LAI utilization rates.

F255. PERSONAL RECOVERY SELF-REPORT OUTCOME MEASURES IN SERIOUS MENTAL ILLNESS: A SYSTEMATIC REVIEW OF MEASUREMENT PROPERTIES

Simon Felix^{*1}, Valery Kevin-Marc¹, Meryl Caiada¹, Sarah Guionnet¹, Julien Bonilla-Guerrero², Jean-Marc Destailhats², Antoinette Prouteau³

¹University of Bordeaux, ²Jonzac Hospital, ³University of Bordeaux, Jonzac Hospital

Background: Consumer movements of people with lived experience of mental illness have long advocated for the acknowledgement of personal recovery. Personal recovery in mental illness can be defined as “a deeply personal, unique process [...] a way of living a satisfying, hopeful, and contributing life even with limitations caused by illness” (Anthony, 1993). By challenging the traditionally established biomedical models and practices surrounding the notion of mental illness, personal recovery thus represents a paradigm shift in mental healthcare (Davidson et al., 2005). The transformation of mental health services towards both person and recovery-centered care has therefore been defined as a priority by the World Health Organization (WHO, 2021). Yet, it has proven difficult to create recovery-oriented health services that consider users subjectivity and perspectives: there is a need to shift from traditional clinical outcome measures to assess specific personal recovery processes (Slade et al., 2014). Validated self-report outcome measures (Patient Reported Outcome Measures, PROMs) are therefore needed to facilitate the transformation towards recovery-oriented practices and services. Objectives were to identify published measures and analyze their measurement properties using a standardized methodology.

Methods: Following the COSMIN guidelines (Prinsen et al., 2018, Mokkink et al., 2017), we conducted a systematic review of personal recovery PROMs in serious mental illness. The MEDLINE, PMC, PsycINFO, PsycARTICLES, PBSC and Scopus electronic databases were searched for articles published between May 2012 and October 2023. Full-text articles from a previous systematic review were also examined. A broad spectrum of psychometric properties was reported and analyzed using standardized criteria. A supplementary content validity analysis was conducted.

Results: 118 studies were included in the review, describing 25 PROMs. Ten of them had not been identified in previous reviews. Quality of evidence was globally poor for most PROM measurement properties. Very little evidence was found for cross-cultural validity, measurement invariance, measurement error and criterion validity. The Recovery Assessment Scale and Questionnaire about the Process of Recovery showed the strongest evidence for sufficient psychometric data on a wide range of measurement properties.

Discussion: Several personal recovery measures are now available. While research is still needed to enhance their validity on some psychometric properties, the current tools appear sufficient to cover most research and clinical needs.

F256. BUILDING A CONTINUUM OF CARE FOR TREATMENT-RESISTANT SCHIZOPHRENIA SPECTRUM DISORDERS

Rocco Marotta*¹, Irene Bihl², Meriwether Brown³, Suma Srishaila³, Sophia Walker⁴, Katharine Cutts Dougherty³, Lisa Mann³, David Rowe³, Robert Laitman⁵

¹*Silver Hill Hospital, Yale University*, ²*Sage Healthcare, Yale University*, ³*Silver Hill Hospital*, ⁴*Silver Hill Hospital, NYU*, ⁵*Bronx Westchester Medical Group*

Background: Schizophrenia Spectrum Disorder (SSD) continues to pose a tremendous burden on human societies. Despite decades of research, treatment outcomes are still not fully encouraging. Clozapine is universally recognized as the most effective antipsychotic available but is still underutilized and in many institutions, is regarded as a last resort treatment choice for resistant cases only.

Methods: We at Silver Hill Hospital (SHH), Project Daniel, and Sage Healthcare at the Bridgeport Rescue Mission, are developing a continuum of care to make clozapine available more widely. The prototype comprehensive program on campus of Silver Hill Hospital, evaluates and treats a unit maximum of 14 patients for SSD, and those with treatment resistance are prescribed clozapine, which, when appropriate, is supplemented with oxytocin, modafinil, lamotrigine, or another antipsychotic. These patients are followed over many months to years and those who have continued in follow-up (N=60), have shown a promising course, with outcomes including finishing their education, many to the graduate level, working, maintaining sobriety, living independently and reconnecting with family. The high cost of such continuity of care in a residential setting has been addressed by the development of Team Daniel, that provides an outpatient program, following over 200 patients, some of whom were referred from SHH. Patients in Team Daniel follow a strict protocol involving clozapine treatment, mixed medication when appropriate, along with group therapy and family involvement. This program has sustained a meaningful recovery rate of over 70%, and reduced hospitalization from 93% in the two years prior to joining the practice to 15% readmitted.

Results: Our work up to this point clearly demonstrates that the five pillars of successful treatment include: 1) sobriety; 2) medication management and compliance; 3) therapeutic alliance between patient, family, and healthcare provider; 4) support in maintaining social connectedness; and 5) long-term, lasting clinical follow-up. Clozapine's particular effectiveness, not only in controlling positive symptoms of psychosis, but also its significant effects in controlling substance use, impulsivity, suicidality, long-term remission, and overall increased survival, compels us to seek ways to use it effectively in vulnerable communities of high risk. We recognize our responsibility to extend this treatment model, including to those with limited economic resources and a high level of illicit substance use.

Discussion: In this presentation, we outline a model of treatment that has evolved as an extension to Silver Hill Hospital's treatment plan but is targeted at the most vulnerable, complex, inner-city population through the operation of a free community healthcare clinic, Sage Healthcare. The model provides for local university faculty and students in various healthcare disciplines to identify clients with the diagnosis of schizophrenia, and implement a detailed clozapine treatment protocol, managing side effects, adjunctive medications, and evaluating outcomes through the use of psychosis rating scales such as PANSS. Group therapy, family engagement, as well as the supportive structure of Bridgeport Rescue Mission itself emulates the SHH program. Experienced SHH clinicians play a major role in the development and support of this program. The goal is to replicate in the community, a residential setting

through which patients can be followed daily, treated primarily with clozapine and return to long-term stability and a meaningful life.

F257. THE LONG-TERM FOLLOW-UP OF THE TREATMENT AND EARLY INTERVENTION FOR PSYCHOSIS PROJECT: LOFT STUDY PROTOCOL

Teya Petrova*¹, Philippe Golay¹, Paul Klauser², Raoul Jenni³, Nadir Mebdouhi¹, Philippe Conus¹, Luis Alameda¹

¹*Service of General Psychiatry, Lausanne University Hospital and University of Lausanne,*

²*Center for Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Lausanne University Hospital,* ³*Center for Psychiatric Neuroscience, Lausanne University Hospital*

Background: Psychotic disorders represent a leading cause of chronic disability. While early intervention (EI) in psychosis is the gold standard to treat patients after a first episode of psychosis (FEP), knowledge of the evolution and the long-term effects of such type of intervention is limited, underscoring the critical importance of early detection and intervention. To date, very few studies have examined the long-term impact of such type of treatments as well as the long-term outcome of FEP patients. The Long-term Follow-up of Treatment and Early Intervention for psychosis (LOFT) is a up to 20-year longitudinal study within a clinical epidemiological cohort of nearly 1000 patients who completed a three-year program specialized in early intervention for the initial stages of psychotic disorders, called Treatment and Intervention in Psychosis Program (TIPP) in Lausanne, Switzerland, and who went through a deep phenotyping during assessment their first years of treatment. Hence, the objective of this study is to gain insight into the long-term evolution of physical and mental health, as well as in term the neurobiological functioning of the patients treated after a first psychotic episode in TIPP.

Methods: Around 700 patients treated in TIPP between 2004 and 2019 will be recontacted and reevaluated at either 5, 10, 15 and 20 years after their entry in the TIPP program. Static factors such as demographics, childhood trauma history and variations in the level of insight, as well as dynamic changes in clinical variables over time will be analyzed using traditional group level and machine learning methods to provide prognostic insights. A subsample of the patients who took part in a research program will be invited to undergo additional neurobiological assessments to explore specific biomarkers.

Results: -

Discussion: The study protocol of the recently funded study will be presented alongside with an update on recruitment. Identifying determinants of the long-term evolution in relation to past TIPP program evaluations should enable us to generate avenues of improvement for clinical treatment strategies and advance the path toward precision medicine for individuals with psychotic disorders. We hope LOFT will help reshape and redefine current interventions for subgroups of patients at risk of poorer outcome.

F258. INTERVENTIONS TARGETING IDENTITY: A TRANSDIAGNOSTIC SCOPING REVIEW WITH IMPLICATIONS FOR ADULTS WITH A SEVERE MENTAL ILLNESS

Lisette Van der Meer*¹, Elske Kronemeijer¹, Hanneke Muthert¹, Ellie van Setten², Marieke (Gerdina) Pijnenborg¹

¹University of Groningen, ²On personal affiliation

Background: People with a severe mental illness (SMI) often face challenging life-experiences that impact their identity. Nevertheless, no overview exists of interventions on the way mental health professionals may support people in the process of regaining (grip on) identity. We conducted a transdiagnostic scoping review of evaluated interventions that target identity or self-concept in people with severe mental illness (SMI), 2) acquired brain injury (ABI), and 3) intellectual disability (ID).

Methods: We conducted a literature search in November 2021 (with an update in November 2023) in the databases PsycInfo, Medline, the Psychology and Behavioral Sciences Collection, CINAHL, Academic Search Premier, EBSCO open dissertations, and Web of Science. Search terms included search strings related to a) relevant concepts (e.g. identity, self-concept, etc.) and b) interventions or evaluation methods and c) target groups.

Results: Thirty studies were included. Most studies included small groups, were feasibility studies or qualitative evaluations. Most interventions were group-based, relatively brief and varied in theoretical background and intervention characteristics. Qualitative data showed positive results for narrative interventions, as well as (un)structured peer group interventions. Quantitative studies suggest that programs explicitly targeting identity or self-esteem may be effective.

Discussion: Some promising identity-based interventions have been developed, but future research is needed to investigate the effect of intervention content and format. In general, quantitative identity outcomes are lacking for less structured supportive peer-groups, while qualitative evaluations are lacking for structured identity-based programs.

F259. HYBRID MHEALTH CARE: PATIENT PERSPECTIVES OF BLENDED TREATMENTS FOR PSYCHOSIS: A SYSTEMATIC REVIEW

Frances Greenway*¹, Mark Weal¹, Emma Palmer-Cooper¹

¹University of Southampton

Background: Disengagement rates for first episode psychosis intervention services are currently higher than those of other mental health services. As such, mHealth interventions have been extensively employed in mental health research, showcasing their potential to address the significant treatment gap. While numerous studies underscore the advantages and functionalities of mHealth, challenges persist regarding patient uptake and sustained engagement, especially among individuals with schizophrenia and non-affective psychosis. There is a growing recognition that integrating mHealth interventions with face-to-face interactions could enhance overall care. Hybrid healthcare, characterised by the interaction of digital tools and in-person care, empowers patients to take more control of their health while benefiting from clinician support. Given the global initiative to incorporate mHealth into traditional mental health care, this review aims to explore individual-level barriers and facilitators to engagement with hybrid digital systems, aiming to uncover strategies for promoting trust and enhancing engagement. By identifying key factors that impact the outcomes of these interventions, particularly understanding participant engagement, this research contributes valuable insights to the development of accessible and effective mental health interventions.

Methods: The search yielded 5,255 studies but only 16 were included in the final review. An inductive approach was taken to derive themes and patterns from the primary data, adhering to the primary studies own interpretations. Four electronic databases were systematically searched (Medline, Web of Science, CINAHL, and PsychINFO) to identify hybrid digital interventions being used to treat psychosis spectrum disorder. The primary interest was to understand individual level barriers and facilitators to engagement with hybrid digital systems. Studies that only reported the efficacy of the interventions were excluded.

Articles of all study designs, written in English and had been featured in a peer reviewed journal between inception and May 2023 were included in the primary search. Reasons for exclusion were primarily due an absence of an in-person presence throughout the intervention and did not explore participants experiences of the intervention.

Results: Seven analytic themes were identified: (1) Tool to Aid Communication; (2) Central Role of the Therapist; (3) Increased Sense of Support; (4) Greater Insight into Voices; (5) Enabling Technologies (6) Sense of Community; (7) Barriers to Engagement. A number of participants conveyed a heightened sense of control and understanding of their symptoms, with daily reflection and monitoring features among the most positively regarded. Obstacles such as difficulties using technology and feelings of paranoia were recognised as challenges to effective engagement with mHealth in 8 of the included studies. However, regular interaction with a therapist was noted to alleviate some of these barriers and helped participants to feel more support.

Discussion: The themes identified in this review highlight the potential impact of hybrid digital interventions within this population. Context-aware systems, customised for each individual, may prove especially valuable in improving engagement and enhancing therapeutic alliance. This review aims to guide and shape the design and development of innovative hybrid digital interventions, offering valuable insight for researchers and clinicians involved in the development of new interventions and the seamless integration of mobile health (mHealth) into conventional healthcare practices.

F260. PERCEIVED SOCIAL DEFEAT AS A MECHANISM BETWEEN CHILDHOOD ADVERSITY AND SUBCLINICAL PSYCHOTIC PHENOMENA: AN EXPERIENCE SAMPLING STUDY

Pilar Torrecilla^{*1}, Manel Monsonet¹, Thomas R. Kwapi², Neus Barrantes-Vidal¹

¹*Universitat Autònoma de Barcelona*, ²*University of Illinois at Urbana-Champaign*,

Background: The experience of social defeat, described as the negative experience of being excluded from the majority group, has been suggested as an underlying mechanism between several psychosocial risk factors and psychosis expression. Increasing evidence has shown that social defeat plays a role explaining the effects of childhood adversity on the development of psychotic symptoms. However, limitations regarding the definition and measurement of social defeat have been acknowledged, and most studies have focused on clinical populations or individuals at clinical high risk for psychosis. The study of the psychological mechanisms underlying psychosis expression may benefit from examining nonclinical populations exhibiting subclinical psychotic-like experiences (PLE) without the burden of a clinical status. To this aim, the present study ecologically assessed the subjective experience of perceived social defeat using Experience Sampling Methodology (ESM), and examined for the first time its association with psychotic-like and affective expression as well as its potential mediating

role between different dimensions of childhood adversity and subclinical experiences in the flow of daily life.

Methods: The study is embedded in the Barcelona Longitudinal Schizotypy Study (BLISS) and comprises data for 159 nonclinical young adults (mean age=28, sd=2.3) with a wide distribution of schizotypy traits. Participants were longitudinally assessed from Time 1 to Time 5 (mean time interval=7.8 years). Participants completed interview-based and self-report measures of childhood adversity at Time 1 and were assessed with ESM at Time 5. Social defeat was measured with two ESM items capturing appraisals of inferiority and outsider status. Multilevel structural equation models were used to assess the relationship between social defeat scores and daily-life subclinical experiences, and a series of multilevel mediation models were conducted to examine the within-person indirect effect of the associations between empirically-derived early adversity dimensions and momentary subclinical experiences (paranoia, positive PLE, negative PLE, disorganization, negative affect and positive affect) through momentary social defeat.

Results: Social defeat was positively associated with momentary levels of paranoia, positive PLE, negative PLE, disorganization and negative affect, and negatively associated with positive affect. Multilevel mediation analyses indicated that the indirect effect of childhood experiences of deprivation and sexual abuse to paranoia, positive PLE, negative PLE, disorganization, low positive and high negative affect through appraisals of social defeat were statistically significant.

Discussion: Perceived appraisals of social defeat impact psychotic and affective experiences in daily life. The study adds on previous literature supporting the mediating role of social defeat in the association of childhood adversity and psychosis expression captured in individuals' real context, and extends findings by suggesting that specific forms of adversity (i.e., deprivation and sexual abuse) may particularly increase the experience of social defeat as compared to other forms of adversity (e.g., physical or emotional abuse). These findings highlight the relevance of exploring different types of adversity when investigating the underlying psychological mechanisms and that socially excluded and minority groups are an important target to implement prevention and intervention strategies to reduce psychosis risk.

F261. HOMELESSNESS, PSYCHIATRIC DISORDERS, AND VIOLENT OFFENDING: A NATIONWIDE, REGISTER-BASED COHORT STUDY

Sandra Nilsson^{*1}, Thomas Munk Laursen², Lars Højsgaard Andersen³, Merete Nordentoft⁴, Seena Fazel⁵

¹*Copenhagen Research Center for Mental Health - CORE*, ²*Aarhus University*, ³*ROCKWOOL Foundation Research Unit*, ⁴*Mental Health Centre Copenhagen*, ⁵*University of Oxford*

Background: Psychiatric disorders are linked to increased risk of violent offending and are prevalent in people experiencing homelessness, but little is known about how homelessness is linked to violent crimes. We aimed to examine the association of homelessness and schizophrenia spectrum disorder with the risk of violent offending.

Methods: We did a nationwide, register-based cohort study of people living in Denmark between Jan 1, 2001, and Dec 31, 2021, aged 15 years or older. The study population was obtained from the Danish Civil Registration System, which was linked to several other registers (The Danish Homeless Register, the Danish Central Criminal Register, the Danish National Patient Register, and the Danish Psychiatric Central Research Register). Outcome was first violent offending, defined as first date of a police-recorded violent crime leading to a conviction. We calculated incidence rates per 10,000 person-years, incidence rate ratios (IRRs)

using Poisson regression analysis, and probability of violent offending. Analyses were stratified by sex. Age, calendar year, country of origin, and highest educational level were included as confounders.

Results: The study cohort included 1,786,433 Danish residents aged 14-42 years living between Jan 1, 2001, and Dec 31, 2021, contributing with 21,336,322 person-years at risk. Overall, 57,084 (3.2%) individuals had a police-record of any violent offending during follow-up. After five years follow-up, the probability of any violent crime in males and females experiencing homelessness was: 15.8% (95% CI 14.8-16.8) and 5.1% (95% CI 4.4-5.9), respectively. The incidence of violent offending in individuals with history of homelessness and schizophrenia spectrum disorder was 395.1 per 10,000 person-years (95% CI 350.9-444.8) in males and 187.9 per 10,000 person-years (95% CI 151.5-233.0) in females; after adjustment for age and calendar year, the IRRs were 20.2 (95% CI 18.0-22.8) in males and 64.9 (95% CI 52.1-80.8) in females compared with those without history of homelessness and no schizophrenia spectrum disorder. The IRRs were higher than in those only experiencing homelessness (IRR 11.1, 95% CI 10.4-11.9 in males and 19.6, 95% CI 17.0-22.6 in females) and in those who only had a schizophrenia spectrum disorder (IRR 4.5, 95% CI 4.3-4.8 in males and IRR 10.6, 95% CI 9.7-11.6 in females). The risk estimates were reduced but remained high after adjustment for country of origin and educational level.

Discussion: Homelessness was associated with increased risk of violent offending independently and in combination with schizophrenia spectrum disorder. Individuals experiencing homelessness and having a schizophrenia spectrum disorder constitute a high-risk group of violent offending. Improved efforts to mitigate and prevent homelessness and support people with schizophrenia spectrum disorder are needed.

F262. OPEN BOARD

F263. EXPOSOME SCORES AND PROTECTIVE FACTORS IN PSYCHOSIS PRONENESS

Eda Karaca¹, Didenur Şahin¹, Seda Arslan¹, Tuba Şahin¹, Simge Merve Vit¹, Su Barış Karakelle¹, Timothea Touloupoulou², Didenur Sahin Cevik*¹

¹*Bilkent University*, ²*Interdisciplinary Neuroscience Program, Bilkent University; National Magnetic Resonance Research Center (UMRAM), Aysel Sabuncu Brain Research Centre (ASBAM), Bilkent University; National and Kapodistrian University of Athens, Icahn School of Medicine at Mount Sinai*,

Background: Psychosis is a mental disorder in which the contribution of the environment, along with genetic factors, in its etiology, is significant. This contribution can be measured in aggregate quantitatively, creating an exposome score. On the other hand, some protective factors that could reduce the likelihood of disease development have been recently identified. For example, healthy relationships, high IQ, and positive self-esteem are some of the factors that are thought to be protective and expected to significantly alter the impact of the environmental risk. We aimed to explore the role of the exposome score on psychosis proneness and whether protective factors moderate this relationship.

Methods: 488 healthy individual twins and siblings, some oversampled for a family history of psychosis (229 twin pairs, 30 healthy siblings of first episode psychosis patients) aged between 14-23, were assessed with CAPE-42 and environmental assessments (17 variables). Exposome

scores of each participant were calculated and included, cannabis use, abuse, neglect, bullying, winter birth and hearing impairment (a measure of environmental risk specific to psychosis). An overall protective factor score was calculated with 12 factors: IQ, social class, relationship status, religious affiliation, number of friends, support, social cohesion, feeling love in the family, having a close family, strong family bonds, positive self-esteem, positive thoughts about others. Each score was calculated according to whether the participant had this protective factor (scored as 1) or not (scored as 0) (mean+ SD was used as a threshold in the continuous variables) out of 12.

Results: Linear regression showed a significant effect of exposome score on psychosis proneness (total CAPE score) (Estimate=4.74, $t=6.99$, SE= 0.68, $p < 0.001$), indicating that higher exposome score was associated with higher psychosis proneness. There was also a significant effect of overall protective factor score on psychosis proneness (Estimate=-2.62, $t=-6.83$, SE= 0.38, $p < 0.001$), implying that a higher overall protective factor score was associated with lower psychosis proneness. The effect of exposome on psychosis proneness was moderated by a significant interaction between exposome and overall protective factor score (Estimate=-1.91, SE=0.39, $z=-4.96$, $p < 0.001$), suggesting that the effects of exposome on psychosis proneness varied depending on the overall protective factors score.

Discussion: The exposome scores, which measure different environmental risk factors, showed a strong relationship with a higher risk of psychosis. Conversely, an overall protective factor score showed an association with a lower risk of psychosis. The interaction analysis suggested that the overall protective factor score moderated the effect of the exposome on psychosis proneness, highlighting the dynamic and interrelated nature of these influences. This nuanced understanding offers a more comprehensive approach to the management and prevention of psychosis by offering insightful information for creating focused interventions and preventive measures.

F264. MAINTENANCE OF EFFICACY OF KARXT (XANOMELINE AND TROSPIMUM) IN SCHIZOPHRENIA

Inder Kaul¹, Elan A. Cohen², Andrew C. Miller¹, Amy Claxton¹, Steven M. Paul¹, Stephen K. Brannan¹, Stephen Brannan*¹

¹Karuna Therapeutics, ²CenExel Hassman Research Institute

Background: A high unmet medical need exists for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action. All currently approved treatments for schizophrenia have D2 dopamine receptor blocking activity; the efficacy and tolerability limitations of these therapies are well known. KarXT, an investigational medication, combines the dual M1/M4 preferring muscarinic acetylcholine receptor agonist xanomeline and the peripherally restricted muscarinic receptor antagonist trospium chloride. KarXT is designed to preserve the beneficial central nervous system effects of xanomeline while reducing adverse events (AEs) due to peripheral muscarinic receptor activation. The efficacy and safety of KarXT in schizophrenia were demonstrated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. The Phase 3, multicenter, 52-week, outpatient, open-label extension EMERGENT-4 (NCT04659174) trial evaluated long-term safety, tolerability, and efficacy of KarXT in adults with schizophrenia.

Methods: The EMERGENT-4 trial enrolled participants who previously completed the treatment period of one of the Phase 3 double-blind studies, EMERGENT-2 or EMERGENT-

3. Regardless of previous treatment, eligible participants were started on KarXT dosing (xanomeline/trospium) at 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID. Efficacy analyses were conducted in the modified intent-to-treat population, defined as all randomized participants who received ≥ 1 trial drug dose and had a baseline and ≥ 1 postbaseline PANSS assessment. Efficacy measures included a change from acute study baseline to Week 52 in Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores.

Results: Prior to receiving KarXT in the EMERGENT-4 study, all participants previously completed the treatment period of one of the Phase 3 double-blind studies and received KarXT or placebo. Participants who had received KarXT in the previous study had a lower mean PANSS total score at baseline compared to those who had received placebo (76.1 vs 86.5), reflecting greater improvement during 5 weeks of active treatment. After initiating treatment with KarXT, participants who received placebo in the previous studies exhibited rapid improvement in symptoms as early as the first assessment point in EMERGENT-4 (Week 2). After 4 weeks of KarXT treatment in EMERGENT-4, there were no meaningful differences in PANSS total score between participants who had previously received KarXT versus those who had received placebo. For all participants, improvements from baseline continued through 52 weeks of treatment for PANSS total score, PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores. Data are continuing to be recorded in this ongoing study, and updated analyses will be available at the time of the meeting.

Discussion: In the interim analysis of the open-label extension EMERGENT-4 trial, average participant improvement continued throughout the 52-week trial regardless of whether participants have received previous treatment with KarXT or placebo. These findings support the potential of KarXT to be first in a new class of medications to treat schizophrenia based on muscarinic receptor agonism and without any direct dopamine D2 receptor blocking activity.

F265. MOTHERHOOD IMPACT ON WOMEN WITH A FIRST EPISODE OF PSYCHOSIS: 3-YEAR FOLLOW-UP STUDY ON CLINICAL, FUNCTIONAL AND NEUROCOGNITIVE OUTCOMES

Alexandre Díaz-Pons¹, Marina Soler-Andrés², Víctor Ortiz-García de la Foz¹, Nancy Murillo-García¹, Ángel Yorca-Ruiz¹, Rebeca Magdaleno Herrero¹, Sara Barrio-Martínez¹, Sergio Castaño-Castaño³, Alexandre González-Rodríguez⁴, Esther Setién Suero⁵, Rosa Ayesa-Arriola¹, Rosa Ayesa-Arriola⁶, Nancy Murillo-García^{*7}

¹IDIVAL, ²University of Oviedo, ³University of Oviedo, ⁴Mutua Terrassa, ⁵European University of the Atlantic, ⁶Valdecilla Biomedical Research Institute, IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria, ⁷Valdecilla Biomedical Research Institute; Research Group on Mental Illnesses

Background: Women facing a first episode of psychosis (FEP) deal with distinct challenges, amplified by the added responsibility of parenthood. Current research suggests that parental rates seem to be higher among FEP women (50-60%) than FEP men, making them more likely to confront this role alongside the inherent challenges connected to the illness. Limited scientific literature on how parenthood affects female with psychosis presents mixed perspectives. The aim of the present study was to explore factors contributing to diminished parental rates in FEP patients and exploring its impact on FEP women.

Methods: This study focused on 610 FEP patients from the PAFIP program in Santander, Spain (2001-2017). Categorizing based on pre-illness-onset parenthood status, men constituted 57.54% (n=351) of the sample, and only 5.41% (n=19) were fathers, while women represented 42.55% (n=259) of the sample, with 36.29% (n=94) of them being mothers. ANCOVA analyses compared baseline and 3-year follow-up outcomes, considering age and education influence.

Results: Parents exhibited older ages at illness onset and program inclusion compared to both non-parent groups ($p \leq 0.001$). Non-mothers surpassed non-fathers in educational levels, IQ, and employment rates ($p \leq 0.05$). Mothers demonstrated a shorter duration of untreated illness and were more likely to come from a low socioeconomic-status family than non-mothers ($p \leq 0.05$). Mothers exhibited superior premorbid adjustment compared to both non-mothers and non-fathers ($p \leq 0.001$). Non-fathers presented higher rates of tobacco, cannabis, and alcohol consumption, along with poorer premorbid adjustment than mothers and non-mothers ($p \leq 0.001$). At three-year follow-up mothers showed lower global neurocognitive deficit scores, and general disability than non-mothers ($p \leq 0.05$). Specifically, mothers exhibited better attention, executive functions, and motor dexterity outcomes ($p \leq 0.05$). Over time, positive and disorganized dimensions were impacted in both groups ($p \leq 0.001$), along with executive functions and motor dexterity ($p \leq 0.05$).

Discussion: Women presented higher rates of pre-illness-onset parenthood status than men. Mothers experienced delayed psychosis onset, suggesting a logical connection between preexisting motherhood and onset age. Prolonged psychosis-free periods may enhance parenthood opportunities, suggesting a potential stability or resilience phase before symptoms. This aligns with findings of superior neurocognitive performance and diminished disability in mothers. Interestingly, these advantages seem present before illness onset, as indicated by better premorbid adjustment. While both groups improved over time, no differences emerged in time by group interaction, suggesting motherhood did not distinctly influence outcomes. An alternative interpretation posits improved initial circumstances or traits, like better premorbid adjustment among mothers, enhancing parenthood likelihood. These considerations have potential implications for treatment planning.

F266. RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND TOLERABILITY OF ELECTROCONVULSIVE THERAPY IN PATIENTS WITH CLOZAPINE-RESISTANT SCHIZOPHRENIA

Helio Elkis^{*1}, Debora Melzer-Ribeiro¹, Isabel Napolitano¹, Samuel Leite¹, Joston A. de Souza¹, Adriana Vizzotto¹, Elaine Di Sarno¹, Marisa Fortes¹, Monica Gomes¹, Graça de Oliveira¹, Belquiz Avrichir¹, Leda Talib¹, Christoph Correll²

¹*Institute of Psychiatry University of São Paulo*, ²*The Zucker Hillside Hospital*

Background: Clozapine is the only antipsychotic indicated for Treatment-Resistant Schizophrenia (TRS) but there is no established treatment for patients with clozapine-resistant schizophrenia (CRS). Clozapine augmentation with antipsychotics or other substances is effective in comparison with placebo while augmentation with electroconvulsive therapy (ECT) showed to be effective in comparison with treatment as usual, but not with placebo (sham-ECT). The aim of the present study was to compare ECT vs Sham- ECT in patients defined as CRS by the Treatment Response and Resistance in Psychosis Working Group Consensus Guidelines on Diagnosis and Terminology (TRRIP).

Methods: This was a double-blind, randomized, controlled-trial that compared 40 outpatients with DSM-5 schizophrenia randomized to receive 20 sessions of ECT (n=21) or sham-ECT

(n=19). All patients received anesthesia by hypnotic induction using intravenously (IV): Propofol, Atropine, and Suxamethonium for muscle relaxation. The sham-ECT procedure used the same drugs, except for muscle relaxation, but, instead, 3 mg of midazolam IV for mild hypnotic induction. ECT or sham-ECT was administered twice weekly, with an inter-treatment interval of ≥ 3 days, until the patients completed 20 sessions (10-12 weeks). All participants and their relatives signed the informed consent. The study was approved by the institutional review board of Hospital das Clínicas of the University of São Paulo and registered in Clinicaltrials.gov. Patients were included based on the TRRIP criteria: 1- a confirmed diagnosis of TRS; 2- use of clozapine for ≥ 3 months, with plasma levels ≥ 350 ng/mL. Additionally, patients needed to have a total Positive and Negative Syndrome Scale (PANSS) score GREATER THAN 60 and a score of ≥ 4 in ≥ 2 of the seven items of the PANSS positive subscale. The primary outcome was the $\geq 50\%$ PANSS Total Score reduction; secondary outcomes were the change in scores of the PANSS subscales, the PANSS five-factor dimensions (Negative, Positive, Anxiety-Depression, Disorganized-Cognitive, Excitement), the PANSS-6 (delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, and lack of spontaneity of conversation flow) and the Calgary Depression Rating Scale (CDRS). Treatment response was analyzed by percentage reduction, Linear Mixed Models and effect sizes.

Results: At baseline, patients were 37.40 (± 9.62) years old, predominantly male (77.5%), and ill for 14.95 (± 8.32) years. The mean total PANSS score was 101.10 (± 24.91), and clozapine plasma levels were 909.25 (± 684.6) ng/mL, both values higher in comparison with the international literature. Groups were similar at baseline except for years of school education (included as a covariate). Two patients in each group dropped out during the study. At endpoint 1/19 of the completers (5.26%) in the ECT group and 0/17 in the sham-ECT group showed a $\geq 50\%$ total PANSS score reduction. Both groups showed no significant differences of the total PANSS score ($F=0.12$; $p=0.73$), Positive ($F=0.27$, $p=0.61$), Negative ($F=0.25$, $p=0.62$), and General Psychopathology scores ($F=0.01$, $p=0.94$) as well for all PANSS five factors, the PANSS-6 and CDRS. There were also no significant statistical differences between groups regarding adverse effects.

Discussion: The present study showed that ECT augmentation of clozapine was tolerable but not more efficacious than Sham-ECT. However, the findings may not be generalizable due to the relatively small sample size and the degree of severity of the population. Future studies with larger number of participants who are less compromised are warranted to assess the potential utility of ECT augmentation of clozapine in patients with CRS.

F267. PROSPECTIVELY ASCERTAINED CHILDHOOD PREMORBID PSYCHOLOGICAL FACTORS IN A COHORT OF 719 PATIENTS WITH SCHIZOPHRENIA AND 49,451 CONTROLS

Javiera Vásquez¹, José Conejeros², Camila Díaz Delarrosa³, Cristian Mena⁴, Juan Undurraga⁵, Alfonso Gonzalez-Valderrama⁶, Susana Claro⁷, Eduardo Undurraga⁸, Nicolas Crossley⁹

¹School of Medicine, Pontificia Universidad Católica de Chile, Santiago, ²Pontificia Universidad Católica de Chile, ³Instituto Psiquiátrico Dr. José Horwitz Barak, ⁴Early Intervention Program, J. Horwitz Psychiatric Institute, ⁵Clínica Alemana Universidad del Desarrollo, Early Intervention Program, José Horwitz Psychiatric Institute, ⁶Early Intervention in Psychosis Program at J. Horwitz Psychiatric Institute, Finis Tearrae University, ⁷Stanford University, ⁸School of Government, Pontificia Universidad Católica de

Chile, ⁹Institute of Psychiatry, Psychology and Neuroscience, KCL; and School of Medicine, Pontificia Universidad Católica de Chile

Background: Understanding the premorbid socioemotional trajectories of severe mental disorders, such as schizophrenia and bipolar disorder, is crucial for early identification and the implementation of effective interventions. Factors such as self-esteem, motivation, growth mindset, and perception of family support, have all been associated with mental health difficulties in adolescence. Studies in adults with severe mental illness have also pointed to the existence of similar premorbid difficulties in their earlier lives and could potentially guide preventive interventions. However, these studies are limited by the retrospective nature of their design. Using information collected from national educational assessments in Chile, we examined potential differences in prospectively-ascertained measures of 1) Self-esteem and School Motivation, 2) Perceived Parental Academic Support, and 3) Growth Mindset, in children who later developed resistant and non-resistant schizophrenia and bipolar disorder compared to their classmates.

Methods: This retrospective cohort included 719 children and adolescents born after 1990, later diagnosed with schizophrenia or bipolar disorder, alongside 49,451 healthy controls. The cohort consisted of 584 participants who subsequently initiated treatment with Clozapine for treatment-resistant schizophrenia, identified through the Chilean National Hematological Monitoring Service, and 135 individuals who were diagnosed with a first episode of schizophrenia at the Horwitz Psychiatric Institute in Santiago between 2007 and 2020 (without Clozapine prescription). As comparators, we included 111 patients diagnosed with bipolar disorder in the same institution during the same years and a group of 49,451 healthy controls consisting of each patient's classmates. We obtained anonymized data from the Chilean Ministry of Education's System for Measurement of Educational Quality (SIMCE) tests conducted in 4th, 8th, and 10th grades between 2012 and 2019. We constructed indicators of 1) Self-esteem and School Motivation, 2) Perceived Parental Academic Support, and 3) Growth Mindset. These metrics were z-normalized for every patient with their school classmates of that year. This normalization procedure controlled for cohort effects and socioeconomic status in the context of the economically-segregated nature of the Chilean education system. We estimated mixed linear models to adjust for repeated measurements and the variable number of observations for each participant. The models included group membership (Resistant and Non-resistant Schizophrenia, Bipolar, and Healthy Controls), grade level, gender, and final grade as covariates, in addition to a random effect for school.

Results: We found that children subsequently diagnosed with schizophrenia perceived less parental academic support than their classmates (effect size -0.286, 95%CI -0.399SD to -0.1736SD p LESS THAN 0.001). They also scored higher in growth mindset (effect size 0.251, 95% CI 0.0397SD to 0.462SD $p=0.019$). After adjusting for gender, grade level, and grades, these differences remained statistically significant compared to the healthy classmates. The bipolar patient group did not show statistically significant differences in any of the analysed outcomes. We did not find differences in self-esteem.

Discussion: Our results suggest that the perception of parental academic support could be an antecedent factor in the development of schizophrenia, possibly indicating a more neglectful parental environment and/or lower trust. Unexpectedly, patients with schizophrenia showed a significantly more flexible mindset in childhood, and similar self-esteem to their peers. Interventions aimed at preventing the development of schizophrenia in young people may benefit from focusing on building trust and supporting parental relationships. We should note that our cohort primarily comprised children who developed severe (treatment-resistant) schizophrenia, and our findings might not necessarily apply to those developing milder forms of the illness.

F268. DIAGNOSIS AND SEX-SPECIFIC DIFFERENCES IN THE SHAPE AND VOLUME OF THE HIPPOCAMPUS IN SCHIZOPHRENIA AND BIPOLAR DISORDERS

Daniel Herrera-Escartín^{*1}, Noemí Hostalet², Erick J Canales-Rodríguez³, Raymond Salvador⁴, Xavier Sevillano⁵, Edith Pomarol Clotet⁴, Pilar Salgado Pineda⁴, Mar Fatjo-Vilas², Neus Martínez-Abadías¹

¹University of Barcelona, ²University of Barcelona, FIDMAG Sisters Hospitaliers Research Foundation, CIBERSAM, Biomedical Research Network in Mental Health, Instituto de Salud Carlos III, ³FIDMAG Sisters Hospitaliers Research Foundation, CIBERSAM, Biomedical Research Network in Mental Health, Instituto de Salud Carlos III, Signal Processing Lab (LTS5), École Polytechnique Fédérale de Lausanne, ⁴FIDMAG Sisters Hospitaliers Research Foundation, CIBERSAM, Biomedical Research Network in Mental Health, Instituto de Salud Carlos III, ⁵GTM-Grup de Recerca en Tecnologies Mèdia, La Salle, Universitat Ramon Llull,

Background: Schizophrenia (SZ) and Bipolar Disorder (BD) are psychiatric conditions with a substantial clinical, neurobiological, and genetic overlap, and no diagnostic-specific biomarkers exist. Neuroimaging studies have shown that patients with these diagnosis show subtle gray matter reductions widespread over the brain. However, volume and shape differences in subcortical structures remain far less unexplored, and there are no consistent results regarding sex effect. Geometric Morphometrics (GM) provides a robust methodology that goes beyond the typical brain volumetric approaches and can be used to detect more detailed dysmorphologies. We hypothesized that combining volumetric and morphometric features could improve the description and analysis of anatomical changes associated with these disorders; and that some of these changes could represent diagnostic and sex-specific biomarkers.

Methods: Head structural Magnetic Resonance Images (MRI, 1.5T) were obtained from 131 patients with schizophrenia (SZ), 94 individuals with bipolar disorder (BD) and 89 healthy controls (HC) of European ancestry. Right and left hippocampi were segmented from the MRIs using FSL FIRST, and volumetric differences between groups were evaluated with a regression model, accounting for sex, age and intracranial volume as covariates. To compare the hippocampal shape between patients and controls, the 3D coordinates of 60 landmarks were registered over the left hippocampus of each individual. After a Generalized Procrustes Analysis and correcting for size and age differences by a multivariate linear regression, we computed the Procrustes distances among groups (globally and separated by sexes) and performed permutation tests to assess the statistical significance of shape differences.

Results: Individuals diagnosed with SZ presented reductions in the hippocampus volume compared to HC ($p_{\text{left}} = 0.001$, $p_{\text{right}} = 0.029$) and the same pattern was observed between patients with BD and HC ($p_{\text{left}} = 0.023$). In all group comparisons, both hippocampi displayed volumetric differences between sexes, with males presenting higher volumes than females ($p < 0.001$). As regards shape analyses, pairwise comparisons showed only differences between BD and HC ($p = 0.018$), with patients presenting anterior and posterior narrowing and a more concave hippocampal shape. Furthermore, the results showed a sex-specific effect, with significant differences in hippocampal shape observed only between BD and HC men ($p = 0.016$).

Discussion: Our results confirm previous data, showing a volume reduction in the hippocampus associated with SZ and BD. In addition, our shape analysis based on landmarking and geometric morphometrics contributes to characterising hippocampal morphological changes between groups, providing novel evidence regarding sex-specific dysmorphologies in

BD. Our approach suggests the potential of future studies combining volumetric and shape data to improve our understanding of the neurobiological basis of psychotic disorders.

F269. RECOGNIZING SCHIZOPHRENIA AND DEPRESSIVE SPECTRUM: PRELIMINARY EVIDENCE FROM MACHINE LEARNING ALGORITHMS

Yating Huang^{*1}, Jiayu He¹, Tongxuan Zheng¹, Chao Yan¹

¹*East China Normal University (ECNU)*

Background: Anhedonia serves as a fundamental transdiagnostic trait present in both schizophrenia and major depressive disorder. Within the Research Domain Criteria framework, the Positive Valence System stands as one of six domains illuminating the shared foundational mechanism of psychotic disorders. This study aimed to the effectiveness of machine learning (ML) for classifying the schizophrenia spectrum and depressive spectrum, grounded in the multidimensional reward processing theory. Additionally, it investigates the degree to which various dimensions of reward processing contribute to the overall classification performance.

Methods: A total of 453 subjects (Mage=23.27, SDage=7.54, 289 females) were recruited from mental health center and community, comprising of 55 schizophrenics (SCZ), 116 major depressive disorders (MDD) and 282 healthy controls (HCs). Among healthy controls, there were 36 individuals with high schizotypy (HS, top 10% of total score) and 112 individuals with subthreshold depression (SD, BDI total score GREATER THAN 16) and 134 individuals with low depressive symptoms and schizotypy. All participants underwent the Monetary Reward Delay Task, the Pleasure Experience Prediction Questionnaire, and the Pleasure Experience Recall Questionnaire. These assessments measure anticipatory pleasure (including the "prediction" and "feeling" components), consummatory pleasure, motivation, and remembered pleasure. These factors were subsequently extracted as predictive features, serving as inputs for training the Machine Learning (ML) model. The aim was to assess the classification performance, differentiating between SCZ and MDD from HCs. Additionally, we extend the model to categorize at-risk groups such as high schizotypy and SD individuals. After model evaluation, we calculate feature weights to determine the significant impact of reward dimensions on classification separately.

Results: The RF model demonstrates moderate performance in distinguishing SCZ from HCs (AUC=92.62%, Sensitivity=61.54%, Specificity=88.00%). In terms of depression, the RF model achieves high classification accuracy for MDD patients (AUC=90.75%, Sensitivity=86.36%, Specificity=78.57%) and individuals with SD (AUC=90.73%, Sensitivity=82.35%, Specificity=84.85%). Combining SD and MDD individuals enhances the model's performance (AUC=96.35%, Sensitivity=93.33%, Specificity=89.29%). However, the sensitivity was low to classify individuals with HS from HCs. We examined the weights (wts) of reward dimensions and identified that "motivation" and "anticipatory pleasure" were the two most influential dimensions in distinguishing the depression and SCZ (Moti: wts=[0.34, 0.41]; Anti: wts=[0.23, 0.29]).

Discussion: Our findings underscore the effectiveness of the RF model in accurately classifying SCZ, MDD, and SD from HCs. However, the model demonstrated limitations in recognizing schizotypy. Notably, within the domain of reward processing, the dimensions of motivation and anticipatory pleasure emerged as pivotal contributors to the classification of both schizophrenia and depression. These insights provide valuable implications for understanding the transdiagnostic mechanisms of anhedonia.

F270. SYMPTOM NETWORK DIFFERENCES BETWEEN SCHIZOPHRENIA AND AUTISM SPECTRUM DISORDER: A NETWORK ANALYSIS

Szilárd Holka*¹, Dániel Sörnyei¹, Ágota Vass¹, Kinga Farkas¹

¹*Semmelweis University*

Background: The overlapping symptoms of schizophrenia and autism are increasingly emphasized in research on the two disorders. Among these symptoms, much attention is focused on psychopathological variables such as mentalization, self-perception, perceptual anomalies, anxiety or depression. For example, an important link between the two disorders lies in mentalizing abilities, which are characterized by atypical neurodevelopment and are significantly influenced by attachment patterns with parents and the wider environment. Although the vast majority of research has examined these factors independently, the transdiagnostic approach is rare. We aim to fill this gap by applying network analysis, which is gaining popularity in the field of psychopathology. This approach allows us to explore complex relationships between theoretically selected variables in a data-driven way.

Methods: Based on previously established psychiatric diagnosis, participants were grouped into people with schizophrenia (SCH), with autism spectrum disorder (ASD), and neurotypical (NTP) without any diagnosis. Altogether 1909 participants (ASD: N=158, 47% female, mean age = 32 years; SCH: N=44, 79% male, mean age = 34 years, NTP: N = 1707, 64% female, mean age = 38 years) have completed questionnaires about social cognition, social support and psychopathological factors. To model conditional independence relationships between the variables we applied network analysis on our cross-sectional data. We estimated Gaussian graphical models with regularization technique graphical LASSO based on extended BIC criterion. To examine the importance of constructs, we identified the most central nodes in the networks through centrality metrics, including strength, closeness, betweenness and expected influence. Finally, we checked the reliability and accuracy of the networks with the nonparametric and case-dropping bootstrap methods. To explore the global and local network structure differences between the groups, we applied the Network Comparison Test. NCT is a permutation test which allows us to assess invariance measures, such as network structure invariance, global strength invariance and edge invariance.

Results: Preliminary analysis showed that only the symptom network structure of ASD differs significantly from the NTP network in global strength ($p < 0.05$). Bootstrapping results showed that the network models are reliable. In the SCH network the narrative subscale of the same questionnaire was the most central regarding strength and expected influence, while the Multidimensional Schizotypy Scale's disorganised subscale had the highest z-score in betweenness and closeness metrics. The ownership subscale of Embodied Sense of Self Scale was the most central node in the ASD network. Self-reflectiveness was the most central node in strength and expected influence in the NTP network, as well as intellect and openness in terms of betweenness and closeness.

Discussion: Our hypothesis was that mentalization would play a central role in the network structure of SCH and ASD. Although this was not the case, our results are still clinically relevant. The crucial role of disorganisation in the SCH network structure confirms its prominent role in the psychotic state as well in the general psychopathology itself. This is supported not only by the centrality indices, but also through a strong positive relationship with ownership in the ASD network. As regards the NTP network, the intellect and openness, as well as self-reflectiveness can be identified as protective factors from the psychotic condition. In this approach the significance of these factors lies in the potential therapeutic targets they may represent.

F271. SUPAR: A POSSIBLE BIOMARKER FOR SCHIZOPHRENIA

Mikkel Soerensen^{*1}, Bahast Biuk², Jimmi Nielsen³, Bjørn H. Ebdrup⁴, Mette ødegård nielsen⁵

¹CNSR, ²Copenhagen University Hospital, ³Psychiatric Centre Glostrup, Unit for Complicated Schizophrenia, Mental Health Services in the Capital Region of Denmark, ⁴Center for Neuropsychiatric Schizophrenia Research, CNSR, Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Centre Glostrup, University of Copenhagen, University of Copenhagen, ⁵Center for Neuropsychiatric Schizophrenia Research

Background: Recent attention to the immunological aspects of schizophrenia suggests heightened inflammatory activity in schizophrenia. A novel biomarker, soluble urokinase-type plasminogen activator receptor (suPAR), exhibits elevated levels in patients with chronic schizophrenia. SuPAR's stability and resistance to freezing make it suitable for longitudinal studies. Positive correlations with immunological biomarkers, such as IL-6 and hs-CRP, position suPAR as a promising marker for chronic inflammation, less influenced by acute changes. This study aims to investigate suPAR as a novel biomarker in different stages of schizophrenia.

Methods: This investigation integrates data from two distinct cohorts, each including a matched healthy control group:

1. PECANS 2 (N=108) which centers on antipsychotic-naïve first episode psychosis (ANFEP) individuals diagnosed with schizophrenia or non-affective psychoses. These patients underwent treatment with Aripiprazole for a duration of minimum 6 weeks.

2. The Clinical Re-examination Cohort (N=137) comprises chronic patients re-evaluated approximately 9.6 ± 3.5 years after their initial diagnosis of either schizophrenia or schizoaffective disorder.

suPAR was analyzed using suPARnostic ELISA assay at Hvidovre Hospital, Denmark. Values were log transformed for statistical analyses.

Results: As indicated by prior literature, female sex, daily tobacco smoking, and higher age emerged as principal factors increasing suPAR levels across the cohorts and patient status. Adjusted for these values, we observed no group difference in the ANFEP cohort before the initiation of medical treatment ($p=.44$). Following a 6-week monotherapy with aripiprazole, the suPAR concentration increased slightly in patients ($t=2.1$, $p=0.02$) and was stable in the healthy controls, although the group time interaction was not significant. Furthermore, the suPAR level in the clinical re-examination cohort is elevated in the patient group ($F=6.3$, $p=0.013$), even when adjusted for age ($F=6.9$, $p=0.01$), sex ($F=11.3$, $p=0.001$), and smoking status ($F=24.6$, $p < 0.001$).

Discussion: These preliminary findings validate suPAR as a potential biomarker for schizophrenia. The rise in suPAR levels is notably significant among schizophrenia patients undergoing antipsychotic treatment compared to matched healthy controls. Interestingly, this signal becomes more pronounced with an increasing duration from the time of initial diagnosis. The current analyses affirm prior observations in individuals with chronic schizophrenia, where elevated suPAR levels have been documented. Our data indicate that this phenomenon does not manifest during the initial stages of first psychotic diagnoses. However, within the first six

weeks, a modest yet significant increase in suPAR is evident. This disparity among groups appears to persist over the years. Further investigation is necessary to determine whether this signal is a result of medication usage or signifies a progression in the underlying pathology of schizophrenia.

F272. A REVAMPED CLINICAL QUALITY REGISTRY FOR PSYCHOSIS IN SWEDEN: LEARNING FROM EXAMPLES OF EXCELLENCE

Simon Cervenka*¹, Lydia Melchor², Maria Skott³, Mikael Landén⁴

¹*Uppsala University*, ²*Sahlgrenska University Hospital*, ³*Karolinska Institutet*, ⁴*University of Gothenburg*

Background: Sweden has a strong tradition in national quality registries, with high coverage and strong output across a wide range of disciplines. The registries contain individualized data about medical interventions, procedures and outcomes, and are typically integrated into clinical workflows resulting in a capacity to generate data in real time. Sweden's more than 100 registries have leveraged the country's position in health care resulting in having among the best survival rates after acute heart infarction, stroke and breast cancer. The Swedish registries are certified by the National Steering Group for Quality Registers, which also performs ongoing monitoring, securing the validity and hence clinical relevance. Examples of successful registries in psychiatry include the ECT and Bipolar registry (Bipolär). A registry was previously established also for psychotic disorders (PsykosR) however coverage and hence the utility for both clinical care and research has been lacking. In parallel, a national audit of psychosis health care showed large interregional differences in quality.

Methods: A revamped version of PsykosR is established and merged with Bipolär. The process for establishing an optimized minimum dataset (MDS) with high relevance for health care providers is described.

Results: The new registry has a module for new registrations, with particular attention to onset of symptoms and loss of function, as well as on the clinical workup. Subsequent data registration is integrated into the yearly follow-up visit which is performed according to current national guidelines, and includes parameters for symptom levels, interventions including pharmacological treatment, hospital admissions and social support, as well as indicators of somatic health. The registry is designed to also include individuals at clinical high risk for psychosis (CHR-P).

Discussion: The establishment of a new version of PsykosR aims to increase quality of health care on a national level by providing real-time feedback to providers, as well as generate data for research that can further leverage treatment algorithms. The inclusion of an arm for CHR-P is an important starting point for developing early detection and intervention practices in Sweden.

F273. STUDY PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL TESTING THE EFFECTS OF METACOGNITIVE TRAINING (MCT) ON NEGATIVE SYMPTOMS IN PSYCHOTIC DISORDERS, AND EXPLORING POTENTIAL MECHANISMS UNDERLYING SYMPTOM REDUCTION

Benjamin Rask*¹, Simon Cervenka¹, Jonas Persson¹, Linda Swanson¹, Tonya Pixton², Ulrika Sällström², Mårten Tyrberg³

¹*Uppsala University*, ²*Centre for Clinical Research Sörmland, Uppsala University*, ³*Centre for Clinical Research Västmanland, Uppsala University*

Background: Negative symptoms in schizophrenia (NS) presents a substantial barrier to daily functioning and quality of life for those affected and current treatment options are limited. The cognitive model (Beck et al., 2009) suggests that NS could be caused and maintained by maladaptive coping strategies such as shutting down the cognitive-affective experience and adopting dysfunctional beliefs. Recent research highlights metacognition (MC) and reflective functioning (RF), processes of understanding internal mental states, as crucial for understanding and treating NS, with deficits in MC linked to more severe NS and decreased RF associated with NS severity. Metacognitive training for schizophrenia (MCT) combine elements from cognitive behavioral therapy (CBT), psychoeducation and cognitive remediation therapy (CRT) to target cognitive biases (Moritz and Woodward., 2007). A recent meta-analysis found support for a magnitude of observed association between MCT and lowered delusions as well as hallucinations (Penney, Sauvé and Mendelson., 2022). Recently, metacognitive training for negative symptoms in schizophrenia (MCT-Minus) (Swanson et al., 2021) was developed, focusing on specific thought patterns common in NS such as negative beliefs about human interaction; low expectations about pleasure, success and acceptance; and defeatist beliefs about performance. Results from a feasibility study indicate that MCT-Minus can lead to improvement including increased reflective functioning, decreased NS, and reduced perceived stigma (Swanson et al., 2022; Swanson et al., 2023). The current project aims to build on these findings, by evaluating MCT-Minus efficacy and by exploring potential psychological and biological mechanisms underlying symptom reduction.

Methods: Participants over the age of 18 with a psychotic disorder will be recruited from tertiary psychiatric care and randomized into 8 sessions of either MCT-Minus (n = 45) or counseling (n = 45), which will be blinded to the subjects. Primary outcome measures are the Positive and Negative Syndrome Scale (PANSS), the Clinical Assessment Interview for Negative Symptoms (CAINS) and Motivation and Pleasure Scale-Self Report (MAP-SR). Secondary outcome measures include the Dysfunctional Attitudes Scale (DAS), the Reflective Functioning Questionnaire (RFQ-8), and the Internalized Stigma of Mental Illness Scale-9 (ISMI-9). Group differences will be evaluated through analysis of variance. Underlying mechanisms will be explored through structural equation modelling using the independent variable (MCT-Minus), the mediator variables (RF, perceived stigma and dysfunctional attitudes) and the dependent variable NS. Quantitative data will be collected at pre-intervention, post-intervention and at follow-up after 12 weeks. Semi-structured interviews investigating the participant experience of MCT-Minus and potential benefits will be conducted at pre-intervention and post-intervention. Thematic analysis will be used to analyze the qualitative data. Resting state functional magnetic resonance imaging (rsfMRI), structural MRI, and MR spectroscopy will be performed in all subjects pre- and post-treatment. Preprocessing and statistical analysis of rsfMRI scans will be performed in conn toolbox in Matlab. The study and the statistical analyses will be preregistered.

Results: We hypothesize that improvements in NS will be greater in the intervention group compared to the counseling control group, and that treatment gains will be maintained at follow-up. In the rsfMRI study the primary aim is to compare changes in connectivity in the default mode network, which is involved in reflective processes such as MC. We hypothesize that, between groups, structural changes are related to NS improvement. Secondary aims are to study change in glutamate levels and structural connectivity in the anterior cingulate cortex.

Discussion: This will be the first RCT to assess MCT specifically targeting NS in schizophrenia. Moreover, to our knowledge no previous study has investigated changes in functional connectivity after psychological treatment targeting NS. Findings may contribute to addressing the unmet therapeutic need for NS in schizophrenia.

F274. VALUE OF GYM-BASED EXERCISE TRAINING VERSUS USUAL CARE FOR YOUNG ADULTS WITH SEVERE MENTAL ILLNESS: A PRAGMATIC, SINGLE-BLINDED, MULTI-CENTRE RANDOMISED CONTROLLED TRIAL - THE VEGA TRIAL

Bolette Skjødtt Rafn^{*1}, Victor Sørensen², Martin Andersen³, Bjørn H. Ebdrup⁴, Julie Midtgaard³

¹*Mental Health Centre Glostrup*, ²*Centre for Applied Research in Mental Health Care (CARMEN) and Center for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Center Glostrup, University of Copenhagen*, ³*Centre of Applied Research in Mental Health Care (CARMEN), Mental Health Centre Glostrup, University of Copenhagen*, ⁴*Center for Neuropsychiatric Schizophrenia Research, CNSR, and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Centre Glostrup, University of Copenhagen*,

Background: People with severe mental illness (SMI) have increased risk of developing obesity, metabolic syndrome, and type II diabetes. The relationship is multifactorial including the mental disorder, psychosocial effects, dietary habits, smoking, adverse effects of antipsychotics, and sedentary lifestyle. Exercise can be a cost-efficient adjunctive treatment in improving personal recovery, symptom burden, cognition, quality of life, and multiple cardiometabolic outcomes. Furthermore, exercise carried out in communities have the potential to reduce the experience of isolation, loneliness, and internalized stigmatization and may improve long-term change of physical activity behaviour. Thus, we aim to evaluate the effectiveness of gym-based group exercise (Vega Exercise Community) compared to usual care for young adults with SMI. We hypothesize that Vega Exercise Community will be superior to usual care for personal recovery after four months.

Methods: The Vega trial is a pragmatic, single-blinded, multi-centre randomised controlled trial that is conducted at three sites across Denmark. We aim to include 400 participants aged 18-35 years and diagnosed with SMI, specifically schizophrenia spectrum disorders, bipolar disorders, or major depression. Initially, an eligibility criterion was current antipsychotic medication, however this criterion was removed since it excluded many people with SMI who could have benefitted from participating, and thus limited the generalizability of the trial. Participants are randomized (2:1) to the Vega Exercise Community or usual care. Vega Exercise Community offers three weekly supervised group-based functional training sessions hosted in commercial centers delivered by certified Vega instructors. Participants in Vega Exercise Community will be randomized (1:1) after four months to minimal versus extended support with regards to sustained physical activity. Per protocol attendance to the exercise community is set at 33% a priori. Assessment of outcomes occurs at baseline, four, six and 12-months. The primary outcome is personal recovery assessed by Questionnaire about the Process of Recovery at four months. Additional outcomes include behavioral and functional symptoms, health-related quality of life, metabolic health, and cardiorespiratory fitness. Finally, the quality of life and physical and mental health of the participants' primary relative is evaluated.

Results: Recruitment began in October 2022. As of Dec 6th, 2023, 270 have been screened for eligibility, where 20 were ineligible and 61 declined with the main reasons being distance to the Vega Exercise Community or exercise schedule conflicted with other commitments. Currently, 124 are enrolled and 94, 70 and 11 have completed the four-, six-, and 12-months assessments, respectively. 34 primary relatives are enrolled and 28 have completed at least one follow-up questionnaire. Participants have attended on average 27% (SD 19) of the available exercise sessions, while 33% of participants have attended the exercise sessions per protocol.

Discussion: Given the pragmatic nature of the trial, attendance is not required nor expected three times per week. Rather the exercise community is available for participants to use when possible. Yet, many participants attend the Vega Exercise Community regularly. The Vega Exercise Community program has the potential not only to improve recovery and health of individuals with SMI but also enable healthcare professionals to promote exercise as an integrated part of treatment. This holds the potential to bridge mental healthcare services and the civil society and subsequently promote physical activity and social inclusion.

F275. PROPOSAL FOR NOVEL PATIENT CLASSIFICATION WITH ENLARGED LATERAL VENTRICLES AND COGNITIVE DECLINE BASED ON DATA-DRIVEN ANALYSIS OF NEUROIMAGING IN PSYCHIATRIC DISORDERS AND CLINICAL CHARACTERIZATION

YUKA YASUDA*¹, Satsuki Ito¹, Junya Matsumoto¹, Naohiro Okada², Masaki Fukunaga³, Kiyotaka Nemoto⁴, Kenichiro Miura¹, Naoki Hashimoto⁵, Kazutaka Ohi⁶, Tsutomu Takahashi⁷, Michihiko Koeda⁸, Hidenaga Yamamori⁹, Michiko Fujimoto¹⁰, Naomi Hasegawa¹, Shinsuke Koike¹¹, Motoaki Nakamura¹², Go Okada¹³, Jun Miyata¹⁴, Shusuke Numata¹⁵, Toshiaki Onitsuka¹⁶, Reiji Yoshimura¹⁷, Shin Nakagawa¹⁸, Yoshiyuki Watanabe¹⁹, Norio Ozaki²⁰, Ryota Hashimoto¹

¹National Institute of Mental Health, National Center of Neurology and Psychiatry, ²The University of Tokyo, ³National Institute for Physiological Sciences, ⁴University of Tsukuba, ⁵Hokkaido University Graduate School of Medicine, ⁶Gifu University Graduate School of Medicine, ⁷University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, ⁸Nippon Medical School, ⁹Japan Community Health Care Organization, Osaka Hospital, ¹⁰Osaka University Graduate School of Medicine, ¹¹University of Tokyo, ¹²Showa University, ¹³Hiroshima University, ¹⁴Aichi Medical University, ¹⁵Tokushima University, ¹⁶National Hospital Organization Sakakibara Hospital, ¹⁷University of Occupational and Environmental Health, ¹⁸Yamaguchi University Graduate School of Medicine, ¹⁹Shiga University of Medical Science, ²⁰Nagoya University Graduate School of Medicine

Background: The creation of a novel diagnostic system using objective biomarkers is expected to take place, due to difficulty of the current diagnostic system based on symptoms in psychiatry. We clustered the 5602 subjects based on brain subcortical volumes and showed a four-biotype classification, namely extremely (Brain Biotype [BB] 1: n=110) and moderately smaller limbic regions (BB2: n=566), larger basal ganglia (BB3: n=679), and normal volumes (BB4: n=4247), being associated with cognitive/social functioning (Okada et al., Mol Psychiatry, 2023). In the present study, we performed a detailed examination of the biological and clinical characteristics of these biotypes.

Methods: A total of 5602 patients in the previous paper, including healthy subjects (n=3077), patients with schizophrenia (SZ: n=1499), bipolar disorder (BD: n=234), major depressive disorder (MDD: n=598), autism spectrum disorder (ASD: n=189) and other psychiatric

disorders (O: n=5), were included. The biological and clinical characteristics of four biotypes were investigated using subcortical volumes from T1-weighted MRI images, cognitive functions, EEG, and genomic information.

Results: We examined the differences in subcortical volume characteristics in each biotype and found that the lateral ventricle volume was remarkably larger ($Z\text{-score} = 5.1 \pm 1.8$) in BB1 (n=110). 99.1% of BBI subjects had the lateral ventricle volume greater than 3 standard deviation (3 SD) of normal subjects, and this brain feature discriminated BB1 with a sensitivity of 99.1% and a specificity of 98.1%. Therefore, BB1 was redefined as a brain structural feature with a lateral ventricular volume of 3 SD or greater. Of the 186 redefined subjects, 33 patients with detailed cognitive function data were stratified into two groups: 9 patients with moderate or higher cognitive decline (SZ8/ASD1) and 24 patients with mild or lower cognitive decline (SZ9/ HC9/ASD4/ MDD1/O1), and compared. EEG abnormalities (71% in the former group, 0% in the latter), a diagnosis of schizophrenia (89% in the former group, 38% in the latter group), and low intelligence (IQ=67 in the former group, IQ=103 in the latter group) were obviously observed in the former group than in the latter. Furthermore, copy number variation analysis of 7 out of 9 cases in the former group showed a high rate of pathological CNV (22q11.21 deletion, 7q11.23 duplication, and DPP6 deletion) in 3 cases, which is only seen in approximately one out of several thousand normal subjects.

Discussion: We have identified a novel candidate for classification of psychiatric disorders with high rates of EEG abnormalities, psychotic symptoms, and pathological rare genomic variants in a stratified group of patients with schizophrenia and other psychiatric disorders with lateral ventricular volumes of 3 SD or greater and moderate to severe cognitive decline. However, the limitation is that the number of patients is still small, and the clinical course, treatment response, outcome and other clinical features have not yet been investigated. We proposed a possible novel psychiatric disorder by going back to each patient based on the clinical significance from a large-scale data-driven analysis screening, and proposed a methodology to find the concept and psychiatric disorders by objective indices for the first time in the world.

This new biotype classification suggests the possibility that objective measurements based on brain imaging data will be incorporated into psychiatric diagnostic systems in the future. Furthermore, it is expected that the creation of animal models that can be objectively validated will become possible, which might reenergize the stalled development of therapeutic drugs.

F276. A SINGLE CASE EXPERIMENTAL DESIGN PILOT OF A CULTURALLY ADAPTED BRIEF POST-TRAUMATIC STRESS DISORDER (PTSD) INTERVENTION FOR PEOPLE WITH FIRST-EPISODE PSYCHOSIS AND PTSD

Vuyokazi Ntlantsana*¹, Usha Chhagan¹, Yusuf Asmal¹, Enver Karim¹, Saeeda Paruk¹, Lindokuhle Thela¹, Andrew Tomita², Lauren C Ng³, Bonga Chiliza¹

¹University of KwaZulu-Natal, ²KRISP, ³UCLA

Background: Post-traumatic stress disorder (PTSD) prevalence is higher in populations with psychosis and is associated with poorer outcomes. Brief Relaxation, Education and Trauma Healing (BREATHE) is a 3-session intervention developed in the USA for patients with PTSD and serious mental illness. The main components are breathing retraining and psychoeducation using videos as aids and includes homework as part of the intervention. BREATHE is suitable for task-shifting. Culturally adapted interventions have been shown to have better efficacy, especially in minority populations, compared to un-adapted interventions. The study aimed to

assess the feasibility, tolerability and acceptability of a culturally adapted BREATHE intervention in patients with first episode psychosis (FEP) and PTSD in Durban, South Africa. **Methods:** Participants with FEP who screened positive for PTSD on the PTSD Checklist for DSM 5 (PCL-5) were recruited into an adapted multiple baseline design type of the single case experimental design pilot study from May to October 2023. The structured clinical interview for DSM-5 was used to confirm a diagnosis of PTSD. Feasibility was assessed using follow-up rates and participant use of intervention techniques. To assess for tolerability, participant discomfort or clinical deterioration were observed. Qualitative interviews and the Treatment Acceptability and Adherence Scale (TAAS) were used for assessing for treatment acceptability. PTSD symptoms, culture-specific PTSD symptoms and PTSD cognitions were measured using the PCL-5, the Zulu Culture-specific Trauma Experience Questionnaire (Z-CTEQ) and Posttraumatic Cognitions Inventory (PTCI), respectively. Weekly measures were conducted for five weeks before the intervention, during the three weeks of the intervention, at one-month and 3-months post intervention. Other quantitative measures such as the positive and negative symptoms scale (PANSS) for psychosis symptom severity, Childhood trauma questionnaire (CTQ) for childhood trauma and WHO Disability Assessment Scale to assess for disability, were used. The pilot was single blinded with only the assessors blinded to intervention allocation. The therapist who administered the intervention was trained by the developers of the intervention and the assessors were two trained research assistants and one psychiatrist.

Results: Four participants were recruited into the study. The follow-up rate was 100% and regular use of intervention techniques indicated good feasibility. No adverse events were reported indicating good tolerability. TAAS median score of 62.5 (IQR 55-69.5), indicated good treatment acceptability. PCL and PCTI scores showed improvement but the Z-CTEQ scores remained stable. Mean PANSS scores were 37.5 (SD 5.1) and 39.25 (10.0) at enrollment and 3-month assessments, respectively, indicating low psychosis symptom severity. Two participants scored positive for childhood trauma domains. WHODAS scores were median 25 (17.5-30.5) and 20.5 (17.5-37), indicating some improvement in disability.

Discussion: Culturally adapted BREATHE intervention is safe, feasible, acceptable, and may be efficacious in populations with early psychosis and PTSD symptoms. It is a suitable for low resource settings as it is a relatively low-cost intervention, allows for agency as patients can manage their own symptoms using breathing techniques as self-regulation. It may be administered to patients as they await higher level care. The study is the first step towards a powered efficacy and implementation sustainability studies, but this will require further cultural adaptation of the intervention for treatment of PTSD related to cultural experiences.

F277. UPPSALA PSYCHOSIS COHORT: A MULTIMODAL STUDY IN EARLY STAGE PSYCHOSIS PATIENTS, HIGH RISK INDIVIDUALS AND HEALTHY CONTROLS

Inez Ebbersten Olivero-Reinius^{*1}, Jonas Persson¹, Martin Cernvall¹, Oscar Aarflot¹, Victoria Arfuch Prezioso¹, Corina Caprariu¹, Johan Bengtsson¹, Simon Cervenka¹

¹*Uppsala University*

Background: Imaging and post-mortem studies reveal cortical grey matter thinning, connectivity loss, and synaptic marker reduction in individuals with schizophrenia. Deviant synaptic activity measured by EEG suggests impaired error detection, contributing to hallucinations, delusions, and cognitive impairments. Several lines of research suggest that

excessive synaptic pruning by microglia, particularly involving complement factor C4A, may be a key mechanism for causing these changes in brain structure and function. Initial studies using Positron Emission Tomography (PET) and radioligands for the synaptic vesicle protein 2A (SV2A) have demonstrated synaptic reduction in patients with long-term schizophrenia, whereas two subsequent studies on early-stage psychosis patients have yielded divergent results (Yoon et al., 2023; Onwordi et al., 2023). Hence, the timing of putative synaptic loss during disease development remains unclear, and the proposed underlying mechanisms remain to be confirmed in vivo. The main aim of the present project is to address these questions.

Methods: The Uppsala Psychosis Cohort (UPC) (ClinicalTrials.gov ID NCT05763966) is a longitudinal, multimodal, observational study that aims to include 60 early-stage psychosis (EPP) patients, 30 clinical high-risk for psychosis (CHR-P) individuals, and age and gender-matched healthy controls (HC). EPP criteria include onset of psychotic symptoms together with functional decline within 3 years. CHR-P individuals meet established criteria using Structured Interview for Psychosis-risk Syndromes (SIPS). Assessments, including clinical, cognitive (using MATRICS Consensus Cognitive Battery), and imaging will be conducted at baseline and follow-ups at 1, 3, and 5 years. A lumbar puncture is performed at baseline. The imaging protocol includes PET with the SV2A radioligand [18F]SynVest-1 (baseline and 1 year), MR modalities (fMRI, DTI, MRS), and neurophysiological examinations (EEG, TMS). Metabolite-corrected arterial input function is used for PET data quantification. Data analysis integrates SV2A PET, MRI modalities, and neurophysiology to evaluate synaptic loss and the consequences for brain function. We hypothesize greater differences in SV2A in each stage of disease development (HC LESS THAN CHR-P LESS THAN EPP), linked to symptom severity and cognitive impairment. Cerebrospinal fluid analysis aims to identify predictive markers for synaptic loss and disease progression, including C4A levels. The analysis considers genetic vulnerability as well as cannabis exposure, which has shown to influence both SV2A binding in in vivo and affect synaptic density in vitro.

Results: The first patient was enrolled in May 2023. Descriptive data from initial patients will be reported, including also results from their experience of participating in the study.

Discussion: By combining cross-sectional and longitudinal analyses, including at-risk individuals, the study addresses the key question of when synaptic changes occur during disease progression, and in which patients. Recognizing heterogeneous disease mechanisms, the proposal's clinical implication lies in developing tools for patient stratification in trials of novel treatments, such as candidate drugs targeting microglia-mediated synaptic pruning.

F278. THE ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND EDUCATIONAL ATTAINMENT, AND COGNITION IN PATIENTS WITH SCHIZOPHRENIA, THEIR UNAFFECTED SIBLINGS, AND HEALTHY CONTROLS: RESULTS FROM THE TURKISH SAMPLE OF THE EU-GEI STUDY

Handan Noyan^{*1}, Sinan Guloksuz², Meram Can Saka³, Köksal Alptekin⁴, Cem Atbasoglu³, Zeynep Baran Tatar⁵, Berna Binnur Akdede⁶, İ. Tolga Binbay⁶, Vesile Altınyazar⁷, Halis Ulaş⁶, Berna Yalınçetin⁸, Guvem Gumus Akay⁹, Burçin Cihan¹⁰, Haldun Soygür¹¹, Eylem Şahin Cankurtaran¹², Semra Ulusoy Kaynak¹³, Bart Rutten¹⁴, Jim Van Os¹⁴, Alp Üçok¹⁵

¹Beykoz University, ²Maastricht University, ³Ankara University, ⁴Dokuz Eylul University, School of Medicine, ⁵Bakirkoy Training and Research Hospital for Psychiatry, Neurology and

Neurosurgery, ⁶Dokuz Eylül University, School of Medicine, ⁷Adnan Menderes University, ⁸Dokuz Eylül University, ⁹Ankara University Brain Research Center, ¹⁰Middle East Technical University, ¹¹Okan University, ¹²Güven Çayyolu Healthcare Campus, ¹³Gülhane, University of Health Sciences, ¹⁴Maastricht University Medical Centre, ¹⁵Istanbul University

Background: Childhood trauma (CT) is suggested to adversely impact educational attainment and cognition. However, few studies have explored the differential effects of CT subtypes on these aspects. This study aims to examine the potential effects of CT subtypes on educational attainment and global cognition in a large Turkish sample, including patients with schizophrenia (SCZs) (n=742), their unaffected siblings (SIBs) (n=718), and healthy controls (HCs) (n=1039).

Methods: CT was assessed using the short form of the Childhood Trauma Questionnaire (CTQ), measuring childhood emotional, physical, and sexual abuse, as well as physical and emotional neglect. Global IQ was assessed with the Brief WAIS -III Revised. Level of education was defined as years of completed education. Psychotic experiences were measured using the Community Assessment of Psychic Experiences (CAPE). Additionally, premorbid social adjustment in childhood and adolescence was evaluated with the Premorbid Adjustment Scale (PAS) (only in SCZs). In statistical analysis, a Brown–Forsythe test (due to asymptotically F distribution) was used to compare mean scores of CTQ sub-scales, education, and IQ among the study groups. Cross-sectional group comparisons based on CT history were conducted with the independent samples t-tests in each group. Associations of the five CTQ mean scores with education and global IQ were separately assessed for each group using hierarchical regression analyses. The regression analyses were conducted with adjustments for the following confounders: sex and age, global IQ (only for CT-education) or education (only for CT-IQ), CAPE total score and mean scores of PAS, and current antipsychotic use (only for SCZs).

Results: Patients significantly had less years of education and global IQ scores (respectively, 10.4 ± 3.9 ; 58.6 ± 34) compared to both their siblings (11.4 ± 4.1 ; 78.4 ± 37.2) and HCs (11.2 ± 4.1 ; 84.6 ± 27.3) (all pcorr. LESS THAN 0.001). SCZs had higher scores in all CTQ sub-scales than both SIBs and HCs (all pcorr. LESS THAN 0.001). SIBs had higher scores of emotional abuse (pcorr. LESS THAN 0.001) and emotional neglect (pcorr.=0.003) than HCs. CT was negatively related to education and cognitive performance in all groups, only with physical neglect being related to educational attainment in all three groups. In the SCZ group, on educational attainment, after adjusting for sex and age, global IQ had a significant effect, and when controlling for all confounders, physical abuse also showed a significant effect ($\beta_{adj} = -0.17$, pcorr.=0.01). However, it was found that global IQ is associated only with confounders including age, education, CAPE, and PAS (LESS THAN 12 age). The relationships between CT and education, and cognition, were found to be more prominent in both SIBs and HCs.

Discussion: The study showed a weak association between CT and lower educational attainment in SCZs, compared to both the other groups. A similar pattern was observed emerged for global IQ. While there was no relationship between global cognition and any type of trauma in SCZs, cognitive performance was negatively affected by CT, especially neglect types, in both SIBs and HCs. Furthermore, in SCZs, only the confounders were associated with global IQ. In patients with SCZ, besides the confounders examined in this study, additional risk factors such as relapses or hospitalizations might negatively play a role in education and cognition. We propose that, in the absence of other risk factors, these relationships are more prominent in SIBs, who share the family environment and genetic risk with SCZs. Our findings

are important revealing that different types of CT may have an impact on educational attainment and cognition, and with these effects diversifying in each group.

F279. IDENTIFICATION OF SUBTLE VISUAL DYSFUNCTIONS IN RECENT ONSET PSYCHOSIS AND DEPRESSION, AND CLINICAL HIGH-RISK STATE USING ENTROPY AND ENERGY FEATURE MAPS.

Alexandra Korda¹, Christina Andreou², Shalaila Haas³, Inga Meyhöfer⁴, Joseph Kambeitz⁵, Stephan Ruhrmann⁵, Raimo K.R. Salokangas⁶, Alessandro Bertolino⁷, Christos Pantelis⁸, Stephen Wood⁹, Matthias Mann¹⁰, Markus Nöthen¹¹, Franco Fabbro¹², Eva Meisenzahl¹³, Paolo Brambilla¹⁴, Rachel Upthegrove¹⁵, Andre Schmidt¹⁶, Udo Dannlowski¹⁷, Lana Kambeitz-Ilankovic⁵, Dominic B. Dwyer¹⁸, Julian Wenzel¹⁹, Pierluigi Selvaggi²⁰, Jarmo Hietala²¹, Anita Riecher-Rössler²², Christos Davatzikos²³, Nikolaos Koutsouleris¹⁸, Stefan Borgwardt²⁴, Rebekka Lencer^{*24}, and the PRONIA Consortium¹⁸

¹UKSH, ²University of Basel Psychiatric Clinics, Center for Gender Research and Early Detection, ³Icahn School of Medicine at Mount Sinai, ⁴University of Bonn, ⁵University of Cologne, ⁶University of Turku, ⁷University of Bari, ⁸Melbourne Neuropsychiatry Centre, The University of Melbourne, ⁹Orygen, the National Centre of Excellence in Youth Mental Health, ¹⁰Max Planck Institute of Biochemistry, ¹¹Life and Brain Center, University of Bonn, ¹²University of Udine, ¹³Heinrich-Heine University Düsseldorf, ¹⁴University of Milan, ¹⁵University of Birmingham, ¹⁶University of Basel, ¹⁷Münster University, ¹⁸Ludwig Maximilian University, ¹⁹University of Cologne, University Hospital Cologne, Clinic for Psychiatry and Psychotherapy, ²⁰Università degli Studi di Bari "Aldo Moro", ²¹University of Turku, ²²University of Basel Psychiatric Clinics, ²³University of Pennsylvania Perelman School of Medicine, ²⁴University of Lübeck

Background: Subtle Visual Dysfunctions (VisDys) are often ignored in clinical studies of patients with schizophrenia, despite being detailed by 50% of patients. Furthermore, the neurobiological underpinnings of VisDys in patients with a first/recent onset psychosis (ROP) or depression (ROD), and a clinical high-risk condition for psychosis (CHR) are unclear. A deeper understanding of VisDys in early psychotic states could not only provide useful information for clinical practice, but also advance understanding of the underlying disease perceptual mechanisms that mediate susceptibility to psychosis. We investigated the utility of entropy and energy texture features for identification of VisDys in ROP and CHR, respectively. Entropy measures the complexity of the texture distribution, and its inverse measure is the energy which reflects the regularity and uniformity of the texture distribution. Then, the identification of VisDys in ROD using both developed models was tested.

Methods: Structural MR images were acquired from 135 ROP (64 patients with VisDys), 134 CHR (71 patients with VisDys) and 140 ROD (23 patients with VisDys). External validation set included 113 ROP (45 with VisDys), 104 CHR (51 patients with VisDys) and 77 ROD (17 patients with VisDys). The mwp0* image produced via SPM12 segmentation was used for discretization of intensities. Next, a voxel-by-voxel sliding 3D cube of 7x7x7 dimension was used for the grey level co-occurrence matrix (GLCM) calculation. Texture features were extracted and imported in a 20x20 nested cross-validation schema for the identification of VisDys. In the inner loop, cross-validated feature selection method selected equal number of ranked-features to the number of the patients. To perform localization, the positive relevance (PR) of voxels for patients with VisDys was calculated using the layer-wise relevance propagation (LRP) algorithm for multilayer neural network. The explanation given by LRP

was a map of voxels in the original texture feature map that contributed to diagnosis. The brain relevance of the external validation group ROP+ROD(CHR+ROD) using the entropy(energy) was associated with clinical scores.

Results: Presence of VisDys in ROP and CHR groups was predicted with classification accuracy GREATER THAN 74%. In ROP, using the energy feature map, regions that contributed most to the classification decision of VisDys were amygdala, right putamen, angular gyrus, left parietal cortex, postcentral cortex, precuneus, gyrus rectus, left thalamus, parts of vermis and occipital lobe. In CHR, using the entropy feature map, cuneus and parts of vermis showed PR for correctly classified VisDys. Shared regions were identified for the prediction of VisDys in ROP and CHR using energy and entropy feature maps, respectively including cerebellar areas, calcarine sulcus left, frontal and temporal lobe, fusiform gyrus, hippocampus, right insula and rectus, and lingual left. The utility of entropy (energy) revealed inverse structural changes in shared regions when VisDys were present in ROP (CHR) patients. Both classification schemas presented good prediction accuracy for ROD in both samples.

In ROP and ROD with VisDys we can predict a) PANSS_Positive, b) PANSS_disorganization, c) PANSS_excitement, d) PANSS_distress and e) functionality, at baseline. In CHR and ROD with VisDys there were no predictability of the clinical scores using the whole brain relevance.

Discussion: Preliminary results suggest that microstructure changes in non-segmented images are associated with the VisDys phenomenon in ROP and CHR and that these changes are differentiated in shared regions between ROP and CHR patients. The proposed framework supports a model of the visual system being implicated in core disease mechanisms of psychosis that may potentially contribute to the identification of structural biomarkers for psychosis. Changes in the cerebellar volume of patients with schizophrenia have been linked to predominantly positive symptoms which is in line with the fact that the cerebellum supports multiple functions including emotion regulation, inhibiting impulsive decision making, attention, and working memory. We can speculate that ROP and ROD with VisDys presents homogeneous brain texture changes highly associated with PANSS scores, functionality at baseline and the outcome in 1-year follow-up. CHR and ROD presents heterogeneous brain texture changes, association can be considered only in the cluster level.

F280. THE EFFECT OF STRESSFUL LIFE EVENTS ON THE RISK FOR PSYCHOSIS: DIFFERENCES BETWEEN MEXICAN AT CLINICAL AND FAMILIAL HIGH RISK

Lourdes Nieto¹, Tecelli Domínguez-Martínez¹, Laura Navarrete¹, Mauricio Rosel-Vales¹, Ricardo Saracco-Álvarez¹, César Celada-Borja¹, Maria Luisa Rascón-Gasca¹, Luis Gerardo Moncayo Samperio¹, Tecelli Dominguez^{*2}

¹*Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz*, ²*Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"*

Background: Stressful life events (SLEs) in the development of early psychosis have been little studied in low-income countries. This study examines differences in the prevalence of SLEs in Mexican at clinical high risk (CHR) and those with familial high risk for psychosis who do not meet CHR criteria (non-CHR FHR). We also analyze the association between SLEs and CHR.

Methods: Participants included 43 persons with CHR and 35 with non-CHR FHR. CHR criteria were assessed with the Comprehensive Assessment of At-Risk Mental State. SLEs were assessed using the Questionnaire of Stressful Life Events.

Results: Participants with CHR reported more SLEs associated with negative academic experiences than those in the non-CHR FHR group. Bullying (OR = 7.77, 95% CI [1.81, 33.32]) and low educational level (OR = 21.25, 95% CI [5.19, 46.90]) were the strongest predictors of CHR, while starting to live with a partner (OR = 0.26, 95% CI [0.10, 0.84]) was associated with a lower risk of CHR.

Discussion: Negative school experiences increase the risk of psychosis, particularly bullying, suggesting that schools may be ideal settings for implementing individual preventive strategies to reduce risk factors and increase protective factors to improve the prognosis of those at risk of developing psychosis. In Latin America, there are multiple barriers to early intervention in psychosis. It is thus crucial to identify risk and protective factors at the onset and in the course of psychosis in order to design effective preventive interventions.

F281. MORE UPDATING, LESS TESTING: NMDA-DEPENDENT CHANGES IN BIMODAL INFERENCE AS A NEUROCOMPUTATIONAL MECHANISM UNDERLYING SCHIZOPHRENIA

Philipp Sterzer^{*1}, Marcus Rothkirch², Merve Fritsch³, Lukas Roediger³, Katrin Reichenbach³, Deniz Yilmaz³, Veith Weilhhammer⁴

¹University of Basel, ²Medical School Berlin, ³Charité - Universitätsmedizin Berlin, ⁴University of California Berkeley

Background: According to predictive-processing theory, the positive symptoms of schizophrenia can be explained by altered inference mechanisms characterized by an overweighting of external sensory data relative to internal predictions. While this account is supported by a large body of behavioral and neuroimaging data, little is known about the neurotransmitter mechanisms involved in such abnormal inference. Here, we tested the hypothesis that hypofunction of the N-Methyl-D-aspartate receptor (NMDAR) may lead to an increased weighting of sensory evidence in perceptual inference.

Methods: Twenty-eight healthy volunteers underwent intravenous infusion of either NMDAR-antagonist s-ketamine or placebo in a randomized, double-blind cross-over design. During infusion, they reported their perception while viewing fully ambiguous or partly disambiguated structure-from-motion stimuli which consisted of random dots constituting two intersecting rings rotating in depth. Changes in the perception of this stimulus occur only when the rings overlap (every 1.5 s), which enabled us to discretize participants' reports into sequences of states. The change in the proportion of stimulus-congruent perceptual states with increasing levels of disambiguation was used to quantify the weighting of sensory evidence in perceptual inference.

Results: Using a generalized linear model (GLM) to predict participants' perceptual states, we found that s-ketamine increased their sensitivity to disambiguating information relative to placebo ($p = 5.8 \times 10^{-4}$), similar to recently reported findings in patients with schizophrenia. Importantly, perceptual inference is known to fluctuate over time between two modes, during which either external input or internal predictions dominate perception. We used Hidden Markov Models to infer transitions between these two states, each linked to an independent GLM that predicted perceptual states from current inputs and preceding states. Under s-ketamine, fluctuations in bimodal inference were shifted towards external mode, i.e. participants spent more time in states during which external input dominated perception ($W = 264$, $p = 0.03$, two-sided Wilcoxon rank sum test). Strikingly, a similar shift towards external mode was found in patients with schizophrenia compared to healthy controls ($n=23$ per group; $W = 578$, $p = 2.32 \times 10^{-3}$).

Discussion: This study shows that NMDAR-antagonist s-ketamine increases the weighting of external sensory data relative to internal predictions, mimicking findings obtained in patients with schizophrenia. Crucially, our analyses indicate that NMDAR antagonism does not result in a uniform change in inference, but rather affects the dynamic fluctuation between externally- and internally-biased states. Such bimodal inference likely represents iterative test-and-update cycles, a strategy by which the brain forms stable internal representations from the stream of sensory information. NMDAR hypofunction and the associated shift towards external mode may thus cause maladaptive updating of internal representations and thus a propensity to making spurious connections between unrelated sensory signals, thus giving rise to the positive symptoms of schizophrenia.

F282. DELAY IN PRESCRIBING CLOZAPINE...WORSE CLINICAL OUTCOMES?

Leticia Irene Muñoz-Manchado*¹, Jose Ildefonso Perez-Revuelta¹, José María Villagrán Moreno³, Miquel Bernardo⁴, Liliana Galindo⁵, Yulia Worbe⁶, Jorge Zimbrón⁷, Emilio Fernandez-Egea⁵

¹Jerez General Hospital, Andalusian Health Service; Severe Mental Disorder Research Group, University of Cádiz, , ³Mental Health Clinical Management Unit, Jerez General Hospital, Severe Mental Disorder Research Group, University of Cádiz, ⁴Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, CIBERSAM, ⁵Cambridgeshire and Peterborough NHS Foundation Trust, Behavioral and Clinical Neuroscience Institute, University of Cambridge, ⁶Sorbonne University, ICM, Inserm, CNRS, Hôpital Saint Antoine, ⁷Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge

Background: We investigate whether an earlier use of clozapine is related to a better response in different clinical domains, namely positive, negative, functioning and well-being.

Methods: We used data from a carefully characterised cohort of 254 clozapine-treated patients, which were evaluated using the positive subscale of the positive and negative syndrome scale (PANSS), the Brief Negative Symptom Scale (BNSS), Global Assessment of Functioning Scale (GAF) and the short version Warwick-Edinburgh Mental Well-being Scale (SWEMWBS). We then used logistic regression models (for positive and negative symptoms remission) and linear regression (for functioning and wellbeing) to evaluate the influence of time to clozapine initiation (TCI; above or below three years), age at the first episode of psychosis (AFE), duration of clozapine treatment (DCT) and gender.

Results: Proportion of negative symptoms remission and higher functioning scores were associated with earlier treatment with clozapine in the first three years after the first episode of psychosis (exp (B)=0.38; p=.02; β =-0.12, p=.046, respectively). No effect of time to clozapine initiation was found on positive symptoms remission rates or well-being scores.

Discussion: Starting clozapine treatment within the first 3 years of illness decreases the severity of negative symptoms and improves functioning in clozapine-treated patients. Clozapine effect on positive symptoms remission rates was not influenced by the time to clozapine initiation.

F283. THE ASSOCIATION OF IMMUNE GENES WITH SCHIZOPHRENIA SUBTYPES

Kosar Teymouri*¹, Clement Zai², Mahbod Ebrahimi², Cheng Cheng Chen², James Kennedy²

¹*Center for Addiction and Mental Health*, ²*University of Toronto and CAMH*,

Background: Immune disturbances have long been implicated in the pathophysiology of schizophrenia. An extensive body of research has been done to further our understanding of the underlying mechanism of the role of the immune system in schizophrenia. 287 loci were associated with the risk of schizophrenia in the most recent genome-wide association study (GWAS). The strongest hit came from the major histocompatibility (MHC) region, which was previously identified by Sekar et al., to belong to the complement C4 gene. The C4 gene codes for two structurally and functionally different isotypes, C4A and C4B with long or short forms (C4L and C4S). While C4 suggests the immune system's involvement in schizophrenia, it's not the sole immune gene linked to the condition. Moreover, subtyping schizophrenia has been an established strategy to dissect its heterogeneity. In this study, we aimed to identify all the immune genes that were fine-mapped in the most recent GWAS and investigate their association with the subtypes of schizophrenia.

Methods: A total of 613 subjects from the Toronto Schizophrenia Sample were included in this retrospective study. Participants were over the age of 18 and were diagnosed with SCZ or schizoaffective disorder. We categorized the genes as immune-related genes if they: had known immune function; were part of an immune pathway; or were expressed in an immune tissue. We individually investigated the associations between the identified genes including C4 with schizophrenia subtypes and phenotypes including PANSS scores, treatment-resistant schizophrenia (TRS), and age of onset. We later looked at their combined predictive power using polygenic risk scores (PRS) of the immune genes. Sex-stratified analyses were conducted for all the phenotypes.

Results: Our preliminary results on the first set of prioritized fine-mapped genes identified over 30 immune-related loci. Our study of the C4 gene showed that C4S was nominally associated with TRS in males only ($p=0.047$). Higher copy numbers of C4S and C4AS were associated with a lower number of hospitalizations in the whole sample (C4S $p = 0.023$ and C4AS $p = 0.007$), Europeans (C4S $p = 0.049$) and non-Europeans (C4AS $p = 0.044$). Moreover, higher copy numbers of C4AS were associated with higher age of first hospitalization in the whole sample ($p = 0.0371$) and females only ($p=0.011$). In male samples, higher copy numbers of C4B ($p=0.036$) and higher predicted brain expression of C4B ($p = 0.034$) were associated with lower age of onset. There was no association observed between C4 and positive, negative, and general psychopathology in the PANSS score. Currently, we are studying the relationship of the immune genes individually and as a PRS score with schizophrenia subtypes.

Discussion: While our study provides further support for C4 having a significant sex effect, it also suggests that C4S may have a protective effect against more severe forms of SCZ. Additionally, it supports the role of the immune system in the development of schizophrenia. Further analyses are in progress to extend and validate our current findings including the effect of inflammatory biomarkers on SCZ subtypes.

F284. THE ASSOCIATION BETWEEN COMPLEMENT PROTEINS AND CYTOKINES IN EARLY PSYCHOSIS

Rachel Davis*¹, Subash Raj Susai¹, David Mongan², Melanie Föcking¹, Inge Winter-van Rossum³, Barnaby Nelson⁴, NEURAPRO Investigators⁵, OPTiMiSE Study group⁵, Rene Khan⁶, G. Paul Amminger⁷, David Cotter¹

¹Royal College of Surgeons in Ireland, ²Queen's University Belfast, ³UMC Utrecht, ⁴Orygen Youth Health Research Centre, ⁵International sites, ⁶Icahn School of Medicine at Mount Sinai, ⁷Orygen, National Centre of Excellence in Youth Mental Health

Background: Consistent evidence demonstrates the involvement of immune dysfunction and associated pro-inflammatory status in the pathophysiology of psychosis. Altered levels of pro-inflammatory cytokines have been observed in blood and cerebrospinal fluid of patients at varying stages of psychosis, from clinical high risk, to first episode and chronic psychosis. The complement cascade is another emerging immune mechanism dysregulated in psychosis. Our team has identified alterations in complement and associated coagulation cascade proteins in early psychosis in relation to psychopathology.

Even though cytokine-related inflammatory alterations are increasingly studied in psychosis, the interrelationship between cytokines and complement cascade in clinical populations is not well understood. Therefore, the primary aim of this study is to evaluate the relationship between levels of peripheral complement proteins and cytokines in clinical cohorts from early psychosis, including clinical high risk of psychosis (CHR) and first episode psychosis (FEP).

Methods: Baseline plasma samples were obtained from two cohorts: the NEURAPRO clinical trial of CHR participants (n=170) and the OPTiMiSE clinical trial of drug-naïve FEP patients (n=243). Complement and coagulation proteins were quantified from baseline plasma samples using mass spectrometry. Cytokines were quantified at baseline using multiplex immunoassays. Linear regression models were developed to establish the relationship between complement proteins and cytokines. These models were adjusted for the potential covariates. P-values were corrected for multiple comparisons using the Bonferroni method ($\alpha = 0.05$).

Results: In CHR cohort, a significant linear relationship was found between several complement and coagulation proteins and four cytokines: CRP, IFN- γ , IL-6, and TNF α . CRP had a significant (p LESS THAN 0.01) positive relationship with complement C4B, complement factor B (CFB), and C9. Significant positive relationships were observed between IL-6 and C4B, CFB, C5, complement factor I (CFI), fibrinogen alpha and gamma chains, and coagulation factor XIII A subunit. IFN- γ had a significant positive relationship with complement C1R and C1S. TNF α had a significant positive relationship with C1R and CFI. Analysis of OPTiMiSE data of FEP patients is currently ongoing.

Discussion: The results have demonstrated a linear relationship between plasma levels of pro-inflammatory cytokines and complement proteins. It is notable that all four cytokines that reached significance have been consistently implicated in the pathophysiology of schizophrenia. Considering that complement proteins are related to inflammatory response in psychosis, complement proteins could have the potential to be a superior inflammatory biomarker for the following reasons. The complement system is central to many biological mechanisms implicated in schizophrenia, such as the coagulation cascade, oxidative stress, lipid metabolism and synaptic pruning. Mass spectrometry, a robust proteomic tool, can be used to quantify complement proteins, but it is difficult to detect cytokines with high sensitivity due to their low abundance and molecular weight. Finally, while cytokines are susceptible to short-term changes in immune status, complement proteins could be a potential biomarker that represents multiple long-term biological alterations in psychosis.

F285. LIVED, LOVED, LABOURED AND LEARNED: A NEW WAY OF THINKING ABOUT EXPERIENCE IN MENTAL HEALTH RESEARCH

Eóin Killackey*¹

Background: Increasingly, young people with lived and living experience of mental ill health are included in research in youth mental health including in ultra-high risk (UHR) and first-episode psychosis (FEP) research. However, for the potential of this inclusion to be realised and for progress to occur in mental health research we need a better way of including and talking about all the parties who are needed to make this happen. This is important to address implicit power dynamics and also to ensure that inclusion of other perspectives does not become tokenistic. Many of the ways that are used to talk about young people being involved in UHR or FEP research (youth participation, youth partnership) do not address the power implicitly held in titles or labels of other stakeholders in youth mental health research. At the same time with a sole focus on the important contribution of the experience of young people, the valuable experiences of other stakeholders can be neglected or lost (e.g. families).

Methods: This presentation describes the development of a framework which recasts the way that experience is thought about in youth mental health research, including research in UHR and FEP. It reconceptualises the various voices in research through the lens of the experience that each group may bring to conversations about the development, execution, interpretation or dissemination of the research.

Results: As a consequence of the development described above, the 4L framework is proposed. This understands the experience that stakeholders bring to a conversation about mental health research as coming primarily from one of four types of experience: Lived, Loved, Laboured and Learned. Importantly these forms of experience are not mutually exclusive.

Discussion: This presentation will introduce a new way of thinking about experience in mental health research that is more inclusive and which through the language it uses, seeks to present a more equal plane from which all voices can be heard. Importantly it acknowledges that various types of experience are not mutually exclusive, and that the lens through which any individual contributes to a discussion about mental health research may evolve over time. It is also possible that this framework has applications beyond youth mental health research. This presentation has important implications for the inclusion of all types of experience in mental health research.

F286. USING AI-DRIVEN PLATFORM TO MEASURE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA THROUGH FACIAL AND ACOUSTIC ANALYSIS

Jean-Pierre Lindenmayer*¹, Anzalee Khan², Vikram Ramanarayanan³, Hardik Kothare³, David Paulter³, Benedicto Parker⁴, Mohan Parak⁴, David Suendermann-Oeft³, Christian Yavorsky⁵

¹New York University, ²Nathan S. Kline Institute for Psychiatric Research and Manhattan Psychiatric Center, ³Modality, ⁴Manhattan Psychiatric Center, ⁵Biovalis

Background: The automatic analysis of facial and acoustic expressions of facial and speech productions in individuals with various psychiatric conditions has been expanding in the past few years. Here we are presenting new data on using an automatic multi-modality platform to measure negative symptoms of patients with schizophrenia. One central feature of negative symptoms is the reduction of facial movements and are referred to as expressive negative symptoms. Current methods of assessing negative symptoms depend on observations during a clinical interview. These interviews can be insensitive to change in treatment, subjective, require extensive training and are subject to cultural disparities. This study assesses whether a

novel artificial intelligence (AI) system analyzing facial and acoustic features can improve rater derived measurement of expressive negative symptoms in schizophrenia.

Methods: Hospitalized inpatients with schizophrenia (SZ: n = 70) and demographically matched healthy controls (HC: n = 75) completed a brief 8-minute assessment using the AI-driven platform NEMSI. Each participant was tested twice within one week in order to assess for test-retest reliability. For the AI software, participants were each provided a valence-neutral sentence to read by an avatar and were engaged in free speech where they were asked open ended probes designed to be emotionally-ambiguous in valence and content (e.g., tell me about yourself?). For the SZ group, at the first visit, the AI-driven recording was supplemented by rater assessed PANSS, BNSS, CDSS, CGI-S, AIMS, SAS, BARS. Concurrent, convergent, divergent, and discriminant validity were assessed. For the HC group, individuals received the AI vocal/speech software. All individuals were asked to assess user experience as measured by the SUTAQ (Service User Technology Assessment Questionnaire). Mann–Whitney test was used for comparison of AI features with clinical measures. Accuracy, sensitivity, specificity, and area under receiver operating characteristics-curve were measured as discriminatory indices of classifications.

Results: The mean age of individuals with SZ was 41.33 (10.35) and the HC group was 37.20 (8.52), and the mean PANSS total at Time 1 was 80.33 (10.18). Comparison of all the extracted features (54 facial and acoustic metrics) between SZ and the HC groups found 40 features to be significantly different ($p < 0.001$) mostly belonging to speech features (syllable alternating motion rate, loudness/articulation, speaking rate and pauses) and some facial features (e.g., average jaw acceleration, lip aperture). Session duration for the AI software was a mean of 8:32 min. Test-retest reliability was high ($ICC=0.91$). Significant correlations were observed between PANSS Motor Retardation and the AI software speaking rate ($r = -0.766$) and average jaw acceleration ($r = -0.820$), PANSS Active Social Avoidance and syllable alternating motion rate ($r = -0.821$), PANSS Marder Negative symptom score with pauses during speech ($r = -0.579$), BNSS Blunted Affect Vocal Expression, and Blunted Affect Expressive Gestures with the AI software speaking rate ($r = -0.777$). Most SZ (85.71%) and HC (93.78%) reported satisfaction with the AI-driven platform. Accuracy of classifying SZ from HC was 89.31%.

Discussion: We show significant correlations between speech and facial AI measures and negative symptoms assessed by raters using symptom scales. We also show a clear separation between facial and speech features of HC and participants with schizophrenia. The features of the AI-driven platform might help in improving the “validity” and reducing the “heterogeneity” in the assessment of negative symptoms and improve tracking and treating negative symptoms.

F287. FIRST EPISODE PSYCHOSIS: EXPLORING CLOZAPINE'S POTENTIAL

Mislav Škrobo¹, Draženka Ostojić², Antonia Puljić³, Ante Silić³, Dalibor Karlović⁴, Vjekoslav Peitl*⁵

¹University Hospital Centre Sestre Milosrdnice, ²University Psychiatric Hospital Vrapče and Faculty of Law, Social Work Study Centre, University of Zagreb, ³University Hospital Centre Sestre milosrdnice; School of Medicine Catholic University of Croatia, ⁴University Hospital Centre Sestre milosrdnice; School of Medicine Catholic University of Croatia, ⁵University Hospital Centre Sestre Milosrdnice; Catholic University of Croatia

Background: Clozapine, an atypical antipsychotic, has demonstrated remarkable efficacy in the treatment of treatment-resistant schizophrenia. However, its use in first-episode psychosis

(FEP) remains controversial due to concerns about potential side effects, limited evidence, and the availability of alternative treatments. This study aims to investigate the safety and efficacy of clozapine in individuals experiencing their first episode of psychosis.

Methods: This open-label prospective trial was carried out at the University Hospital Center Sestre Milosrdnice in Zagreb, Croatia, and involved 58 participants between the ages of 18 and 35 who had been diagnosed with First Episode Psychosis (FEP). These participants were randomly allocated into two groups: one group received clozapine as their initial treatment, while the other group received a standard antipsychotic medication. The study involved the assessment of clinical parameters, which included the administration of the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning (GAF), and monitoring for potential side effects. These assessments were conducted both at the beginning of the study and at regular intervals throughout a one-year follow-up period. Furthermore, data on social and occupational functioning, quality of life, and medication adherence were also collected.

Results: Preliminary results at the six-month mark show significant differences in symptom reduction between the clozapine and standard antipsychotic groups, with the clozapine group exhibiting a greater reduction in PANSS scores. Additionally, the clozapine group showed improved social and occupational functioning as assessed by the GAF scale. While the clozapine group experienced more side effects, particularly related to sedation and weight gain, these were generally manageable, and medication adherence remained high in both groups.

Discussion: This study provides important insights into the potential use of clozapine as a first-line treatment in FEP. Our findings suggest that clozapine may offer significant advantages in symptom reduction and functional improvement over standard antipsychotic medications. While the occurrence of side effects highlights the importance of careful monitoring and management, they do not appear to outweigh the benefits in this population. The long-term implications of initiating clozapine in FEP require further investigation. This study contributes to the ongoing discussion about treatment options for individuals experiencing their first episode of psychosis and may have important implications for clinical practice and treatment guidelines.

F288. MODELING AUDITORY MAGNETOENCEPHALOGRAPHIC RESPONSES IN 15-YEAR OLD OFFSPRING TO PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Oskar Jepsen^{*1}, Anette Fauriskov Bundgaard¹, Andreas Færgemand Laursen¹, Sinnika Birkehøj Rohd², Martin Wilms², Doris-Helena Feodora Bjarnadóttir Olsen², Marta Schiavon², Maja Gregersen², Mette Falkenberg Krantz², Aja Neergaard Greve¹, Nicoline Hemager², Anne Amalie Elgaard Thorup³, Merete Nordentoft², Ole Mors¹, Karl Friston⁴, Yury Shtyrov⁵, Martin Dietz⁵

¹Aarhus University Hospital, ²Copenhagen University Hospital, ³Child and Adolescent Mental Health Center Capital Region of Denmark, ⁴University College London, ⁵Aarhus University

Background: Patients with schizophrenia and bipolar disorder display altered neurophysiological responses, as measured with electroencephalography (EEG) or magnetoencephalography (MEG). By applying neuronal models to neurophysiological data, recent studies have found in vivo evidence for reduced synaptic gain on superficial pyramidal cells in patients with schizophrenia, in line with neuropathological evidence. However, whether synaptic changes are related to illness state or underlying liability remains unsettled. To address

this gap, we recorded auditory responses using MEG from 15-year-old adolescents at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and modeled auditory responses using dynamic causal modeling (DCM).

Methods: We recruited 15-year-old subjects taking part of the third wave of The Danish High Risk and Resilience Study – VIA (VIA15). Subjects were either at FHR-SZ, FHR-BD, or matched population-based controls (PBC). We recorded MEG data during two auditory paradigms: the roving auditory oddball paradigm and the 40-Hz auditory steady-state response (ASSR). We compared sensor-level oddball responses between groups and applied DCM to study underlying changes in extrinsic and intrinsic connectivity.

Results: Data collection is ongoing. Preliminary sensor-level analyses reveal no evidence for group differences in auditory oddball responses. Preliminary DCM revealed evidence for modulation of both extrinsic and intrinsic connectivity in adolescents at FHR-SZ and FHR-BD, relative to PBC.

Discussion: Computational modeling of magnetoencephalographic auditory responses reveals altered effective connectivity in adolescents at familial high risk of schizophrenia and bipolar disorder.

F289. OPTIMIZING HEALTH FOR YOUTH AT CLINICAL HIGH RISK (CHR) FOR PSYCHOSIS: EARLY INDICATORS OF FEASIBILITY

Muhammad Husain^{*1}, Lisa Hawke², Nicole Kozloff¹, Michael Kiang¹, Gillian Strudwick², Wei Wang², David Castle³, George Foussias¹

¹University of Toronto, ²Center for Addiction and Mental Health, ³Tasmania Mental Health Service

Background: functioning and have a high lifetime risk of suicide. The CHR period is an important phase where indicated interventions may reduce the risk of progression to several negative outcomes, including the development of schizophrenia. Given that up to 80% of individuals with CHR have another diagnosable mental illness and almost half experience poor psychosocial functioning, developing interventions that address poor functioning in CHR youth is of great importance. We aimed to adapt and evaluate the efficacy of the Optimal Health Program (OHP), a 12-week skills-based illness self-management program, in improving functioning, reducing distress, and building resilience in CHR individuals.

Methods: The study consists of three phases: (1) Adaptation of OHP for CHR through youth engagement: A six-member advisory group consisting of youth with lived experience convened on a weekly basis to adapt the OHP intervention, tailoring OHP to the needs of CHR youth; (2) OHP-CHR will be evaluated for feasibility, acceptability, and preliminary efficacy in a single arm pre-post intervention trial (n=30). Measures of clinical, functional, and cognitive outcomes will be completed at study entry and repeated post-intervention at 12-weeks; (3) Qualitative evaluation of OHP-CHR: Post-intervention semi-structured qualitative interviews will be conducted at the end of study to obtain views of OHP-CHR, experiences participating, perception of the program, and barriers/facilitators to participation.

Results: (1) Adaptations were informed through engagement with individuals with lived experience and focused on: youth-friendly language; incorporation of personal stories; emphasis on personalized recovery; enhancement in graphic design; thus, tailoring to the CHR population. (2) Participants are currently being recruited to the clinical trial from the CHR Clinical Research Service at CAMH. Over the course of 5 months, from September 2023 to January 2024, 23 referrals were received, of which 16 met study inclusion criteria, and over

60% of eligible participants were recruited (n=10). All participants completed baseline assessments (60% male, mean age=20.5±3.9 years). Most participants have attended all planned sessions (n=8; 80%). 50% (n=5) attended in-person, 20% (n=2) attended virtually, 30% (n=3) attended with a hybrid format. So far 7 participants have completed the 12-week intervention with 86% (n=6) attending all 9 sessions. one participant dropped out after completing 5 sessions.

Discussion: The present study was able to engage individuals with lived experience to clinically adapt the OHP intervention to the needs of CHR youth. The preliminary results suggest that OHP-CHR may be a feasible and acceptable intervention for CHR youth.

F290. PSYCHOTIC EXPERIENCES AND PROBLEMATIC GAMING: NEW UNKNOWN ASSOCIATION

Andre Fernandes^{*1}, Renan Biokino², Andrew Miguel¹, Viviane Machado¹, Gabriela Koga Tonsig², Lais Fonseca¹, Pedro Pan², Thiago Henrique Roza³, Giovanni Salum⁴, Ives Passos⁵, Luis Augusto Rohde⁵, Euripedes C Miguel⁶, Carolina Ziebold⁷, Ary Gadelha¹

¹Federal University of Sao Paulo/Univ. of Sao Paulo Medical School, ²Federal University of Sao Paulo, ³Federal University of Paraná (UFPR), ⁴UFRGS, ⁵Federal University of Rio Grande do Sul (UFRGS), ⁶USP, ⁷PROESQ - EPM/UNIFESP

Background: Problematic Gaming (PG) is a serious mental health condition related to several psychiatric disorders, such as anxiety, social phobia, depression or attention-deficit/hyperactivity disorder. However, the association between PG and Psychotic experiences (PE) remains poorly explored in literature. Both disorders can share common physiopathological mechanisms, as they may involve changes in the salience network and dopamine neurotransmission. Also, subjects with psychotic symptoms may be more reclusive, increasing their vulnerability to gaming time. We hypothesized that adolescents with PG were more likely to report PE compared with those without the disorder. The aim of our study was to examine the association between both conditions in a large Brazilian community sample.

Methods: We utilized a cross-sectional subsample of a large Brazilian cohort (n=1,616; 13-to-21-year age range), from whom it was evaluated the presence of PE, measured by Community Assessment of Psychic Experiences - Positive Dimension (CAPE-Pos). We also classified the participants according to their gaming status, using the 7-item version of the Game Addiction Scale (GAS): no PG, PG, or Gaming Addiction (GA). Linear regression analyses were used to examine the association between GD and PE, adjusted for the presence of significant covariates, including other psychiatric conditions.

Results: 53.5% (n=865) of the participants were male, with a mean age of 18.4 years; 60.9% (n=981) had higher family risk for psychiatric disorder. 9.5% (n=154) presented problematic gaming and 2.7% (n=43) gaming addiction. 28.0% received any DSM-IV diagnosis and 9.39% had PE. Participants presenting PG had greater levels of PE compared with participants without PG. PG remained significantly associated with PE in multivariate analyses (b=0.96, 95% CI 0.17-1.75, p=0.017).

Discussion: We found a statistically significant association between problematic gaming and PE in a sample of Brazilian young people. Also, comorbid gaming addiction and any other psychiatric disorders substantially increased the level of PE. Further longitudinal studies may help to disentangle common neurobiological and/or behavioral pathways between these two phenomena. This could provide a new perspective into vulnerability for disorders such as schizophrenia, during a viable period for early intervention.

F291. OPEN DIALOGUE AS "LIVE", EFFICIENT TRAINING IN SOCIAL COGNITION FOR PSYCHOTIC CONDITIONS

Maria Gariup*¹

¹*OPUS YOUNG Study, Child and Adolescent Psychiatric Center Glostrup*

Background: Social cognition (SC) refers to the way people perceive, think about, interpret, categorize, and judge their own social behaviors and those of others (APA 2018). It includes: emotion processing, mentalizing, social perception and attributional bias (Green et al., 2019). Mounting evidence suggests that SC is impaired in psychotic disorders (Savla et al., 2013), and that SC domains may have an important influence on functional outcomes (Halverson et al., 2019). There is increasing interest in interventions targeting SC in this patient group (Halverson et al., 2019; Peña et al., 2016): most interventions are interactive, groupbased treatments including a range of visual, auditory, video stimuli depicting social stimuli (Kurtz et al., 2016). Interventions appear effective in improving SC domains, but it has not yet been consistently demonstrated whether they generalize to real improvements in daily life functioning, (Green et al., 2019). In this work we argue that Open Dialogue (OD) approach for psychosis (Seikkula et al., 2011) may constitute an effective training on SC.

Methods: Open Dialogue (OD) is an approach started in Finland for treating psychotic crises. It is a need-adapted approach, involving families and social network from the very beginning (SEIKKULA and OLSON, 2003). OD has shown preliminary, excellent results in terms of functional- and symptoms recovery, when compared to standard treatment (TAU) (Seikkula et al., 2011). More importantly, these results have shown to hold also at 19-yrs follow-up: durations of hospital treatment, disability allowances, and the need for antipsychotic medication remained significantly lower in the OD group vs TAU (Bergström et al., 2018). This is especially important, as other high-intensive care programs with good effects in the short period, have failed to prove sustained benefits vs TAU at 20-years follow-up (e.g. Hansen et al., 2023). OD has gained international interest, with pilot studies happening worldwide, and a RCT trial just carried out in the UK, with outcomes expected for next summer (Pilling et al., 2022). Many of OD principles are common to other first-episode programs: quick help, flexibility, involvement of families and of social instances (Olson et al., 2014). Two characteristics though, are peculiar to OD.

1. "Dialogicity": an extensive use of family and network meetings, where the focus is not so much on finding a shared agreement, but more on encouraging dialogue and polyphony, where all points of view are considered legitimate.

2. The use of "reflective talks" between therapists during meetings (Andersen, 1995): therapists share together, in front of the network, the feelings they are experiencing at the meeting, and give place to their wonders and to what still has been unsaid (Olson et al., 2014; Sidis et al., 2022). This often can lead to a better mutual understanding, and a resolution of stressful circumstances (Bergström et al., 2018).

Results: Other benefits can come along. OD encourages the emergency of the different points of view and needs, and provides "live training" about which emotions can be activated in a situation. The "person in concern" can naturally appreciate feelings and motifs that have been at stake in the lived situation, both for oneself and one's closest ones. This insight could easily

translate in higher mentalization skills. Besides, it is expectable that the experience of overcoming communication difficulties, and reaching a closeness and mutual understanding, could modify one's trust and one's attributional bias. In this line, it is noticeable that at the 19-th year follow-up, what many participants recalled about the approach, was not so much one therapeutical relation, but rather, that the approach helped them and their families to better communicate together (Bergström et al., 2018).

Discussion: OD stands out as a putative effective training in social cognition: "Dialogue increases reflexivity" (Seikkula, 2023). This possibility could contribute to explain the good results the approach has shown so far (Bergström et al., 2018) and deserves further investigation.

F292. ADAPTING BIDS FOR MULTI-SITE AND MULTI-SESSION STUDIES

Tobias Goodwin-Allcock^{*1}, Rhea Thukral², Lei Wang¹, Nina Kraguljac¹

¹The Ohio State University, ²The University Of Alabama at Birmingham

Background: In neuroimaging studies, the sheer volume of data, both acquired and derived, can be overwhelming. To that end, the Brain Imaging Database Structure (BIDS) was developed so that researchers could more easily manage, process, and share their data. BIDS has been successful and widely adopted with examples such as: the NIH supported OpenNeuro data sharing platform, and a collection of neuroimage processing tools called BIDS Apps. A feature of BIDS is that it is designed to handle multiple sessions. This simplifies the management of longitudinal data. However, BIDS is only in its first iteration, and the authors themselves admit that it was not designed for multi-site studies. They do provide two suggestions for multi-site studies:

1. Consider each site as a separate BIDS database
2. Encode the siteID in the subject name. Both suggestions have issues for multi-site multi-session (MSMS) studies. The issues arise when a subject changes sites between sessions. A subject may change sites for many reasons, e.g. longitudinal studies may include new sites or no longer include sites for their follow up sessions, or a subject may have moved houses between sessions and live much closer to a different site. To demonstrate this issue with BIDS for MSMS studies, let's suppose three subjects (subjectID=001,002,003) and two hospitals (siteID=01,02) over two sessions. Subject 001 goes to site 01 for both sessions, subject 002 goes to site 02 for both sessions and subject 003 has their first session at site 02 and their second session at site 01. Following the first BIDS suggestion, we have two databases: (BIDS_Hospital01 and BIDS_Hospital02). In BIDS_Hospital01 there are two subjects, sub-001 and sub-003. In this case, sub-001 contains two sessions whereas sub-003 contains only the second session. Now let's consider the second BIDS suggestion. One database (BIDS) that contains all the data. In there, the subject names contain the siteID. In our example, this results in 4 subject files: sub-01001, sub-02002, sub-01003, sub-02003. In both suggestions, Subject 003's data has been split into two different folders. This is confusing and leads to unnecessary complications when attempting to view all the sessions for a given subject. This example demonstrates the need for a system that appropriately stores the data for multi-site multi-session studies.

Methods: We propose encoding the site information in with the session ID: sessionID= LESS THAN sessionIdx GREATER THAN LESS THAN siteID GREATER THAN. The subjects' IDs will not contain the siteIDs and the database will be considered as one combined database.

Results: Storing the information in this way keeps all the data in one directory and keeps all a subject's data together. Additionally, the data will be ordered in the subject's file in order of the sessions due to the sessionIdx coming first. Finally, the siteID's are clearly identified within the session names. In our example, subject 003's data would be stored in one file, sub-003, that contains ses-102 and ses-201.

Discussion: Encoding the siteID into the sessionID has been shown to be beneficial compared to the current methods. A limitation is that this is not a current suggestion from BIDS so some tools may need adaptation to be compatible with this new database design. People may see this and think an alternative method could be to have a site referenced folder as a subfolder within the session folder, however, unless there were multiple sites for a given session, this would be an unnecessary extra folder to navigate through, e.g. "BIDS/sub-003/ses-1/site-02/..." instead of "BIDS/sub-003/ses-102/...". Given the unnecessary extra folder, we believe that storing multi-site multi-session data in the way proposed in this abstract is simpler than other alternatives as well as an improvement over the current suggestions.

F293. ULOTARONT IN THE TREATMENT OF SCHIZOPHRENIA: POST-HOC ANALYSES OF TWO 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 TRIALS

Heather Dworak¹, Robert Goldman¹, Yan Li¹, Kenneth S. Koblan¹, Armin Szegedi¹, Nicholas DeMartinis*¹

¹Sumitomo Pharma America, Inc.

Background: Ulotaront, an investigational TAAR1 agonist with 5-HT1A agonist activity, has demonstrated efficacy in a flexible-dose (50 mg/d to 75 mg/d) Phase 2 trial [Koblan KS, et al., N Engl J Med.2020;382(16):1497] in acutely psychotic patients with schizophrenia (PANSS effect size [ES] 0.45). We previously reported [Kane J, et al., Neuropsychopharmacology. 2023;48:351] results from two Phase 3 fixed-dose studies designed to further evaluate the efficacy and safety of ulotaront (ULO) in schizophrenia, which both failed to meet their primary endpoint (DIAMOND 1 [D1], NCT04072354; and DIAMOND 2 [D2], NCT04092686). We now report results of post-hoc analyses undertaken to better understand possible contributors to the lack of ulotaront-placebo (ULO-PBO) separation in the Phase 3 studies.

Methods: Both studies were double-blind, placebo-controlled, 6-week trials evaluating the efficacy of ulotaront (50 mg/d and 75 mg/d; 75 mg/d and 100 mg/d) in adult patients with schizophrenia who were acutely psychotic (PANSS total score $\geq$ 80). In D1 and D2, enrollment was limited to patients with $\leq$ 2 or 3 prior hospitalizations for acute psychotic episodes, respectively. The primary endpoint was Baseline-to-Week-6 change in PANSS total score.

Results: Neither D1 or D2 met the primary endpoint for any ULO dose group (D1: ULO-50 mg and ULO-75 mg vs. PBO were -16.9 and -19.6 vs. -19.3; D2: ULO-75 mg and ULO-100 mg vs. PBO were -16.4 and -18.1 vs. -14.3). The previously reported flexible-dose (50-75 mg) Phase 2 trial [Koblan KS, et al., 2020] was significant for ULO-50-75-mg vs. PBO (-17.2 vs. -9.7). A review of 14 PBO-controlled NDA trials in schizophrenia conducted from 2009-2015 [Gopalakrishnan M, et al. J Clin Psychiatry. 2020;81(2):19r12960] found mean endpoint PANSS change scores of -16.9 for drug vs. -10.5 for placebo. These results suggest that the effect of ULO in the D1/D2 studies was comparable to active drug in both post 2009 NDA

trials and in the previous Phase 2 ULO trial. However, the PBO response was unusually high in both D1 and D2 studies, with D1 PBO response (-19.3) the highest recorded in any pre-or-post-2009 NDA trials in schizophrenia [Gopalakrishnan et al., 2020]. In a pre-specified pooled D1/D2 analysis, patients enrolled prior to onset of the COVID pandemic demonstrated significant efficacy for ULO-50-100 mg vs. PBO on PANSS total score (-15.8 vs. -8.8; $p=0.017$; $ES=-0.47$). No difference was observed for ULO vs. PBO in the post-COVID sample (-17.7 vs. -17.5), potentially linked to observed regional differences in placebo response. Finally, elevated serum prolactin (PRL) at screening was a predictor of higher PBO response. For ULO vs. PBO in D1/D2 pooled, $PRL \leq 40$ ng/mL: -17.8 vs. -14.4; $p=0.014$; compared with $PRL > 40$ ng/mL: -14.1 vs. -21.7. Elevated PRL was associated with increased dose or newly initiated antipsychotic (AP) treatment proximal to study entry.

Discussion: A large PBO effect was observed in both studies (most notable in D1) which may have masked the ability to detect a significant efficacy signal for ULO. Patients enrolled pre-COVID demonstrated notably larger effect sizes for ULO, though this finding may be due to geographic factors, as most pre-pandemic patients were recruited in the US. Initiation of a new AP or a dose increase for ongoing AP just prior to study entry appears to have contributed to a lack of drug-placebo separation. Finally, it appears that limiting enrollment to patients with ≤ 2 or 3 prior hospitalizations may have resulted in a sampling bias that favored patients who had either less illness chronicity/severity or with a history of illness that was more readily responsive to outpatient AP therapy without requiring recurrent hospitalizations.

F294. EXPLORING THE ROLE OF ANTICHOLINERGIC MEDICATION BURDEN ON COGNITION IN PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Valentina Mancini^{*1}, Caren Latreche², Jack Fanshawe¹, Ioana Varvari¹, Chambrez-Zita Zauchenberger¹, McGinn Nova², McGuire Philip¹, McCutcheon Robert¹

¹*Oxford University*, ²*University of Geneva*

Background: There is preclinical and human evidence that cholinergic antagonists may have deleterious cognitive effects. Cognitive deficits are a core feature of psychosis but may be exacerbated by the use of psychotropic medications with anticholinergic properties. However, the impact of anticholinergic activity on cognitive functioning in psychosis is not clearly established. In this systematic review and meta-analysis, we aimed to synthesize evidence from studies quantifying anticholinergic medication burden in psychosis to determine if subjects with a higher burden have worst cognitive outcomes. Additionally, we explored studies that investigated if reducing cholinergic medications can improve cognition in psychotic subjects.

Methods: We searched Medline, EMBASE, and PsycINFO, from inception until October 2023. Studies reporting objective cognitive assessment and quantification of cholinergic burden using clinical scales (ACB), serological quantification (SAA), or studies tapering anticholinergic medications were included. Cognitive measures were grouped into domains of the MATRICS battery. All the analyses were carried out in R using the metaphor package. Given high heterogeneity was expected, we employed a random-effects meta-analysis model to pool results across studies. Heterogeneity was assessed with Cochrane Q statistic and I² index. Effect sizes were estimated as R-values for correlational studies (ACB and SAA) and as standardized mean difference (Cohen's d) for tapering studies. Publication bias was evaluated by visually inspecting funnel plots and performing the Egger's test. Study quality was evaluated using a modified version of the Newcastle-Ottawa scale.

Results: Of 212 eligible studies screened, 39 met inclusion criteria, comprising 25 ACB studies (4620 patients), 6 SAA studies (382 patients) and 8 (157 patients) tapering studies. We identified a negative correlation between ACB and the following MATRICS domains of cognition: Global cognition ($r=-0.37$, 95% CI, [-0.48,-0.25]), Verbal learning ($r=-0.28$, 95% CI, [-0.36,-0.21]), Visual learning ($r=-0.17$, 95% CI, [-0.28,-0.06]), Working Memory ($r=-0.22$, 95% CI, [-0.29,-0.14]), Processing Speed ($r=-0.24$, 95% CI, [-0.35,-0.13]), Attention ($r=-0.19$, 95% CI, [-0.29,-0.08]), Executive functions ($r=-0.17$, 95% CI, [-0.27,-0.06]), and Social cognition ($r=-0.12$, 95% CI, [-0.19,-0.05]). Similarly, we identified a negative correlation between SAA and the following MATRICS domains: Verbal learning ($r=-0.26$, 95% CI, [-0.38,-0.14]), Working Memory ($r=-0.19$, 95% CI, [-0.35,-0.03]), Executive functions ($r=-0.16$, 95% CI, [-0.27,-0.04]). Finally, tapering off cholinergic medication improved the scores in the following MATRICS domains: Verbal learning ($d=0.72$, 95% CI, [0.36,1.09]), Working Memory ($d=0.94$, 95% CI, [0.63,1.26]), Processing Speed ($d=1$, 95% CI, [-0.51,2.5]), and Executive Functions ($d=0.44$, 95% CI, [0.26,0.62]).

Discussion: Findings from this meta-analysis support a role of cholinergic burden in the cognitive impairment observed in psychosis. From a clinical perspective, tapering off anticholinergic medication in psychotic patient may be beneficial for cognition. However, randomized clinical trials are needed for an unbiased quantification of benefit.

F295. EXTERNALIZING PLAY IN PSYCHOSIS THERAPY – EXPERIENCES FROM THE FACE YOUR FEARS TRIAL

Sanne Bekker*¹, Louise Angelou Stokbro¹, Anne Sofie Due², Lise Mariegaard², Mads Juul Christensen¹, Ulrik Nykjær Jeppesen³, Merete Nordentoft⁴, Louise Birkedal Glenthøj³, Ditte Lammers Vernal⁵

¹Psychiatry, Aalborg University Hospital, ²VIRTU Research Group, Copenhagen Research Center for Mental Health, Mental Health Center Copenhagen, ³VIRTU Research Group, Copenhagen Research Center for Mental Health, Mental Health Center Copenhagen, University of Copenhagen, ⁴Copenhagen Research Center for Mental Health, Mental Health Center Copenhagen, , ⁵Psychiatry, Aalborg University Hospital, Aalborg University

Background: FaceYourFears is a randomized controlled trial (RCT) which explores the impact of exposure therapy rooted in cognitive behavioral principles in the treatment of paranoia in patients with schizophrenia-spectrum disorders. The project has two manualized intervention arms, cognitive behavioral therapy (CBT) vs. virtual reality (VR)-assisted CBT, both aiming to mitigate avoidance behaviors and harm expectancies. Exposure fosters new learning experiences, challenge exaggerated perceptions, and helps the patient become more aware of cognitive and behavioral patterns in interacting with the surrounding world.

Methods: This presentation draws from the therapist's experiences in the trial. Exposure is pivotal for reducing avoidance and enabling cognitive shifts. In the VR intervention, exposure consist of a constructed VR environment with triggers known to cause paranoid ideas and strong emotion in the patient. By trying different behavioral experiments and role play in both VR and real life, the patient is able to test paranoid ideas which potentially can allow for more adequate coping and better functioning in daily life. In the CBT intervention, exposures are planned as homework in the real world between sessions.

Creativity and play can be integrated in the therapy in both treatment arms, with certain elements being particularly important:

- Safety circle or cognitive diamond enhances the psychoeducation by using concrete and visual presentation to explain the rationale behind the treatment.
- Window of tolerance provides the therapist with information on hyper- and hypo arousal to use the appropriate level of exposure in which the patient is able to take in new information and generate appropriate cognitive structures. When hyper aroused, the patient is not able to take in new information or regulate emotions; when hypo aroused, the patient is learning from the experience due to lack of engagement.
- Importance of therapeutic alliance: To be able to use play, humor and creativity, a thorough knowledge of the patient's history, experiences, personality, and boundaries is paramount. If a therapeutic alliance is not formed or adequate, use of novel ideas or humor may be perceived as insensitive or inappropriate.

Play or creative behavioral testing can take many forms, e.g., an intense worst case scenario role play, trying out a novel response, externalization an internal strategy such as humor or by the patient using their imagination to alter paranoia in a new way (imaginary rescripting).

Results: Illustrative examples from the trial include unconventional approaches like employing Harry Potter incantations, introducing unusual scenarios, or referencing horror movie characters. Small, funny elements like sticking out one's tongue to the hostile people in the VR bus or waving at hallucinations may engage the patient in laughter instead of fear and paranoia. Creative interventions, such as imaginary rescripting and worst-case scenario role play enhance patient engagement, self-worth, and commitment to and belief in symptom reduction. This commitment may result in continued efforts to decrease symptoms even after the end of treatment.

Discussion: Explicitly addressing patient comfort or discomfort early in treatment and generally fostering a collaborate environment is crucial in CBT for psychosis. Integrating creative play may enhance therapy outcomes for some, though it is not a universal goal. Timing is key – ensuring the patient feels supported and not ridiculed. The therapists' clinical experiences from the trial, integrating unconventional ideas and funny elements, seem to foster a good alliance with some patients which is something that may be explored further in psychosis research.

F296. CORTICAL MYELIN MAPPING IN NEUROBIOLOGICAL SUBGROUPS OF PATIENTS WITH PSYCHOSIS-SPECTRUM DISORDERS

Victoria King*¹, Natalie Remiszewski², Matthew Defenderfer¹, Adrienne Lahti¹, Nina Kraguljac²

¹The University of Alabama at Birmingham, ²The Ohio State University

Background: Psychosis-spectrum disorders are typically diagnosed in late adolescence or early adulthood, interestingly coinciding with peak myelination in the brain. Additionally, processing speed has been identified as a core deficit in schizophrenia. The T1w/T2w ratio was developed as a proxy measure of myelin content in vivo and has been used to examine 'myelin maps' of healthy people and people with psychiatric and other myelin-related disorders. Moreover, normative modeling is a technique designed to study patient populations at an individual level, assessing interindividual differences as opposed to typical 'case-control'

studies. We used this method to group our patients into subgroups based on cortical thickness. We then compared myelin maps between each group. Our hypothesis was that normative-based subgroups of patients with psychosis-spectrum disorders would differ in myelin content in regions associated with processing speed.

Methods: Similar to a pediatric growth chart, the normative model generates normative curves of cortical thickness based on more than 58,000 healthy individuals, accounting for age and sex, in 148 brain regions using the Destrieux atlas. We adapted the model to our site data using healthy controls, then plotted our patients on the curves to produce individual z-scores for each subject in each region. We then used these z-scores to determine ‘extreme’ positive and negative deviations from each normative curve, using a cutoff of ± 2 . To control for false positives, we used a cutoff of 4 extreme deviations per subject to determine 4 subgroups of patients: those with mostly positive deviations, those with mostly negative deviations, those with under 4 positive and negative deviations, and those with over 4 positive and negative deviations. Myelin maps for all subjects were generated using the Minimal Preprocessing Pipelines from the Human Connectome Project. a priori regions were identified based on a recent meta-analysis. We performed an ANCOVA to compare global average myelin content between the groups, and a MANCOVA to compare myelin content in regions associated with processing speed between the groups.

Results: We compared myelin values of 98 first-episode psychosis patients - 28 ‘positive’ patients, 32 ‘negative’ patients, and 38 ‘none’ patients - and 111 healthy controls. Due to a small sample size of 7 patients, we excluded those who fell into the ‘both’ group. The spatial patterns of deviations among all patients were highly heterogeneous, with only a few regions showing more than 4% overlap between all subjects. Using age, sex, and SES as covariates, the results of the ANCOVA revealed a significant difference between the groups on global average myelin content ($F = 2.822$, $p = 0.04$). The results of the MANCOVA revealed that patients in the positive group exhibit increased myelin compared to healthy controls in regions associated with processing speed ($F = 1.350$, $p = 0.012$); however, these results did not survive multiple comparison correction.

Discussion: This study expands on previous findings of heterogeneous spatial patterns of deviations from a normative model in patients with psychosis-spectrum disorders. This method highlights the importance of examining interindividual differences in addition to case-control studies which describe an overall group trend. Further, our data suggest that first-episode psychosis patients who exhibit positive deviations from a normative model of cortical thickness present significantly higher myelin content in areas associated with processing speed. While the exact mechanism is unclear, this finding may help explain why first-episode psychosis patients exhibit deficits in processing speed.

F297. CAREGIVING AND CLINICAL OUTCOMES IN FIRST EPISODE PSYCHOSIS

Michelle Worthington^{*1}, Laura Yoviene Sykes², Nina Levine², Shannon Imetovski², Vinod Srihari², Carrie Veilliette²

¹*Yale University*, ²*Yale University School of Medicine*

Background: Family involvement is an important part of treatment for young people recovering from a first episode of psychosis; however, the experience of caregiving and the effects of caregiver burden within family members in this population are not well understood. As a young person’s social environment has the potential to shape the course of their recovery, understanding how to inform robust family-based interventions is an essential component of overall recovery. In this study, we examine the experience of caregivers in a first episode

psychosis clinic and examine the relationship between the experience of caregiving and the young person's symptoms. We hypothesize that a more challenging caregiving experience is associated with a higher severity of symptoms.

Methods: Data was collected at the Specialized Treatment in Early Psychosis (STEP) clinic at the Yale University School of Medicine. To measure the caregiving experience, we administered the Experience of Caregiving Inventory (ECI) to families upon entering treatment at STEP, and at 6- and 12-months following admission to STEP. The ECI is a 35-item questionnaire with both positive and negative subscales that measure multiple dimensions of caregiving for relatives with serious mental illness. Clinical variables measuring symptoms and levels of functioning administered to the young person included the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF), Global Functioning: Role and Social Scales (GF:S and GF:R). Pearson's correlations were used to examine the relationships between scores on the caregiving inventory positive and negative subscales and clinical measures.

Results: A total of 24 survey responses were received. Of the caregivers who responded, 17 (71%) identified as primary caregivers and 13 (54%) reported having additional caregiving responsibilities. The mean number of hours spent caregiving per week was 57 (SD = 61). The mean age of the young person was 22.7 years (SD = 3.5) and the median duration of untreated psychosis (DUP) was 8.1 months (IQR = 0.03-11.4). Primary caregivers reported higher scores on the ECI negative subscale (mean = 92.4, SD = 49.2) than secondary caregivers (mean = 57.6, SD = 24.0). The ECI negative subscale showed a trend positive correlation with the PANSS total score ($R^2 = 0.42$, $p = 0.07$) and the negative ECI subscale was positively correlated with the PANSS positive subscale ($R^2 = 0.50$, $p = 0.03$). This demonstrates an overall more negative caregiving experience with higher levels of symptoms of psychosis early in treatment, primarily driven by the presence of increased positive symptoms. Further, longer DUP was associated with lower scores on the negative scale of the ECI ($R^2 = -0.46$, $p = 0.04$), potentially indicating that more acute or shorter onset of symptoms may be associated with a more negative caregiving experience. Functioning as measured by the GAF, GF:R and GF:S was not associated with positive or negative caregiving experiences.

Discussion: Caregiver burden as indicated by higher scores on the negative subscale of the ECI was higher for primary caregivers and for caregivers of young people experiencing higher levels of positive symptoms, but was decreased for caregivers of young people with longer duration of psychosis. In total, these findings begin to elucidate risk factors for higher caregiver burden and potential burnout in first episode psychosis. Continued examination of the caregiving experience in first episode psychosis, including examining changes over time, would be necessary to best inform mechanisms of support for caregiving family members involved in first episode psychosis treatment for their young person.

F298. PARSING HETEROGENEITY IN MEDICATION-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS WHO PRESENT FEATURES OF THE DEFICIT SYNDROME: A NORMATIVE MODELING APPROACH

Matheus Teles*¹, Natalie Remiszewski¹, Adrienne Lahti², Saige Rutherford³, Andre F. Marquand⁴, Nina Kraguljac¹

¹The Ohio State University, ²The University of Alabama at Birmingham, ³Donders Institute,

⁴Donders Institute of Brain, Cognition, and Behaviour, Radboud University, Radboud University Medical Centre, Institute of Psychiatry, King's College London

Background: The deficit syndrome is a clinical subtype of schizophrenia characterized by enduring negative symptoms and thought to be more homogeneous than the non-deficit form of the illness, but it is not clear if this is also true for abnormalities in cortical thickness. Normative modeling is a novel way to capture inter-individual neurobiological heterogeneity and can be utilized to assess heterogeneity in the cortical thickness of clinically distinct patient groups. Here we hypothesized that medication-naïve first episode psychosis patients with features of deficit syndrome, when compared to patients without, will be more homogenous in cortical thickness pathology.

Methods: We recruited 101 antipsychotic medication-naïve first episode psychosis patients at the University of Alabama at Birmingham for the study. Twenty-nine patients included in the analysis displayed clinical features of the deficit syndrome, while seventy-two patients did not. We used the Schedule for the Deficit Syndrome to assess if patients display features of the deficit syndrome. We used T1-weighted structural MRI on a 3-T Siemens Magnetom Prisma with a 20-channel head coil to quantify individual region-level structural normative deviations (defined as GREATER THAN 2SD) in cortical regions in patients with or without clinical features of the deficit syndrome. We quantified individual region-level structural normative deviations based on a normative reference model using the Predictive Clinical Neuroscience and brain charts toolkits. We used BrainPainter to generate all brain renderings. We performed Levene's test for the equality of variances to assess patient groups differences in variance in the number of cortical deviations. Independent samples t-test was utilized to examine differences in the mean number of cortical deviations among patient groups. We performed a two-sample Komolgorov-Smirnov test to compare the distributions of the number of cortical deviations among the patient groups.

Results: Non-deficit patients had a higher mean number of cortical negative deviations, (4.98 ± 6.50), i.e. cortical thinning, than deficit patients (2.44 ± 2.92), $t(97.73)=2.703$, $p=.008$ (Figure 1). The effect size was moderate (Cohen's $d=.44$). Non-deficit patients have significantly more variance in the number of cortical negative deviations than deficit patients, $F=7.56$, $p=.007$. There were no patient group differences in variance ($F=.057$, $p=.812$) and mean number ($t(99)=-.342$, $p=.733$) of cortical positive deviations. Negative deviations were generally more widespread across the cortex in non-deficit compared to deficit patients.

Discussion: Patients with features of deficit syndrome presented significantly reduced mean and variance in the number of cortical negative deviations compared to patients without, which supports the idea that deficit syndrome is a more homogeneous distinct subtype of schizophrenia. Using a normative modeling approach allowed us to capture inter-individual variability in medication-naïve first episode psychosis patients who do or do not present features of the deficit syndrome. These findings provide additional evidence supporting the existence of the deficit syndrome as a distinct and more homogenous disease entity within schizophrenia, compared to the non-deficit form of the illness. This contributes to a better understanding of the pathophysiology of the deficit syndrome and may guide future research on effective treatment strategies, given the current absence of viable options.

F299. NORMATIVE MODELING-DERIVED DEVIATIONS IN ANTIPSYCHOTIC MEDICATION-NAÏVE FIRST-EPISODE PSYCHOSIS PATIENTS OF DIFFERING COGNITIVE FUNCTION

Natalie Remiszewski^{*1}, Eric Nelson², Andre Marquand³, Adrienne Lahti², Nina Kraguljac¹

¹The Ohio State University, ²University of Alabama at Birmingham, ³Donders Centre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition, and Behavior, Radboud University

Background: The central premise of precision medicine is that an individual's unique characteristics play a role in disease vulnerability. Studies have shown that regional normative modeling-based measures can capture inter-individual heterogeneity – however, little is known about their clinical relevance. Here, we investigate if significant deviations from a healthy reference cohort are associated with cognitive performance, a key illness dimension in schizophrenia, in antipsychotic medication-naïve first-episode psychosis patients (FEP).

Methods: Structural neuroimaging was performed using an MPRAGE [TR/TE/TI: 2400/2.22/1000ms; 0.8mm³ voxels] sequences. Data were processed in FreeSurfer 7.1.1. to quantify region-level cortical thickness measures using the Destrieux parcellation. We used the Predictive Clinical Neuroscience braincharts toolkit to compute individual-level deviations from the reference norm for cortical thickness in antipsychotic medication-naïve FEP. A z-value cutoff of ± 2 was used to define extreme deviation, with extreme positive deviations being regions with a z-value of greater than 2 and negative deviations being regions with a z-value of less than -2. Score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess cognition. Grouping based on cognitive function was done in two ways: based on total RBANS score as well as by overall cognitive profile determined by scores on five RBANS subscales. The total extreme deviation loads were compared between these groups.

Results: Using a cutoff score of 85 on total RBANS (mean score minus standard deviation; 100-15) yielded 73 cognitively impaired (LESS THAN 85) and 21 cognitively intact (≥ 85) individuals. K-means clustering based on the 5 RBANS subscales (immediate memory, visuospatial, language, attention, delayed memory) yielded five clusters for overall cognitive profile. T-tests of positive, negative, and total cortical deviation load between cognitively impaired and intact individuals yielded no significant difference in deviation load between the two groups. Additionally, ANOVAs comparing cortical deviation loads between the 5 cognitive profile clusters also yielded no significant differences except for a significant difference between clusters 3 (mostly higher RBANS scores) and 4 (mostly average RBANS scores).

Discussion: Overall, there were no differences in deviation load between FEP of differing cognitive functioning regardless of grouping method. These results inform us that a more generalized metric such as total deviation load by individual may not be an appropriate structural measure for understanding the underlying etiology of cognitive dysfunction in FEP. It is also possible that macrostructural abnormalities do not underly cognitive deficits. Future work should focus on spatial localization of deviations in each of these groups to investigate anatomical patterns in significant deviation.

F300. EXERCISE4PSYCHOSIS: THE EFFECTS OF A MODERATE-TO-VIGOROUS EXERCISE INTERVENTION ON INFLAMMATORY BIOMARKERS AND NEGATIVE SYMPTOM PROFILES IN FIRST-EPISODE PSYCHOSIS

Connor Dunleavy*¹, Richard Elsworth¹, Rachel Upthegrove¹, Stephen Wood², Kelly Allott², Sarah Aldred¹

¹University of Birmingham, ²Orygen

Background: First-episode psychosis (FEP) is a devastating mental illness that tends to emerge during early adulthood, characterised by a disconnect in perception of reality. Perturbations in immune responses and elevated inflammatory biomarkers are suggested as important in the manifestation of FEP, and potentially the emergence of specific negative symptom profiles. Exercise is a potent anti-inflammatory stimulus that is known to reduce inflammation and improve mood profiles, therefore physical activity may represent a novel adjunct therapy for pathological mechanisms of FEP, and negative symptoms unalleviated by currently prescribed antipsychotic medication. This study aims to assess the effects of regular exercise on parameters of immune function, and psychological outcomes in FEP.

Methods: Seventeen young men were recruited from Birmingham 'Early Intervention in Psychosis' services and randomised to a 6-week exercise programme or treatment as usual, consisting of 2-3 sessions per week targeting 60-70% heart-rate maximum. Immune-inflammatory T-helper cell phenotype (Th1, Th2, Th17, Treg) and cytokines (interleukin (IL)-4, IL-6, IL-8, IL-10), growth factors (BDNF, VEGF) symptom severity (PANSS, TEPS), functional outcomes (WHO Quality of Life, Assessment of Disability), and cognition (Digit Span) were measured at baseline, and after 6-weeks of regular exercise.

Results: Participants in the exercise intervention achieved 81.11% attendance, with an average exercise intensity of $67.54\% \pm 7.75\%$ HRMax. This led to favourable changes in immune cell phenotypes, and a significant reduction in the Th1:Th2 ratio (-3.86% , $p = 0.014$). After exercise there was also a significant reduction in plasma IL-6 concentration (-22.17% , $p = 0.006$). IL-8, IL-10, BDNF, and VEGF all increased, but these changes were not statistically significant. Symptomatically, there was a significant reduction in negative symptoms after exercise (-13.54% , PANSS Negative, $p = 0.008$). There was no significant change in positive or general symptoms, functional outcomes, or cognition (all p GREATER THAN 0.05). In the TAU group, there were no significant changes in any biomarkers, symptom severity, functional outcomes, or cognition (all p GREATER THAN 0.05).

Discussion: Exercise as therapy is useful for tackling multiple symptom profiles that are unalleviated by antipsychotic medication, including negative symptoms which are most debilitating with reference to quality of life. Exercise-induced alterations in immune profiles may uncover mechanisms that relate directly to the manifestation of negative symptoms, which may aid in providing precision therapy for people suffering with FEP.

F301. RESHAPING BOUNDARIES BETWEEN SCHIZOPHRENIA, BIPOLAR DISORDER, AUTISM SPECTRUM DISORDERS, AND RESISTANT DEPRESSION: DEVELOPMENT OF THE COHORT « FRENCH MINDS » IN THE FRENCH NETWORK PROGRAM-PROJECT IN PRECISION PSYCHIATRY

Jasmina Mallet^{*1}, Ophelia Godin², Charles Laidi³, Anouck Amestoy⁴, Ariane Cartigny⁵, Boris Chaumette⁶, Ariel Frajerman⁷, corentin gosling⁸, Anton Iftimovici⁹, Renaud Jardri¹⁰, Aline Lefèvre¹¹, Antoine Lefrère¹², Baptiste Pignon¹³, Céline Portalier¹⁴, Romain Rey¹⁵, Ludovic Samalin¹⁶, Linda Scoriels¹⁷, Florian Stephan¹⁸, Nathan Schneider¹⁵, Antoine Yrondi¹⁹, Florence Joseph²⁰, Imène Ben Mohamed²⁰, Federico Cevoli²⁰, Umar Salem²⁰, Marie-Hélène Soto²⁰, Véronique Briquet-Laugier²⁰, Pierre-Michel LLORCA²¹, Marion leboyer²²

¹Alliance FondaMental, APHP (The Greater Hospital of Paris), Institute of Psychiatry and Neurosciences of Paris (IPNP), ²Alliance FondaMental, Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, F-75013, Paris, France, INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé

Publique, F-75013, Fondation FondaMental, ³Alliance FondaMental, INSERM U955, Institut Mondor de la Recherche Biomédicale (IRMB), Univ. Paris Est Créteil, Equipe 15 Neuropsychiatrie Translationnelle La Fondation Fondamental, Créteil, France NeuroSpin, Neuroimaging Platform, CEA, UNIACT Lab, PsyBrain Team, Saclay, France, ⁴Alliance FondaMental, Université de Bordeaux, CH Charles Perrens, ⁵Alliance FondaMental, CHU Robert Debré, APHP, Paris, ⁶Alliance FondaMental, CHSA, GHU Paris Neurosciences, Paris, ⁷Alliance FondaMental, CHU Kremlin-Bicêtre, APHP, ⁸Alliance FondaMental, Laboratoire Dysco, Université de Nanterre, ⁹Alliance FondaMental, GHU Paris Neurosciences, CHSA, ¹⁰Alliance FondaMental, CHU Lille, Université de Lille, ¹¹Alliance FondaMental, CH Fondation Vallée, ¹²Alliance FondaMental, APHM, ¹³Alliance FondaMental, APHP GH Mondor; INSERM U955 team 15; Fondation Fondamental, Créteil; department of psychiatry, CHRU de Lille, FRANCE., ¹⁴Alliance FondaMental, APHP, CHU Louis Mourier, ¹⁵Alliance FondaMental, CH Vinatier, ¹⁶Alliance FondaMental, CHU Clermont-Ferrand, ¹⁷Alliance FondaMental, fInstitute of Psychiatry and Neurosciences of Paris, France, ¹⁸Alliance FondaMental, CHU Brest, ¹⁹Alliance FondaMental, CHU Toulouse, ²⁰Alliance FondaMental, ²¹Alliance FondaMental, CMP B, CHU, EA 7280 Faculté de Médecine, Université d'Auvergne, BP 69 63003 Clermont-Ferrand Cedex 1, Fondation FondaMental, France., ²²Alliance FondaMental, Translational Psychiatry Department, H Mondor Hospital, DHU Pe-Psy, Inserm U955 eq15, Paris-Est University, Fondation FondaMental, France

Background: Schizophrenia (SZ) is a severe mental disorder, but few therapeutic innovations have been developed recently due to a lack of physiopathological knowledge. Psychiatry precision can improve treatment response and clinical outcomes through patient stratification and holds great potential for SZ and other mental disorders. The program-project PROPSY, funded by the French government and launched in 2023, focuses on 4 overlapping and heterogeneous disorders: schizophrenia (SZ), autism spectrum disorders (ASD), bipolar disorder (BD), resistant depression (RD). Five work packages (WP) were defined by the PI Prof. Leboyer, her team, and the institutions CNRS and INSERM. WP1 aims at developing a 3000-patient longitudinal cohort called French Minds upon the existing cohorts FACE and RHU-PSYCARE; WP2 will uncover cellular mechanisms with preclinical studies; WP3 will develop clinical trials; WP4 will create a French Biomedical ecosystem to trigger the public-private partnerships; WP5 is dedicated to the Early Career to increase the attractiveness of psychiatry and awareness of civil society. Considering the importance of better defining homogeneous phenotypes, about 40 Million euros out of 80 of PROPSY are dedicated to the WP1, giving the opportunity to reshape clinical and nosographical boundaries between SZ, ASD, BD and RD.

The aims of this WP1 are to:

1. Identify homogeneous subgroups with specific biological signatures
2. Identify clinical and/or biological dimensions shared by all included participants included, regardless of psychiatric diagnosis.
3. Compare clinical and biological data to replicate similar strategies with international cohorts.
4. Improve the organization of care, ie diagnostic accuracy and therapeutic strategies.

Methods: WP1's leaders and the authors of this abstract were particularly involved in defining unmet needs and meaningful clinical dimensions. Bimonthly meetings involving psychiatrists, researchers and psychologists were organized, named "French minders" meetings. The

participants also met once a month with the leader of another international cohort (US, UK, EU...), to ensure coherence and complementarity between all international cohorts and future collaborations. WPI team contacted peer workers and users of psychiatry to help define unmet needs for patients in a participatory approach.

Results: The following dimensions have been targeted:

1. Neurodevelopment
2. Cognitive flexibility
3. Motivation and emotional regulation
4. Comorbidities, including metabolic syndrome
5. Social Withdrawal
6. Sensori-motor dimension

All subjects will benefit from an extensive clinical (including sleep and neurological soft signs), neuropsychological and paraclinical evaluation (biological, genetic, EEG and MRI). The clinical and paraclinical management platform for patient monitoring will be integrated into healthcare systems in real-life settings. A digital tool will assess real-life clinical parameters. Inclusion criteria are:

1. Age between 16 and 60
2. Signed informed consent
3. Ability to read, write and understand French
4. Confirmed diagnosis of at least one of the 5 following DSM5 diagnoses: 1st episode of psychotic disorder, SZ, BD, RD, ASD without intellectual disability
5. Compatible clinical condition
6. Membership of a social security scheme

Discussion: In a transnosographic approach, patients included in the "French Minds" cohort will be thoroughly phenotyped by collecting and combining clinical, behavioral, numerical, omics, brain imaging data and environmental variables. This research will help reshape clinical boundaries, improve knowledge of the prognostic factors of these four diseases and allow the development of new therapeutic strategies. Precision psychiatry needs large and transnosographic data sets of prospective real-world data.

F302. THE EFFECT OF INTERNALIZED STIGMA ON SOCIAL ANXIETY, FUNCTIONING AND SUBJECTIVE RECOVERY AFTER GROUP COGNITIVE INTERVENTIONS FOR FIRST-EPISODE PSYCHOSIS

Libby Lassman^{*1}, Élisabeth Thibaut², Olivier Percie du Sert², Tania Lecomte³, Ashok Malla², Martin Lepage⁴

¹McGill University, ²Douglas Research Centre, McGill University, ³University of Montreal, ,

⁴Douglas Research Centre; Prevention and Early Intervention Program for Psychoses; McGill University,

Background: Social anxiety disorder is among the most prevalent comorbidity in first-episode psychosis (FEP) and is associated with significant social disability and poor prognosis. An important factor that contributes to social anxiety and impedes recovery in this population is internalized stigma, which involves endorsing and applying negative stereotypes about mental

illness to oneself. Certain group-based cognitive interventions have shown promising results for improving social anxiety and functioning in FEP, including cognitive behavioral therapy (CBT) in which internalized stigma is directly targeted, along with standard cognitive remediation. Thus, internalized stigma stands as an important predictor of treatment response to consider within these interventions. However, this factor has not yet been investigated as a predictor in the context of a group CBT intervention tailored to address internalized stigma for people with FEP and comorbid social anxiety. This study aims to examine whether reduced internalized stigma predicts improvements in social anxiety after receiving group CBT that directly addressed internalized stigma, compared to group cognitive remediation for FEP. Additionally, the effect of internalized stigma on functioning and subjective recovery after treatment will be examined as secondary outcomes.

Methods: Data from the current study was based on a randomized controlled trial comparing the effect of group CBT with group cognitive remediation for people with FEP and comorbid social anxiety disorder. Ninety-six participants aged 18-35 were recruited from five FEP clinics in Montreal and completed measures of social anxiety, functioning, subjective recovery, and internalized stigma at baseline, post-intervention, and two follow-ups (three months and six months). Linear mixed models were conducted to predict primary and secondary outcomes. In each statistical model, the fixed effects consisted of internalized stigma, time, treatment group, and the interaction between internalized stigma and these two factors. Age and sex were entered into the models as covariates.

Results: Linear mixed models revealed a significant and positive main effect of internalized stigma on social anxiety [$F(1, 205) = 75.36, p < .001$], functioning [$F(1, 159) = 9.80, p < .001$], and subjective recovery [$F(1, 200) = 77.82, p < .001$], while controlling for age and sex. However, there was no significant interaction between internalized stigma and treatment group, nor with each time point for all three outcomes (p s GREATER THAN .05). Moreover, no significant baseline differences between the two treatment groups were found.

Discussion: Despite internalized stigma being addressed through group CBT, it was not found to be a significant predictor of social anxiety, functioning, and subjective recovery within this intervention, relative to group cognitive remediation. The positive treatment response of these group interventions may therefore be due to a general therapeutic factor, such as group therapy, which is known to create a sense of belonging with peers and normalize their difficult experiences. This study lays the groundwork for future research to explore the active ingredients of group CBT that specifically target internalized stigma relative to standard group CBT for a population with FEP and comorbid social anxiety.

F303. USING HIERARCHICAL LEARNING MODELS TO INFER NEUROCOMPUTATIONAL MECHANISMS UNDERLYING SCHIZOPHRENIA SYMPTOMS

Teresa Katthagen^{*1}, Stella Zimmermann¹, Tal Geffen¹, Fabien Carruzzo², Mariia Kaliuzhna², Stefan Kaiser², Florian Schlagenhaut¹

¹Charité-Universitätsmedizin, ²University of Geneva

Background: In schizophrenia patients (PSZ), reinforcement learning dysfunctions like reward prediction error coding proposedly contribute to central aspects of the disorder including aberrant salience attribution as well as motivational impairments. Hierarchical learning models, like the novel Volatility Kalman Filter (VKF; Piray and Daw, PLoS Comput Biol 2020), describe such process of prediction error driven belief updating on various levels.

Here, the weight ascribed to prediction errors is informed by estimated noise as well as the inferred belief about the volatility of the environment, which we found to be increased in PSZ in previous studies using the Hierarchical Gaussian Filter (Mathys et al., 2011). However, whether these effects, specifically the relationship between prediction errors and negative symptoms as well as overestimation of volatility, can serve as clinical biomarkers with sufficient stability across time, sites and modelling frameworks, still needs to be addressed in longitudinal designs.

Methods: The current study aimed at assessing the associations between alterations in belief updating and negative symptoms in the multicentre, longitudinal SyMoNe study. A total of 120 (PSZ n=67, healthy controls n=53) participants performed the novel volatile reversal learning paradigm during fMRI at two time points with three months in-between. The task probes higher-level learning and its related neural signatures. In addition to reversals, we introduced another source of uncertainty by varying levels of probabilistic noise. Analyses of choices focused on the effects of noise level and group on performance in terms of correct responses. We further assessed the intra-class correlation as a measure of retest reliability of task performance. Then, we setup a model space with static (Rescorla Wagner) and dynamic (VKF) learning rates as well as control “no learning” model. We concatenated choices across time points and applied a hierarchical Bayesian inference approach for model fitting. FMRI data were pre-processed following a standardized protocol (fMRIPrep). First-level analyses investigating group differences on prediction errors, stimulus beliefs and volatility beliefs are currently ongoing.

Results: There was a main effect of probabilistic noise level on correct responses, which decreased with higher noise levels ($F=122.4$, $p < 0.001$). PSZ chose the correct stimulus less often than healthy controls did ($F=14.14$, $p < 0.001$), but there was only a trend-wise significant interaction between group and noise ($p=0.07$). The novel paradigm showed a good retest reliability in terms of correct responses ($ICC=0.66$). Concurrent model-comparison revealed that the most complex model with a dynamic learning rate (VKF), stable learning parameters and decision noise betas varying over time explained data best (protected exceedance probability: $pxp=0.64$). PSZ underestimated the systematic noise parameter ω ($F=8.99$, $p < 0.01$) and this correlated with higher positive symptoms (beta coefficient=-4.32, $t=-2.38$, $p < 0.05$). There were no group differences in starting points for volatility ($p > 0.1$) or volatility learning rate ($p > 0.7$).

Discussion: In line with previous findings, we found deficient reward learning in schizophrenia patients. However, and in contrast to our previous findings, this was not due to overestimating volatility, but to underestimating the noise. Methodologically, this highlights that both levels of uncertainty, systematic changes and probabilistic noise, should simultaneously be addressed in tasks and models to disentangle both constructs. This might be crucial for identifying the computational parameters underlying symptom dimensions.

F304. EFFECTS OF CANNABIS USE ON GABA-A $\alpha 5$ RECEPTOR BINDING IN CLINICAL HIGH-RISK AND FIRST EPISODE PSYCHOSIS

Zerrin Atakan^{*2}, Paulina Lukow¹, Julia Schubert², Samuel Knight², Amanda Kiemes², Nicholas R Livingston², Jacek Donocik³, A DeMichelli², Thomas Spencer², Paolo Fusar-poli⁴, Federico Turkheimer⁵, Mattia Veronese⁶, Steven Williams², Philip McGuire⁷, Gemma Modinos²

¹University College London, ²Institute of Psychiatry, Psychology and Neuroscience, King's College London, ³South London and Maudsley NHS Foundation Trust, ⁴King's College London, University of Pavia, ⁵Center for Neuroimaging Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, ⁶University of Padua, ⁷University of Oxford,

Background: The impact of cannabis use and GABA dysfunction are both highly researched topics in schizophrenia. Evidence linking the endocannabinoid (ECS) and GABAergic systems involves cannabinoids inhibiting GABA release in the hippocampus through the inhibition of voltage-dependent calcium channels. Furthermore, the ECS ligand AG-2 was shown to also be a ligand for the GABAA receptor. Early use of cannabis increases the risk of developing schizophrenia, but the mechanism by which this happens is not yet clear. Findings in clinical high-risk (CHR) individuals are less conclusive but suggest a dose-response relationship between cannabis use and transition to psychosis. We investigated the links between cannabis use and GABAA $\alpha 5$ receptor binding in CHR individuals and people with first-episode psychosis (FEP) using PET imaging with the tracer [11C]Ro15-4513.

Methods: A total of 58 participants (healthy controls, HC=24; CHR=24; FEP=10) completed the study. Participants underwent PET-MRI scanning with the tracer [11C]Ro15-4513, which has high affinity for GABAA $\alpha 5$ receptor subunits and completed the Cannabis Experience Questionnaire. PET data were analysed with MIAKAT 4.3.24 in Matlab R2017a; data from 2 CHR individuals was excluded due to insufficient acquisition or poor quality. Total volume of distribution (VT) in the hippocampus, selected due to its high expression of both GABAA $\alpha 5$ and ECS, was estimated through a two-tissue compartmental model.

Results: There was a significant group effect of cannabis use ($X^2(2,56)=7.883$, $p=0.019$), by which more individuals in the CHR and FEP groups had ever tried cannabis compared to the HC group ($p=0.024$ and $p=0.029$, respectively). There were no significant group differences in current cannabis use ($p=0.777$), age first tried ($p=0.520$), type ($p=0.635$) or frequency of use ($p=0.173$). Within each group, no significant difference was found in hippocampal VT between individuals currently smoking and not smoking cannabis, or in those who had ever used or never used cannabis (all p GREATER THAN 0.05). However, CHR individuals who started cannabis before age 18 ($n=11$) showed significantly higher hippocampal VT compared to those who started cannabis after age 18 ($n=7$) [$F(1,17)=6.520$; $p=0.023$]. Hippocampal VT in CHR with early cannabis use was significantly negatively correlated with negative symptom severity ($r=-0.686$, $p=0.041$). Furthermore, CHRs who used cannabis regularly ($n=10$) showed a trend-level elevation in hippocampal VT compared to CHR who used only a few times per year ($n=7$) [$F(1,16)=7.540$; $p=0.077$]. No significant differences were found between these variables within FEP or HC.

Discussion: Consistent with previous literature, a higher proportion of CHR and FEPs reported past cannabis use compared to HC. There were no group differences in current use, starting age, type or frequency of cannabis use. This may be due to increased awareness among clinical groups regarding the mental health impacts of cannabis. GABA-A $\alpha 5$ availability was elevated in CHR individuals who started cannabis early, compared to those who started at adulthood, consistent with findings of increased GABA release in hippocampal cultures under conditions of prolonged cannabis use. This elevation, which correlated with lower severity of negative symptoms, may reflect a compensatory upregulation of GABAergic receptors involved in mediating tonic inhibition. Further investigation with larger samples and longitudinal follow-up is required to elucidate the effect of early and frequent exposure to cannabis on GABA receptors in high-risk groups.

F305. ASSOCIATION OF HIPPOCAMPAL GABAA RECEPTOR AVAILABILITY AND RESTING PERFUSION OF A HIPPOCAMPAL-STRIATAL-MIDBRAIN CIRCUIT IN CLINICAL HIGH-RISK AND FIRST-EPISODE PSYCHOSIS

Samuel Knight^{*1}, Paulina Lukow², Amanda Kiemes³, Nicholas R Livingston³, Fernando Zelaya³, Andrea De Micheli⁴, Zerrin Atakan³, James Davies⁵, Tom Spencer³, Paolo Fusar-poli³, Jacek Donocik⁶, Beate Haegel⁶, Mattia Veronese⁷, Federico Turkheimer⁷, Julia Schubert¹, Steven CR Williams⁷, Owen O'Daly³, Philip McGuire⁸, Gemma Modinos³

¹King's College London, ²University College London, ³Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁴Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁵Invivo Imaging Services, ⁶South London and Maudsley NHS Foundation Trust, ⁷Center for Neuroimaging Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁸University of Oxford,

Samuel Knight

Background: Multiple lines of evidence suggest that the hippocampus is vulnerable to dysfunction in psychosis. In vivo neuroimaging research has identified hippocampal, basal ganglia, and midbrain hyperactivity by regional cerebral blood flow (rCBF) in people with psychotic disorders and individuals at clinical high-risk for psychosis (CHR-P). Rodent models suggest that this hippocampal hyperactivity is a result of GABAergic inhibitory interneuron dysfunction, which promotes aberrant downstream hyperactivity of dopaminergic cells in the striatum and midbrain. However, whether GABAergic activity in the hippocampus is linked to rCBF in a hippocampal-striatal-midbrain circuit in individuals at CHR-P and experiencing the first episode of psychosis (FEP) is unknown. We sought to address this question through a multimodal PET/MRI study in antipsychotic-naïve individuals at CHR-P, as well as FEP patients using [11C]Ro15-4513, a PET tracer with high selectivity for GABAA-A5 receptor subunits which are predominantly expressed in the hippocampus.

Methods: Participants included 24 CHR individuals (mean [±SD] age: 25.2 [±4.6] years, 15 female), 24 healthy controls (HC) (25.2[±4.4] years, 15 female), and 10 FEP (mean [±SD] age: 29.2 [±5.2] years, 3 female) scanned in a single session with a 3T GE PET/MR scanner in a cross-sectional, case-control design. GABAA-A5 receptor availability was obtained using [11C]Ro15-4513 PET with arterial blood sampling. One CHR-P participant was excluded due to insufficient acquisition and one due to technical issues with blood sampling. rCBF data were obtained using pseudo-continuous arterial spin labelling (ASL). PET data were analysed with MIAKAT 4.3.24 in Matlab R2017a. Total volume of distribution (VT) in the hippocampus was estimated through a two-tissue compartmental model, which was fitted to each participant using a population-based input function with individualised corrections from discrete blood samples. ASL data were pre-processed using the ASAP toolbox in SPM12. Correlations between individual hippocampal [11C]Ro15-4513 VT and rCBF in the left/right hippocampal, basal ganglia, and midbrain circuit (defined using coordinates from a previous CHR-P study), were assessed using ANCOVA in SPM12. Significance was determined at p LESS THAN 0.05 FWE.

Results: In FEP individuals, lower levels of hippocampal [11C]Ro15-4513 VT were significantly associated with higher rCBF in the right hippocampus ($t=3.14$, $p_{FWE}=0.038$) and trended towards a significant association with higher rCBF in the left hippocampus ($t=2.98$, $p_{FWE}=0.057$). In CHR-P individuals, lower levels of hippocampal [11C]Ro15-4513 VT

trended towards an association with higher rCBF in the left midbrain ($t=2.98$, $p_{FWE}=0.057$). In HC individuals, lower levels of hippocampal [11C]Ro15-4513 VT trended towards an association with higher rCBF in the left pallidum/putamen ($t=2.9$, $p_{FWE}=0.056$). There were no significant differences in the associations of rCBF and hippocampal [11C]Ro15-4513 VT between groups.

Discussion: Our findings suggest that lower hippocampal GABAA-A5 levels were associated with higher hippocampal rCBF in FEP individuals, but not in CHR or HC. This evidence partially supports the hypothesis that GABAergic dysfunction underlies elevations in resting perfusion of a hippocampal-striatal-midbrain circuit in the context of early psychosis.

F306. ATTITUDES TOWARDS PHYSICAL ACTIVITY IN INDIVIDUALS WITH FIRST EPISODE PSYCHOSIS TREATED IN AN EARLY PSYCHOSIS INPATIENT UNIT

Melanie Trimmel^{*1}, Joachim Rockenschaub¹, Antonia Renner¹, Barbara Hinterbuchinger¹, Nilufar Mossaheb¹, Fabian Friedrich¹

¹*Medical University of Vienna*

Background: People with severe mental illnesses (SMI), such as schizophrenia, often suffer from multiple somatic comorbidities. Physical activity (PA) is a crucial factor in preventing cardiovascular diseases and numerous studies have also shown positive effects of PA on mental health. Despite this, people with SMI have been found to be less physically active. Addressing motivational factors and barriers seems decisive to support adherence to regular PA. This study aims to investigate preferences, motivation and barriers towards PA in people with first episode psychosis (FEP).

Methods: In order to explore attitudes towards PA in individuals with FEP aged 18-65 years a comprehensive self-completion questionnaire was developed to collect socio-demographic data as well as previous levels of PA, exercise patterns throughout life, PA preferences, motivational factors and perceived barriers. Recruitment and survey took place during treatment at an early psychosis inpatient unit. The data was analysed descriptively. The study was approved by the local ethics committee.

Results: Overall, eighteen individuals with FEP (thereof five women = 27.8%) aged 18-64 years (mean 26.4) were included. Fifteen were diagnosed with schizophrenic psychosis and three with affective psychosis. Fourteen (= 77.8%) reported regular physical activity within the last 3 months, whereby the majority were physically active on average between two and three days per week between 20 and 60 minutes per PA session. Half of them stated that they practised only one type of PA. The most frequently performed PA was walking (64.3%), followed by training at home (42.9%), yoga/stretching (28.6%), and gym activities (28.6%). Most of them indicated that the extent of their PA had changed during the inpatient treatment: ten reported that the amount of PA had decreased and six that it had increased compared to the period before. Fourteen (= 77.8%) were former sports club members, and eleven (= 61.1%) have been or are currently members of a gym. Eight (= 44.4%) prefer to exercise alone, while eight favour exercising together with a training partner. Regarding the training location, two-thirds preferred outdoor, seven (= 38.9%) at home, five in an institution (= 27.8%), and four in the gym (= 22.2%). Twelve (= 66.7 %) of the respondents would prefer a moderate PA intensity. Eleven (= 61.1%) expressed an interest in sports programs specifically designed for people with psychiatric disorders. Seventeen (= 94.4%) stated that they would like to exercise more regularly, with most of them indicating that trainers or an exercise program would help them to do so. At least half stated that they would do more exercise if their doctors

recommended it. Walking (61.1%) and hiking (55.6%) were the most preferred types of exercise, followed by swimming (44.4%), yoga/stretching (38.9%), training at home (38.9%), cycling (33.3%), gym (33.3%) and running (27.8%). When asked about motivational factors for exercise, the following were stated most frequently: improve physical and mental well-being (100%), strengthen self-confidence (94.4%), improve mood (94.4%), improve energy (88.9%), improve fitness (88.9%), and maintain/improve general health (88.9%). The most frequently experienced barriers to exercise were lack of energy/too exhausting (77.8%), lack of motivation (77.8%), lack of training partners (61.1%), and mental health status/symptoms (55.6%).

Discussion: Individuals with FEP show great interest in PA and would like to be more physically active. Interventions such as medical recommendations, specific training programs (addressing exercise preferences), instructors, and training partners could be supportive to achieve this goal.

F307. DATA-MINING ANALYSIS OF MEDIA EFFECTS ON SOCIAL STIGMATA OF SCHIZOPHRENIA

Joonho Choi^{*1}, Il Bin Kim², Yoon Young Nam³

¹Hanyang University Guri Hospital, ²CHA Gangnam Medical Center, CHA University School of Medicine, ³National Center for Mental Health

Background: In 2011, Korean Neuropsychiatric Association renamed schizophrenia from ‘mind split disorder’ (‘Jungshinbunyeolbyung’ in Korean) to ‘attunement disorder’ (‘Johyeonbyung’ in Korean), in a strategic way to reduce social stigma toward people with schizophrenia. However, there remains an elusive consensus that how the renaming effort has contributed to changes in the social perception of schizophrenia in Korea.

Methods: With this regard, we explored whether media frames alter the social perception, in ways of respecting or disrespecting schizophrenia patients before and after the renaming. This study extensively investigated media keywords related to schizophrenia across the time by applying both language and epidemiologic analyses.

Results: In results, the media keywords have been negatively described for schizophrenia patients both before and after the renaming. Further, from an analysis using the regression model, a significant correlation was observed between the frequency of negative keywords and the hospitalization frequency of schizophrenia patients.

Discussion: These findings suggest that the social perception of schizophrenia has been scarcely changed, but rather remained negatively biased against schizophrenia patients, in spite of the renaming effort. Notably, the biased media frames have been demonstrated to negatively impact on the social perception, and even on the medical use patterns of general schizophrenia patients. In conclusion, we suggest that the unbiased media frames along with the renaming effort may collectively help reduce the negative social perception of schizophrenia.

F308. HIPPOCAMPAL PERFUSION IN FIRST EPISODE SCHIZOPHRENIA AND ITS ASSOCIATION WITH DURATION OF UNTREATED PSYCHOSIS AND TREATMENT RESPONSE

Hao Hu^{*1}, Mengqing Xia¹, Qian Guo¹, Lihe Chen¹, Yao Hu¹, Xiaohua Liu¹, Donald C. Goff², Henry Rusinek³, Guanjin Li¹, Jijun Wang¹

¹Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, ²New York University Langone Medical Center, ³Center for Biomedical Imaging, NYU Grossman School of Medicine

Background: Abnormal hippocampal function has been implicated in first episode schizophrenia (FES) and is regarded as a promising target for intervention. Longer duration of untreated psychosis (DUP) has been associated with hippocampal atrophy and medication resistance in FES. FES patients with longer DUP are often managed with antipsychotics plus modified electroconvulsive therapy (MECT). The relationship between hippocampal perfusion pattern and DUP in FES is not known. The present study aimed to clarify the hippocampal perfusion pattern and its association with DUP in FES and further to investigate whether baseline hippocampal perfusion predicts treatment response.

Methods: At baseline, 85 participants (51 FES/ 34 healthy controls) were enrolled. Because of the association of long DUP and treatment resistance, patients with long DUP are often managed with medications plus MECT. For our study, 20 FES were allocated to the Drug group (medications only) according to clinical practice and 31 FES allocated to the MECT group (medications plus MECT). At baseline, all participants completed clinical assessment and a magnetic resonance imaging scan (T1 and TrueFisp sequence). The TrueFisp sequence was optimized to acquire the arterial spin labeling (ASL) perfusion in hippocampus, by obtaining the 6mm-thickness slice containing the hippocampus. At 6 weeks' follow up, participants completed the same study procedures as at baseline. Baseline cerebral blood flow (CBF) of hippocampus and global cortex were used to predict change in PANSS total and subscale scores.

Results: The three groups didn't differ in age and gender, however, education levels differed significantly. At baseline, DUP was negatively associated with hippocampal CBF ($r=-0.372$, $P=0.007$), and global cortical CBF ($r=-0.387$, $P=0.007$) in all FES subjects. Compared with the Drug group, patients in the MECT group had a longer DUP and took higher mean dose of antipsychotics (chlorpromazine equivalent, CPZ), prior to enrollment. Hippocampal CBF level was lower in FES group than that in healthy controls (HC), which was a trending significant level ($F = 3.080$, $P = 0.083$), while global cortical perfusion didn't yield a significant group difference ($F = 1.017$, $P = 0.316$). Controlling for education level, both hippocampal CBF and global cortical CBF differed significantly among the three groups (hippocampal CBF: $F=4.824$, $P=0.011$; global cortex CBF: $F=3.786$, $P=0.027$). Post-hoc analysis showed hippocampal CBF and global cortex CBF in the MECT group were significantly lower than in HC group (hippocampal CBF: MECT 38.73 ± 1.69 mL/100g/min vs HC 46.437 ± 0.439 mL/100g/min, $P=0.004$; global cortex CBF: MECT group 41.859 ± 0.940 mL/100g/min vs HC 48.107 ± 0.243 mL/100g/min, $P=0.005$), and also lower than in Drug group (hippocampal CBF: 38.73 ± 1.69 mL/100g/min vs Drug 46.067 ± 1.446 mL/100g/min, $P=0.0236$; global cortex CBF: 41.859 ± 0.940 mL/100g/min vs Drug 49.576 ± 0.802 mL/100g/min, $P=0.026$). We further applied the baseline hippocampus and cortex CBF to predict Positive and Negative Syndrome Scale (PANSS) total and subscale reductions at 6 weeks' follow-up visit, controlling for education level, total intracranial volume, DUP and CPZ. For the Drug group but not for the MECT group, the baseline hippocampal CBF predicted reductions in PANSS total score and positive subscale score (PANSS total score reduction: $\beta=-0.027$, $p=0.004$; positive subscale score reduction: $\beta=-3.665$, $p < 0.001$); the global cortical CBF also predicted clinical improvement (PANSS total score reduction: $\beta= 0.023$, $p < 0.001$; positive subscale score reduction: $\beta=3.312$, $p < 0.001$) in the Drug group, such that higher CBF in hippocampus and lower CBF in cortex were associated with larger response.

Discussion: FES patients may manifest different patterns of hippocampal and global cortical CBF based on their DUP; we found DUP to be negatively associated with CBF in hippocampus

and global cerebral cortex. A higher level of hippocampal CBF along with a lower level of cortical perfusion may predict a poorer clinical response to antipsychotics for FES patients.

F309. PERINATAL AND CHILDHOOD INSULT EFFECTS ON PSYCHOTIC-LIKE EXPERIENCES IN MIDDLE CHILDHOOD

Eric Larson*¹, Alexandra Moussa-Tooks¹

¹*Indiana University*

Background: Early life insults (ELIs) occurring during perinatal (e.g., obstetric complications, maternal substance use) and childhood (e.g., trauma exposure, socioeconomic disadvantage) periods often co-occur and are robust, known risk factors for psychotic-like experiences (PLEs) throughout development. ELI exposure during these distinct sensitive periods, as well as different exposures within these periods, may differentially affect PLE phenotypes. To date, understanding the role of ELIs in the etiology of PLEs is limited by reliance on older aged samples that are also typically clinical high risk. Moreover, analyses often examine only one temporal or conceptual domain of ELIs. Characterizing the cumulative and specific effects of diverse perinatal and childhood ELIs on PLEs in a nonclinical, heterogeneous sample of youth is critical for advancing both prediction efforts and the mechanistic understanding of psychosis-spectrum phenotypes.

Methods: The current analysis leverages data from 5,954 non-twin, non-adopted, youth enrolled in the Adolescent Brain Cognitive Development (ABCD) study. Seven perinatal and eight childhood insult exposures were adapted from previous characterization of the ABCD baseline sample and aggregated into cumulative risk scores. Hierarchical linear models tested main effects and interactions of early life insult burden (cumulative number of perinatal and childhood insults) on PLE quantity and associated distress at ages 9-10. Follow-up analyses examined the effects of individual perinatal and childhood insult exposures on PLE quantity. All models controlled for age in months, biological sex, and maternal age at birth. Study sites were included as random effects.

Results: Over 80% of youth in the sample experienced at least one of the 15 assessed ELIs. As expected, perinatal and childhood insult exposure burden were moderately correlated ($\rho = 0.22$). Independently, perinatal and childhood insult exposure was significantly associated with elevated PLE quantity ($B = 0.16$ and 0.30 , respectively), but only childhood insults were associated with PLE distress ($B = 0.70$). However, perinatal and childhood insults did not interact to affect PLE quantity or associated distress. Post-hoc analyses indicated that exposure to substances in utero after knowledge of pregnancy, obstetric complications, and premature birth were the most potent perinatal insults ($Bs = 0.40-0.69$), whereas socioeconomic disadvantage, parental substance use problems, and family conflict were the most potent childhood insults ($Bs = 0.40-0.56$).

Discussion: Consistent with previous research, ELIs occurring during perinatal and childhood periods independently confer risk for PLEs. However, temporally distinct ELIs did not interact to amplify or attenuate PLEs in this sample, suggesting their effects may be temporally restricted to systems most vulnerable at their distinct sensitive windows. Further, our results highlight that diverse ELIs are independently associated with PLEs, the impact scaling with the quantity of ELIs experienced. Also notable is the robustness of childhood insult findings to PLE distress, compared to quantity of PLE experiences, suggesting that these environmental factors may confer additional risk for the appraisal and emotional impact of these experiences above and beyond the emergence of psychosis-spectrum phenomena alone. Altogether, the co-occurrence of perinatal and childhood insults, combined with their independent effects on

PLEs, warrants careful consideration of potential timing effects in ELI outcomes. Future research utilizing longitudinal approaches is needed to elucidate how temporally and conceptually distinct ELIs affect PLE trajectories across childhood and adolescence.

F310. EFFECTS OF EARLY-LIFE ADVERSITY AND ACUTE STRESS ON THE EXPERIENCE OF EMOTION IN SCHIZOPHRENIA

James Waltz^{*1}, Jacob Nudelman¹, Olivia Hutchinson¹, Eric Neutzling¹

¹*Maryland Psychiatric Research Center, University of Maryland School of Medicine*

Background: It has been established that early-life adversity (ELA) can alter sensitivity to rewarding, stressful, and neutral events and stimuli. Psychosis is also associated with increased sensitivity to acute stressors, perhaps engendered by elevated rates of ELA. Using images from the International Affective Pictures Set (IAPS; Lang et al., 2005), our goal was to examine effects of ELA on sensitivity to pleasant, aversive, and neutral stimuli. We also sought to determine whether diagnosis interacted with physical abuse (PA) history in predicting ratings of affective pictures, as well as differences in ratings between stressed and non-stressed conditions. We hypothesized that acute and cumulative stress would increase affective reactivity to unpleasant stimuli and decrease affective reactivity to pleasant stimuli, with stress exposure interacting with diagnosis in modulating sensitivity to pleasant, aversive, and neutral stimuli.

Methods: In our study, 52 patients with schizophrenia spectrum disorders (SZ) and 32 healthy volunteers (HVs) performed the Emotional Experience Task (EET; Ursu et al., 2011) twice, on separate study days at least a week apart (once 10 minutes after presentation of an acute stressor, once 10 minutes after a control task). The Socially Evaluated Cold Pressor Task (SECPT; Schwabe et al., 2008) was used as the acute stressor. In the stress condition, participants submerged their non-dominant arm in a bucket of ice water for as long as they could tolerate, up to three minutes, while being filmed by an unsympathetic research assistant. The control condition used warm water. During performance of the EET, subjects viewed 72 IAPS picture stimuli (24 pleasant, 24 unpleasant, 24 neutral) in four runs of 18 trials each. On each trial, subjects were asked to rate both the “positivity” and “negativity” of the emotion experienced, during the presentation of a picture, on a 5-point scale, by means of a three-button response unit. To ask about experiences of abuse, we administered the 28-item Childhood Trauma Questions (CTQ).

Results: We observed an effect of diagnosis on mean picture ratings, such that SZ patients exhibited reduced dynamic range, relative to HVs, in their ratings. Specifically, we found that SZ patients, in comparison to HVs, rated positive pictures as less positive ($t = 1.958$; $p = 0.05$) and more negative ($t = 3.640$; $p < 0.001$). SZ patients also rated negative pictures as more positive ($t = 2.911$; $p = 0.005$) and less negative ($t = 2.711$; $p = 0.008$) than HVs. We observed no significant interactions between diagnosis and abuse history predicting ratings of pictures (all F-values < 1). When we examined correlations between PA scores on the CTQ and ratings of IAPS pictures from the EET, we found significant associations between PA scores and mean ratings of aversive images ($r = 0.309$; $p = 0.035$), as well as the effect of the acute stressor on ratings of positive ($r = 0.333$; $p = 0.022$) and neutral stimuli ($r = 0.300$; $p = 0.040$), with patients with higher PA scores showing a greater impact of the acute stressor on ratings of IAPS pictures.

Discussion: We observed that both diagnosis and abuse history impacted ratings of affective pictures. Abuse history also modulated the effect of the acute stressor. However, diagnosis and abuse history did not produce interacting effects on ratings of affective pictures in our study.

Future analyses will investigate whether diagnosis and abuse history exerted interacting effects on brain activity related to sensitivity to pleasant and aversive stimuli. A better knowledge of the processes by which ELA sensitizes susceptible individuals to the noxious effect of future stressors, is critical to our ability to reduce the severity and impact of psychotic symptoms through interventions.

F311. TUNE-UP: A COMPREHENSIVE APPROACH TO THE MANAGEMENT OF REFRACTORY POSITIVE, NEGATIVE, AND COGNITIVE PSYCHOTIC SYMPTOMS

Ioana Varvari¹, Chambrez-Zita Zauchenberger¹, Valentina Mancini¹, Jack Fanshawe¹, Sharon Musiiwa², Saik DeLaMotte², Philip McGuire³, Robert McCutcheon³

¹University of Oxford, Oxford Health NHS Foundation Trust, ²Oxford Health NHS Foundation Trust, ³Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, University of Oxford, Oxford Health NHS Trust,

Background: Pharmacological treatment of the positive symptoms of psychosis typically consists of dopamine antagonism, but this approach seldom addresses the cognitive (e.g., concentration and memory) and negative (e.g., anhedonia and avolition) symptoms of the disorder. Additionally, a notable subset of patients remain affected by positive symptoms despite standard dopamine antagonist treatments, highlighting the need for innovative approaches to tackle intractable symptoms.

Methods: In response to this challenge, the TUNE-UP (Treating Unmet Needs in Psychiatry) clinic was launched in Oxford in September 2023. This novel approach aims to: (A) Conduct thorough evaluations of cognitive, negative, and positive symptoms, (B) Determine changeable factors that may contribute to these persistent symptoms (for example, cholinergic overload, sleep issues, physical health problems, and mood disorders), and (C) Develop treatment strategies that may include starting clozapine in a community setting when needed. An analysis of data from the clinic's first five months has been conducted to understand the demographics and symptom patterns of the patients referred.

Results: During its initial five months, the TUNE-UP clinic received 21 referrals, with males making up 80.9% of the patient population (average age 43.3 years, SD 13.7). Referral reasons were diverse, including cognitive symptoms (3), combined negative and cognitive symptoms (1), positive symptoms (11), medication reviews (3), and clozapine re-titration (3). Among those assessed (N=17), the average total symptom score, as measured by the Positive and Negative Syndrome Scale (PANSS), indicated mild/moderate severity (70.5, SD 18.4). Objective cognitive assessments using the Screen for Cognitive Impairment in Psychiatry (SCIP) revealed an average score of 54.1 (SD 12.1), significantly below the expected score in a comparable control group (76.3). Lower cognitive scores correlated with older age ($r = -0.62$, $p = 0.01$). The Subjective Scale to Investigate Cognition in Schizophrenia was used to measure perceived cognitive deficits, revealing that worse subjective cognition correlated with more severe negative symptoms ($r = 0.57$, $p = 0.03$), but not with the objective SCIP outcomes ($r = 0.12$, $p = 0.85$).

Discussion: While managing refractory positive symptoms is critical, the prevalence of cognitive and negative symptoms underscores the importance of a holistic treatment approach. Implementing routine, structured evaluations of all symptom areas is necessary and achievable in clinical settings. Future studies will focus on the long-term effects of various treatments across different symptom domains in a naturalistic setting.

F312. ATTACHMENT REPRESENTATIONS IN PRE-ADOLESCENTS AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER AND POPULATION-BASED CONTROLS – LONGITUDINAL CHARACTERISTICS OF ATTACHMENT, ITS RELATION TO MENTAL DISORDERS AND PARENTAL FUNCTIONING.

Mette Krantz*¹, Maja Gregersen², Lotte Veddem³, Carsten Hjorthøj⁴, Åsa Prøsch⁴, Jessica Ohland⁴, Julie Marie Brandt⁵, Sinnika Birkehøj Rohd⁵, Christina Bruun Knudsen³, Anna Krogh Andreasen³, Nicoline Hemager⁵, Anne Søndergaard⁶, Aja Greve⁷, Ole Mors⁷, Merete Nordentoft⁵, Elia Psouni⁸, Anne A.E. Thorup¹

¹Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR, ²CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, ³The Psychosis Research Unit, Aarhus University Hospital; Aarhus University, ⁴Copenhagen Research Center for Mental Health - CORE, ⁵CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, ⁶CORE - Copenhagen Research Centre for Mental Health, ⁷Psychosis Research Unit, Aarhus University Hospital, Psychiatry⁸Lund University,

Background: Secure attachment, created from the first years of life through loving, sensitive, and stable relationships with caregivers, is crucial for a positive mental development and for establishing healthy relations with other people through life. For children born to parents diagnosed with schizophrenia or bipolar disorder, such relationships may face challenges when parental illness makes it difficult to provide the attentive responses needed for secure attachment development. We aimed to examine 1) attachment representations from middle childhood to early adolescence among children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) compared with population-based controls (PBC), 2) whether non-secure attachment in middle childhood predicted non-secure attachment in early adolescence, 3) whether non-secure attachment in middle childhood predicted early adolescence psychopathology, 4) whether parental level of functioning and 5) levels of stimulation and support provided at home predicted secure early adolescence attachment.

Methods: Methods:: In a nationwide cohort of 510 same-aged children born to parents with schizophrenia or bipolar disorder and population-based controls, attachment representations were examined through the use of the age-appropriate assessment of attachment scripts, the Story Stem Assessment Profile (SSAP) at age 7 and the Secure Base Script Test (SBST) at age 11. Child psychopathology was assessed with the Schedule for Affective Disorders and Schizophrenia for school-age children – present and lifetime version (K-SADS-PL). Parental level of functioning was measured with the Personal and Social Performance Scale (PSP).

Results: A total of 482 children participated in the SSAP at age 7 and a total of 409 children (FHR-SZ=157, FHR-BP=92 and PBC=160, mean (SD) age 11.9 (0.23)) participated in the SBST assessment at age 11. No difference in secure attachment prevalence was found between risk and control groups. The parental level of functioning at the child's age 7 predicted richer secure base content at age 11 ($p=0.01$, Partial Eta Squared= 0.02), as did the child's level of attachment security at age 7 ($p < 0.001$, Partial Eta Squared= 0.10). The child's level of disorganization at age 7 predicted prevalence of mental disorder at age 11 ($p=0.002$, Partial Eta Squared=0.02).

Discussion: Non-differential attachment prevalence across groups might relate to assessment sensitivity in this setting and to actual adequate overall attachment in the included families.

Selection bias may be relevant to consider in the topic of attachment since families which had been subject to concern reports from the municipality, and families in which children were placed out of home, were slightly underrepresented as compared with the nation-wide total sample. If findings are replicated in other studies, awareness of parental functioning in middle childhood, and awareness of level of disorganization in middle childhood, can be relevant to support healthy attachment development.

F313. MAPPING THE RELATIONSHIPS BETWEEN PSYCHOTIC EXPERIENCES AND DEPRESSIVE SYMPTOMS: A CROSS-LAGGED PANEL NETWORK MODEL

Keith Ho-Fung Cheng¹, Anson Kai Chun Chau^{*2}, Hong Wang Fung³, Stanley Kam Ki Lam⁴, Wai Tong Chien⁴

¹*The University of British Columbia*, ²*The University of New South Wales*, ³*Hong Kong Baptist University*, ⁴*The Chinese University of Hong Kong*

Background: Individuals with psychosis often experience depression. Their common comorbidity may suggest a dynamic relationship between the two conditions, contributing to their formation and maintenance. Their subclinical expressions also often co-occur in both clinical and non-clinical populations. Given the heterogeneity of psychotic symptoms, specific psychotic symptoms may display differential relationships with depression. While some longitudinal studies have demonstrated the bidirectional association between depression and positive symptoms including paranoia and hallucinations, the relationship between depression and negative symptoms is less clear. In addition, the co-occurrence of positive and negative symptoms is rarely considered in a single study. Therefore, it would be important to model the interactive relationship between these depressive and psychotic psychopathologies, which develop over time as a dynamic network. Recently, cross-lagged panel network model (CLPN) is available to capture the dynamics between multiple symptoms of interest with longitudinal data. The current study aimed to apply CLPN to explore the predictive relations between multiple positive and negative psychotic experiences (PEs), and depressive symptoms (DSs) by using two-wave longitudinal data.

Methods: We analysed longitudinal data from an international sample with self-report DSs and PEs at baseline and 1-year follow-up. PEs and DSs at baseline and 1-year follow-up were measured by the Community Assessment of Psychotic Experiences - Positive and Negative Dimension, and the Patient Health Questionnaire-9, respectively. Three positive (i.e., delusional ideations, bizarre experiences, perceptual anomalies), three negative PEs (i.e., social withdrawal, affective flattening and avolition), and nine DSs were modelled as nodes in the CLPN. Edges between nodes indicated cross-lagged relationships between the nodes across time, controlling for their levels at baseline. Cross-construct in-prediction (i.e., the extent to which a variable is predicted by variables in other constructs in the network) and out-prediction (i.e., the extent to which a variable predicts variables in other constructs in the network) indices of each node were also computed.

Results: The final sample consisted of 152 participants (age: $M = 26.18$ ($SD = 8.78$), 94.1% female), of which 115 (75.0%) reported at least one psychiatric diagnosis (major depressive disorder: $n = 58$, 38.2%). Participants were mainly from North America (40.8%) and Europe (22.4%). The CLPN revealed dynamic relationships between positive and negative PEs and DSs. In particular, the DS of 'feelings of worthlessness' was associated with an increase in 'delusional ideations' over time ($B = 0.24$), while the DS of 'psychomotor retardation or agitations' was associated with an increase in avolition over time ($B = 0.33$). The DSs of 'depressed mood' ($B = 0.16$), 'feelings of worthlessness' ($B = 0.14$) and 'loss of energy' ($B =$

0.13) were associated with an increase in social withdrawal over time. Cross-construct in-prediction and out-prediction indices suggested that DSs could predict PEs (especially negative PEs) to a larger extent than the reverse.

Discussion: Using CLPN, our results highlight the complex relationships between DSs and PEs, which are not necessarily confined by traditional diagnostic boundaries. More specifically, our findings unveil specific DSs and PEs that are especially important to the development and maintenance of depression and psychosis. Our findings suggest that individual DSs may be more predictive of the development of specific positive and negative PEs than vice versa.

F314. EFFECT OF ULOTARONT ON BRAIN DOPAMINE SYNTHESIS CAPACITY IN SUBJECTS WITH SCHIZOPHRENIA ON STABLE DOSES OF A D2 ANTIPSYCHOTIC: RESULTS OF AN 18F-DOPA PET STUDY

Oliver Howes¹, Luke Vano¹, Grazia Rutigliano², Rob McCutcheon³, Robert Lew⁴, Snezana Milanovic⁴, Lisa Lennek⁴, Seth Hopkins*⁴, Kenneth S. Koblan⁴

¹*Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, Imperial College London, Psychiatric Imaging Group, Institute of Clinical Sciences (ICS), Imperial College London, Institute of Psychiatry, Psychology and Neuroscience, Kings College London,* ²*Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, Imperial College London, Psychiatric Imaging Group, Institute of Clinical Sciences (ICS), Imperial College London,* ³*Institute of Psychiatry, Psychology and Neuroscience, Kings College London, University of Oxford, Oxford Health NHS Foundation Trust,* ⁴*Sumitomo Pharma America*

Background: 18F-DOPA PET imaging studies have found higher striatal dopamine synthesis capacity is associated with symptoms of psychosis and is correlated with illness severity [Jauhar S, et al. JAMA Psychiatry. 2017;74(12):1206]. In a mouse model, ketamine-induced elevations in dopamine synthesis capacity were reduced by single doses of ulotaront (3 mg/kg i.p.) with no effect on baseline dopamine synthesis capacity [Kokkinou M, et al. Mol Psychiatry. 2021;26(6):2562]. Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A activity that has demonstrated efficacy in a Phase 2 trial in patients with schizophrenia [Koblan KS, et al. N Engl J Med. 2020;382(16):1497]. The aim of the current study was to evaluate the effect of ulotaront adjunctive to a D2 antipsychotic on brain dopamine synthesis capacity, as measured by 18F-DOPA PET imaging, in adults with schizophrenia.

Methods: Subjects, ages 18-45, were enrolled who met DSM-5 criteria for schizophrenia and were on a stable dose of a D2 antipsychotic for a ≥ 3 weeks prior to screening. At screen, an 18F-DOPA PET scan was performed. Subjects were continued on their antipsychotic, and treatment with ulotaront was added for 14 days at an initial dose of 50 mg/d for 3 days followed by 75 mg/d for the remaining time period. On day 14, the 18F-DOPA PET scan was performed approximately 2-4 h after the final dose. The primary endpoint was change from baseline in dopamine synthesis capacity in the striatum at day 14 by 18F-DOPA PET scan. Imaging data were analyzed with Patlak modelling with cerebellum as reference region, resulting in the influx constant K_{icer} reflecting dopamine synthesis capacity. For the whole striatum and its subregions (associative, motor, limbic), averaged regional K_{icer} values were calculated, and correlated with PANSS total and subscale scores (Marder Positive). Change from baseline in DA synthesis was calculated and a repeated measures ANOVA was used to test treatment, and

treatment by region, interaction effects. Efficacy measures included the PANSS total and subscale scores.

Results: 22 patients with schizophrenia were enrolled; 19 had useable baseline and day 14 scans: male (n=14), female (n=5); mean age, 32.9; baseline mean (SD) PANSS total 79.3 (7.3) and PANSS positive subscale 19.2 (4.6). There was a significant effect of treatment (p LESS THAN 0.05) and striatal subregion (p LESS THAN 0.05) on Kicer but no treatment by subregion interaction (p GREATER THAN 0.8). Mean percent changes from baseline, and respective treatment effect size were: whole striatum= -3.98% (95% CI: -8.68%, 0.72%) and Cohen's d= -0.46 (95% CI: -0.97, 0.05), associative striatum= -3.38% (95% CI: -8.09, 1.34) and Cohen's d= -0.39 (95% CI: -0.89, 0.11); motor striatum= -3.89% (95% CI: -9.61, 1.81%) and d= -0.39 (95% CI: -0.89, 0.11); and limbic striatum= -5.79% (95% CI: -9.66, -1.92%) and d= -0.74 (95% CI: -1.28, -0.19). The mean reduction in dopamine synthesis capacity for all 3 striatal subregions was greater than the estimated minimal threshold (0.0005/min) likely to be clinically meaningful. There was a significant moderate correlation between change in striatal 18F-DOPA Kicer and change in Marder Positive Factor score on the PANSS (r=0.5, p LESS THAN 0.05) but no significant relationship with change in PANSS total symptom score (r=0.2, p GREATER THAN 0.05).

Discussion: Consistent with preclinical findings, this study found that 14 days of treatment of patients with schizophrenia with ulotaront added to a stable dose of a D2 antipsychotic resulted in potentially clinically meaningful reductions in dopamine synthesis capacity in the striatum that were correlated with a reduction in the severity of the PANSS-positive subscale score. These results, despite stable baseline treatment with a D2 antipsychotic, provide confirmation of the potential efficacy of the novel TAAR1 agonist mechanism of action of ulotaront.

F315. GABA-A RECEPTOR BINDING IN CLINICAL HIGH-RISK FOR PSYCHOSIS AND FIRST-EPISODE OF PSYCHOSIS: A [11C]RO15-4513 PET STUDY

Paulina Lukow*¹, Julia Schubert², Samuel Knight², Amanda S Kiemes², Nicholas R Livingston², James Davies³, Andrea De Micheli², Thomas Spencer², Paolo Fusar-Poli², Beate Haege⁴, Natasha Vorontsova², Jacek Donocik⁴, Eugenii Rabiner³, Steve Williams², Philip McGuire⁵, Mattia Veronese⁶, Federico Turkheimer², Modinos Gemma²

¹University College London, ²King's College London, ³Invicro Imaging Services, ⁴South London and Maudsley NHS Foundation Trust, ⁵University of Oxford, ⁶University of Padua **Background:** Dysfunction of the GABAergic neurotransmitter system is proposed to play a role in the pathophysiology of schizophrenia. Human post-mortem and preclinical evidence suggest that alterations to the excitation-inhibition balance in the hippocampus may be associated with the development of psychosis. GABA-A $\alpha 5$ subunit-containing receptors are primarily expressed in the hippocampus and mediate tonic inhibition of neuronal firing. These receptors have been suggested by preclinical research as a potential new therapeutic target for psychosis-relevant behavioural and physiological phenotypes. Our study sought to investigate whether hippocampal GABA-A $\alpha 5$ receptor binding is altered in antipsychotic-naïve individuals at clinical high-risk for psychosis (CHRp) and people with a first-episode of psychosis (FEP).

Methods: Twenty-four healthy controls (HC), 24 individuals at CHRp, and 10 people with an FEP underwent positron emission tomography (PET) acquisition with arterial blood sampling using the radiotracer [11C]Ro15-4513, which has relatively high affinity for GABAA receptors containing the $\alpha 5$ subunit. One CHRp participant was excluded due to insufficient PET acquisition, and another due to technical issues with blood sampling. PET data were analysed

with MIAKAT 4.3.24 in Matlab R2017a. A two-tissue compartmental model was employed using a population-based input function with individual corrections from discrete blood samples, which estimated the total volume of distribution (V_t) within the hippocampus. Hippocampal V_t values were compared between groups using a type III AN(C)OVA in R 4.3.2 with the `lm` and `Anova` functions, with and without age and sex as covariates of no interest. Results were considered significant at $p \leq 0.05$.

Results: The HC, CHRp and FEP samples had an average age of 25.2 (SD=4.4), 25.2 (SD=4.6) and 29.2 (SD=3.7) years, respectively. The percentage of females in each group was 62.5%, 68% and 33%, respectively. There were no significant differences in hippocampal V_t values between the HC (mean 9.63, SD=1.72), CHRp (mean 9.20, SD=1.51) and FEP (mean 9.25, SD=2.29) groups, either without ($F=0.38$, $p=0.68$) or with nuisance covariates ($F=0.46$, $p=0.64$).

Discussion: This study did not find evidence for an alteration in binding to GABA-A receptors containing the $\alpha 5$ subunit in the hippocampus in antipsychotic-naïve individuals at CHRp or in people with an FEP. Further investigations focussing on less subunit-specific GABAergic dysfunction or on glutamatergic neurotransmission may help elucidate the putative role of hippocampal excitation-inhibition mechanisms in psychosis spectrum symptoms.

F316. THE INTERSECTIONALITY OF DEMOGRAPHIC FACTORS AND SOCIAL DETERMINANTS OF HEALTH AMONG INDIVIDUALS IN EARLY PSYCHOSIS PROGRAMS: A LATENT CLASS ANALYSIS

Yen-Ling Chen^{*1}, Susie Xiong², Tzuahzia Lee², Kathleen E. Nye¹, Valerie Tryon¹, Laura M. Tully¹, Stephania Hayes¹, Mark Savill¹, Sabrina Ereshefsky¹, Chelyah Miller¹, Katherine Pierce¹, Madison J. Miles¹, Merissa Kado-Walton³, Khanh Linh H. Nguyen¹, Nitasha Sharma¹, Amanda McNamara³, Christopher Hakusui¹, Viviana Padilla¹, Maliha Safdar³, Rachel Loewy⁴, Daniel Shapiro¹, Khalima A. Bolden¹, Karina Muro¹, Yi Zhang⁵, Andrew Padovani⁶, Adam Wilcox⁷, Lisa Dixon⁸, Cameron Carter², Tara A. Niendam¹, EPI-CAL Group²

¹University of California, Davis, School of Medicine, ²University of California, Davis, ³Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, ⁴University of California - San Francisco, ⁵Center for Healthcare Policy and Research, University of California-Davis, ⁶Center for Healthcare Policy and Research, University of California Davis, ⁷Washington University St. Louis, ⁸NYSPI/Columbia University Medical Center,

Background: Disparities in health care and health outcomes have been compared among racial groups. For example, Black individuals with first-episode psychosis experience more negative pathways to care (e.g., Anderson et al., 2014) and more severe symptoms when presenting to treatment (e.g., Nagendra et al., 2018) compared to White individuals. However, viewing differences in health outcomes as simply comparing a single dimension of demographic features (e.g., race) creates potential risk of overlooking a broader picture in within-group heterogeneity and the intersectionality between demographic and other social, environmental, and structural factors. Specifically, various social determinants of health (SDoH) factors are associated with psychopathology, including psychosis (e.g., Jester et al., 2023), as well as treatment effectiveness (e.g., Bennett and Rosenheck, 2021). Therefore, it is imperative to incorporate an intersectional lens to view individual's experiences as being shaped by their position and experience in a society, in addition to their socio-cultural identity. To achieve this

goal, the current study utilized latent class analysis (LCA) modeling to identifying more meaningful clusters in classifying individuals who accessed early psychosis care.

Methods: Data was collected from individuals enrolled in California's EPI-CAL early psychosis (EP) programs using the Beehive application. Inclusion criteria included individuals being enrolled in one of the EPI-CAL programs and enrolled in Beehive as part of their clinical care. Individuals who did not agree to sharing their data for research were excluded. Distinct clusters were empirically derived from LCA based on the intersection of demographic and SDoH factors, using the R package "poLCA" (Linzer and Lewis, 2011). Differences in symptom severity and lifetime hospitalization/emergency room (ER) visits were compared by racial categories and by the LCA-identified classes, using one-way ANOVA and chi-square. Logistic regression was conducted to further examine whether LCA-identified classes predicted the likelihood of lifetime hospitalization or ER visits after adjusting for symptom severity.

Results: The sample included 316 individuals (42% female, Mage=19.88 years, SDage = 4.59 years). Approximately 31% of individuals identified as White, 11% Black, 31% Latinx, 10% Asian, 14% multiracial, and 3% other. Results of LCA suggested four distinct classes (entropy=.77). Class 1 (n=100) included more Black and Latinx individuals, showed higher level of economic instability, but had more positive social and community support. Class 2 (n=86) was predominantly White and Asian American and more economically advantaged. Class 3 (n=84) included more sexual minoritized groups, had highest rate of lifetime homelessness, experienced more community violence and discrimination. Class 4 (n=48) was racially diverse, experienced discrimination, and received the least social and community support among all groups. Symptom severity, lifetime hospitalization and ER visits did not show significant differences among racial groups (p s GREATER THAN .05). Class 3 reported more severe symptoms compared to other classes (p s $\leq$.01). Lifetime hospitalization significantly differed by classes (p =.03). Compared to Class 2, Class 1 predicted lower lifetime hospitalization rates (OR=.41, 95% CI [.20, .82]) and lower ER visits (OR=.35, [.12, .93]) after adjusting for symptom severity.

Discussion: Current findings highlight the value of an intersectional approach to examining health outcomes. Using race itself as a single classifier did not yield statistically or clinically meaningful differences in symptom severity or history of hospital/ER visits among individuals enrolled in EP programs. Instead, empirically derived classes that included both demographic and SDoH factors indicated adverse community experiences and discrimination may exacerbate symptom in minoritized groups. Additionally, social and community support may act as a protective factor reducing lifetime hospitalization and ER visits.

F317. WHAT HAPPENS AFTER EARLY INTERVENTION IN FIRST EPISODE PSYCHOSIS? LIMITATIONS OF EXISTING SERVICE MODELS AND AN AGENDA FOR THE FUTURE

Emily Wilner*¹, Andrew Hyatt², Victoria Hasler²

¹Cambridge Health Alliance/Harvard Medical School, ²Cambridge Health Alliance

Background: The last decade has provided hope for individuals with schizophrenia-spectrum illnesses and their families with the advent of specialized, recovery-oriented, and patient-centered programs to treat psychotic disorders from the earliest signs of illness to the first episode of psychosis (FEP). While ample evidence provides support for the positive outcomes associated with FEP programs, there is concern that these gains are not sustained over time and that not all individuals benefit equally from such programs, especially those from minority

backgrounds. Additionally, there is disagreement about the optimal length of FEP programs, and step-down or discharge practices vary widely, ultimately reflecting a lack of clear guidance on how to best maintain the hard-won gains in FEP programs. This review aims to examine the extant literature on the efficacy of FEP programs, as well as that of step down or discharge practices and long-term outcomes with the goal of identifying ways to extend the gains made in FEP programs.

Methods: To conduct this literature review, we searched PubMed in August 2021 for published research on outcomes and step-down/discharge practices of first episode (FEP) programs using the following keywords and combinations: 'coordinated specialty care' or 'early intervention' with 'psychosis' and 'discharge' or 'transition' or 'aftercare' or 'step down' or 'extension program.' The articles obtained from these searches were supplemented by key FEP program efficacy studies (e.g., RAISE trial, OPUS study).

Results: Efficacy of FEP programs: A growing body of literature supports the efficacy of specialized early intervention programs for FEP. However, these benefits may vary depending on demographic factors (e.g., race, ethnicity).

Step down/Discharge practices: There is a lack of a uniform approach to step down or discharge practices from FEP programs. Upon completion of a FEP program, many individuals return to usual community treatment. However, qualitative studies underscore the benefits of a more nuanced approach, including an individualized, patient-centered, coordinated and flexible transition plan aided by a strong therapeutic alliance between service user and provider, as well as collaboration between existing and future providers. Long-term Outcomes following FEP care: There is a body of literature focused on improving long-term outcomes for individuals with psychosis through the extension of FEP programs, though the results of extending FEP care are mixed. Lower intensity or more targeted psychosocial support (e.g., support from peers, vocational specialists) following completion of FEP care have been shown to improve functional outcomes.

Discussion: FEP programs have long been associated with positive treatment outcomes, however when many individuals complete such a program, they return to usual community treatment, which typically includes psychiatric management and some access to individual supportive therapy and/or case management. What tends to be lost are psychosis-specific interventions (e.g., CBT for Psychosis, Social Skills Training), family interventions, and perhaps most importantly, psychosocial supports crucial to maintaining and improving function in the community (e.g., peer support, supported employment/education services). The beneficial role of psychosocial supports following the end of a FEP program suggests an urgent need to provide sustainable funding sources for these traditionally non-reimbursable services. Further research investigating the impact of continuing these services during and after FEP care, as well as the addition of psychosis-specific interventions (e.g., CBTp) that have a growing evidence base for preventing relapse, would assist policymakers in designing a smoother and more effective continuum of care for service users leaving FEP programs. Dismantling studies could also assist in identifying the service users who benefit from specific aspects of FEP programs. This would be a further step in tailoring aftercare to the preferences and values of the service user.

F318. IMPROVEMENT IN COGNITION DURING COGNITIVE REMEDIATION IS RELATED WITH EPIGENETIC CHANGES IN BDNF GENE

Rafael Penadés*¹, Carmen Almodovar-Paya², Clemente García-Rizo¹, Victoria Ruíz¹, Rosa Catalán¹, Sergi Valero³, Til Wykes⁴, Mar Fatjó-Vila², Bàrbara Arias⁵

¹Hospital Clinic Barcelona, ²FIDMAG Germanes Hospitalàries Research Foundation, ³ACE Alzheimer Center Barcelona, ⁴Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁵Universitat de Barcelona

Background: Cognitive remediation (CRT) produces cognitive benefits in schizophrenia, but we do not yet understand whether molecular changes are associated with this cognitive recovery. A gene central to synaptic plasticity, the BDNF, has been proposed as one potential route. This study assesses whether BDNF methylation change following CR-produced cognitive improvement.

Methods: We tested the effect of CRT on cognition using Mixed Models, where the interaction (treatment by moment, pre-post) was the main effect of interest. Participants were randomized into a two-arm (CRT, n=40) and treatment as usual (TAU, n=20) randomized controlled trial. Cognitive domains were assessed before (T0: 0 weeks) and post-treatment (T1: 16 weeks). Next, we tested the association between the treatment group and methylation changes in three CpG islands of the BDNF gene. Correlations between changes in cognitive domains and changes in methylation were also analyzed.

Results: CRT group showed significant improvements in some cognitive domains compared with TAU. Between-groups differential changes in methylation over time were observed at CpG1.2, CpG1.7, CpG1.10, CpG1.17 and CpG3.2. In those five CpG units, differences in the degree of methylation between T0 and T1 were associated with changes in Speed of Processing, Working Memory, and Verbal Learning within the CRT group.

Discussion: Cognitive improvement could be mediated by epigenetic changes in BDNF gene. That could provide a neurobiological insight into biological mechanisms of cognitive recovery in terms of DNA methylation of a key gene in neuroplasticity regulation. If these data were replicated, BDNF methylation patterns could represent a biomarker of response that would help clinicians provide more personalized treatments.

F319. USING COGNITIVE BEHAVIORAL THERAPY TO TREAT BINGE EATING DISORDER IN A PATIENT WITH SCHIZOPHRENIA: A CLINICAL CASE STUDY

Martin Cernvall*¹, Simon Cervenka¹

¹Uppsala University

Background: Schizophrenia is associated with an increased risk for obesity, diabetes, metabolic syndrome and cardiovascular disease compared to the general population. Although not well studied, there is emerging evidence that people with psychotic disorders and receiving antipsychotic medication have elevated rates of binge eating symptomatology. Detecting and managing binge eating in psychotic disorders may be an important part of clinical management of these patients. However, there is a lack of documentation regarding the use of psychological treatments targeting binge eating symptoms for persons with schizophrenia.

Methods: This clinical case study describes the use of cognitive behavioral therapy (CBT) to target binge eating disorder in a 45-year old male patient diagnosed with schizophrenia. Concomitant medication included quetiapine (200 mg), risperidone (2mg) and venlafaxine (225 mg). He had previously been prescribed clozapine which had to be withdrawn due to severe sedation. Body mass index (BMI) pre-treatment was 33. A previous cognitive assessment indicated an estimated full IQ somewhat below average and pronounced deficits in certain cognitive domains. The treatment took place at an outpatient unit at an academic

medical center. The patient lived alone with continuous informal support from his parents and attended a vocational rehabilitation program 2-3 times per week.

Results: The patient had a long history of binge eating episodes. At time for assessment, he described 8 objective binge episodes during the last 28 days, but no compensatory behaviors. During binge episodes, the patient was eating more rapidly than normal and this resulted in feeling uncomfortably full and also feelings of disgust and guilt. The clinical picture was consistent with DSM-5 criteria for binge eating disorder (mild). Assessment with the eating disorder questionnaire (EDE-Q) indicated elevated levels of concerns about body shape and weight. A functional analysis indicated that binge episodes occurred mainly in the evenings and were associated with reduced intake of food during the day, which precipitated anxiety and also the experience of voices. The patient rated the overall frequency of voices to 2 (scale 0-10) and their associated distress to 6 (scale 0-10). In the functional analysis, binge episodes were hypothesized to serve emotion regulating functions. Treatment included 16 sessions of CBT over 8 months and a follow-up after 18 months. In line with current empirical support, treatment focused on reducing restraint and normalizing patterns of regular eating in order to prevent binge episodes. This was achieved mainly with self-monitoring of eating patterns and planning of meals. Dysfunctional thoughts and beliefs regarding body shape, weight and self-worth were also addressed. The frequency of binge eating episodes and body shape and weight concerns were significantly reduced at end of treatment (monthly binge episodes from 8 to 0 and body shape and weight concern index from 3.3 to 1.0, respectively). Improvements were maintained at 18 months follow-up (0 binge episodes, shape and weight concern index 0.5) and the patient no longer fulfilled criteria for binge eating disorder. Furthermore, distress associated with voices was reduced to 3 (0-10).

Discussion: This clinical case study demonstrates how CBT can be applied successfully for patients with schizophrenia and co-occurring binge eating disorder. This indicates the importance of assessing binge eating symptoms and developing CBT methods targeting such problems in people with schizophrenia.

F320. “MOTIV8”: A CLUSTER-RANDOMIZED FEASIBILITY TRIAL OF A WEIGHT MANAGEMENT INTERVENTION FOR ADULTS WITH SEVERE MENTAL ILLNESS IN SECURE FORENSIC SERVICES

Rebekah Carney^{*1}, Hany El-Metaal¹, Heather Law¹, Siobhan Savage¹, Ingrid Small¹, David Shiers², Mark Hann³, Gemma Shields³, Parise Carmichael-Murphy³, Richard Jones¹, James Farrell¹, Sophie Parker¹

¹Greater Manchester Mental Health NHS Foundation Trust, ²Greater Manchester Mental Health NHS Foundation Trust, University of Keele, ³University of Manchester

Background: People with severe mental illness experience a 25-year reduction in life expectancy, mainly from physical disorders. This is driven by medication side-effects, high rates of adverse health behaviours, and poor physical healthcare. It is particularly compromised in secure services, where there are restrictions on movement, increased confinement, reduced access to outdoor space and high dosages of medication. Motiv8 is a 9-week weight management programme aiming to address this issue. It was co-produced with service users, and includes exercise sessions, cooking classes, physical health/sleep sessions, and a pharmacy review.

The aim was to conduct a randomised waitlist-controlled trial to assess the feasibility of Motiv8+treatment as usual for individuals on forensic inpatient units. Objectives were to assess feasibility and acceptability via recruitment/retention rates, adherence, engagement/attendance, drop-out rates, assessment completion, and qualitative interviews. The overall aim was to use outcome data to refine a protocol for a definitive trial.

Methods: A randomised waitlist-controlled trial of Motiv8+TAU compared with TAU was conducted in forensic inpatient services at Greater Manchester Mental Health NHS FT (ISRCTN13539285). 29 participants were recruited into four cohorts and randomised to either Motiv8+TAU (n=12) or TAU+waitlist Motiv8 (n=17). Assessments were completed at baseline, 10-weeks and 3-months. Qualitative interviews (developed with service users) were conducted with a subsample of participants (n=8) to capture unique experiences of Motiv8 and inform a refined intervention. A sub-study was conducted with staff to explore the ward environment and assess confidence/knowledge of physical health. A lived experience group was established prior to study set-up to inform trial procedures, develop recruitment materials and inform session content. The group was co-facilitated by service user researchers, who were consulted throughout the trial, and included in the interpretation/dissemination.

Results: 29 participants (4 cohorts) were recruited from secure services in Greater Manchester Mental Health NHS Foundation Trust, and 100% were randomised. Two cohorts were randomised to receive Motiv8 straight away (n=12) and two randomised to the waitlist condition to receive TAU followed by Motiv8 (n=17). Participants were predominantly male (n=25, 89.7%), white (n=22, 75.9%) and average age was 36.5 (range 20-61). All but one was diagnosed with a psychotic related disorder. Retention to the trial was good (93.1% 10-weeks, 72.4% 3-months), the main reason for participant loss was discharge from the ward (n=5, 71.4%). 72.4% participants (n=21) started the intervention and received a dose. Engagement with the intervention was good, particularly for the first two cohorts. The blind was successfully maintained, and no safety concerns were raised. The trial was not powered to detect differences between groups; however, qualitative feedback revealed that participants enjoyed being involved in the trial, reported numerous benefits of the intervention including physical improvements (feeling fitter, losing weight), increased knowledge and hope, and finding it valuable and worthwhile.

Discussion: The data suggests evidence for the acceptability/feasibility to conduct a rigorous, methodologically robust study comparing Motiv8 with TAU+waitlist for adults on forensic inpatient units. Our study adds to the growing evidence base regarding physical health interventions for adults on secure forensic inpatient mental health units. Further work is needed to refine an application to explore potential effectiveness of Motiv8 in forensic services.

F321. TOOLKIT FOR CANADA'S LOWER-RISK CANNABIS USE GUIDELINES FOR PSYCHOSIS (LRCUG-PSYCH)

Lucy Chester*¹, François-Olivier Hebert², Didier Jutras-Aswad²

¹*Centre de Recherche du CHUM*, ²*Research Center, Centre Hospitalier de l'Université de Montréal (CRCHUM), Université de Montréal, Centre Hospitalier de l'Université de Montréal (CHUM), Université de Montréal*,

Background: Cannabis use has been associated with an increased risk of developing a psychotic disorder, and with greater symptom severity, increased risk of relapse and poor treatment response in individuals with a psychotic disorder. Certain modifiable factors associated with cannabis use have been shown to increase or reduce these psychosis related

risks. These factors are the subject of the Lower-Risk Cannabis Use Guidelines for Psychosis (LRCUG-PSYCH), a set of evidence-based and public health-oriented recommendations designed to mitigate and reduce psychosis-related risks associated with cannabis use. Guidelines were developed by international expert consensus following an extensive review and evidence grading of scientific literature, a description of which can be found in the evidence review published in the Journal of Dual Diagnosis in 2023 (Fischer et al.). They are structured into 11 recommendation clusters for individuals seeking to modify their cannabis use and minimize associated risks. Here, we present knowledge dissemination materials designed to promote awareness, education, and implementation of the LRCUG-PSYCH into clinical practice.

Methods: The LRCUG-PSYCH toolkit consists of public and clinician-oriented knowledge summaries and a suite of resources for cannabis and psychosis-related education, prevention, and harm reduction. These resources are the result of an international collaboration between experts in psychiatry, addiction, knowledge transfer and communication, and in consultation with clinicians, patient partners and people with lived experience of psychosis and cannabis use. Endorsement for the LRCUG-PSYCH has been granted by prominent national public health and substance use organizations, including the Schizophrenia Society of Canada (SSC), Canadian Public Health Association (CPHA), and Canadian Research Initiative on Substance Misuse (CRISM).

Results: The following resources are available as web and print versions, in both English and French: LRCUG-PSYCH Evidence Brief – a summary of the 11 evidence-based recommendations for reducing psychosis-related risks when using cannabis written for clinicians, professionals, organisations, and government entities dedicated to improving the health of people who use cannabis. LRCUG-PSYCH Brochure – a summary brochure of the 11 evidence-based recommendations written for the general public. This resource is targeted towards individuals who are thinking about using cannabis or who are actively using cannabis, and individuals who have a history of, or are at an elevated risk of developing psychosis. Harm reduction posters – two public-facing posters recommending individuals to talk to their healthcare providers about cannabis and the risk of psychosis. Patient decision Aid: My reflection Journal – a tool for individuals who use cannabis to log and reflect on their cannabis use, the impact of their use, and how they may alter their consumption habits in line with their own lifestyle and preferences. Dialogue Support Tool for Clinicians – a tool designed to help guide clinicians in their conversations about cannabis with people who have experienced psychotic episodes and/or been diagnosed with a psychotic disorder, aligning with evidence-based approaches for health behaviour change such as motivational interviewing and brief interventions. Communication Bridges and Roadblocks Infographic – a short visual list of common communication approaches that may support or impede communication for clinicians discussing cannabis use with people who have experienced psychotic episodes and/or been diagnosed with a psychotic disorder.

Discussion: Dissemination and implementation of the LRCUG-PSYCH toolkit offers a promising avenue to improve public and clinician awareness, understanding and response to cannabis-related psychosis risks. By bridging expert consensus with practical tools, these resources aim to empower individuals and healthcare professionals in navigating conversations and decisions related to cannabis use, ultimately fostering a reduction in psychosis-related risks.

F322. INDIVIDUALIZED SMARTPHONE-BASED PATIENT-REPORTED OUTCOMES IN OUTPATIENT PSYCHIATRIC CARE: FEASIBILITY, CLINICAL ENDPOINTS AND IMPACT ON RECOVERY

Felix Machleid¹, Anette Schönewald¹, Luise Balzer², Linda Kokwaro¹, Louisa Schröder-Frerkes³, Caspar Wiegmann⁴, Jakob Kaminski*¹

¹Charite University Medical Center Berlin, ²Humboldt Universität Berlin, ³Vivantes Klinikum am Urban Berlin, ⁴Kliniken im Theodor-Wenzel-Werk

Background: Outpatient care for people with severe and chronic mental illness is complex due to various challenges. One challenge is monitoring of outcomes that are relevant to the patient and engage in self-management. This pilot study aims to investigate the feasibility and usability of a smartphone-based application for recording individually formulated electronic patient-reported outcomes (dynamic ePROs) between treatment appointments to promote self-management.

Methods: In this non-randomized case-control pilot study, patients with schizophrenic and affective disorders (F20, F25, F31, F32/33) used a newly developed smartphone application over a period of 90 days between their outpatient appointments to regularly record pre-defined and individualized dynamic ePROs. The control group received the usual treatment in the form of regular outpatient appointments. Psychometric data including data on specific symptom severity, quality of life, daily functioning and healthcare utilization were collected in both groups at baseline and at the end of the study.

Results: At the time of submission of this abstract, the study has not yet been completed. It is planned to present preliminary data on adherence, quality of life and symptom change as a proof-of-concept at the conference.

Discussion: The results of our study contribute to the investigation of the impact of digital recording of individual symptom trajectories on patient self-management and the therapeutic alliance and thus provide an important contribution to this field of research.

F323. DIFFERENCES IN RESTING-STATE OSCILLATIONS IN EEG BETWEEN ULTRA-HIGH-RISK, CLINICAL CONTROL AND HEALTHY CONTROL GROUPS

Julia Adams*¹, Ilvana Dzafic¹, Magdalene de Rozario¹, Gregor Leicht², Moritz Haaf³, Marija Krcmar⁴, Cassandra Wannan⁴, Suzie Lavoie¹, Kelly Allott¹, Christopher G Davey¹, Hok Pan Yuen¹, Thomas Whitford⁵, Melanie Formica¹, Sarah Youn¹, Jashmina Shetty¹, Rebecca Beedham¹, Victoria Rayner¹, Graham Murray⁶, Andrea Polari¹, Lukasz Gaweda⁷, Dan Koren⁸, Louis Sass⁹, Josef Parnas¹⁰, Andreas Rasmussen¹¹, Patrick McGorry¹, Jessica A Hartmann¹, Barnaby Nelson¹, Stephen Wood¹

¹Orygen Youth Mental Health, ²University Medical Center Hamburg-Eppendorf, ³University Medical Center Hamburg, ⁴University of Melbourne, ⁵University of New South Wales, ⁶University of Cambridge, ⁷Institute of Psychology, Polish Academy of Science, Warsaw, Poland, ⁸University of Haifa, ⁹Rutgers University, ¹⁰University of Copenhagen, ¹¹Mental Health Center Amager

Background: We are investigating whether there are distinct differences in resting-state gamma oscillations across ultra-high-risk (UHR), clinical control (CC) and healthy control (HC) populations. Gamma band oscillatory activity has previously found to be increased during resting-state in psychotic populations, and with ketamine administration in healthy controls.

Gamma disturbances in ultra-high-risk populations have been compared with clinical controls during response tasks, but not at resting state. We hypothesize that there would be increased gamma oscillations in the UHR group than in the CC group at rest, and no difference between CC and HC.

Methods: Data was collected from 12–25-year-olds who were classified as Ultra-High-Risk (UHR), Clinical Control (CC) and Healthy Control (HC). Final group frequencies were 68 UHR, 44 CC and 16 HC. Clinical controls are other individuals in the service experiencing psychiatric symptoms but no threshold or sub-threshold psychotic symptoms. Raw EEG data was then prepared for analysis using a pre-processing pipeline in EEGLAB and FOOOF, a python-based tool for neural power spectra analysis. Spectral parameterization will be used to look at the aperiodic components for accurate identification of oscillatory activity. Cluster-based permutation testing with multiple comparisons corrections will be used to identify group differences.

Results: Statistical analysis is currently underway, as such results will be available by the time of presenting. Preliminary results using fast Fourier transform suggests a difference between UHR and CC groups.

Discussion: Gamma disturbances in ultra-high-risk populations may indicate gamma disturbances are uniquely present with psychotic and psychotic-like symptomatology and could contribute to psychotic-like symptoms. Further work around the role of gamma disturbances may clarify the relationship further. These findings suggest a connection between gamma disturbances and the psychosis continuum.

F324. WHOLE-GENOME SEQUENCING OF SCHIZOPHRENIA FAMILIES FROM THE AZORES AND MADEIRA

Hamed Kazemi¹, John Drake², Tim Bigdeli³, Silviu Bacanu⁴, Kelly Benke⁵, Brion Maher⁵, James Knowles⁶, Steven McCarroll⁷, Celia Carvalho⁸, Joana Moura Cabral⁸, Helena Medeiros⁹, Rute Ferreira¹⁰, Michele Pato⁶, Carlos Pato⁶, Vladimir Vladimirov¹, Ayman Fanous^{*11}

¹University of Arizona, ²University of Arizona, Texas A and M University, ³SUNY Downstate Medical Center, ⁴VIPBG, ⁵John Hopkins University, ⁶Rutgers University, ⁷Harvard Medical School, ⁸University of the Azores, ⁹University of Southern California, ¹⁰Instituto S. Joao de Deus, ¹¹University of Arizona College of Medicine

Background: While genome-wide association studies (GWAS) have been successful in identifying common risk alleles contributing to schizophrenia (SCZ) etiology, a highly heritable psychiatric disorder with substantially increased mortality risk, these studies often ignore the contribution of rare variants. Using whole genome sequencing (WGS) data from the Portuguese Island Collection (PIC) sample (n = 171), which contains families with affected and unaffected individuals and controls. We applied a two-pronged analytical approach to assess the impact of common and rare variants in PIC. First, common variants were used to calculate the polygenic risk score (PRS) for SCZ. Second, within a linear mixed models (LMM) framework, we assessed the impact of rare deleterious variants in the PIC cohort to predict schizophrenia status based on the presence of the alternative, disease-associated, risk allele within genes. For variants with evidence of familial segregation, we further 1) compared the presence of alternative alleles within groups and 2) conducted permutations on the likelihood of familial segregation to calculate a whole-genome p-value for rare deleterious variants.

Methods: Prior to analysis, summary statistics of gnomAD v3.1.2 were used to select 5,217,104 common single nucleotide polymorphisms (SNPs) with a $MAF \geq 0.01$ and 7,538,699 rare single nucleotide variants (SNVs) with a $MAF \leq 0.01$. The PRS was calculated using PRSice-2, using common variants in 44 SCZ patients, 65 Unaffected, and 62 population control subjects. For the quality-control step, subjects with excessive Mendelian errors, sex-check failures, and/or low-quality reads were removed. To define rarity, variants with $MAF \leq 0.01$ in the control population and 1000 Genome (if present) were defined as rare. All other variants were defined as common. For defining deleterious rare variants, Combined Annotation Dependent Depletion (CADD) v1.6 with hg38 was used to define phred-like scores, and ANNOVAR v2020.06.08 with GRCh38 and refGene was used to define exonic variants.

Results: The p-value threshold of 0.001 explained the largest variation of risk for SCZ with $R^2 = 0.054$ (p-value = 0.013) when comparing cases vs. unaffected family members and the p-value threshold of 0.05 explained the largest variation of risk for SCZ with $R^2 = 0.251$ (p-value = 2.2×10^{-5}) for cases vs. population controls analysis. Results from the linear mixed model showed the association strength between genes carrying rare and deleterious variants (PHRED score ≥ 10) and SCZ status in the PIC cohort including LIG3, A3GALT2, BMP2K, C15orf39, MCM4, SIGLEC14, and SIGLEC5 which have been implicated in numerous psychiatric conditions, including SCZ.

Discussion: We conducted a permutation analysis with rare and deleterious variants (PHRED score ≥ 10) displaying signs of segregation. This analysis aimed to assess the probability of familial segregation within affected families across the entire genome (p-value: 0.0041). Through the identification of particular genes and genetic variations linked to SCZ, we can attain a deeper understanding of the biological mechanisms underlying the onset of this disorder.

F325. DECODING LANGUAGE ENTROPY: A DISTINCTIVE SIGNATURE IN INDIVIDUALS WITH SCHIZOPHRENIA

Maria Francisca Alonso^{*1}, Jorge Portal², Alvaro Cavieres³, Monica Otero⁴, Pedro Alfaro⁵, Lucia Zepeda³

¹Western University, ²USM, ³UV, ⁴USS, ⁵PUCV

Background: Language disturbances are a core feature of schizophrenia and are often expressed as through formal thought disorder which encompasses speech disorganization and impoverishment. Recent advancements in computational linguistics offer new avenues for exploring language features, such as word frequency, syntactic organization, and more complex semantic dimensionalities. The language entropy captures the amount of certainty or uncertainty in a time series. Some authors have associated the entropy differences with rigid and flexible states when applied to text analysis. Suggesting that low entropy relates to highly rigid use of linguistic features while high entropy denotes flexible use of specific linguistic features. This study aimed to compare the language entropy between individuals with schizophrenia, bipolar disorder and controls.

Methods: We recruited a sample of 90 participants, 30 with schizophrenia (SZ), 30 with bipolar disorder (BD) and 30 matched controls (HC). For the neurocognitive assessment, we used the SCIP neuropsychological battery while the symptoms were rated with the Brief Psychiatric Rating Scale. They all went through a picture description task that was recorded and later transcribed. We analyzed the entropy of the text samples as the additive inverse of the sum of products calculated by multiplying the probability of each category by the natural log of the probability of that category. All participants provided written informed consent

before the assessment. Clinical and demographic data were analyzed using descriptive and Bayesian statistics. We first compared groups' entropy with a Bayesian ANOVA. To address the interaction with cognitive and symptom variables, a Bayesian correlation was conducted between entropy, SCIP and BPRS scores.

Results: Healthy controls and the patient groups did not significantly differ in age or gender distribution, however, the educational level of the SZ group was lower. All the participants had Spanish as their only transactional language. As expected, the HC group performed better on the cognitive assessment. In the description task, we observed a difference in the entropy of the language samples between the groups (HC: 6.851, SD: 0.2; BD: 6.741, SD: 0.2; SZ: 6.099, SD: 0.5, BF10: GREATER THAN 10000). In the posthoc analysis the results showed that the BD group did not differ with the HC group (BF10: 0.762). Regarding the cognitive performance, the entropy correlated with all the measures. When comparing the symptoms, the entropy was correlated with negative symptoms (Pearson's r : -0.64, BF10: GREATER THAN 10000) but not with positive (Pearson's r : -0.23, BF10 : 0.791).

Discussion: We observed a difference in entropy among the groups, noting that the Bipolar Disorder (BD) group exhibited greater similarity to the control group than the Schizophrenia (SZ) group. Our findings imply a more inflexible language use among SZ patients, while such rigidity was not evident in BD. This rigid linguistic pattern may serve as a distinctive signature of schizophrenia. Notably, the entropy was correlated with negative symptoms, aligning with the observed language impoverishment characteristic of schizophrenia.

F326. EXPLORING THE INTERPLAY OF CANNABIS USE AND GENETIC FACTORS IN EDUCATIONAL ATTAINMENT AMONG FIRST-EPISODE PSYCHOSIS PATIENTS, THEIR SIBLINGS, AND CONTROLS

Nancy Murillo-García^{*1}, Sergi Papiol², Rosa Ayesa-Arriola¹

¹*Valdecilla Biomedical Research Institute; Research Group on Mental Illnesses,* ²*Max Planck Institute of Psychiatry*

Background: Patients with first-episode psychosis (FEP) achieve lower educational attainment (EA) than their unaffected siblings and healthy controls. Lower rates of cannabis use have also been described in controls and siblings of FEP patients. As EA is a trait significantly influenced by genetic factors, the genetic load could also be related to the difference in academic outcomes between the groups. The aim of this study was to investigate whether cannabis use and the polygenic score for EA influence EA, operationalised as years of formal education completed.

Methods: We included 390 subjects enrolled in PAFIP-FAMILIAS from Santander, Spain (122 FEP, 175 controls, 93 siblings). All provided data on their EA, cannabis use at baseline and a DNA sample. Quality control before polygenic scoring was performed according to standard procedures. The polygenic score for EA was calculated using the PRS continuous shrinkage method (Ge et al., 2019). Statistical analysis was performed using linear mixed modelling. The main model included the dependent variable (EA), fixed effects (cannabis use, polygenic scores, group membership, intelligence, sex, age) and a random effect (family code). A null model was fitted for comparison effects. In this model, polygenic scores and cannabis use were removed.

Results: The main model explained 56% of the variance in EA ($R^2= 0.56$). This model was better than the null model in predicting the outcome ($\chi^2= 30.35$, p LESS THAN 0.001). Polygenic score, intelligence and female sex were positively associated with EA (p LESS

THAN 0.001). Cannabis use was not a significant predictor of EA on its own, but showed a significant interaction with group membership ($p = 0.003$). FEP group membership was associated with cannabis use, and this interaction significantly predicted EA.

Discussion: Our research suggests that EA is influenced by both genetic factors and cannabis use. These variables may play a role in mediating the lower academic performance observed in FEP patients. Our findings highlight the potential risk of cannabis use in relation to psychosis and its potential impact on cognitive outcomes.

Lunch and Poster Session III

S1. COMPARING FORENSIC AND NON-FORENSIC FEMALE PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: AN EUROPEAN STUDY

Giovanni de Girolamo*¹, EU-VIORMED EU-consortium²

¹IRCCS St. John of God Clinical Research Centre, Brescia, ²IRCCS St. John of God Clinical Research Centre, Italy

Background: Violent behaviour is much more frequent in male than in female subjects and there is a paucity of studies regarding violent behavior displayed by women. The specific aim is to analyse a sample of female subjects, diagnosed with schizophrenia spectrum disorders (SSD), included in an European study on forensic psychiatry, the EUVIORMED study: women with SSD who were admitted to forensic facilities were compared to women with SSD who never exhibited violent behaviour.

Methods: Sociodemographic, clinical, neuropsychological, and treatment-related characteristics of the two samples of female patients have been compared. Standardised assessment instruments included psychopathology (PANSS), psychosocial functioning (WHODAS 2.0), and cognition (Brief Assessment of Cognition in Schizophrenia-BACS covering six cognitive domains: verbal memory and learning, working memory, motor function, verbal fluency, processing speed and executive function. HCR-20 v. 3 has been used to produce a quantification of violence risk assessment.

Results: In the overall European sample there were 26 women violent cases, with an SSD and a history of at least one act of serious interpersonal violence and 36 matched women with an SSD but who had never been violent. The vast majority of both groups were white (92.3% of female cases and 94.4% of female controls, $p=.538$). The female cases were significantly younger than the female controls ($p=.012$). Marital status did not significantly differ between cases and controls ($p=.265$). Most participants in both groups were single (69.2% of cases, 83.4% of controls), even though among cases a higher percentage (23.1%) were also divorced/widowed. On the contrary, the controls were more likely than cases to have children (88.9% vs 61.5%, $p=.011$). There was also a significant difference in the level of education between the two groups ($p=.027$), with the control group reporting more years of education (14, SD= 3.4) compared to cases (12.3, SD= 2.5). No significant differences were found in the occupational status. Although there was no significant difference in age at first contact with mental health services between cases and controls ($p=.133$), the control group had a shorter disease duration (mean years of 9.3; SD=7.9) compared to the cases who had a mean duration of 15.4 (SD=10.6) years. Overall, the most common diagnosis in both groups was schizophrenia (84.6% among cases compared to 77.8% in the control group); delusional disorders (3.8%) and schizophreniform disorders (3.8%) were diagnosed in a tiny minority. Cases were more likely to have a comorbid diagnosis of personality disorders (36%) than controls (5.7%) ($p=.003$). Lifetime substance use was common in both groups (53.8% in the cases and 62.9% in the control group) ($p=.479$). Almost half of the sample reported at least one suicide attempt or an act of deliberate self-harm in the past (46.2% of cases vs 47.1% of controls, $p=.944$). The total mean PANSS score was 72.1 (SD=22.9) for female cases and 69.0 (SD=22.8) for controls suggesting similar levels of positive symptoms, negative symptoms, general psychopathology, and overall symptom severity results among cases and controls. About WHODAS 2.0, controls had a higher mean score (16.7, SD=7.6) compared to cases (7.0, SD=6.8), ($p < .001$), reflecting higher disability and a worse functioning. In terms

of cognition forensic female patients achieved lower scores for all BACS, domains but one (verbal memory), although the difference were not significant. We found no significant difference in the incidence of violence exposure between female forensic participants and control subjects. However, there was a notable difference in the frequency with which they were exposed to violence in the past ($p=.034$). Cases were more likely to report exposure to violence often (62.5%), whereas controls predominantly reported that as a rare experience (66.7%). More cases were also often victims of violence compared to their non-forensic counterparts ($p=.023$), and had been beaten, kicked or punched by someone ($p=.020$). We then conducted a multivariable logistic regression using all the factors that differed between the female forensic participants/cases and control subjects from the first three tables. Age in years, number of years in education, comorbidity with personality disorders, WHODAS 2.0 total score, and having experienced physical violence, that was being beaten, kicked, or punched by someone, significantly predicted the likelihood of being a female forensic case as compared to a female control.

Discussion: Despite the potential for bias and underestimation, our research affirms that the emergence of aggressive conduct in women with SSD is shaped by various factors. Elements such as the extended duration of illness, a history of being victimized, and the presence of a comorbid borderline personality disorder are influential in the expression of aggressive behaviour in female patients with SSD.

S2. TIME WILL TELL: ASSOCIATIONS BETWEEN UNBALANCED TIME PERSPECTIVES AND SYMPTOM SEVERITY IN INDIVIDUALS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

Giovanni de Girolamo*¹, DIAPASON Consortium²

¹*IRCCS St. John of God Clinical Research Centre, Brescia, ²Italy*

Background: Time Perspective (TP) is an essential, albeit elusive, psychological phenomenon with profound consequences on human emotions, cognition, judgment, and behaviors (Strathman and Joireman, 2015; Zimbardo and Boyd, 1999, 2008). The term refers to the “nonconscious personal attitude that each of us holds towards time and the process whereby the continual flow of existence is bundled into time categories that help to give order, coherence, and meaning to our lives” (Zimbardo and Boyd, 2008). Individuals use past, present, and future temporal frames to encode, store, and recall experienced events as well as to form expectations. Patients with schizophrenia spectrum disorder (SSD) experience disrupted temporality on the immediate timescale. However, insufficient information is available for longer time frames, and the interaction of temporal perspectives with the clinical manifestations of SSD is unknown.

Methods: We aimed to explore the associations between TP, daily time use, and levels of functioning among 620 patients (313 residential patients and 307 outpatients) with a diagnosis of SSD recruited from 37 different centres in Italy. The Brief Psychiatric Rating Scale and the Specific Levels of Functioning (SLOF) were used to assess psychiatric symptoms severity and levels of functioning. Daily time use was assessed using an ad hoc paper and pencil Time Use Survey. The Zimbardo Time Perspective Inventory (ZTPI) was used to assess TP. Time perspective biases were measured using the Deviation from the Balanced Time Perspective-revisited (DBTP-r) indicator, based on Zimbardo Time Perspective Inventory (ZTPI) scores. Preliminary analyses examined the associations between ZTPI/DBTP-r and BPRS/BNSS total scores. In secondary analyses, we first tested the associations between the ZTPI/DBTP-r and BPRS/BNSS subscales and then compared ZTPI differences between patients with and without

hallucinations, delusions, and conceptual disorganisation. Statistical significance was set at Holm-Bonferroni corrected p LESS THAN 0.05.

Results: Low-to-moderate positive correlations were found between the DBTP-r and BPRS/BNSS total scores ($r = 0.29/0.22$). The strongest associations were between DBTP-r/ZTPI_Past-Negative and anxiety/depression ($r = 0.34/0.36$), followed by DBTP-r/ZTPI_Present-Fatalistic with thought disturbances ($r = 0.22/0.20$). DBTP-r was associated with BNSS anhedonia and avolition ($r = 0.21/0.24$). DBTP-r was higher in patients with hallucinations ($ES = 0.391$) and conceptual disorganisation ($ES = 0.397$) than in those without these symptoms. Unbalanced time perspective was positively associated with the severity of primary and secondary SSD features. The amount of time spent on non-productive activities (NPA) was positively predicted by DBTP-r ($Exp(B): 1.36; p .003$), and negatively predicted by the Past-Positive ($Exp(B): 0.80; p .022$), Present-Hedonistic ($Exp(B): 0.77; p .008$), and Future ($Exp(B): 0.78; p .012$) subscales. DBTP-r significantly negatively predicted SLOF outcomes ($p .002$), and daily time use, in particular the amount of time spent in NPA and Productive Activities (PA), mediated their association.

Discussion: These findings provide a rationale for empirical tests focused on balancing time perspectives in patients with SSD. According to our findings, more inactive patients had unbalanced temporal perspectives. These individuals manifested a decreased positive attitude toward the past, believed that uncontrollable forces determine their current fate, and displayed a strongly limited future foresight (i.e., avoided setting and realising future goals). To the best of our knowledge, this is the first study to report the association between TP and time spent “doing nothing” in both the general and clinical populations. Our results suggest that desirable levels of the three TP dimensions (i.e., high Past-Positive and Future, as well as low Present-Fatalistic TP) may play a protective role against

inactivity or wasting time and, subsequently, against the negative consequences of inactivity in individuals with SSD listed earlier. We found that the more balanced patients are in their TP, the better daily functioning levels they have (including social functioning, daily life, and working abilities). We found that the effect of BTP on functioning levels was mediated by the time spent in non-productive and productive activities. The present results suggest that fostering BTP (e.g., restructuring past memories, encouraging a greater focus on the future, and reducing fatalistic life perspectives) might lead to a reduction of inactivity in patients with SSD, with an increase in productive activity levels and psychosocial functioning. Such changes may have notable effects on

patients’ levels of functioning and rehabilitation outcomes. TP can be effectively changed via both individual psychotherapy and group-level training interventions, and such changes may lead to highly desirable outcomes, including increased well-being and decreased clinical symptoms.

S3. A MULTI-COUNTRY STUDY ON THE RELATIONSHIP BETWEEN WAR-RELATED MEDIA EXPOSURE AND PSYCHOTIC EXPERIENCES IN THE AFTERMATH OF THE OCTOBER 2023 ISRAEL-GAZA WAR: RESILIENCE AND RELIGIOSITY AS MODERATORS

Feten Fekih-Romdhane^{*1}, Ahmad Abu-Akel², Mai Helmy³, Amthal Alhuwailah⁴, Hanaa Shuwiekh⁵, Emna Maalej⁶, Abdallah Y Naser⁷, Sahar Obeid⁸, Alexandre Andrade Loch⁹, Majda Cheour⁶, Souheil Hallit¹⁰

¹Tunis El Manar University, Faculty of Medicine of Tunis, ²University of Haifa, ³Sultan Qaboos University, ⁴Kuwait University, ⁵Fayoum University, ⁶Tunis Al Manar University, Faculty of Medicine of Tunis, ⁷Isra University, ⁸Lebanese American University, ⁹Universidade de Sao Paulo, ¹⁰Holy Spirit University of Kaslik (USEK)

Background: After the 7th of October 2023, millions of individuals across the globe have been facing an unprecedented indirect exposure to war and terror through media coverage. Young people exposed to such early, extensive and repeated war-related media content are at increased risk for detrimental and long-lasting psychological consequences, including the development or exacerbation of psychotic experiences (PEs), particularly when mitigating resources are lacking. In this context, the current study sought to test the hypothesis that resilience and religiosity are involved as moderators in pathways linking early war-related media exposure and PEs in community emerging adults.

Methods: This is a cross-sectional study that was conducted two to four weeks following the start of Israel's war on Gaza on the 7th of October 2023. Young adults from the general population of Egypt, Jordan, Kuwait, Oman, and Tunisia (N= 2424; mean age= 22.15 ± 4.05 years; 74.1% females) took part in the study through an online survey.

Results: The results of the moderation analysis showed that higher war-related media exposure was significantly associated with higher PEs. Higher resilience was significantly associated with lower PEs. The interaction war-related media exposure by resilience was significantly associated with PEs; at low and moderate levels of resilience, more war-related media exposure was significantly associated with higher PEs (Beta = .10 and Beta = .06 respectively). This effect was not significant at high levels of resilience. In addition, the interaction war-related media exposure by religiosity was significantly associated with PEs; at low and moderate levels of religiosity, more war-related media exposure was significantly associated with higher PEs (Beta = .10 and Beta = .06 respectively). This effect was not significant at high levels of religiosity.

Discussion: As anticipated, resilience had a moderating influence on the relationship between war-related media exposure and PEs. More specifically, the findings suggest that this relationship ceases to be significant when resilience is high, thus advocating the role of resilience in trauma and how it can be protective against PEs in face of media exposure to collective trauma. In addition, the relationship between war-related media exposure and PEs severity was moderated by religiosity, suggesting that highly religious young adults may withstand the adverse psychological effect of war-related media exposure on psychotic symptoms better than those with low to moderate levels of religiosity. Overall, it can be suggested that war-related media exposure should be assessed and monitored on a regular basis in young individuals who experience psychotic symptoms, resilience-related factors that may be available should be identified, and timely resilience-based interventions can be considered for alleviating PEs among those heavily exposed to war coverage on media. Furthermore, the current results suggest a possible importance of high religiosity in buffering the association between early war-related media exposure and the severity of PEs. This is especially of relevance in Arab settings, where religion has a significant influence on both public and private lives and has consistently been found to play a protective role in the occurrence of mental health problems. All these findings hold the promise of enriching the epidemiological landscape of media exposure to mass violence and PEs pathogenesis within the growing context of conflicts and wars. More intensive research efforts in this area are needed and might be of paramount importance from a public health perspective for early intervention and prevention.

S4. SOCIAL RESPONSIVENESS IN FAMILIES WITH PARENTAL SCHIZOPHRENIA OR BIPOLAR DISORDER – THE DANISH HIGH RISK AND RESILIENCE STUDY

Lotte Veddem^{*1}, Maja Gregersen², Anna Krogh Andreassen³, Christina Bruun Knudsen⁴, Julie Marie Brandt⁵, Mette Falkenberg Krantz⁵, Anne Søndergaard², Birgitte Klee Burton⁶, Jens Richardt Jepsen⁷, Nicoline Hemager⁸, Anne Amalie Elgaard Thorup⁹, Merete Nordentoft¹⁰, Ole Mors¹¹, Vibeke Bliksted¹², Aja Neergaard Greve¹³

¹*The Psychosis Research Unit, Aarhus University Hospital; Aarhus University; iPSYCH - The Lundbeck Foundation Initiative for Integrative Psychiatric Research,* ²*CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen,* ³*The Psychosis Research Unit, Aarhus University Hospital Psychiatry The Lundbeck Foundation Initiative for Integrative Psychiatric Research,* ⁴*Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research - iPSYCH; Aarhus University,* ⁵*CORE-Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital University of Copenhagen – Faculty of Health and Medical Services The Lundbeck Foundation Initiative for Integrative Psychiatric Research,* ⁶*Child and Adolescent Mental Health Centre, Mental Health Services Capital Region, Copenhagen,* ⁷*Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) and Center for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Center, Copenhagen University Hospital - Mental Health Services CPH,* ⁸*Research Unit of Mental Health Centre Copenhagen at Gentofte University Hospital; Mental Health Services in the Capital Region of Denmark,* ⁹*Child and Adolescent Mental Health Center, Capital Region of Denmark,* ¹⁰*Research Unit at Mental Health Center, Capital Region of Denmark and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH),* ¹¹*Research Department P, Aarhus University Hospital, Risskov, Denmark and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH),* ¹²*Psychosis Research Unit, Aarhus University Hospital, Risskov,* ¹³*Aarhus University Hospital*

Background: Individuals with schizophrenia or bipolar disorder exhibit social impairments, and their partners display poorer functioning and more psychopathology. However, nonrandom mating and transmission of social abilities from parents to their children remain under-investigated. Therefore, we aimed to examine social responsiveness in families with parental schizophrenia or bipolar disorder.

Methods: The Danish High Risk and Resilience Study – VIA 11 is a nationwide cohort study consisting of 11-year-old children with at least one parent diagnosed with schizophrenia (n = 179) or bipolar disorder (n = 105) and population-based controls (PBC, n = 181). Children and both parents were assessed with The Social Responsiveness Scale, Second Edition (SRS-2). Parents completed the SRS-2 Adult Self-report Form, and the SRS-2 School-Age Form was completed by the teacher who knew the child best in school settings. Duration of time each parent and child have lived together until age 11 was ascertained through interviews.

Results: Parents with schizophrenia and parents bipolar disorder exhibited poorer social responsiveness compared with PBC parents. Parents with schizophrenia displayed poorer social responsiveness compared with parents with bipolar disorder. Co-parents to parents with schizophrenia exhibited poorer social responsiveness compared with co-parents to parents with bipolar disorder and PBC parents. We found significant positive associations between parents'

and children's social responsiveness in all groups, with no interaction effect of duration of time living together.

Discussion: This study is the first to investigate social responsiveness in families with parental schizophrenia or bipolar disorder compared with PBC. Offspring of parents with schizophrenia or bipolar disorder are more likely to be exposed to poor social responsiveness. However, this appears to be more pronounced in families with parental schizophrenia where both parents display poorer social responsiveness. Furthermore, social responsiveness was positively associated between parents and children, irrespectively of familial high-risk status. The familial transmission of social responsiveness presumably occurs due to both genetic factors. Considering that social impairments are suggested as a vulnerability marker, this knowledge calls for increased attention towards vulnerable families, particularly those where both parents have social impairments. More research in the field is warranted, and future studies should aim at applying various measures capturing different aspects of social impairment.

S5. WHAT COULD HELP PREVENT PSYCHOSIS IN ADOLESCENTS WITH CANNABIS USE DISORDER? PRELIMINARY RESULTS FROM THE RESCATE STUDY

Inmaculada Baeza^{*1}, Daniel Ilzarbe², María Moya³, Juan Ignacio Mena⁴, Patricia Camprodon-Boadas⁵, Gisela Sugranyes⁶, Elena De la Serna⁷

¹Hospital Clinic de Barcelona, ²Department of Child and Adolescent Psychiatry, Institute of Neuroscience, Hospital Clinic de Barcelona, CIBERSAM, ³Child and Adolescent Psychiatry and Psychology department, FCRB-IDIBAPS, ⁴Psychiatry and Psychology department, Hospital Clinic de Barcelona, ⁵Fundacio Clinic per la Recerca Biomèdica-IDIBAPS, ⁶IDIBAPS (August Pi i Sunyer Biomedical Research Institute) / Hospital Clínic Barcelona, CIBERSAM, ⁷Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM

Background: Cannabis use disorder has been associated with the onset of psychotic symptoms, and earlier age at onset of use could be linked to earlier development of the prodromal psychotic symptoms (Dragt et al, 2010; Mustonen et al, 2018). A recent systematic review of risk and protective factors of negative consequences of cannabis use (Grigsby et al, 2023) did not found studies about the role of cognitive reserve or diet.

The objective of this study is to assess in a sample of adolescents who fulfil criteria for cannabis use disorder the role of cognitive reserve and adherence to Mediterranean diet in prodromal psychotic symptoms.

Methods: This is cross-sectional study of adolescents attending a mental health outpatient clinic with a specialized unit for substance use disorders. A clinical, cognitive and neuroimaging assessment is performed as well as drug urine analysis. The CORE-A (Camprodon-Boadas et al, in press) was used to assess cognitive reserve and the KIDMED questionnaire (Serra-Majem et al, 2004) to evaluate adherence to Mediterranean diet.

Results: 20 patients were included, with a mean age of 16.5±0.9 years and 50% girls. Mean positive and negative prodromal symptoms according to SOPS scale were 4.1±4.1 and 6.4±3.2, respectively, with a mean GAF score of 64.2±13. The mean adherence to Mediterranean diet was moderate (5.2±2.4), with a score on cognitive reserve below the cut-off point (33.6±9.4). Moreover, there was a significant correlation of negative SOPS score and adherence to Mediterranean diet ($R=-0.656$, $p=0.008$) and a tendency between positive SOPS score and

adherence to Mediterranean diet ($R=-0.507$, $p=0.054$). Nevertheless, CORE-A score was not significantly correlated with any SOPS subscale or total score.

Discussion: Adherence to mediterranean diet could have a role mediating prodromal psychotic symptoms in adolescents with cannabis use disorders. The association between cannabis and psychosis and the harmful effects of cannabinoids in adolescents (Solmi et al, 2023) requires studying protective factors to try to decrease negative consequences of cannabis use in young populations.

This study has been funded by the Spanish Ministry of Health (National Drugs Plan, 2022I053).

S6. THE ROLE OF ENVIRONMENTAL FACTORS ASSOCIATED WITH DIET IN CHILDREN AND ADOLESCENTS AT PSYCHOSIS RISK: RESULTS FROM THE CAPRIS STUDY

Inmaculada Baeza^{*1}, Elena De la Serna², Daniel Ilzarbe³, Gisela Sugranyes⁴, Olga Puig-Navarro⁵, Ana Meseguer⁶, Adriana Fortea⁷, Jordina Tor⁸, Daniel Muñoz-Samons⁸, Marta Rodríguez-Pascual⁸, Xavier Álvarez-Subiela⁸, Montserrat Dolz⁹

¹Hospital Clinic de Barcelona, ²Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM, ³Department of Child and Adolescent Psychiatry, Institute of Neuroscience, Hospital Clinic de Barcelona, ⁴Instituto de Investigaciones Biomedicas de Barcelona, CSIC-IDIBAPS-CIBERSAM, ⁵Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic of Barcelona, , ⁶Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. CIBERSAM, Barcelona, Spain, ⁷Department of Child and Adolescent Psychiatry, Hospital Clinic / Fundació Clinic per la la Recerca Biomèdica (FCRB) / Universitat de Barcelona, ⁸Hospital Sant Joan de Déu, Barcelona, ⁹Hospital Sant Joan de Déu

Background: Environmental factors such as poor diet and low vitamin intake have been associated with schizophrenia and first-episode of psychosis (Aucoin et al, 2020), but research in subjects at psychosis risk is scarce (Provenzani et al, 2023). In children and adolescents with psychosis risk syndrome (PRS, also named clinical high risk) there are no studies about the role of adherence to Mediterranean diet (AMD) as well as vitamin B12 and folate levels.

The objective of this study was to assess serum vitamin B12 and folate levels as well as AMD in children and adolescents with PRS and healthy controls (HC).

Methods: An 18-month prospective longitudinal study (CAPRIS) in which help-seeking minors meeting PRS criteria were recruited from two hospitals in Barcelona, Spain. A sample of HCs were also included. At baseline, the Semistructured Interview for Prodromal Syndromes and Scale (SIPS/SOPS) were administered, as well as a clinical scale battery. The KIDMED questionnaire (Serra-Majem et al, 2004) was used to evaluate MDA. This scale consists of 16 yes/no questions. Three categories of adherence (good, average and poor) were defined according to scores that were ≥ 8 , 4-7, and ≤ 3 . Serum B12 and folate levels were measured.

Results: 90 PRS subjects and 95 HC were included. No differences were found on age (15.2 ± 1.6 vs 15.3 ± 1.8 years) but there were more girls in the PRS group (76.7 vs 57%, $\chi^2 = 7.825$, $p=0.027$). Sex was use as a covariate in the statistical analyses.

50.8% of PRS subjects vs 25.9% of HC had a folate insufficiency ($\chi^2_{29, 290}$, $p=0.003$) while 18.9 of PRS vs 6.4% of HC had a B12 insufficiency ($\chi^2_{25.433}$, $p=0.027$).

Related to AMD, mean scores were 5.6 ± 3 in PRS subjects vs 7.1 ± 2.1 in HC ($F=15.318$, p LESS THAN 0.001). Also, 22.6% of PRS participants vs 5.1% of HC had a low AMD while 35.8 vs 57.7% of the same groups were in the high AMD category ($\chi^2=11.159$, $p=0.004$). There was a significant lower correlation between the total KIDMED scores and the total SOPS scores ($R=0.391$, p LESS THAN 0.001), as well as with all the SOPS subscales.

Discussion: B12 and folate insufficiency as well as a low AMD are associated with PRS children and adolescents compared to HC. The role of these vitamins and MD should be taken into account in assessing this young population as well as in the possible interventions to decrease psychopathology.

This study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects PI21/00391 and PI21/0009, and co-funded by the European Union.

S7. THE EFFECT OF SARS-COV-2 VIRUS ON RESTING-STATE FUNCTIONAL CONNECTIVITY DURING ADOLESCENCE: INVESTIGATING BRAIN CORRELATES OF PSYCHOTIC-LIKE EXPERIENCES AND SARS-COV-2 RELATED INFLAMMATION RESPONSE

Helin Yılmaz Kafalı*¹, Hacer Dasgin², Didenur Sahin², Sara Sinem Sozan³, Kader K. Oguz², Muge Mutlu⁴, Aslinur Ozkaya Parlakay⁵, Timothea Touloupoulo⁶

¹Işık University, ²National Magnetic Resonance Research Center (UMRAM), ³Ankara Social Sciences University, ⁴Ankara City Hospital, ⁵Ankara City Hospital, ⁶Bilkent University,

Background: We first aimed to investigate resting-state functional connectivity (rs-FC) differences between adolescents exposed to SARS-CoV-2 and healthy controls. Secondly, considering the possible association between psychotic-like experiences (PLEs) and the SARS-CoV-2, the moderator effect of PLEs on group differences in rs-FC was examined. Thirdly, brain correlates of inflammation response during acute SARS-CoV-2 infection were investigated.

Methods: Eighty-two participants aged between 14-24 years (SARS-CoV-2 ($n=35$), controls ($n=47$)) were examined using rs-fMRI. Seed-based rs-FC analysis was performed. The positive subscale of the Community Assessment of Psychotic Experiences-42 (CAPE-Pos) was used to measure PLEs.

Results: The SARS-CoV-2 group had a lesser rs-FC within sensorimotor network (SMN, left precentral gyrus), central executive network (CEN, the right precentral gyrus), and language network (LN, left supramarginal gyrus, left angular gyrus); but an increased rs-FC within visual network (VN, left superior and middle frontal gyrus) compared to controls. No significant differences were detected between the groups regarding CAPE-Pos scores. However, including CAPE-Pos as a covariate, we found an increased rs-FC within CEN and SN in SARS-CoV-2 compared to controls. Among the SARS-CoV-2 group, neutrophil/lymphocyte and thrombocyte*neutrophil/lymphocyte ratio was correlated with decreased/increased FC within DMN and SN, and increased FC within CEN.

Discussion: This cross-sectional study showed rs-FC alterations within the SMN, CEN, LN, and VN among adolescents exposed to SARS-CoV-2. Moreover, changes in rs-FC associated with PLEs existed in these adolescents, in spite of the absence of clinical changes. Furthermore, inflammation response was correlated with alterations in FC within the triple network system.

S8. THE ASSOCIATION BETWEEN AUTISM AND PSYCHOSIS AND THE TOOLS USED TO MEASURE IT

Michael Miles*¹, Emma Palmer-Cooper¹, Dennis Golm¹

¹*University of Southampton*

Background: Recent research has found that autistic individuals are at an increased risk of experiencing psychosis and are more likely to receive diagnosis of a psychotic disorder. It has been proposed, and there is some evidence to suggest, that autistic individuals may struggle to interpret the intended meaning of questions pertaining to psychosis due to a propensity to interpret language hyper-literally, possibly leading to false-positive responses. If the strength of the association between these two conditions were to vary significantly depending on the measure used to assess it, this difference may be explained by the literality of the language used. This study, therefore, aimed to meta-analyse data examining this comorbidity, and to examine whether the measures used to assess it moderate the strength of the association.

Methods: A systematic review and three meta-analyses were conducted. The first analysis examined data from correlational studies that used trait score measures to assess both conditions within general population samples. The second examined data from studies that compared comorbidity rates of the two conditions to general population prevalence data. The third examined whether diagnosis of either condition was associated with an increased trait score of the other, compared to general population samples. For each of these, moderation analyses were then conducted on the measures of assessment used.

Results: Preliminary results for all three analyses revealed a significant positive effect between the two conditions. The first analysis found that the effect between total autism and psychosis symptomology ($z = .483$, 95% CI = 0.404 - 0.561, p LESS THAN .0001, $k = 22$) was moderated by the psychosis questionnaire used, with three of the ten measures producing significantly lower effects. Data for each of these moderating measures were, however, limited. Sub-analyses found a large effect between overall autistic symptomology and negative psychosis traits ($z = .584$, 95% CI = 0.505 - 0.664, p LESS THAN .0001, $k = 20$), and lower, yet still significant effects, were found for both positive ($z = .273$, 95% CI = 0.224 - 0.322, p LESS THAN .0001, $k = 28$) and disorganized psychosis traits ($z = .376$, 95% CI = 0.319 - 0.433, p LESS THAN .0001, $k = 16$). No moderating effect of measure used was found, however, for any of these sub-analyses. The second analysis found autistic individuals were over twice as likely to receive a diagnosis of a psychotic disorder (LogOR = 2.201, 95% CI = 1.646 - 2.755, p = LESS THAN .001, $k = 17$) compared to the general population. The third analysis found that diagnosis of one condition was associated with an increased trait score of the other, compared to the general population (SMD = 1.184, 95% CI = 0.995-1.372, p = LESS THAN .0001, $k = 11$). No moderating effect of measures or methods used was found for the second or third analyses, but again, data for each measure or method used was limited.

Discussion: These findings add further evidence to the association between autism and psychosis. Due to limited data, however, reliable conclusions regarding the moderating effect of measures and methods used are difficult to draw. Results of the sub-analyses of the correlational data may suggest that the association between autistic and psychosis trait scores are largely due to the shared negative symptomology between the two conditions. Due to limited data, we were not able to perform similar sub-analyses for the second and third analyses. Future research should investigate further how autistic individuals interpret questions regarding psychosis, to ensure that these measures of assessment are truly capturing psychotic symptomology.

S9. GENETIC EVIDENCE FOR ASSOCIATION BETWEEN ESTROGEN AND AGE AT ONSET IN FEMALES WITH SCHIZOPHRENIA: A PRELIMINARY EMPIRICAL STUDY USING POLYGENIC RISK SCORES

Na Zhan^{*1}, Justin Tubbs², Yuanxin Zhong¹, Perry Bok Man Leung¹, Tomy C.K. Hui¹, Karen K.Y. Ho¹, Karen S.Y. Hung¹, Eric F.C. Cheung¹, Hon-Cheong So³, Pak C. Sham¹, Simon S. Y. Lui¹

¹The University of Hong Kong, ²Massachusetts General Hospital, ³The Chinese University of Hong Kong

Background: Estrogen may have protective effects on liability for schizophrenia, as evidenced by the bimodal distribution of age at onset (AAO) in female patients, with the second peak during the post-menopausal period, compared with the unimodal distribution in male patients. It is plausible that the age of menarche and the age of menopause reflect an individual's cumulative exposure to endogenous estrogen. Evidence also suggests that early-onset schizophrenia in females is associated with older age of menarche, and delayed puberty in males is associated with more severe prodromal symptoms. However, genetic evidence regarding the relationship between estrogen, puberty, and AAO in schizophrenia is scarce.

Methods: We recruited a cohort of 302 female and 255 male schizophrenia patients from outpatient clinics. DNA samples and AAO information were collected from each participant. Genotyping was performed using the Illumina Asian Screening Array. We constructed the polygenic risk scores (PRS) of the phenotypes of age of menarche and age of menopause for each participant, based on the summary statistics of two large-scale Genome-Wide Association Studies (GWAS), and a higher PRS is indicative of a later age of onset. We then examined the association between schizophrenia AAO and the PRS of age of menarche in all patients, the inclusion of males was informed by previous research suggesting a significant overlap in the genetic architecture of age of menarche in females and age of voice breaking in males, so age of menarche was used as a proxy for puberty timing here in both genders. The first five genetic principal components and gender were included as covariates in the linear regression model. The correlation between schizophrenia AAO and the PRS of age of menopause was conducted exclusively in female patients.

Results: In our cohort, we observed a positive association between gender and the AAO of schizophrenia, indicating that females have a significantly later AAO than males ($p < 0.01$). Conversely, the PRS for the age of menarche was negatively associated with schizophrenia AAO ($p < 0.05$). Using a threshold of $p = 0.1$, the PRS for age of menarche and gender collectively explained 2.82% of the variance in AAO ($p < 0.01$). In subgroup analysis, a trend was observed across the three groups: early-onset female patients ($AAO \leq 18$) exhibited the highest PRS (mean = 0.084) for the age of menarche, while late-onset female patients ($AAO > 40$) showed the lowest PRS (mean = -0.192). Furthermore, the PRS for age of menopause was negatively associated with AAO in female patients ($p < 0.05$). In subgroup analysis, a significant difference was detected, suggesting that late-onset schizophrenia female patients had the lowest PRS (mean = -0.337) for age of menopause, whereas the early-onset schizophrenia group had the highest PRS (mean = 0.149).

Discussion: Our findings provide preliminary genetic evidence that later menarche is associated with early-onset ($AAO \leq 18$) schizophrenia, and earlier menopause is associated with late-onset ($AAO > 40$) schizophrenia. Our results are consistent with previous epidemiological findings, supporting the protective effects of estrogen against

schizophrenia in females. Interestingly, the association between later puberty timing and earlier AAO also exists in our male sample. However, our findings should be interpreted with caution due to our small sample size. Future research should verify our findings, and investigate how the reproductive hormones could influence mood, behavior, and cognition through various pathways.

S10. FAMILY FUNCTIONING IN FAMILIES WITH 11-YEAR-OLD CHILDREN OF PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER AND POPULATION-BASED CONTROLS – THE DANISH HIGH RISK AND RESILIENCE STUDY

Nicoline Hemager*¹, Ida Gjøde², Maja Gregersen³, Julie Brandt⁴, Anne Søndergaard³, Mette Falkenberg Krantz⁵, Lotte Vedum⁶, Christina Bruun Knudsen⁷, Anna Krogh Andreasen⁷, Ole Mors⁸, Merete Nordentoft⁹, Aja Greve¹⁰, Anne Amalie Elgaard Thorup²

¹Research Unit of Mental Health Centre Copenhagen at Gentofte University Hospital; Mental Health Services in the Capital Region of Denmark, ²Child and Adolescent Mental Health Center, Capital Region of Denmark, ³CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Mental Health Centre Copenhagen, ⁴Copenhagen Research Center for Mental Health - CORE, ⁵CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital University of Copenhagen – Faculty of Health and Medical Services The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ⁶Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research - iPSYCH; Department of Clinical Medicine, Faculty of Health and Medical Sciences, Aarhus University, ⁷Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research - iPSYCH; Aarhus University, ⁸Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark, ⁹CORE- Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, University of Copenhagen – Faculty of Health and Medical Services, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ¹⁰Psychosis Research Unit, Aarhus University Hospital Psychiatry

Background: Childhood family dysfunction is a predictor of psychosis and affective disorders in adult life and poor emotional family climate is associated with psychopathology in children in the background population. Being born to a parent with schizophrenia or bipolar disorder is a major risk factor for developing the same disorder as the parent as well as other mental disorders. Investigating the complex interaction of environmental and genetic risk factors is important to understand the shared and distinct aetiology of these disorders and to inform preventive interventions. However, evidence regarding family functioning in families with parental severe mental disorders is sparse. Therefore, we aimed to examine family functioning in the families of preadolescent children at familial high-risk of schizophrenia or bipolar disorder.

Methods: This population-based cohort study of 11-year-old children included 160 families with parental schizophrenia, 95 families with parental bipolar disorder, and 176 control families. Family functioning was measured with the 12-item version of the McMaster Family

Adjustment Device – General Functional Scale reported by the primary caregiver. The primary caregivers' social functioning was measured with the Personal and Social Performance Scale, whereas the offspring's global functioning was measured with the Children's Global Assessment Scale. Offspring problem behavior was measured with the Child Behavior Checklist School-Age Version.

Results: Families with parental schizophrenia and bipolar disorder demonstrated significantly poorer family functioning than control families. Also, a significantly higher proportion of the families with parental schizophrenia and parental bipolar disorder demonstrated levels of family dysfunction that were clinically significant compared with controls. Family functioning in the two high risk groups did not differ from each other. Preliminary analyses suggest that poorer family functioning was related to poorer social functioning of the primary caregiver and higher levels of offspring dimensional psychopathology in all study groups but only with poorer global functioning in the offspring with parental bipolar disorder.

Discussion: Preadolescent children at familial high-risk of schizophrenia and bipolar disorder have not only an increased risk of developing a severe mental disorder but also an increased risk of living in dysfunctional families. The interaction of both genetic and environmental risk factors in these preadolescent children in families with parental schizophrenia or bipolar disorder warrant early detection and may inform future intervention studies and programs.

S11. EYE MOVEMENTS AND EYE STRUCTURE IN CLINICAL HIGH RISK FOR PSYCHOSIS

Cemal Demirlek*¹, Merve Ekin², Merve S. Gurbuz³, Berna Yalincetin³, Ferdane Atas⁴, Koray Kocoglu³, Muge Akkoyun³, Hatice Eraslan-Boz³, Simge Uzman-Ozbek⁵, Mahmut Kaya⁶, Gulden Akdal⁷, Emre Bora⁵

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Institute of Psychology, SWPS University,* ³*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University,* ⁴*Department of Ophthalmology, Cerkezkoy State Hospital,* ⁵*Department of Psychiatry, Dokuz Eylul University Medical School,* ⁶*Private Practice,* ⁷*Department of Neurology, Dokuz Eylul University Medical School*

Background: Eye movement and retinal abnormalities have been observed in chronic psychosis, and recent investigations have highlighted the presence of similar abnormalities in individuals at clinical high risk for psychosis (CHR-P). Accumulating research emphasizes the interconnected changes in both eye and brain anatomy and physiology in neuropsychiatric conditions, positioning the eye as a promising avenue for non-invasive exploration and biomarker development. This study utilizes antisaccade (AS), involving looking in the opposite direction of the target, and memory-guided saccade (MGS), characterized by maintaining fixation and recalling the target's location. The objective is to unravel the intricate interplay between eye movements and retinal structure in individuals at CHR-P, providing valuable biomarkers for psychosis.

Methods: The CHR-P criteria is ascertained through the Turkish version of the Structured Interview for Prodromal Syndromes (SIPS). The SIPS includes three UHR-P syndromes: Attenuated Psychosis Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), and Genetic Risk and Deterioration Syndrome (GRDS). To ensure a thorough clinical evaluation, all participants underwent interviews utilizing the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Ophthalmic imaging involved the application of

spectral-domain optical coherence tomography (OCT), was administered by an experienced ophthalmic technician using the Spectralis system (Heidelberg Engineering; Heidelberg, Germany). The total retinal thickness and volume were computed for all participants. Following OCT imaging, participants underwent eye movement recording using the EyeLink 1000-Plus eye-tracker. Assessment of AS-MGS (antisaccade - memory-guided saccade) involved measuring parameters such as correct saccades, anticipatory saccades, and peak velocity.

Results: This study included 23 individuals at risk for CHR-P. Saccadic peak velocity in AS was significantly associated with both total central retinal thickness ($p = 0.031$, $r=0.451$) and volume ($p = 0.038$, $r = 0.434$). The number of anticipatory saccades in MGS was significantly associated with both total central retinal thickness ($p = 0.039$, $r=0.433$) and volume ($p = 0.036$, $r = 0.440$). The number of anticipatory saccades in MGS was significantly associated with both total central retinal thickness ($p = 0.019$, $r=0.486$) and volume ($p = 0.012$, $r = 0.515$). The correct saccades in AS and saccadic peak velocity in both paradigms were not significantly associated with the central retinal macular thickness or volume in individuals at CHR-P.

Discussion: To our knowledge, this is the first study to identify relationship between eye movements and retinal structure in individuals at CHR-P. The significant associations found between antisaccade (AS) and memory-guided saccade (MGS) parameters with retinal thickness and volume offer a compelling case for the eye as a non-invasive window into neuropsychiatric conditions. This suggests a potential underlying neurophysiological mechanism that links retinal structure to the efficiency of eye movements. The significant association found with anticipatory saccades in MGS further emphasizes the intricate relationship between eye movement control and retinal structural integrity. The eye's accessibility and the non-invasive nature of the techniques used suggest a promising potential for these biomarkers in clinical settings.

S12. ASSOCIATION BETWEEN PROCESSING SPEED AND RETINAL THICKNESS IN ULTRA-HIGH RISK FOR PSYCHOSIS

Cemal Demirlek^{*1}, Merve S. Gurbuz², Berna Yalincetin², Ezgi Cesim², Muhammed Demir², Burcu Verim², Ferdane Atas³, Simge Uzman-Ozbek⁴, Ekin Sut⁵, Burak Baykara⁵, Berna B. Akdede⁴, Mahmut Kaya⁶, Emre Bora⁴

¹*Institute of Health Sciences, Dokuz Eylul University*, ²*Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University*, ³*Department of Ophthalmology, Cerkezko State Hospital*, ⁴*Department of Psychiatry, Dokuz Eylul University Medical School*, ⁵*Department of Child and Adolescent Psychiatry, Dokuz Eylul University Medical School*, ⁶*Private Practice*

Background: Both neurocognitive impairments and retinal abnormalities represent important facets of psychosis, with recent investigations shedding light on the presence of cognitive deficits in young individuals at ultra-high risk for psychosis (UHR-P) seeking assistance. Notably, impairments in processing speed, memory, and executive functions have been identified in this population. Emerging research underscores parallel changes in both retinal and cerebral anatomy and physiology in neuropsychiatric conditions, presenting the retina as a promising avenue for non-invasive exploration and the development of biomarkers. Additionally, retinal abnormalities have been linked to the severity of psychotic symptoms and cognitive dysfunction in individuals with chronic schizophrenia. This study aims to unravel the

intricate interplay between cognitive functions and retinal thickness in individuals at UHR-P, offering valuable insights into the pathophysiology of neuropsychiatric diseases.

Methods: Participants seeking help were required to fulfill the UHR-P criteria as determined by the Turkish version of the Structured Interview for Prodromal Syndromes (SIPS). The SIPS encompasses three UHR-P syndromes: Attenuated Psychosis Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), and Genetic Risk and Deterioration Syndrome (GRDS). To ensure comprehensive clinical evaluation, all participants underwent interviews using the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Ophthalmic imaging involved the use of spectral-domain optical coherence tomography (OCT) conducted by an experienced ophthalmic technician employing the Spectralis system (Heidelberg Engineering; Heidelberg, Germany). While OCT images were obtained for both eyes of each participant, analysis focused solely on the right eye to prevent any potential bias. The central macular thickness was computed for all participants. Prior to OCT imaging, participants underwent an assessment of premorbid abilities utilizing either the Wechsler Intelligence Scale for Children-R (WISC-R) or the Wechsler Adult Intelligence Scale-R (WAIS-R) information subtests. Processing speed was gauged using the Digit Symbol Substitution Test (DSST), and visual memory (both immediate and delayed recall) was evaluated using the Visual Reproduction Test. Executive functions were scrutinized through the Wisconsin Card Sorting Test (WCST) and the Stroop Color and Word Test. Outcome variables included the number of categories completed and perseverative errors from the WCST, along with the Stroop interference score and Stroop error score.

Results: This study included 34 individuals at UHR-P. UHR-P group consists of 8 individuals with BLIPS, 22 individuals with APS, 5 individuals with GRD. The central retinal macular thickness was positively correlated with Stroop interference score ($p = 0.019$, $r = 0.413$) and DSST score ($p = 0.002$, $r = 0.525$). Additionally, the other cognitive domains were not significantly associated with the central retinal macular thickness in individuals at UHR-P.

Discussion: The findings of this study elucidate a significant association between processing speed, as measured by the Digit Symbol Substitution Test (DSST), and central retinal macular thickness in individuals at ultra-high risk for psychosis (UHR-P). The positive correlation between DSST scores and central retinal macular thickness implies that increased processing speed is associated with increased retinal thickness. Furthermore, the positive correlation between Stroop interference scores and central retinal macular thickness suggests that greater retinal thickness may be linked to higher cognitive interference, a hallmark of executive dysfunction. These relationships underscore the potential of retinal imaging as a non-invasive biomarker for identifying neurocognitive impairments in UHR-P individuals. However, it is noteworthy that other cognitive domains did not show a significant association with retinal thickness.

S13. CHOROIDAL VASCULARITY INDEX IN CLINICAL HIGH-RISK FOR PSYCHOSIS

Cemal Demirlek^{*1}, Ferdane Atas², Berna Yalincetin³, Burak Baykara⁴, Berna Akdede⁵, Mahmut Kaya⁶, Emre Bora⁵

¹*Institute of Health Sciences, Dokuz Eylul University,* ²*Department of Ophthalmology, Cerkezoy State Hospital,* ³*Department of Neuroscience, Dokuz Eylul University,* ⁴*Department of Child and Adolescent Psychiatry, Dokuz Eylul University Medical School,* ⁵*Department of Psychiatry, Dokuz Eylul University Medical School,* ⁶*Private Practice*

Background: The eye is recognized as a component of the central nervous system and is often referred to as a gateway to the brain. The eye, along with its microvascular system, exhibits numerous shared features with the brain in both anatomy and pathophysiology. Anomalies associated with the choroid and retina have been observed in psychotic disorders, particularly in cases of schizophrenia. The Choroidal Vascularity Index (CVI) serves as a valuable tool for evaluating structural changes in the choroid, defined as the ratio of luminal area (LA) to the total choroidal area (TCA).

Methods: This study marks the inaugural investigation into the choroidal vascularity index among individuals at clinical high risk for psychosis (CHR-P), employing optical coherence tomography (OCT). Thirty-two patients at CHR-P and 30 age and gender-matched healthy controls (HC) included in this study. Each participant underwent clinical evaluations in psychiatry and ophthalmology. Choroidal imaging was conducted utilizing the enhanced deep imaging (EDI) protocol through spectral domain OCT. Central choroidal thickness (CCT) was manually measured with EDI-OCT, from the inner border of the sclera to the outer border of the retinal pigment epithelium (RPE), using the calipers of the Heidelberg reader positioned subfoveally. The choroidal vascularity index was evaluated based on the EDI-OCT images.

Results: The CCT measurement was $374.08 \pm 72.82 \mu\text{m}$ in CHR-P and $355.20 \pm 46.37 \mu\text{m}$ in HCs ($p > 0.05$). CVI was $63.66 \pm 2.83\%$ and $61.30 \pm 1.81\%$ in CHR-P and HCs groups, respectively ($p = 0.002$). CVI was $63.63 \pm 3.67\%$, $63.60 \pm 2.63\%$, $64.02 \pm 3.06\%$ in the brief limited intermittent psychotic symptoms syndrome (BLIPS), the attenuated psychosis symptoms syndrome (APS), the genetic risk and functional decline prodromal syndrome (GRD) subgroups of CHR-P, respectively, and it was not statistically different ($p = 0.96$).

Discussion: These findings indicate that prodromal psychosis is marked by irregularities in choroidal vasculature. The use of in vivo ophthalmological imaging through OCT, a non-intrusive, rapid, and secure technological method, holds promise as a potential biomarker for the quantitative assessment of microvasculature abnormalities in individuals experiencing prodromal psychosis.

S14. LEVELS OF STIMULATION AND SUPPORT PROVIDED AT HOME, STRESSFUL AND TRAUMATIC LIFE EVENTS, AND RISK OF PSYCHOPATHOLOGY AMONG PREADOLESCENT CHILDREN OF PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Mette Krantz*¹, Maja Gregersen², Julie Marie Brandt³, Anne Søndergaard⁴, Sinnika Birkehøj Rohd³, Lotte Vedddum⁵, Christina Bruun Knudsen⁶, Anna Krogh Andreasen⁷, Carsten Hjorthøj⁸, Aja Greve⁹, Nicoline Hemager¹⁰, Ole Mors¹¹, Anne Thorup¹², Merete Nordentoft¹³

¹Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR, ²CORE - Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR, ³CORE- Copenhagen Research Centre for Mental Health, ⁴CORE - Copenhagen Research Centre for Mental Health, ⁵Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research; Aarhus University, ⁶Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for Integrative Psychiatric Research - iPSYCH, ⁷Psychosis Research Unit, Aarhus University Hospital - Psychiatry; The Lundbeck Foundation Initiative for

Integrative Psychiatric Research, ⁸CORE - Copenhagen Research Center for Mental Health; The Lundbeck Foundation Initiative for Integrative Psychiatric Research; University of Copenhagen; University of Copenhagen, Section of Epidemiology, ⁹Psychosis Research Unit, Aarhus University Hospital; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ¹⁰CORE - Copenhagen Research Center for Mental Health; Child and Adolescent Mental Health Center; University of Copenhagen, ¹¹Psychosis Research Unit, Aarhus University Hospital - Psychiatry, Aarhus; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ¹²Mental Health Services in the Capital Region of Denmark, Child and Adolescent Mental Health Centre - BFOR; Copenhagen University Hospital; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, ¹³CORE - Copenhagen Research Centre for Mental Health; University of Copenhagen; The Lundbeck Foundation Initiative for Integrative Psychiatric Research

Background: It is well-established that children of parents with schizophrenia or bipolar disorder are at increased risk of having the same disorder as their parent as well as increased risk of developing other mental disorders. Causes are presumed to include gene-environment interactions through epigenetic mechanisms. Childhood adversity is also a risk factor for mental disorder. Childhood adversity can be subdivided into at least two subdimensions; adversity related to deprivation, meaning the lack of factors expected to be present in the rearing environment and which support healthy development, and adversity related to threat, meaning the presence of factors which the child perceives as a severe stressor, or threat, to its life conditions. Previous studies have indicated that childhood adversity related to the deprivation dimension such as living in a home environment with little stimulation and support increases risk of psychopathology including psychotic disorder among children at risk of severe mental disorder. Concerning the threat dimension, experiencing stressful or traumatic life events has in general population, and high risk, studies been shown to increase risk of later psychopathology, especially psychotic disorder. The prevalence of childhood adversity is higher among children of parents with severe mental disorder compared to controls. Combined with their genetic risk, children of parents with schizophrenia or bipolar disorder thus face an accumulation of risk factors for mental disorder. Knowledge concerning subcategories and combined effects of these types of adversity is needed to identify children at high risk of developing mental disorders including psychotic disorders. We therefore aim to examine how adversity risk factors related to deprivation and threat moderate risk of mental disorder and psychotic experiences among children at familial high risk of schizophrenia or bipolar disorder. We hypothesize that both dimensions of adversity increase risk respectively, and that this risk is further increased when combined.

Methods: In a nationwide population-based cohort study of 522 same-aged children of parents with schizophrenia or bipolar disorder and population-based controls, levels of stimulation and support provided at home was assessed with the semi-structured, age-appropriate at-home interviews MC-HOME at age 7 and EA-HOME at age 11. Stressful life events were assessed through anamnestic interviews with parents at age 7. Child psychopathology and trauma exposure was assessed at age 7 and 11 with the Schedule for Affective Disorders and Schizophrenia for school-age children – present and lifetime version (K-SADS-PL).

Results: Preliminary results will be presented.

Discussion: Knowledge concerning specific risk factors and possible cumulative risks of the social environment of children at familial high risk of schizophrenia or bipolar disorder is needed to inform preventive mental health interventions targeting the rearing environment. Evidence informing future interventions is lacking, although this group of children is

substantial in size, identifiable in health systems, and at increased risk of developing mental disorder which is a major human and economic burden.

S15. CLINICAL AND NEUROCOGNITIVE PROFILES OF A COMBINED CLINICAL HIGH RISK FOR PSYCHOSIS AND CLINICAL CONTROL SAMPLE: A LATENT CLASS ANALYSIS

Miriam Stübke¹, Frauke Schultze-Lutter², Michael Kaess³, Franscini Maurizia⁴, Nina Traber-Walker⁵, Petra Walger⁶, Benno G. Schimmelmann⁷, Kai Vogeley⁸, Joseph Kambeitz⁹, Jochen Kindler¹⁰, Chantal Michel^{*1}

¹University Hospital of Child and Adolescent Psychiatry and Psychotherapy, ²Heinrich-Heine University Düsseldorf, ³Department of Child and Adolescent Psychiatry, Center for Psychosocial Medicine, University Hospital Heidelberg, Germany., ⁴University Hospital of Psychiatry/University of Zurich, ⁵Psychiatric University Hospital Zurich, ⁶University Hospital of Child and Adolescent Psychiatry and Psychotherapy, Cologne, Germany, ⁷University of Bern, University Hospital of Child and Adolescent Psychiatry and Psychotherapy, ⁸Department of Psychiatry and Psychotherapy, University of Cologne, Germany, ⁹Department of Psychiatry, University of Cologne, Germany, ¹⁰University Hospital of Child and Adolescent Psychiatry, University of Bern

Background: The clinical high-risk (CHR) state for psychosis demonstrates considerable clinical heterogeneity, presenting challenges for clinicians and researchers alike. Basic symptoms (BS), to date, have largely been ignored in explorations of clinical profiles. Therefore, we examined clinical profiles using a broader spectrum of CHR symptoms including not only (attenuated) psychotic symptoms but also BS.

Methods: CHR patients (N=875) of early intervention centers in Germany and Switzerland were assessed using the Schizophrenia Proneness Instruments and the Structured Interview for Psychosis-Risk Syndromes. Latent Class Analysis was applied to CHR symptoms to identify clinical profiles. Additionally, demographic, other symptoms, current non-psychotic DSM-IV axis I disorders and neurocognitive variables were assessed to further describe and compare the profiles.

Results: A three-class model was best fitting the data (BIC: 11517.68; AIC: 11236.01; entropy: 0.871), whereby BS (e.g., disturbance of receptive speech: eta square=0.52, p GREATER THAN 0.001; thought perseveration: eta square=0.47, p GREATER THAN 0.001) best differentiated between the profiles. Class 1 (n=523) had a low probability of CHR symptoms, highest functioning and lowest other psychopathology, neurocognitive deficits and transition-to-psychosis rate (1.3%). Class 2 (n=97) had the highest probability of BS and (attenuated) positive symptoms but hallucinations, lowest functioning and the highest symptom load, most neurocognitive deficits and highest transition rate (55.1%). Class 3 (n=255) was mostly characterized by attenuated hallucination and otherwise intermediate between the other two classes (transition rate: 19.6%). Comorbidity rates were comparable across classes with some class differences in diagnostic categories.

Discussion: Our profiles based on BS and (attenuated) psychotic symptoms provide clinically useful entities by parsing out heterogeneity in clinical presentation. In future they also might guide class-specific intervention.

S16. AUDITORY PREDICTIVE CODING DURING A ROVING STANDARD MISMATCH NEGATIVITY PARADIGM IN YOUTH AT CLINICAL HIGH-RISK FOR PSYCHOSIS: RESULTS FROM NAPLS-3

Holly Hamilton*¹, Jessica Hua², Spero Nicholas³, Brian Roach³, Aysenil Belger⁴, Ricardo Carrion⁵, Erica Duncan⁶, Jason Johannesen⁷, Matcheri Keshevan⁸, Sandra Loo⁹, Margaret Niznikiewicz¹⁰, Jean Addington¹¹, Carrie Bearden⁹, Kristin Cadenhead¹², Tyrone Cannon⁷, Barbara Cornblatt⁵, Thomas McGlashan⁷, Diana Perkins⁴, William Stone⁸, Ming Tsuang¹², Elaine Walker⁶, Scott Woods⁷, Daniel Mathalon¹³

¹University of Minnesota/Minneapolis VA Health Care System, ²University of California, San Francisco/San Francisco Veterans Affairs Health Care System, ³San Francisco VA Health Care System, ⁴University of North Carolina, ⁵Zucker Hillside Hospital, ⁶Emory University, ⁷Yale University, ⁸Harvard Medical School / Beth Israel Deaconess Medical Center, ⁹University of California, Los Angeles, ¹⁰Harvard Medical School, ¹¹University of Calgary, ¹²University of California, San Diego, ¹³University of California, San Francisco/San Francisco VA Health Care System

Background: Identifying prognostic biomarkers may improve clinical outcome prediction and clarify mechanisms associated with psychosis onset. Several studies suggest that reduced mismatch negativity (MMN) event-related potential (ERP) component amplitude is associated with greater likelihood of future psychosis onset among individuals at clinical high-risk for psychosis (CHR-P). According to predictive coding models, the MMN is a prediction error signal elicited when a deviant sound violates the prediction that a frequent standard sound will recur, with successive standard repetitions strengthening this prediction. Consistent with this framework, successive standards presented during MMN paradigms produce a progressively increasing repetition positivity (RP) thought to reflect strengthening of the memory trace for the standard. Likewise, deviant tones preceded by a longer series of standard repetitions elicit a larger negativity (i.e., deviant negativity; DN), reflecting a stronger prediction error signal. Parsing these components of MMN is optimally achieved using a “roving standard” paradigm, in which a series of standard tone repetitions are followed by a deviant tone that becomes the new standard stimulus. However, no studies have separately examined these components during a roving standard paradigm in CHR-P individuals to determine if deficits in specific aspects of predictive coding underlying MMN generation are risk factors for psychosis.

Methods: Baseline EEG data were collected during a roving standard MMN paradigm from 710 CHR-P and 96 healthy comparison (HC) participants as part of NAPLS-3. Participants were followed for two years, and those who developed psychosis (CHR-Converters) were compared with those who continued to meet CHR-P criteria (CHR-Persisters) and those who remitted from the CHR-P syndrome (CHR-Remitters). ERP amplitudes to increasing standard stimulus repetitions (RP), immediately subsequent deviants (DN), the corresponding MMN deviant-standard difference wave, and the “traditional” MMN averaged over trials regardless of the number of preceding standards were measured. Analyses were completed in the full sample and in a subset of CHR-P (n=559) who were not taking antipsychotics at baseline.

Results: In an initial analysis of 589 CHR-P and 89 HC, both CHR-P and HC showed significant memory trace effects. For DN and MMN, amplitudes were greater when deviants were preceded by longer trains of standards (33 GREATER THAN 8 GREATER THAN 3; ps LESS THAN .001). For RP, amplitudes increased with standard stimulus repetitions (ps LESS THAN .001). Similar effects were evident for MMN, DN, and RP (ps LESS THAN .001)

across outcome groups. These main effects of task and lack of association with outcomes were evident in the full and unmedicated samples. Differences between outcome groups were present for the DN in the unmedicated subsample only ($p=.03$), with future CHR-Remitters showing greater DN amplitudes across standard stimulus repetitions relative to future CHR-Converters ($p=.01$). The traditional MMN amplitude did not differ between CHR-P and HC in the full or unmedicated sample (p s GREATER THAN .05). In the unmedicated subsample only, however, there was an effect of outcome on the traditional MMN ($p=.03$), such that future CHR-Remitters had greater amplitudes than future CHR-Converters ($p=.04$) and CHR-Persisters ($p=.01$).

Discussion: CHR-P individuals, regardless of future outcomes and medication status, show similar RP, DN, and MMN memory trace effects to HC, suggesting intact predictive code formation and maintenance. However, greater DN and traditional MMN amplitudes among future CHR-Remitters relative to CHR-Converters in the unmedicated subsample suggests the integrity of prediction error signaling may be sensitive to future CHR-P outcomes.

S17. DISRUPTION OF ULTRASONIC VOCALISATION BOUT SEQUENCES IN A RAT MODEL OF SCHIZOPHRENIA RISK

Kieran Scott^{*1}, Lucinda J. Speers², David K. Bilkey¹

¹*University of Otago*, ²*Grenoble Institut de Neurosciences, Inserm*

Background: Timing and sequencing is disrupted in schizophrenia. This could reflect disruption in underlying brain mechanisms and may underlie the disorganisation that is a major symptom dimension in the disorder. Disorganisation symptoms, such as loose associations and illogicality, are strongly related to negative social and vocational outcomes, and to treatment resistance. Thus, understanding how the underlying brain mechanisms are disturbed is an important goal in the search for treatment options. In our lab we have investigated the sequential structure of ~50 kHz ultrasonic vocalizations (USVs) that rats use to communicate. USV structure may be an indicator of the integrity of sequencing mechanisms, and thus, a marker of the effectiveness of potential treatments in preclinical models. We have previously studied USV call structure in rats exposed to Maternal Immune Activation (MIA), a risk factor for schizophrenia in humans. We found changes to transition probabilities between individual USV calls in MIA rats, which may be due to disruptions in sequencing mechanisms. However, vocalizations tend to occur in a series of calls, termed a bout. These bouts have a non-random sequential structure and may be a more meaningful communicative unit than single vocalizations. Thus, we hypothesised that bout structure would be disturbed in MIA rats.

Methods: We recorded USVs in control and MIA rats in two different conditions where animal pairs were able to communicate without physical contact. In the paired animal paradigm, we recorded from 25 control rats, and 27 MIA rats. In our reward paradigm, we recorded from 18 control rats, and 20 MIA rats. The machine learning program VocalMAT was used to detect and categorise. Bouts were then identified as call sequences with less than two seconds between individual calls. Bout structure was analysed using a Levenshtein distance analysis, which generates a measure of the similarity between two sequences, with a higher score indicating greater similarity. To these ends, we calculated set median string candidates for each dataset and group. These candidates were then analysed for similarity with the bout pool using a Levenshtein similarity index (LSI), which normalised for bout length. The candidate with the highest mean LSI was selected, and then compared with the other group set median, and against the other group bout pool. Significance was assessed using Mann-Whitney U tests.

Results: In our paired animal paradigm we recorded 638 bouts from control rats ($\bar{x} = 24.5 \pm 4$), and 570 bouts from MIA rats ($\bar{x} = 25 \pm 3.4$). Bouts from control rats had greater similarity ($\bar{x} = 0.31 \pm .008$) to their set median string when compared to MIA bouts ($\bar{x} = 0.28 \pm .008$; $p < .0001$), indicating greater bout variability in the MIA group. Consistent with this, we also found that the MIA set median was less distant to control bouts ($\bar{x} = 0.32 \pm .008$), than to MIA bouts ($\bar{x} = 0.32 \pm .008$; $p = .005$). In our reward paradigm, we recorded 785 bouts from control rats ($\bar{x} = 42.6 \pm 4.1$), and 942 bouts from MIA rats ($\bar{x} = 46.1 \pm 3.5$). As previously, bouts from control rats had a greater similarity to their set median ($\bar{x} = 0.21 \pm .006$), relative to MIA bouts ($\bar{x} = 0.18 \pm .005$; $p = .0007$). Again, we also found the MIA set median was less distant to control bouts ($\bar{x} = 0.21 \pm .006$), than to MIA bouts ($\bar{x} = 0.18 \pm .005$; $p = .004$).

Discussion: In summary, these findings indicate that there is greater variance in USV bout composition in MIA rats compared to control animals, suggesting a disruption in the mechanisms that control USV sequencing. If this reflects broader sequencing problems in MIA rats then it may provide a useful marker of disorganization that can be used in preclinical studies aimed at finding novel treatments for this characteristic of schizophrenia.

S18. THE ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND ATTENUATED PSYCHOTIC SYMPTOMS IN A GENERAL ADULT POPULATION

Rachel Reeves^{*1}, Ciaran Shannon², Donncha Hanna³, Ryan McIlwaine², Julie-Ann Jordan², Adrian Boyd², Ciaran Mulholland³

¹Impact Research Centre Northern Health and Social Care Trust, ²IMPACT Research Centre, Northern Health and Social Care Trust, ³Queens University Belfast

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder. There is a recognised symptomatic overlap between symptoms of ADHD and attenuated psychotic symptoms, yet there is a dearth of research exploring the association between these two conditions. The study aimed to investigate this association and to determine whether ADHD symptoms made a unique contribution in predicting attenuated psychotic symptoms whilst examining and controlling for Adverse Childhood Experiences (ACES), depression and anxiety.

Methods: Amazon's online crowdsourcing service Mechanical Turk (MTurk) was used to conduct an online survey of a US-based general population. 1052 adults (18-38) completed the Adverse Childhood Experiences Questionnaire (ACE-Q), the Prodromal Questionnaire (PQ-16), the Patient Health Questionnaire 9 (PHQ-9), the Generalised Anxiety Disorder 7 (GAD-7) and the Adult ADHD Self-Report Scale (ASRS). Multiple regression analysis explored the predictors of PQ-16 total score.

Results: The average total PQ-16 score was 4.67 out of a possible 16, average ACE-Q score was 2.21 out of a potential 10, average PHQ-9 score was 7.26 out of a possible 27 and average GAD-7 score was 6.75 out of a possible 21. The final regression model, which combined ACES, anxiety, depression and ADHD explained 49.7% of the variance in relation to the total number of items endorsed on the PQ-16. ACES, depression, and ADHD subscales of impulsive motor and impulsive behavioural were significant predictors of PQ-16 total score; anxiety and the ADHD subscale of inattention were not. After controlling for ACES, anxiety and depression, ADHD symptoms made a unique contribution of 7.5% of the variance in PQ-16 total score.

Discussion: The results demonstrate the association between ADHD and attenuated psychotic symptoms in the general population. Impulsive behavioural and motor were important predictive factors, yet exploration of this association has been neglected to date. Future research should consider exploring this association and investigating the possible mechanisms through which impulsivity predicts attenuated psychotic symptoms. A greater understanding of these mechanisms and the symptomatic overlap between ADHD and attenuated psychotic symptoms may aid clinical decision making, diagnostic procedures and early intervention.

S19. DEPERSONALIZATION AND SELF-DISTURBANCE IN INDIVIDUALS AT RISK FOR PSYCHOSIS

Julia Lebovitz^{*1}, Katrina Rbeiz¹, Sohee Park¹

¹*Vanderbilt University*

Background: Self-disturbance is central to schizophrenia (Hur et al., 2013), but less is known about anomalous self-experiences in relation to psychosis-risk. Individuals at risk for psychosis report poor self-concept clarity (Cowan et al., 2023), anomalous embodiment (Torregrossa et al., 2023), porous self-boundary (Benson and Park, 2019), depersonalization (Büetiger et al., 2020) and basic self-disturbances (Nelson et al., 2012). However, the role of depersonalization in psychosis-risk has not been systematically investigated even though it is a common feature of schizophrenia (Černis, 2022). We examined aberrant self-experiences (depersonalization, body disturbance and interoceptive impairment) in relation to psychosis-risk. Furthermore, we assessed loneliness and trauma history, which have been shown to increase psychosis risk (Steenkamp et al., 2022).

Methods: 232 adults (mean age =33.7; 129 women) completed a web-based survey which included measures of psychosis risk (Prodromal Questionnaire-16; PQ-16), depersonalization (Černis Felt Sense of Anomaly Scale; CFSA), interoception (Multidimensional Assessment of Interoceptive Awareness; MAIA), and bodily self-disturbances (Body Disturbances Inventory; B-BODI). In addition, a measure of loneliness (UCLA Loneliness Scale; UCLA) and trauma (Brief Trauma Questionnaire; BTQ) were included to assess social adversity. Psychosis risk was defined using the PQ-16; the low-risk group (LR) scored below 6, and the high-risk group (HR) scored 6 or above (Ising et al., 2012).

Results: There were 64 HR and 168 LR participants. 107 (46%) had received a prior psychiatric diagnosis. There were no group differences in age or sex. Depersonalization and self-disturbances were clearly elevated in HR. Both FSA ($F(1,229) = 9.477$ p LESS THAN .001) and B-BODI ($F(1,229) = 13.173$, p LESS THAN .001) scores were higher in HR than LR. While the MAIA total score was approaching significance ($p=.056$), there were significant differences in the MAIA subscales: not distracting (p LESS THAN .001), not worrying (p LESS THAN .05), and emotional awareness (p LESS THAN .05). The HR group also reported elevated UCLA ($F(1,229) = 5.425$, p LESS THAN .001) and BTQ scores ($F(1,229) = 4.703$, p LESS THAN .001). Separate logistical regression models revealed that CFSA total, (OR=1.06, p LESS THAN .001), B-BODI total (OR=1.76, p LESS THAN .011), MAIA Not Distracting (OR=1.08, p LESS THAN .001), MAIA Not Worrying, (OR=1.12, p LESS THAN 0.01), and MAIA Emotional Awareness (OR=1.11, p LESS THAN 0.01) predicated psychosis HR when controlling for loneliness and trauma history.

Discussion: Depersonalization, bodily self-disturbances, and some aspects of altered interoception were present at higher rates in HR. Although social adversity was also elevated in HR, core symptoms of self-disturbance remained significant after controlling for loneliness

and trauma. Despite the importance of depersonalization, body disturbance, and interoception schizophrenia, they are not routinely assessed in prodromal studies. The results of the present study support the notion of investigating self-disturbances as a risk factor for psychosis and incorporating clinical interventions focused on self-disturbances.

S20. THE ASSOCIATION BETWEEN ADVERSE AND BENEVOLENT CHILDHOOD EXPERIENCES ON ATTENUATED PSYCHOTIC EXPERIENCES USING THE PRODROMAL QUESTIONNAIRE-16 (PQ-16) IN A STRATIFIED YOUTH POPULATION

Ciaran Shannon^{*1}, Joshua Kearns², Clare Howie¹, Mark Shevlin³, Gavin Davidson², Lisa Bunting², Julie Cameron⁴, Anne Grant², Orla McBride³, Claire McCartan¹, Jamie Murphy³, Emma Nolan³, Dirk Schubotz², Ciaran Mulholland²

¹IMPACT Research Centre, Northern Health and Social Care Trust, ²Queen's University Belfast, ³Ulster University, ⁴Mental Health Foundation

Background: There has been a wealth of research published on the negative impact of adverse childhood experiences on the development of mental health disorders, including psychosis and the at-risk mental state. In contrast, less work has been conducted on the protection that may be offered by benevolent childhood experiences. Benevolent childhood experiences are the antithesis to childhood adversity and refers to positive early life experiences, including support, security, predictability and safety. This study aimed to examine the association between adverse and benevolent childhood experiences and attenuated psychotic symptoms in a youth population sample.

Methods: Participants were recruited as part of the Northern Ireland Youth Wellbeing Survey (n=541; mean age = 14.56), a stratified random household survey. Participants completed the Prodromal Questionnaire-16 (PQ-16), Adverse Childhood Experiences Questionnaire (ACES-Q) and the Benevolent Childhood Experiences questionnaire (BCE-Q), as well as demographic information and questions on Troubles-related exposure to paramilitaries. Three separate hierarchical multiple regression analyses were ran, each with four models, to determine predictors for total PQ-16 score, PQ-16 Hallucinations score and PQ-16 General Unusual Experiences score.

Results: The average total PQ-16 score was 2.36 out of a possible 16, average ACE score was 0.73 out of a potential 10 and average BCE score was 7.86 out of a possible 10. For total PQ-16 score, the final regression model indicated that urban/rural living, higher ACE Abuse/Neglect score, higher ACE Household dysfunction score and lower BCE total score were significant predictors of PQ-16 score. For PQ-16 Hallucination score, the final model indicated that higher ACE Abuse/Neglect score and higher ACE Household dysfunction score were significant predictors of rating this subscale. For PQ-16 General Unusual Experiences score, the final model indicated that higher ACE Neglect score, higher ACE household dysfunction score and lower BCE total score were significant predictors of subscale scoring.

Discussion: This study supports previous evidence of the association between childhood adversity and attenuated psychotic symptoms, including hallucinations. It also highlights that an increasing number of benevolent childhood experiences predict a lower number of attenuated psychotic symptoms. These findings can provide potential factors to be aware of when conducting screening of psychotic symptoms in general population settings and also help develop strategies for early intervention.

S21. A LONGITUDINAL MRI STUDY OF RECENT STRESSFUL LIFE EVENTS AND GREY MATTER VOLUME IN INDIVIDUALS AT CLINICAL-HIGH RISK FOR PSYCHOSIS

Cheryl See*¹, Emily P. Hedges¹, Stefania Tognin², Gemma Modinos¹, Mark van der Gaag³, Lieuwe De Haan⁴, Patrick D. McGorry⁵, Barnaby Nelson⁵, Anita Riecher-Rössler⁶, Rodrigo Bressan⁷, Neus Barrantes Vidal⁸, Marie-Odile Krebs⁹, Merete Nordentoft¹⁰, Stephan Ruhrmann¹¹, Gabriele Sachs¹², Bart P. Rutten¹³, Jim Van Os¹³, Gareth J. Barker¹, EU-GEI High Risk Study¹⁴, Steven Williams¹, Philip McGuire¹, Lucia R. Valmaggia¹, Matthew J. Kempton¹

¹King's College London, ²King's College London, ³VU University Amsterdam, ⁴AMC, University of Amsterdam, ⁵University of Melbourne, ⁶University of Basel, ⁷Universidade Federal de Sao Paulo - UNIFESP, ⁸Universitat Autònoma de Barcelona, Spain, ⁹University Paris Cité - INSERM, ¹⁰Mental Health Centre Copenhagen, ¹¹University Hospital - University of Cologne, ¹²Medical University of Vienna, ¹³Maastricht University Medical Centre, ¹⁴EU-GEI High Risk Study

Background: Meta-analytical evidence has confirmed that recent stressful life events (SLEs) are associated with the onset of psychosis, but the related neural mechanisms remain unclear. The present study aims to investigate whether recent SLEs may be associated with smaller grey matter volumes (GMV) observed in the clinical high-risk (CHR) state for psychosis. To our knowledge, there are only two CHR studies that have examined this relationship; both studies focused only on pituitary volumes and neither found a significant association. In healthy adults, six studies found significant reductions in prefrontal cortex and hippocampal volumes associated with recent SLEs, suggesting these areas may represent a vulnerability to stress. By understanding the neural correlates of recent SLEs in CHR individuals, we can better understand how stress is involved in the development of psychosis. In the current study, we have examined if brain volumes in CHR individuals were negatively associated with recent SLEs using a longitudinal dataset.

Methods: 218 CHR individuals between the ages of 15-45 years were recruited through the EU-GEI high risk study from Europe, Australia, and Brazil. 45 participants transitioned to psychosis. T1-weighted images and clinical data were obtained for up to four timepoints over a 24-month period. The List of Threatening Experiences (LTE) questionnaire measured SLEs from 12-months prior and was quantified as the LTE score at each timepoint. A linear mixed model was used to analyse the effects of recent SLEs on changes in GMV over time. LTE score, time, and the interaction term LTE score $\times$ time were included as fixed effects, with site and participant as random effects. Separate models were fitted for six a priori brain regions: 1) total GMV; 2) hippocampus; 3) anterior cingulate cortex (ACC); 4) orbitofrontal cortex (OFC); 5) amygdala; and 6) insula. All models were adjusted for sex and total intracranial volume. We further adjusted for childhood trauma as a potential confounder. We investigated whether sex or transition status (whether an individual transitioned to psychosis) affected the association between recent SLEs and brain volumes. The statistical significance level was set at two-tailed p LESS THAN 0.05, and a 5% false discovery rate correction was applied to adjust for multiple comparisons.

Results: The main effect of LTE score on GMV across all brain regions was not significant, indicating recent SLEs were not associated with changes in GMV. While total GMV, ACC,

and OFC volumes exhibited a significant reduction over time, the interaction term LTE score $\times$ time was not significant, suggesting SLEs did not affect the rate of reduction in GMV. Adjusting for childhood trauma did not affect the significance of the results. There were no significant effects on recent SLEs associated with changes in GMV due to sex or transition status. Sensitivity analyses to test for the effects of scanner model did not change the significance of the results.

Discussion: The results indicated the number of recent SLEs may not have a detectable effect on brain volumes in CHR individuals. The main strength of our study lies in the use of longitudinal data, which enabled us to model the trajectory of changes in GMV relating to recent SLEs. In addition, our sample was larger than those used in previous studies. It is possible the effects of recent SLEs on brain structure are only apparent in individuals who are closer to psychosis onset. As CHR samples are heterogeneous especially in terms of psychosis progression, such effects may be obscured in the current study. The results may also mean the number of events is not relevant to changes in GMV, but instead personal experience of the event could be more important. Future work could consider including subjective stress measures.

S22. EXPLORING COMPONENTS OF ANTICIPATORY PLEASURE AND THEIR IMPACT ON NEGATIVE SCHIZOTYPY AND SUICIDAL IDEATION

Rebecca Salzano*¹, Richard Linscott¹

¹*University of Otago*

Background: Negative schizotypy is a major risk factor for suicidal ideation. Deficiencies in anticipatory pleasure have been identified as a mediator of the relationship between the two constructs. Impairment in anticipatory pleasure encompasses various aspects, including a lack of positive beliefs about future experiences, expectations that future events will not cause pleasure, and reduced ability to mentally represent the value of future experiences. This research investigated these elements of pleasure capacity, exploring their contribution to the relationship between negative schizotypy and suicidal ideation.

Methods: Psychology undergraduates ($n = 335$) completed self-report assessments. These included measures of schizotypy (Brief Revised Updated version of the Schizotypal Personality Questionnaire, SPQ-BRU), dysfunctional beliefs (17-item Dysfunctional Attitudes Scale – Form A, DAS-A-17), expectancy appraisals (Success and Resource Appraisals Questionnaire, SARA-Q) reward valuation (Monetary Choice Questionnaire, MCQ), affective forecasting (Affective Forecasting Questionnaire, AFQ), and suicidal ideation (Columbia-Suicide Severity Rating Scale, C-SSRS). Probit regression was used to investigate whether variables of interest predicted suicidal ideation. A structural equation model with a probit link was tested to assess the mediating roles of expectancy appraisals, dysfunctional beliefs, reward valuation, and affective forecasting. Bias-corrected bootstrapped confidence intervals were used to assess statistical significance.

Results: Probit model results revealed positive effects of expectancy appraisals ($\beta_3 = .01$; 95% confidence interval = $[0.004, 0.026]$, $p = .01$) and perfectionism beliefs ($\beta_4 = .02$ $[0.005, 0.039]$, $p = .01$) on suicidal ideation. The significance of interpersonal schizotypy's association with suicidal ideation was borderline ($\beta_1 = .02$ $[.00, .05]$, $p = .05$). Social anxiety, valuation of future rewards, and affective forecasting were not significant predictors of suicidal ideation.

Interpersonal schizotypy (standardised beta $c1 = .14$; bootstrapped 95% confidence interval = [.08, .29]) and social anxiety ($c2 = .08$ [.03, .29]) had significant total relationships with suicidal ideation. Expectancy appraisals ($a1b1 = .034$ [.01, .07]) and perfectionism beliefs ($a1b2 = .029$ [.01, .07]) fully mediated both associations ($c1' = .07$ [-.004, .12]; $c2' = .02$ [-.04, .07]).

Discussion: Our findings suggested a stronger association of expectancy appraisals and perfectionism beliefs with suicidal ideation than interpersonal schizotypy and social anxiety. Further, these beliefs fully mediated the relationship between negative schizotypy and suicidal ideation. This suggests that beliefs about one's inability to experience pleasure in the future play a key role in the emergence of suicidal ideation among those with negative schizotypy. Addressing these beliefs may offer prevention and intervention strategies for this population.

S23. AN EXPLORATORY STUDY OF PSYCHOSIS RISK FACTORS IN INDIVIDUALS REFERRED BUT NOT MEETING CRITERIA FOR AN EARLY INTERVENTION IN PSYCHOSIS SERVICE

Sean Naughton^{*1}, Aoife Brady², Mary Clarke²

¹*DETECT, Early Intervention in Psychosis Service, Dublin*, ²*DETECT, Early Intervention in Psychosis Service, Dublin, Ireland*

Background: The 'at-risk mental state' (ARMS) for psychosis has been critiqued for its limited prognostic ability and low capacity to prospectively identify those who will develop a first episode of psychosis (FEP). Only a minority of individuals with an incident FEP will have presented to an ARMS service, even in areas where these are well established. Population based studies challenge the assumption that the ARMS model, as currently constructed, represents a universal, or even common entry point to psychosis. This has resulted ARMS services having a negligible effect on FEP incidence and outcomes overall.

Recent work has highlighted the importance of referral pathway and pre-test risk enrichment in ARMS studies. In addition 'clinical pathway risks,' which do not incorporate any specific test for psychotic symptoms, have demonstrated an ability to prospectively identify at-risk populations. Various factors outside of the current attenuated positive symptom model have been reported as important risk markers. Therefore, we hypothesise that those referred to an Early Intervention in Psychosis (EIP) service, but not meeting criteria for an ARMS or FEP remain enriched for psychosis risk factors, and may be an important group for further investigation. Broadening the search for groups at high-risk of psychosis is key to improving population-level ascertainment of psychosis risk.

The aim of the current study is to explore risk-enrichment in diagnostic, demographic and socio-functional domains amongst individuals referred to an EIP service but not meeting ARMS or FEP criteria. The second aim is to compare the demographic and functional markers of this cohort to a FEP cohort as a point of reference.

Methods: A retrospective file review was undertaken in an Irish EIP service of all referrals from its foundation in 2005, to the end of 2021, a sixteen year timespan. All individuals agreeable to review underwent a standardised clinical assessment, including the Structured Clinical Interview for DSM Disorders (SCID). Outcomes of specific DSM disorders met were reported for the 'not meeting criteria' cohort. Totals were compiled and also grouped in diagnostic categories. Demographic (age, gender, family history of psychosis, nationality) and

socio-occupational (relationship status, living status, working status) variables were compiled. The functional markers of the cohort were compared, in an adjusted model, with individuals diagnosed with a FEP during the same period.

Results: From 2005-2021 inclusive, there were 2025 completed index assessments. 27.6% (n=558) did not meet either FEP or ARMS criteria, notably higher than the 5.4% (n=110) meeting ARMS criteria. 60.9% (n=1233) met criteria for a FEP, and 6.1% (n=124) met criteria for a psychotic disorder, but not first episode. The relative proportion of each group varied over the study period. The 'not meeting criteria' group were enriched for non-psychotic psychiatric morbidity, with 65.4% (n=366) meeting criteria for at least one DSM Axis I disorder and 36.4% of those meeting criteria for more than one. The most common diagnostic groups met were substance use disorders, 22.5% (n=164), anxiety disorders, 22.2% (n=162) and depressive disorders, 20.4% (n=149). They were more likely than an FEP cohort to be younger (OR 0.97, CI 0.96-0.98) and male (OR 1.12, CI 1.03-1.71). They were less likely to be of non-Irish nationality (OR 0.85, CI 0.77-0.91). They had an equivalent proportion of family members with a psychotic disorder. They were less likely to be inpatients or undergoing involuntary treatment. Their functional markers were poor and broadly equivalent to a FEP cohort. On one indicator, long term unemployment (GREATER THAN 12 months), they were more impaired than an FEP cohort (adjusted OR 2.83, CI 1.65-4.85).

Discussion: This group is enriched for demographic, diagnostic and functional risk-factors for psychosis. The proportion of their non-psychotic psychiatric morbidity is consistent with what has been reported in ARMS samples, indicating that this characteristic is shared with other EIP service referrals. They are functioning poorly. This is both an important early risk factor, and indicates their high current need. They are a substantially larger group than those meeting ARMS criteria.

The potential significance of these findings is that those 'not meeting criteria' may represent an important, high capacity, risk-enriched population for psychosis. They are easily accessible as they are already in contact with both general adult and EIP services, despite the fact that they currently do not meet criteria for monitoring. In view of these findings, they should be an important focus for further study in the search for at-risk populations beyond the current ARMS model.

S24. ASSOCIATION BETWEEN PSYCHOPATHY TRAITS AND PSYCHOSIS LIKE EXPERIENCES IN A CLINICAL ADOLESCENT SAMPLE

Niklas Granö*¹

¹*Helsinki University Hospital, Department of Adolescent Psychiatry*

Background: Psychopathy and psychosis have been associated with dangerous behavior and hence, must often be assessed together for diagnostic reasons. However, little is known, how psychopathy traits and psychosis like experiences (PLEs) are associated in adolescent years in clinical populations at sub-diagnostic level. While psychopathy describes stable trait dimensions of personality, PLEs are more often dynamic symptoms and reactions to external factors, having multiple biological and psychological vulnerability factors in the background. It is important to understand how stable personality traits are associated with PLEs in the early years of development.

Methods: We assessed 88 adolescents (25 boys and 63 girls) between 13-18 years of age, who were entering psychiatric services at Helsinki University Hospital, Finland, with Youth

Psychopathy Inventory (YPI), Prodromal Questionnaire-Brief (PQ-B) and Beck Depression Inventory (BDI-21). Associations were analyzed between these self-report scales.

Results: Psychopathy sum score (YPI) correlated significantly with PLE (PQ-B) sum score (.366, $p < .001$). Of psychopathy subscales Lying (.346, $p < .001$), Impulsiveness (.410, $p < .001$) and Thrill-seeking (.319, $p = .002$), Remorselessness (.266, $p = .012$), Callousness (.217, $p = .042$) and Irresponsibility (.214, $p = .046$) correlated significantly with PLE sum score. In regression analysis psychopathy sum score explained significantly PLE sum score when age and gender were controlled for ($\beta = .403$, $p < .001$) and association remained significant ($\beta = .341$, $p < .001$) after adjusting regression model with depression sum score (BDI-21).

Discussion: In this study we found an association between psychopathy traits and psychosis like experiences. Association was found especially with some sub scales of psychopathy with PLEs. The association remained significant after adjusting the model with depression. Results suggest that psychopathy traits and PLEs can be discovered already at early stage on subclinical psychopathy dimensions in adolescent years and could be considered in preventive or psychiatric care of adolescents. More studies in the future are needed to explore mechanism between PLEs and psychopathy traits in adolescents.

S25. EYE MOVEMENTS IN THE GAZE PERCEPTION TASK: IMPLICIT SOCIAL COGNITIVE PROCESSING AND A POTENTIAL BIOMARKER FOR DETECTING CLINICAL HIGH RISK FOR PSYCHOSIS

Kam Hung Harry Tsui^{*1}, Janet Hsiao¹, Wing Chung Chang¹, Christy Lai Ming Hui¹, Ho Ming Edwin Lee¹, Eric Yu Hai Chen¹, Sherry Kit Wa Chan¹

¹*Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong*

Background: The early detection of individuals with at-risk mental states (ARMS) is crucial for initiating preventative interventions and improving long-term outcomes. While eye movement abnormalities have been well-established in schizophrenia, less is known in ARMS subjects, especially in response to social stimuli and gaze perception. This study aims to investigate the atypical eye movements in ARMS subjects and evaluate the potential of eye movement behaviors and the gaze perception task as an early detection method for psychosis risk.

Methods: Thirty-six help-seeking ARMS subjects were identified using the Comprehensive Assessment of At-Risk Mental States (CAARMS) and recruited from the psychiatric outpatient clinics at Queen Mary Hospital, Hong Kong. Fifty healthy controls without previous psychiatric history were recruited from the community.

A computerized gaze perception task was implemented with the eye-tracker method (Chan et al., 2021). The gaze perception task consists of 6 blocks with 30 trials of randomly selected stimuli of faces each. Subjects were asked to judge if the averted gaze with different levels of ambiguity (centre: 0° and 5°; ambiguous gaze: 10° and 15°; unambiguous gaze: 20°, 25° and 30°) were looking at themselves. Self-Referential Gaze Perception (SRGP) rates were calculated for each gaze condition. Fixations and saccades variables during the task were extracted. The group differences of eye movement variables and SRGP rates were assessed using ANCOVA controlling for age and gender. Linear Discriminant Analysis (LDA) was employed to identify the variables best differentiating between ARMS and HC. LDA models were constructed based on SRGP rates, eye movement variables, and a combination of both.

Results: Our results revealed significant differences in eye movement variables between ARMS and control subjects. ARMS had a larger total number of fixation than HC ($F = 18.035$, $p = 0.001$); the duration of fixation in HC was longer than those in ARMS ($F = 8.202$, $p = 0.005$). In terms of saccadic movements, FEP and ARMS had a trend of greater saccade amplitude than HC ($F = 2.888$, $p = 0.093$); and ARMS had a significantly higher velocity of saccade than HC ($F = 4.858$, $p = 0.030$). Also, ARMS exhibited significantly higher ambiguous ($F = 27.409$, $p \text{ LESS THAN } 0.001$) and unambiguous SRGP rates ($F = 14.508$, $p \text{ LESS THAN } 0.001$) than HC. For the ARMS and HC classifications, the LDA model using only SRGP rates exhibited a very good AUC-ROC (0.824, 95% CI: 0.735– 0.913), while the model using only eye movement variables had a good AUC-ROC of 0.781 (95% CI: 0.682– 0.879) (Table X). The model combining both SRGP rates and eye movement variables performed the best with a very good to excellent AUC-ROC of 0.893 (95% CI: 0.825 – 0.962), which was significantly better than the models with only SRGP ($Z = 2.145$, $p = 0.032$) and only eye movement variables ($Z = 2.402$, $p = 0.016$).

Discussion: Our findings indicated that ARMS individuals exhibited erratic and rapid eye movements and distinct SRGP during the gaze perception compared to healthy controls. The combined model, incorporating eye movement and behavioral data, demonstrated superior classification performance, indicating that a multidimensional approach may be more effective for differentiation. This study revealed the eye movement abnormalities in the ARMS population during the gaze perception task, shedding light on their potential utility in the early identification of psychosis risk. Further research is warranted to validate these findings in larger and more diverse samples, and to explore the underlying mechanisms of these observed differences.

S26. AT-RISK MENTAL STATES CONVERSIONS THROUGH NON-VERBAL VARIABLES: LOOKING AT MOVEMENT ABNORMALITIES AS A POSSIBLE INDICATOR

Ana Lopes Rocha^{*1}, Willian Henrique de Paula Ramos², Felipe Argolo¹, Anderson Ara³, João Medrado Gondim⁴, Natalia Mansur Haddad¹, Lucas Hortêncio¹, Leonardo Peroni¹, Julio Cesar Andrade¹, Mauricio Henriques Serpa⁵, Guillermo Cecchi⁶, Cheryl Corcoran⁷, Martinus Theodorus van de Bilt¹, Wagner Gattaz¹, Natalia Mota⁸, Alexandre Andrade Loch¹

¹*Institute of Psychiatry, Laboratory of Neuroscience (LIM 27), University of Sao Paulo, Brazil,*
²*Statistics Department, Federal University of Paraná, Curitiba, PR, Brazil,* ³*Department of Statistics, Federal University of Paraná, Curitiba-PR, Brazil,* ⁴*Federal University of Bahia,*
⁵*Institute of Psychiatry, Laboratory of Psychiatric Neuroimaging (LIM 21), University of Sao Paulo, Brazil,* ⁶*IBM Research,* ⁷*Icahn School of Medicine At Mount Sinai,* ⁸*Federal University of Rio de Janeiro*

Background: Movement abnormalities are commonly seen in schizophrenia spectrum disorders. They affect social interaction interfering in the amount of movement and in the use of expressive gestures, contributing to the blunted affect observed in those individuals. Furthermore, these deficits appear not only to be present in the prodromal stages, called at-risk mental states (ARMS), but also to be indicators of conversion to a psychiatric disorder. In the first stage of the study, we found a reduced movement and increase erraticism in ARMS when compared with healthy control individuals. No differences in gesticulation were observed. Here our aim was to use these variables collected in previous studies to verify, after follow-up, if

there is a difference between ARMS individuals who converted to a psychiatric diagnosis and those who did not.

Methods: In the initial sample formed by fifty-six ARMS and sixty-nine healthy controls, subjects were recorded while performing two speech tasks: the Structured Interview for Prodromal Syndromes (SIPS) subject's overview (SO), and a memory report paradigm (MR) based on the recall of a recent dream, an old dream and memory reports based on positively affective pictures. Data was submitted to an automated motion energy analysis (MEA) software where the variables mean amplitude, frequency, and coefficient of variability of head and torso were obtained. Also, frequency of self-stimulating movements and four gestures categories—iconic, metaphoric, beats and deictic—were manually coded. After a mean of 30 months of follow-up, 27 subjects did not develop a psychiatric disorder (control group), 8 ARMS subjects developed a psychotic syndrome (Psychotic group) and 24 ARMS subjects developed other DSM-5 disorders, what we will refer as General Disorders group.

Results: Kruskal-Wallis test was used to analyze differences between control, psychotic and General Disorders group. No differences were observed for MEA mean amplitude or any category of gesticulation and self-stimulatory movement. However, during the SO video, frequency of torso movement and coefficient of variability for both regions presented significant differences, with Dwass-Steel-Critchlow-Fligner (DSCF) multiple comparisons analysis showing that the General Disorders group presented lower frequency ($W=3.41$, $p=0.042$) compared with the Psychotic group and higher coefficient of variability compared with both the Psychotic group (Head: $W=-4.09$, $p=0.011$; Torso: $W=-4.84$, $p < 0.002$) and controls (Head: $W=-4.09$, $p=0.011$; Torso: $W=-4.31$, $p=0.007$).

Discussion: These results are consistent with our hypothesis that movement behavior differences would be observed after conversion of ARMS individuals. However, contrary to what we expected, the greatest difference was observed between the conversion's groups and not with controls. This finding showed that considering risk states as a single group can lead to the loss of important information. Furthermore, the importance of looking at conversion beyond psychosis and for the possibility of using variables obtained through more naturalistic ways, such as movement during speech.

S27. BIOMARKERS OF NEGATIVE SYMPTOMS IN ULTRA-HIGH-RISK FOR PSYCHOSIS INDIVIDUALS

Amelia Ang^{*1}, Marko Milicevic², Alison Yung², Stephen Wood³, Luba Sominsky²

¹Deakin University, ²Deakin University, ³Orygen, the National Centre of Excellence in Youth Mental Health

Background: Negative symptoms are difficult to treat and cause marked disability in schizophrenia. The underlying causes of negative symptoms are still unclear. There are several lines of evidence linking disturbances in oxidative stress and inflammation to negative symptoms in people with schizophrenia. However, further research is needed especially in the early stages of schizophrenia. The Ultra-high risk (UHR) state identifies individuals at high risk of schizophrenia and could be conceptualised as the earliest detectable stage of schizophrenia. Some studies have shown that alterations in inflammation and oxidative stress are evident in UHR individuals, but what is unknown is whether these processes are associated with negative symptoms in the UHR group. This project will examine:

- 1) if disturbances in oxidative and inflammatory biomarkers can be detected early in UHR individuals.
- 2) whether these processes are associated with negative symptoms in UHR individuals.

Methods: A systematic review was conducted to determine the presence of oxidative stress and inflammation in UHR individuals, and to determine its association to negative symptoms. A comprehensive search strategy was used to search Medline, PsycINFO and Embase. Studies of any design and setting were included if they discuss about topics on altered inflammatory or oxidative stress processes in UHR individuals. Articles were screened by two reviewers independently for inclusion. Relevant data will be extracted according to the pre-determined criteria, and study quality will be assessed using Covidence's quality assessment and data extraction template. Key findings from included studies will be synthesized in narrative form according to the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews.

Results: The database search yielded 878 results. After the removal of 480 duplicates, 398 articles were imported into Covidence for screening. Preliminary results to date suggests that elevated levels of inflammatory and oxidative markers are observed in UHR individuals, but it did not allow the confirmation of our hypothesis that there is a link between negative symptoms and inflammatory/oxidative stress processes.

Discussion: This study will provide important information on oxidative stress and inflammation in UHR which is crucial for the development of therapeutic interventions and for preventative measures to be put in place. It is anticipated that findings from this study will be relevant to clinical and community services and provide the necessary groundwork for future studies to be built on.

S28. CLINICAL HIGH RISK STATE FOR PSYCHOSIS: CLINICAL, NEUROCOGNITIVE AND REDOX PHENOTYPING

Martine Cleusix^{*1}, Elodie Sprungli-Toffel¹, Caroline Conchon¹, Alessandra Solida², Kerstin von Plessen³, Marco Armando³, Kim Q Do⁴, Philippe Conus¹, Paul Klauser⁵, Ines Khadimallah⁴, Luis Alameda¹

¹*Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne,* ²*Department of Adult Psychiatry, Neuchâtel Psychiatric Center,* ³*Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne,* ⁴*Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne,* ⁵*Center for Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital*

Background: The Clinical High Risk state for psychosis (CHR-P) concept was implemented to promote the early detection of help-seeking youth with emerging symptoms of psychosis. Because of a drop in the reported proportion of conversion to psychosis in those with CHR-P in the latest years, other clinical phenotypes that reflect the poor trajectories of the CHR-P patients need to be identified. We aimed to: 1) Identify subgroups of patients with CHR-P with principal components analysis (PCA) using psychopathological and cognitive domains as profiling criteria and examine their clinical, functional and cognitive characteristics, as well as biological profile in terms of markers involved in the oxidative stress pathway; 2) Explore the

validity of the proposed stratification by examining the clinical and functional trajectory over a period of 2 years.

Methods: A total of 55 young help-seeking patients aged 14 to 30 were referred by health care providers for a specialized evaluation in case of suspicion of a prodromal psychotic state. They all met CHR-P criteria according to the Structured Interview for Prodromal Syndromes (SIPS) and/or the Comprehensive Assessment of At-Risk Mental States (CAARMS). Individuals included in the study performed an extensive psychopathological assessment, neuropsychological battery and blood test for redox markers (Glutathione Peroxidase (GPx) and Glutathione Reductase (GR) activities). Based on their clinical and cognitive profile, we made a stratification of the patients using PCA.

Results: Cognitive and psychopathological outcome stratification revealed two subgroups of CHR-P patients with distinct profiles. At baseline, individuals in Group 1 showed a poorer profile with weaker self-esteem, lower autonomy and lower cognitive scores compared to Group 2. Analysis of redox markers revealed a positive correlation between GPx and GR activities (which is a marker of good redox regulation) in Group 2, a correlation disrupted in Group 1 (which has previously been associated with poor clinical outcomes in several studies). The poorer clinical profile in Group 1 remained the same or even worsened at 24 months of follow-up, whilst the clinical trajectory of patients in Group 2 tended to stabilize or improve.

Discussion: Our stratification appears to be a promising option to categorize CHR-P patients with distinctive clinical and biological vulnerability. Validation of these groups in larger cohorts is warranted.

S29. PREDICTING CLOZAPINE INITIATION AMONG PATIENTS WITH SCHIZOPHRENIA USING MACHINE LEARNING ON ELECTRONIC HEALTH RECORD DATA

Erik Perfalk^{*1}, Jakob Grøhn Damgaard¹, Andreas Aalkjaer Danielsen¹, Søren Dinesen Østergaard¹

¹*Department of Affective Disorders, Aarhus University Hospital—Psychiatry, Aarhus, Denmark*

Background: Clozapine is the optimal treatment of treatment-resistant schizophrenia, which affects a quarter of patients with schizophrenia. However, initiation of clozapine treatment is often unduly delayed. If it was possible to predict which patients that ultimately would be prescribed clozapine, the delay in treatment initiation could potentially be reduced, leading to a better prognosis for patients with schizophrenia.

We aimed to develop and subsequently validate a prediction model for clozapine initiation at the level of the individual patient by training machine learning models on routinely collected electronic health record (EHR) data.

Methods: EHR data from patients diagnosed with schizophrenia in the Psychiatric Services of the Central Denmark Region in the period from 2016-2021 will be retrieved. From this dataset, we will derive potential predictors from both structured data (covering e.g., prior diagnoses, medication, and number of hospital contacts) and from EHR descriptions of patients in free text (by means of term frequency – inverse document frequency and sentence transformers). At inpatient- and outpatient hospital contact, we will aim to predict clozapine initiation 12 months ahead using machine learning. Elastic Net regularized logistic regression- and

XGBoost models will be trained on 85% of the dataset after which the best performing model will be tested on the remaining 15% of the data.

Results: The study is in progress. The results will be presented at the conference.

Discussion: If a machine learning model trained on routinely collected EHR data can accurately predict initiation of clozapine, it may be implemented as a clinical decision support tool for earlier identification of patients in need of clozapine treatment.

S30. THE IMPACT OF THE SLEEP-WAKE CYCLE ON COGNITION IN INDIVIDUALS WITH SCHIZOPHRENIA

Bruna Assis¹, Raffael Massuda², Joao Vinicius Salgado¹, Joao Salgado*³

¹*Universidade Federal de Minas Gerais*, ²*Universidade Federal do Parana - Brazil*, ³*Federal University of Minas Gerais*

Background: Schizophrenia is associated with sleep disturbances in up to 80% of cases, indicating numerous circadian rhythm alterations (Chan et al., 2017; Cung et al., 2018). Insomnia is the most frequent sleep disorder in schizophrenia (Kaskie et al., 2017).

Circadian rhythm disturbances may be a pathophysiological risk factor for schizophrenia (Delorme et al., 2020). A manifestation related to circadian rhythm is chronotype, which is divided into morning, evening, or intermediary types (Duarte, 2018). Literature suggests an association between chronotype and mental illness (Taylor and Hasler, 2018). The hypothesis is that individuals with schizophrenia exhibit alterations in circadian rhythm, and these alterations are associated with cognitive impairment.

Methods: In this quasi-experimental study, 67 individuals with schizophrenia were evaluated, recruited from the Schizophrenia Outpatient Clinic of the Federal University of Paraná in Curitiba-PR, the Raul Soares Institute (FHEMIG) and the UFMG Clinics Hospital in Minas Gerais, Belo Horizonte. Inclusion criteria included a confirmed diagnosis of Schizophrenia by SCID-V, age between 18 and 60 years, scoring below 20 points on the PANSS positive subscale, and being without a crisis episode in the last three months.

The tools used were: Socio-demographic Questionnaire, Pittsburgh Sleep Quality Index; Morningness-Eveningness Questionnaire-Self Assessment version (MEQ-SA); Brief Assessment of Cognition in Schizophrenia Short Form (BACS-SF); Lysaker Emotion Recognition Task (BLERT); Hinting Task (Hinting); Insomnia Severity Index (ISI) and Berlin Questionnaire (Berlin). Spearman's correlation tests were applied between cognitive variables and sleep-related variables. Regression models were used for controlling intervening variables. The comparison of cognitive performance among the chronotype categories evaluated by MEQ-SA was done using the Kruskal-Wallis test.

Results: In Spearman's correlation matrix, several significant associations were highlighted, including Education with Hinting (p LESS THAN 0.001) and with Blert (p LESS THAN 0.002), ISI with Hinting (p LESS THAN 0.02). In the linear regression model, which included both education and ISI, this factor did not significantly explain the variation in the Hinting Task (p LESS THAN 0.143; p LESS THAN 0.053).

The Kruskal-Wallis test indicated a significant difference between chronotypes assessed by MEQ in performance on the Hinting Task (p LESS THAN 0.04; sum of squares = 6.34). The post-hoc Tukey analysis indicated a significant difference between morning and intermediary MEQ chronotypes (p LESS THAN 0.023) in performance on the Hinting Task.

Discussion: The results suggested that higher levels of education are associated with enhanced performance in both social cognition and emotional recognition abilities. Chronotype appears to impact social cognition as assessed by the Hinting Task, with morning-type individuals showing better results. Limitations of the study include the small number of participants and the absence of a control group.

S31. THE QUALITY OF LIFE OF PATIENTS WITH SCHIZOPHRENIA IS ASSOCIATED WITH FUNCTIONAL CONNECTIVITY IN THE DEFAULT MODE NETWORK

Miki Ishizuka^{*1}, Syuraku Son², Yukako Nakagami³, Takahiko Kawashima², Yuko Kobayashi², Manabu Kubota², Yujiro Yoshihara², Toshiya MURai², Jun Miyata⁴

¹Kyoto University Graduate School of Medicine, ²Department of Psychiatry, Graduate School of Medicine, Kyoto University, Japan., ³Agency for Student Support and Disability, Kyoto University, Japan., ⁴Department of Psychiatry, Aichi Medical University, Japan.

Background: There has been a growing interest in the quality of life (QoL) of patients with schizophrenia (SCZ) as their independence and social participation have been promoted. There have been many reports on the relationship between QoL of SCZ and neurocognitive impairment (Green et al., 1996), as well as alterations in brain structure (Ubukata et al., 2012). Pathophysiology of schizophrenia, like other psychiatric disorders, is considered a disruption of the brain network recently. However, associations between the QoL of SCZ and brain networks are still unclear. The purpose of this study is to identify the association of QoL with functional connectivity (FC) between brain regions in schizophrenia.

Methods: In this study, 58 schizophrenia patients (SCZ) and 80 healthy controls (HC) were enrolled. We used the WHOQOL, a 26-item self-report questionnaire, as a scale of QoL. It assesses 4 domains: physical, psychological, social, and environmental, as well as overall quality of life. Higher scores in all items indicate better QoL. All subjects underwent magnetic resonance imaging (MRI) on a Siemens 3T scanner to obtain resting-state functional MRI data. After preprocessing and denoising, the FC between each cortical region of interest (ROI) and subcortical region of interest (ROI) in default mode with no ROI set was calculated as a Pearson correlation coefficient using the CONN toolbox. We first identified FCs that differed significantly between groups and then used Spearman's rank correlation to examine correlations between significant FCs and the four domains of WHOQOL and overall QoL. This study was approved by the Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, Kyoto University. After receiving a description of the study, all participants provided written informed consent.

Results: Patients' QoL score was significantly lower in the psychological and social domains than HC's ($p < 0.05$). Among FCs with significant connections detected ($p < 0.05$, false discovery rate (FDR) corrected at seed level), the FCs with different Z-scores among the groups were Occipital - OP r, Occipital - OP l, OP r - OP l, LP(L) - s LOC r ($p < 0.05$). In the SCZ group, a significant correlation was found between their FCs which were different between groups and physical subscale, psychological subscale, social subscale, environmental subscale, and overall QoL ($r > 0.35$, $p < 0.05$).

Discussion: Overall QoL, as well as psychological and social domains, are associated with functional connectivity of the cortical regions in the DMN. DMN is known to play a key role in the reflective/introspective process. Therefore, our findings indicate the importance of

associating an extrospective process overall QoL included such as the psychological and social domains with the introspective process. These findings may contribute to the working on introspective processes and may help improve the QoL of patients.

S32. COMMUNICATIVE-PRAGMATIC IMPAIRMENT IN SCHIZOPHRENIA: ANALYZING ERROR PATTERNS THROUGH SIGNAL DETECTION THEORY

Alberto Parola*¹, Claudio Brasso², Paola Rocca³, Francesca M. Bosco⁴

¹*Centre for Language Technology, University of Copenhagen*, ²*Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin*, ³*Department of Neuroscience "Rita Levi Montalcini", University of Turin and SC Psichiatria U, Dipartimento di Neuroscienze e Salute Mentale, AOU Città della Salute e della Scienza di Torino, Turin*, ⁴*Department of Psychology, University of Turin, and Institute of Neurosciences of Turin*

Background: Individuals with schizophrenia (SCZ) show a severe impairment in the communicative-pragmatic domain. Previous studies reported a wide range of communicative deficits, such as difficulties in the comprehension of non-literal, figurative, and deceitful communicative acts, as well as narrative and conversational impairment. However, few studies provided an analysis of the errors committed in understanding communicative acts. Error performance may be highly informative of the clinical and cognitive factors underlying patients' failures in communicative-pragmatic tasks, and may thus provide a critical insights into the condition and its clinical and social dimensions. In this study, we evaluated the ability of patients with SCZ to recognize communicative intentions during the comprehension of different communicative acts, and we specifically focused on the analysis of error performance by using signal detection analysis.

Methods: Twenty-six Individuals with schizophrenia and 26 healthy controls (HC), matched for age, gender and education, took part in the study. Participants completed a computerized pragmatic task assessing the comprehension of literal, deceitful and ironic communicative acts, and a battery of tests evaluating cognitive (planning, cognitive flexibility, working memory, verbal intelligence) and theory of mind (ToM) abilities. Signal detection analysis was employed to assess how well participants could identify the communicative intentions of speakers, i.e. sensitivity, and their tendency to mistakenly attribute communicative intentions, i.e. response bias. Additionally, we explored correlations between sensitivity and response bias, clinical aspects and cognitive and ToM functions.

Results: Patients showed a reduced sensitivity ($\beta = -0.75$, $p < .01$), i.e. lower ability in recognizing the speaker's communicative intention, for all pragmatic phenomena, i.e. sincere, deceitful and ironic acts. Further, patients performed worse in recognizing deceit ($\beta = -0.45$, $p < .01$) and irony ($\beta = -0.36$, $p < .01$) compared to sincere acts. Patients also exhibited a stronger response bias for deceitful communicative acts ($\beta = -0.41$, $p < .05$) compared to HC, as they showed a strong tendency compared to HC to respond "deceit" either in deceitful or especially in not deceitful trials. We found significant correlations between planning ability and sensitivity for sincere, deceitful and ironic acts ($p < .05$), between ToM and sensitivity for sincere and deceitful acts ($p < .001$), and between cognitive flexibility and sensitivity for ironic acts ($p < .05$). We found no significant correlation between response bias and cognitive functions.

Discussion: The results showed that the ability to understand communicative intentions is impaired in SCZ. We found that patients showed reduced sensitivity to all pragmatic

phenomena, i.e. sincere, deceitful and ironic acts, compared to HC. Crucially, when committing errors, patients selected the “deceitful” category more frequently than the others. This was reflected in a stronger response bias for deceitful communicative acts and indicated a strong a priori tendency for patients to respond “deceit” for either deceitful or non-deceitful trials. The patients were clinically stable, but most of them had a history of paranoid symptoms such as persecutory delusions. This tendency could persist and result in a bias in the interpretation of other people's communicative intentions and explain their strong tendency to interpret communicative acts as deceptive regardless of context. We also found that the ability to correctly infer communicative intentions was related to various cognitive functions such as planning, cognitive flexibility and ToM. However, we did not find a relationship between response bias and specific cognitive functions. The present study demonstrates the importance of using an error performance analysis to disentangle the relationship between communicative-pragmatic difficulties and socio-cognitive abilities in schizophrenia.

S33. USING MOBILE HEALTH APPLICATION TO ENHANCE MEMORY AND ATTENTION IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

Huijun Li^{*1}, Hongmei Chi¹, Shuwen Yang², Jijun Wang³

¹Florida A & M University, ²Shanghai Mental Health Center, ³Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine

Background: Mental health applications (MHA) have been rapidly designed and are in urgent need of evaluation. Existing evaluation methods are mostly based on application design, such as platform, development, and subjective overall user observations. The purpose of this study was to evaluate the functionality and feasibility of an MHA to train cognitive function in youth at clinical high risk (CHR) for psychosis with a tool that allows a comprehensive user experience evaluation of mobile applications from multiple dimensions.

Methods: Eighty participants with CHR for psychosis were recruited and randomly assigned to the intervention and the group control. Participants in the intervention group used Specific Memory Attention in Real Time (SMART) application for three months. Functionality and feasibility were measured by Mobile Application Rating Scale and qualitative tools.

Results: Participants in the SMART group report that the form and design of this app are simple to operate and the content are trustworthy. They reported improvement of cognitive function and more motivation to seek help to improve their cognitive function. They also pointed out areas of improvement.

Discussion: Clinical implications of MHA in mental health services and research and clinical gaps are discussed.

S34. PROCESSES OF AUDITORY HALLUCINATIONS IN A NON-CLINICAL AND CLINICAL SAMPLE

Camille Jacquet^{*1}, Clément DONDÉ¹, Catherine Bortolon¹

¹Université Grenoble Alpes

Background: Around 80% of people with schizophrenia experience auditory hallucinations (AH). However, from 5% to 15% of non-clinical individuals also report such experiences (Toh et al., 2022). Having both clinical and non-clinical samples allows the discrimination of processes associated with AH from those associated with the need for care.

Disruptions in both top-down and bottom-up processes are suggested to be implicated in AH (Waters et al., 2012). Reduced sensitivity/accuracy for signal-noise discrimination and increased expectation biases for sensory input are among the altered cognitive functions related to AH (Moseley et al., 2021). Perceptual decision-making in AH has often been studied with the auditory Signal Detection Task (aSDT). However, the choice of noises has been poorly justified and has neglected the role of specific frequencies that compose these noises. Few studies have explored the association between basic auditory processing and AH (Dondé, 2019) and most of these studies have important limitations (e.g., related to the definition of AH). Therefore, in this study, we aim to measure bottom-up and top-down processes linked to AH. We hypothesized (1) that patients with schizophrenia will have a poorer ability to discriminate pure tones compared to the general population, even more if they have AH, (2) that individuals with AH will do more false alarms (FA) and have a more liberal response bias, compared to individuals without AH, and even more in the human-noise condition.

Methods: We recruited (and still are) individuals with schizophrenia or schizoaffective disorder, with or without AH, and individuals from the general population, with or without proneness to AH (based on the Launay and Slade Hallucination Scale). Participants completed a series of questionnaires (i.e. Launay and Slade Hallucination Scale – Extended (modified), Hamilton Program for Schizophrenia Voices Questionnaire (patients only) and Creative Experience Questionnaire). They also completed, in a randomized order, the Tone Matching Task (TMT; Dondé, 2019) and the auditory Signal Detection Task (aSDT; Moseley et al., 2021). The TMT assesses early auditory processes. Two different noises were used in the aSDT to assess perceptual decision-making processes: human, with human speech frequencies, or non-human, without these frequencies (Laloyaux et al., 2022).

Results: Our preliminary results (75 non-clinical participants from 100) indicated no significant difference in TMT scores between individuals with and without proneness to AH ($\chi^2=0.23$, $p=.63$, $\varepsilon^2=.003$). Regarding the aSDT, there was no interaction between groups and noises for response bias ($F=0.277$, $p=.6$, $\eta^2=.001$) nor FA ($F=0.29$, $p=.59$, $\eta^2=.001$). In the human noise condition, there was no significant difference between groups for the number of FA ($\chi^2=2.66$, $p=.10$, $\varepsilon^2=.036$) or the response bias ($\chi^2=3.03$, $p=.08$, $\varepsilon^2=.041$). In the non-human noise condition, there was a significant difference between groups for the number of FA ($\chi^2=4.22$, $p=.04$, $\varepsilon^2=.057$) but not for response bias ($\chi^2=3.54$, $p=.06$, $\varepsilon^2=.048$). However, those with a proneness to AH had more FA on both noises but not significantly ($F=2.74$, $p=.10$, $\eta^2=.022$).

Discussion: Our preliminary results indicate that basic auditory processing does not seem to be associated with the presence of AH in the non-clinical sample. As such, these results indicate that these bottom-up processes might not be implicated in the AH, at least, not in non-clinical samples. Depending on noise conditions, differences between groups regarding the number of false alarms and response bias did not always reach significance. Here, it seems that overall, individuals with or without AH tend to have similar response bias.

S35. THE EFFECTS OF EMOTION REGULATION DEFICITS ON NEGATIVE SYMPTOMS AND FUNCTIONING IN PSYCHOSIS: COMPARING SELF-REPORT, BEHAVIORAL, PHYSIOLOGICAL, AND NEURAL MEASURES

Alexander Sahm^{*1}, Lara Wallenwein¹, Daniela Mier¹

¹*University of Konstanz*

Background: Current evidence suggests a close relationship between difficulties in emotion regulation, negative symptoms, and poor functional outcomes in patients with psychosis. However, there is an ongoing debate on how to measure emotion regulation impairments and which measure is most predictive of functional outcome – a necessary first step towards conceiving new therapeutic interventions. To this end, we examine the correlations of self-report, behavioral, physiological, and neural measures of emotion regulation with negative symptoms and global functioning in psychosis.

Methods: We collected data from 17 patients with a psychotic disorder (15 Schizophrenia spectrum disorders, 1 substance induced psychosis, 1 affective psychosis, $M(\text{Age}) = 28.17$, $SD(\text{Age}) = 6.61$, 18 % female) during their inpatient stay at a psychiatric ward and 15 healthy controls from the community ($M(\text{Age}) = 30.67$, $SD(\text{Age}) = 11.70$, 67% female). Data collection is currently ongoing. Negative symptoms and global functioning were assessed via clinical interviews in the patient group (Positive and Negative Syndrome Scale and Personal and Social Performance Scale). All participants completed the Emotion Regulation Questionnaire (ERQ), indicating trait reappraisal and trait suppression tendencies, and heart rate was measured at rest and root mean square of successive differences (RMSSD) was computed as an index of vagal tone. In addition, we conducted a negative emotion regulation experiment with the conditions observe and reappraisal during functional magnetic resonance imaging (fMRI). We defined emotion regulation success as the difference in self-reported valence between the reappraisal and observation condition. fMRI results were analyzed at an exploratory threshold of $p \text{ LESS THAN } .001$ (uncorrected) and $k = 10$. We extracted the eigenvariate of activation from key regions for emotion regulation, i.e. ventromedial prefrontal cortex, dorsolateral prefrontal cortex, anterior insula, anterior cingulate cortex, and amygdala in the patient group. RMSSD, ERQ, emotion regulation success, and extracted eigenvariates were subsequently correlated to negative symptoms and global functioning.

Results: Patients showed significantly higher suppression scores in the ERQ than controls, significantly lower RMSSD, but no differences in their performance in the emotion regulation task. Among controls, our fMRI results showed activation in the left superior temporal sulcus, tempo-parietal junction, orbitofrontal, dorsolateral-prefrontal, and anterior cingulate cortices, as well as bilateral activation of the caudate, polus temporalis and cerebellum. In the psychosis group we found activation in the left supplementary motor and right dorsolateral prefrontal cortices. In direct comparison to controls, patients had higher activation in the right cuneus and precuneus, anterior and posterior cingulate, dorsolateral prefrontal cortex, and temporo-parietal junction, as well as the bilateral insula and rolandic operculum. Only the RMSSD was correlated to global functioning ($r = .70$, $p = .002$) and showed a tendency of association to negative symptoms ($r = -.41$, $p = .100$).

Discussion: We found differences in neural, self-report, and physiological indices of emotion regulation between patients with psychosis and controls. However, only vagally mediated heart rate variability was correlated to global functioning in patients. These results show the usefulness of the multi-modal assessment of emotion regulation difficulties and might inform future interventional research in psychosis. However, collection and analysis of the complete data set is necessary to draw firm conclusions.

S36. REFERENCE CHOICES IN THE NARRATIVE SPEECH OF PEOPLE WITH SCHIZOPHRENIA DURING A WELL-CONTROLLED JOINT TASK: THE STORYTELLING IN SEQUENCE TASK

Maxime Rancourt*¹, Marion Fossard², Dominique Knutsen³, Marc-André Roy⁴, Caroline Cellard⁴, Marie-France Demers⁴, Luc Vigneault⁵, Sara Amrani⁶, Amélie M Achim⁷

¹Université Laval; VITAM - Centre de recherche en santé durable, ²Université de Neuchâtel, ³Université de Lille, ⁴Université Laval; Centre de recherche CERVO, ⁵Patient partner, ⁶Université Laval, ⁷Université Laval; VITAM - Centre de recherche en santé durable; Centre de recherche CERVO

Background: Language production deficits are common in people with schizophrenia spectrum disorders (SSD). While it is clear that people with SSD often produce unclear or ambiguous references, one aspect of reference production that has received little attention so far is their use of reference markers. From the literature in healthy participants, we know that indefinite markers (e.g., “a girl”) are preferred when introducing new referents (e.g., a new story character) in the discourse, pronouns (e.g., “she”) are preferred when maintaining a referent in focus in the discourse and definite references (e.g., “the girl”) are preferred when shifting the focus of the discourse to a different referent. The current study aimed to determine whether people with SSD differ from healthy controls in their use of reference markers when the stages of narrative elaboration (introduction, maintaining and shift) can be separately examined using a well-controlled verbal communication task.

Methods: 51 outpatients (34.8 years, 37 men) with a SSD and 68 healthy controls (28.3 years, 34 men) participated in this study. They all completed the Storytelling in Sequence Task (STST), a collaborative verbal communication task based on the referential communication paradigm. The STST is composed of 9 stories, each illustrated on 6 images. The participant’s task is to tell each story to an interaction partner (a research assistant) who holds the same 6 images in a random order, so that the partner can place her/his images in the correct order. The interaction partner is separated from the participant by an opaque panel and can provide feedback or ask for clarifications if needed. The STST contains several manipulations shown to influence referential choices (i.e., the terms used to refer to the story characters). First, there are 3 different levels of referential complexity, manipulated between stories based on the number of characters in the stories (1 or 2) and, for the stories with 2 characters, their genders (different or same gender). Second, each image of the stories is linked to a specific stage of narrative elaboration (introduction, maintaining or shift of the character in focus). The verbal interactions were tape-recorded and transcribed verbatim. Two independent raters extracted the first reference to the character in focus in each image of each story and coded the type of reference (indefinite, definite, pronoun or other). Logistic mixed models were performed separately for each stage of narrative elaboration and each type of reference marker, to examine whether the probability of using that marker was influenced by group membership and/or levels of referential complexity.

Results: When focusing on the introduction stage, main effects of group emerged such that people with SSD were less likely to use indefinite markers ($F(1,120) = 6.26$, $p < .013$) and more likely to use definite markers ($F(1,147) = 8.34$, $p < .004$) than the healthy controls, without any effects of referential complexity. During the maintaining stage, main effects of levels of complexity emerged such that both groups were more likely to use

pronouns ($F(2, 7.8) = 30.78$, $p < .001$) and less likely to use definite markers ($F(2, 6.9) = 33.84$, $p < .001$) for stories containing only one character relative to the stories with two characters. For the shift stage, none of the effects were statistically significant.

Discussion: Alterations in the use of reference markers in people with SSD were specifically observed when they had to introduce new characters as part of their storytelling. Using well-controlled verbal communication tasks is a good way to examine verbal productions, including choices of reference markers, while the participants speak about predetermined story content.

S37. INDIVIDUAL PERCEPTIONS OF CLUSTERING AND SWITCHING DURING VERBAL FLUENCY TESTS IN A PILOT SAMPLE OF PARTICIPANTS WITH AND WITHOUT A SCHIZOPHRENIA-SPECTRUM DISORDER

Nancy Lundin^{*1}, Bess Bloomer², Emily Gildea³, Peter Todd³, William Hetrick³

¹The Ohio State University Wexner Medical Center, ²National Institutes of Health, ³Indiana University

Background: Verbal fluency tests (VFT) have been used to study thought disorder (i.e., tangential, disorganized speech) among individuals with psychotic disorders. These tasks index retrieval of related concepts in memory and may provide a window into the cognitive architecture of how people connect thoughts and express these thoughts through speech. In VFT, people generate words belonging to a particular category or beginning with a particular letter in a limited time, and people who tend to alternate between "clustering" and "switching" strategies among groupings of related responses produce more words in these tasks. One challenge in this work is determining which responses to classify as clusters or switches, as the relatedness between concepts is multifaceted. Common classification approaches include subcategory-based norms and more recently natural language processing (e.g., using thresholds of semantic similarity between words). A less common but useful approach is to ask individuals performing VFT to share their perceptions of where they think they switched between related concepts. This approach can capture unique features of individuals' semantic memory organization in ways that are particularly relevant for understanding thought disorder among individuals with psychosis.

Methods: In an ongoing study, participants with a schizophrenia-spectrum disorder ($n=10$) and without a psychiatric diagnosis ($n=7$) engaged in four 3-minute category VFT (animals, cities, foods, occupations) and four 3-minute letter VFT (A, F, M, S) trials during functional magnetic resonance imaging (fMRI). After scanning, participants designated consecutive responses that they thought were related (clusters) in the word lists they generated. Participant VFT responses were coded as cluster-related or switch-related based on these participant evaluations for all domains and on subcategory norms for animal and food domains. Animal subcategories were extended from the commonly used Troyer norms and prior research (e.g., canines, farm animals, African animals). Food subcategories were created based on common food groups and regional cuisines (e.g., fruits, grains, East Asian cuisine).

Results: Initial pilot analysis of the behavioral data showed that participants in both the schizophrenia and comparison groups generated a similar number of verbal fluency responses. Participants generated more responses and reported greater percentages of clustered responses for category VFT (particularly in the food and animal domains) than letter VFT. Additionally, groups showed similar match rates between participant-designated and subcategory-based cluster and switch responses (animal VFT ~76% match; food VFT ~67% match). Examination

of discrepancies between these cluster-switch designation methods revealed some participant-designated clusters not captured by the subcategory-based norms which were associative in nature (e.g., pizza toppings, United States Thanksgiving holiday dishes, taco ingredients) or which combined semantic and phonetic cues (e.g., grouping guinea pig and pig within the same cluster).

Discussion: This pilot analysis demonstrates feasibility of collecting VFT responses for 3-minute generation periods during fMRI among individuals with schizophrenia. This work also highlights the value of asking participants to share their individual perceptions of how concepts are related, which may index components of semantic memory organization relevant to thought disorder. Analyses in the larger future sample are needed to determine whether individual perceptions of semantic memory organization differ in individuals with schizophrenia as well as the neural correlates of these processes. Finally, discrepancies between participant-designated and subcategory-based clusters indicate the need for using and refining models of computational linguistic analysis which may better capture associative and combined semantic and phonetic cues used in cognitive search.

S38. CHEMOSENSORY ANHEDONIA IN PATIENTS WITH SCHIZOPHRENIA

Özge Akgül¹, Emine Ilgın Hosgelen^{*2}, Taha Selim Bilgin³, Berna Binnur Akdede⁴, Köksal Alptekin⁴

¹*Izmir Democracy University*, ²*Dokuz Eylül University, Institute of Health Science*, ³*Health Sciences University*, ⁴*İzmir Tepecik Education and Research Hospital*, ⁴*Dokuz Eylül University*,

Background: Anhedonia, defined as the decrease or impairment of the capacity to experience pleasure, is one of the clinical features of schizophrenia (SZ). SZ patients exhibit pronounced levels of physical and social anhedonia. In recent years, there has been a notable focus in schizophrenia research on the analysis of chemosensory hedonic capacities, which pertain to the individual's capacity to perceive pleasure through smell or taste. There exists a convergence of brain regions involved in the regulation of olfactory function and the processing of emotions, including orbitofrontal cortex, amygdala, and hippocampus. Previous research has indicated that olfactory anhedonia is a significant symptom of schizophrenia. Hence, in comparison to other sensory modalities, olfaction may exhibit greater sensitivity in detecting anhedonia. The primary objective of this study was to investigate the relation between chemosensory anhedonia and hedonic features in patients with schizophrenia.

Methods: The data were obtained from individuals who were on treatment at the Schizophrenia Outpatient Unit of Dokuz Eylül University School of Medicine. The study included 92 healthy controls (HC) and 61 patients with schizophrenia based on the diagnostic criteria outlined in the DSM-5. The researchers evaluated the degree of chemosensory anhedonia by employing the Chemosensory Pleasure Scale (CPS), whereas the assessment of hedonic features was conducted using the Chapman Scales for Physical and Social Anhedonia (PAS and SAS). Also, the social functioning of patients was assessed by the Personal and Social Performance Scale (PSP).

Results: There was no significant difference in terms of age between the SZ and HC groups ($p=0.15$). The mean age and total education years are reported as follows: for SZ patients 38.15 ± 9.69 years and 12.13 ± 4.27 years, respectively; and for HC 35.39 ± 12.43 years and 17.06 ± 4.92 years, respectively. The SZ group showed higher physical, social, and chemosensory anhedonia compared to HC ($p < 0.05$), and their PSP score was 57.58 ± 14.07 . In

SZ, CPS was negatively correlated to PAS ($r=-0.322$, $p=0.011$). Especially, the nature subdomain was negatively correlated to PAS ($r=-0.518$, $p < 0.001$) and SAS ($r=-0.291$, $p=0.023$). In HC, both PAS and SAS showed negative correlations to CPS ($r=-0.41$, $p < 0.001$; $r=-0.403$, $p < 0.001$ respectively). Moreover, the PSP was negatively correlated to PAS ($r=-0.364$, $p=0.008$) and SAS ($r=-0.358$, $p=0.009$) in SZ.

Discussion: This study represents the first investigation that employs the self-reported chemosensory pleasure scale regarding to assess and compare the chemosensory hedonic capacity between patients with schizophrenia and healthy controls within the Turkish population. The discovery of reduced pleasure derived from chemosensory stimulation in the SZ group in comparison to HC is consistent with previous studies that reported heightened levels of olfactory anhedonia. Furthermore, patients with SZ demonstrated higher levels of social and physical anhedonia. In line with the literature, CPS showed a correlation with PAS. In addition, as in line with other studies, the schizophrenia group exhibited an association between impaired social functioning and increased levels of physical and social anhedonia. It is known that heightened olfactory anhedonia and elevated negative symptoms are associated. In comparison to other sensory stimuli, olfaction may demonstrate a potentially elevated sensitivity in detecting anhedonia. Moreover, considering the importance of social functioning is mostly dependent on anhedonia, studying chemosensory anhedonia would be important to enhance comprehension of anhedonia as a negative symptom.

S39. THE RELATIONSHIP BETWEEN THE LEVEL OF EXPRESSION OF EMOTIONS OF THE CAREGIVERS IN PATIENTS WITH SCHIZOPHRENIA AND THE LEVEL OF THOUGHT DISORDER IN PATIENTS WITH SCHIZOPHRENIA

Dilşah Gençaslan¹, Köksal Alptekin¹, Emine Ilgin Hosgelen¹, Berna Akdede¹, Tolga Binbay¹, Emine Ilgin Hosgelen*²

¹Dokuz Eylul University, ²Dokuz Eylul University, Institute of Health Science

Background: Schizophrenia significantly impacts individuals and caregivers, influencing their attitudes towards patients. Emotional expression between the patient and caregiver involves concepts like attitude, perspective on the illness, and critical or hostile behavior. The caregiver's emotional expression significantly affects both the patient and clinical symptoms. Emotional expression levels notably impact positive symptoms, depression, and anxiety, despite not being directly linked to negative symptoms. Thought disorder is a crucial symptom, manifesting as difficulties in organizing and expressing thoughts. This study explores the relationship between schizophrenia patients' thought disorder and their caregivers' expressed emotions.

Methods: Sixty-six patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-V criteria and their corresponding 66 caregivers, a total of 132 participants were included into the study. The patient group consists of 27 females (40.9%) and 39 males (59.1%). Of the patients, 49 (74.2%) were diagnosed with Schizophrenia, and 17 (25.8%) were diagnosed with Schizoaffective Disorder. Among the caregivers, 39 (59.1%) are female, and 27 (40.9%) are male. Patients' average age is 45.50, while caregivers' average age is 57.20

Results: In this study we found no significant relationship between the patients' scores on structural thought disorder and caregivers' scores on emotional expression ($r= .23$, $p=.06$). There was a positive correlation between the perceived emotional expression level by patients and the patients' thought disorder scores ($r= .29$, $p= .01$). A negative correlation existed between caregivers' emotional expression levels and neuropsychological test scores. Positive

correlation was observed between patients' perceived emotional expression scores and PANSS scores.

Discussion: The primary objective of this study was to examine the relationship between patients' structural thought disorders and caregivers' levels of emotional expression, representing verbal or non-verbal behaviors. Our core hypothesis, assuming a positive correlation between the caregiver's emotional expression level and the patients' structural thought disorders, was not statistically significant, despite existing a positive relation. However, patients' perceived emotional expression were related to their increased severity of thought disorders. Thought disorder in patients with schizophrenia may be related to their perceived emotional expression of their caregivers.

S40. THE ROLE OF MOTIVATION IN CLINICAL PRESENTATION, TREATMENT ENGAGEMENT AND RESPONSE IN SCHIZOPHRENIA-SPECTRUM DISORDERS: A SYSTEMATIC REVIEW

Helen Thai*¹, Élodie C. Audet¹, Richard Koestner¹, Martin Lepage², Gillian A. O'Driscoll¹

¹*McGill University*, ²*McGill University, Douglas Mental Health University Institute*

Background: Schizophrenia, the most disabling psychiatric disorder, imposes long-term impairments in social and occupational functioning. Negative symptoms, including amotivation, are poor prognostic factors, but patient motivation as a positive force has been less studied. Self-Determination Theory (SDT) is an established theory of human motivation that considers motivation on a continuum from amotivation, to controlled, identified and intrinsic motivation, and emphasizes autonomy, competence, and relatedness as factors that sustain intrinsic motivation. To identify how motivation as framed by SDT has been studied in treatment contexts, we conducted a systematic review.

Methods: PRISMA-P guidelines were used to investigate the question, “How does motivation impact clinical presentation, treatment engagement and response in schizophrenia-spectrum disorders?” Eligible studies were conducted in adult schizophrenia-spectrum disorders (GREATER THAN 50% of the sample), peer-reviewed, quantitative, in English and used a motivation scale. Results were grouped into cross-sectional correlates of motivation at baseline, longitudinal correlates, and the effects of motivational interventions as measured in RCTs.

Results: Fifty-six independent studies, involving 6,829 participants, met inclusion criteria. Twenty motivation scales were used: the Intrinsic Motivation Inventory-Schizophrenia Research (Choi et al., 2010), which measures task-specific motivation across the SDT continuum, and a 3-item Quality-of-Life subscale (Heinrichs, 1984) that assesses intrinsic motivation in one's life generally, were most used. Cross-Sectional Correlates of Baseline Motivation: Social and occupational functioning were positively associated with motivation in 7/8 studies. Neurocognitive global scores were positively correlated with motivation in 7/9 studies. Negative and positive symptoms were both negatively associated with motivation (9/14 and 7/11 studies respectively), with significant results found primarily with the QLS. Longitudinal Correlates: Motivation at treatment initiation predicted treatment response in 6/10 studies. Cognitive remediation studies generally did not observe this effect (1/5 studies) but did find an association with treatment engagement (4/5 studies). Of 15 studies examining whether motivation changed during treatment, 9 found it did. Additionally, 5 found that these changes correlated with treatment response. RCTs of Motivational Interventions: 15 RCTs evaluated the effect of adding a motivation enhancement condition to an established treatment.

The most common motivation enhancement methods were individualized goal-setting and goal-attainment support (12/15 studies), targeting defeatist beliefs to increase perceived competence (7/15), and increasing contact to improve sense of relatedness (7/15). Participants in the motivational intervention groups showed increased motivation (10/13 studies), higher treatment engagement (8/10), and greater treatment response (11/13) than controls.

Discussion: Baseline motivation was found to be associated with clinical presentation and with the magnitude of response to treatments that targeted social and occupational functioning. Relatively few RCTs have been conducted, but they were consistent in finding that motivational interventions increase motivation and enhance treatment engagement and response. More studies are needed that monitor motivation during treatment, as proximal assessments could better identify treatment factors that impact motivation. Such information could allow modification of treatments to enhance the patient experience and improve efficacy.

S41. COGNITIVE MODEL OF PERCEPTUAL ANOMALIES: THE ROLE OF TOP-DOWN INFLUENCE, SOURCE MONITORING AND INHIBITORY CONTROL PROCESSES FOR HALLUCINATIONS IN SCHIZOPHRENIA AND FOR HALLUCINATORY-LIKE EXPERIENCES IN THE GENERAL POPULATION

Adrianna Aleksandrowicz^{*1}, Steffen Moritz², Joachim Kowalski¹, Łukasz Gawęda¹

¹*Institute of Psychology, Polish Academy of Sciences*, ²*University Medical Center Hamburg-Eppendorf*,

Background: Cognitive models emphasize that top-down processes, source monitoring, and inhibitory control contribute to perceptual anomalies such as auditory hallucinations (AHs) and hallucinatory-like experiences (HLEs). The prevalence of perceptual abnormalities such as illusions or even hallucinations is not restricted to the clinical population and represents a continuum. This account assumes that the further one is on the continuum, the more these experiences should be prominent. Still, there is little evidence to confirm such a hypothesis, often presenting mixed findings. The present study aims to investigate whether there are gradual differences in these postulated mechanisms along the continuum of psychosis. We expect that people with a diagnosis of schizophrenia spectrum disorders, people with frequent HLEs and healthy controls will differ in functioning regarding top-down processes, source monitoring and inhibitory control.

Methods: Eighty-six patients with schizophrenia spectrum disorders (SSD) were divided into two groups based on AHs presence - 45 with auditory hallucinations (present in the week prior to the study) and 41 - non-hallucinating (in the month prior to the study), 43 matched healthy controls (HC), and a sample selected from the general population of 26 participants with high HLEs and 33 with low HLEs performed three experimental tasks assessing top-down processes (False Perception Task - FPT), source monitoring (Action Memory Task - AMT), inhibitory control (Go/No-Go Task). Patients were assessed with the Positive and Negative Syndrome Scale, and all groups were screened using the Mini International Neuropsychiatric Interview (MINI) for the presence of mental disorders. Exclusion criteria were as follows: age below 18 years and above 45 years, hearing impairments, neurological disorders, alcohol dependence in the past 12 months, and intellectual impairments. Additionally, for the non-clinical groups, the presence of the current mental disorders was the exclusion criterion. All patients were stable during the assessment and had no major changes in pharmacological treatment in the past two weeks before the study. Group differences between two clinical groups (AH and non-AH), HC,

and two non-clinical groups (high HLEs and low HLEs) were analyzed with Kruskal-Wallis ANOVA and post hoc tests with Dunn's Test.

Results: Both clinical groups committed significantly more false perceptions in the FPT than HC. However, there were no significant differences between clinical groups (SSD with AH vs SSD without current AH) and non-clinical groups (high HLEs vs low HLEs). Moreover, both clinical groups significantly more often misattributed imagined actions as being performed than the HC group. However, there were no significant differences between the clinical groups (SSD with AH vs SSD without current AH) and the non-clinical groups (high HLEs vs low HLEs). Finally, we found no significant differences between groups for false alarms in the Go/No-Go Task.

Discussion: This study sheds further light on the mechanisms of perceptual anomalies in clinical and non-clinical populations.

S42. EXECUTIVE DYSFUNCTIONS IN PATIENTS WITH SCHIZO-OBESSIVE DISORDER

Min-yi Chu^{*1}, Shuai-biao Li¹, Raymond C. K. Chan²

¹Translational Neuropsychology and Applied Cognitive Neuroscience Laboratory, Shanghai Mental Health Centre, Shanghai Jiao Tong University School of Medicine, ²Neuropsychology and Applied Cognitive Neuroscience, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China; Department of Psychology, University of Chinese Academy of Sciences; Translational Neuropsychology and Applied Cognitive Neuroscience Laboratory, Shanghai Mental Health Centre, Shanghai Jiao Tong University School of Medicine

Background: Schizo-obsessive disorder (SOC) has been proposed to describe patients with schizophrenia (SCZ) exhibiting obsessive-compulsive symptoms or co-morbid the diagnostic criteria for obsessive-compulsive disorder (OCD). These patients are characterized by earlier onset, more severe psychiatric symptoms, and poorer outcomes. However, the underlying pathological mechanisms of SOC are still yet understood. On the other hand, executive dysfunction, the potential endophenotype for both SCZ and OCD, is thought to be a specific alteration in patients with SOC. However, it is still not clear the features of executive dysfunction in patients with SOC. This study adopted a transdiagnostic approach to exploring the features of the specific executive dysfunction in patients with SOC, SCZ, and OCD.

Methods: A total of 38 SOC patients, 82 SCZ patients, 59 OCD patients, and 47 healthy controls (HC) were recruited for this study. We administered the Hayling Complement Sentence Test (HCST), the Sustained Action to Response Task (SART), the n-back task, and the Six-Element Test (SET) to assess the inhibition, updating, shifting, and planning components of executive function to all the participants. All patients also received the assessment of the Positive and Negative Syndrome Scale (PANSS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for evaluation of symptom severity.

Results: SOC patients exhibited significantly more prominent negative and positive symptoms in subscales of PANSS compared to SCZ patients, but they showed no difference in Y-BOCS scores comparing to OCD patients. Findings from one-way ANOVA analysis showed that SOC, SCZ and OCD groups exhibited significantly higher total error numbers of HCST compared with HCs. Both SOC and SCZ patients also exhibited significantly poorer

performances in SET shifting and planning scores, and n-back task than HC. Moreover, SOC patients also performed significantly poorer than OCD patients in SET planning scores.

Discussion: These findings suggested that the poor inhibition ability is a shared impairment among the SOC, SCZ, and OCD patients, and SOC and SCZ patients exhibited more pronounced impairments in other components of executive function, including updating, shifting, and planning abilities. These results supported the notion that SOC may represent a subtype of SCZ with distinct cognitive characteristics.

S43. EVALUATING SOCIAL INTERACTIONS IN SCHIZOTYPY USING ECOLOGICAL MOMENTARY ASSESSMENT

Madisen Russell^{*1}, Tess Filip², Sarah Akhras², Heather Busanet³, Katharine Thakkar³, Amanda Mccleery², Kyle Minor¹

¹Indiana University; ²Purdue University, ³The University of Iowa, ³Michigan State University,

Background: Social functioning deficits are prevalent in individuals with high levels of schizotypal traits (Debbané et al., 2015; Kwapil et al., 2013). Much of the research in this area has been limited to laboratory-based assessments such as interview-rated, self-report, or performance-based measures, where the accuracy of participants' recalled information is compromised by reconstructive processes (Moskowitz and Young, 2006). Ecological momentary assessment (EMA), which collects self-reported information closer in time to its occurrence, can offer a more advantageous approach to assessing individuals' functioning and day-to-day experiences (e.g., Minor et al., 2020). To date, no prior research has evaluated how specific types of schizotypal traits predict key real-world social interaction variables, including: 1) likelihood of interacting; 2) depth of interactions; and 3) enjoyment of interactions. This study seeks to fill this gap by examining if positive, negative, and disorganized schizotypal traits predict these aspects of social functioning in individuals' daily lives. In turn, this will contribute to a deeper understanding of social functioning deficits within schizotypy. I hypothesized that negative schizotypal traits would exhibit the strongest inverse association with social interaction likelihood, depth, and enjoyment.

Methods: Across three midwestern U.S. universities, 185 college student participants completed an online measure of schizotypy (SPQ-BR; Cohen et al., 2010), as well as one or two weeks of EMA to assess daily social interactions. Participants were prompted six times per day to provide information on their social interactions: 1) whether they were interacting with anyone; 2) the depth of that interaction (e.g., small talk, sharing opinions, expressing feelings); and 3) their enjoyment of the interaction. Multilevel modeling was used to examine if schizotypal traits (i.e., positive, negative, and disorganized) can predict the likelihood, depth, and enjoyment of individuals' everyday social interactions.

Results: The average EMA adherence rate was 70.32% (SD=15.76%) and did not significantly differ between sites ($p=.330$). Negative schizotypal traits significantly predicted individuals' likelihood of interacting ($b=-.005$, $SE=.002$, $p=.016$) and ratings of social interaction enjoyment ($b=-.066$, $SE=.019$, $p < .001$), but did not predict individuals' social interaction depth, $b=-.014$, $SE=.008$, $p=.079$. Positive and disorganized traits did not significantly predict individuals' likelihood of interacting (p -values GREATER THAN .552), enjoyment (p -values GREATER THAN .116), or depth (p -values GREATER THAN .090) of social interactions.

Discussion: Negative schizotypal traits inversely predicted the likelihood of whether an individual was interacting with others in their daily lives and how much they enjoyed their interactions. Positive and disorganized traits did not significantly predict any of the social interaction outcome variables. These findings are complementary to the growing body of evidence that suggests negative schizotypal traits play a more significant role in social functioning deficits than positive or disorganized traits (e.g., Abu-Akel et al., 2018; Kwapil et al., 2012). Given the complex relationship between schizotypal traits, affect, and social outcomes (e.g., Kwapil et al., 2020; Minor et al., 2020), future research should examine these interactions and their implications for social functioning in individuals with increased schizotypal traits.

S44. EXAMINING THE CONTRIBUTION OF SOCIAL COGNITIVE BIAS TO SYMPTOMS AND MOMENTARY EXPERIENCES OF PARANOID IDEATION AND NEGATIVE AFFECT IN PSYCHOSIS

Ryan Orth^{*1}, Imani Todd², Laura Hemphill², Melanie Bennett³, Jack Blanchard²

¹*University of Maryland - College Park*, ²*University of Maryland- College Park*, ³*University of Maryland- School of Medicine*

Background: Hostile social cognitive bias, the tendency to interpret the actions of others as intentional and hostile (Combs et al., 2007), is a major component of the social cognitive deficits common in psychosis (Mancuso et al., 2011). Social cognitive bias relates to negative affect and positive symptoms (Mancuso et al., 2011) and predicts paranoid ideation in both clinical psychosis (Buck et al., 2016; Combs et al., 2009) and in non-clinical community samples (Combs et al., 2013). Additional work suggests that social cognitive bias contributes to social impairment in psychosis (Buck et al., 2018; Pinkham et al., 2016), and that this contribution is unrelated to negative symptoms (Mancuso et al., 2011). While social cognitive bias appears to be an important factor in both symptoms and functioning in psychosis, research to date has largely relied upon symptom self-reports and clinician ratings with very little work utilizing methods such as ecological momentary assessment (EMA). Thus, it remains unclear how laboratory and self-report measures of social cognitive bias may predict daily experiences of symptoms.

Methods: The current study seeks to expand current literature by examining how social cognitive bias relates to daily experiences of negative affect and paranoid ideation. We hypothesize that 1) social cognitive bias will relate to greater paranoid ideation and negative affect; 2) social cognitive bias will relate to greater momentary paranoid ideation and negative affect; 3) social cognitive bias will remain related to momentary paranoid ideation and negative affect when controlling for baseline levels of these constructs.

Data were collected from a transdiagnostic sample of adults with clinical psychosis and non-clinical participants living in the Baltimore-Washington metropolitan area of the United States. Social cognitive bias was measured using the overall “blame score” (based on the subscores of perceived intentionality, anger, and blame) of the Ambiguous Intentions Hostility Questionnaire (AIHQ; Combs et al., 2007). Paranoid ideation was measured using the Revised Green Paranoid Thoughts Scale (R-GPTS; Freeman et al., 2021) and negative affect was measured using previously established factors of Brief Psychiatric Rating Scale (BPRS; Kopelowicz et al., 2008; Ventura et al., 1993). Momentary paranoid ideation and negative affect were calculated using average responses from a week of EMA (Orth et al., 2022).

Results: Analyses (N = 86) indicated that the total blame score of the AIHQ was related to R-GPTS ($r = .49$, p LESS THAN .001) and BPRS negative affect ($r = .36$, p LESS THAN .001). The AIHQ was not related to EMA paranoid ideation ($r = .22$, $p = .07$) or negative affect ($r = .13$, $p = .25$). Post-hoc analyses revealed a component of the AIHQ, perceived intentionality, was related to greater EMA paranoid ideation ($r = .24$, $p = .04$). However, when controlling for R-GPTS scores, perceived intentionality was no longer related to EMA paranoid ideation ($t = -1.12$, $p = .26$).

Discussion: As hypothesized, social cognitive bias was related to symptom ratings of paranoid ideation and negative affect. A component of social cognitive bias, perceived intentionality, was also related to momentary paranoid ideation, indicating that individuals more likely to assign hostile intent to ambiguous social situations experienced greater momentary paranoid ideation. However, this relation was no longer significant when controlling for paranoid ideation. These results replicate previous findings regarding the relation between social cognitive bias and paranoid ideation and extend findings to indicate that these biases manifest in momentary experiences of paranoid ideation. Implications of current results will be discussed further at the time of presentation.

S45. EXAMINING THE RELATIONSHIP BETWEEN SCHIZOPHRENIA, CREATIVITY, AND COGNITIVE FUNCTIONING: INSIGHTS FROM THE REMOTE ASSOCIATES TEST

Hanna Kucwaj^{*1}, Bartłomiej Krocze², Zdzisław Gajewski³

¹SWPS University, ²Jagiellonian University in Cracow, ³Barbara Borzym Psychiatric Hospital

Background: The relationship between psychopathology and creativity has been the subject of debate for decades, with some researchers suggesting that mental disorders might be related to enhanced creativity. The findings on the relationship between creativity and schizophrenia remain ambiguous. We aimed to investigate this issue by applying the Remote Associates Test (RAT), which has been rarely used in clinical groups. The RAT allows us to not only compare general accuracy but also examine the pattern of errors, providing a deeper insight into potential differences in the process of generating creative ideas. In the RAT, participants are asked to find one word that is somehow related to each of three given words (e.g., 'hotel,' 'captain,' 'sky'; response: 'stars'). We sought to verify whether schizophrenia patients differ from healthy controls in their performance on this task in two respects: (1) general accuracy and (2) effectiveness in evaluating and rejecting incorrect associations. Importantly, we applied a fluid intelligence test to control for an important source of variation, as previous research has shown that creativity benefits from intelligence.

Methods: We administered the RAT to 68 schizophrenia patients and 75 healthy controls. To assess the ability to reject incorrect associations, we computed an incorrect response rate (the number of incorrect responses to all errors after accounting for general accuracy in the task). Additionally, in the patients' group, we evaluated symptom severity using PANSS-6 and ACE-III.

Results: After controlling for fluid intelligence, the patients and the healthy controls did not differ significantly in either general accuracy or incorrect response rate (p 's GREATER THAN .05). Within the patients' group, performance in the RAT did not correlate with symptom severity measured with PANSS-6 assessing positive and negative symptoms (p GREATER THAN .05). However, it exhibited a positive correlation with cognitive functioning measured using ACE-III ($p = .367$, $p = .002$).

Discussion: After adjusting for fluid intelligence, patients performed comparably to controls on a creative thinking task that assessed both divergent thinking (at the stage of idea generation) and convergent thinking (at the stage of rejecting invalid associations). The absence of correlations between the RAT performance and positive/negative symptoms, coupled with its significant relationship with the ACE-III score, suggests that cognitive functioning is vital for successful creative thinking.

S46. DAILY VARIATIONS IN INTENTION TO BE PHYSICALLY ACTIVE AND AFFECT IN PEOPLE WITH PSYCHOTIC DISORDERS

Valérie Chauvin*¹, Paquito BERNARD², Yannick FRANCILLETTE³, Sébastien GABOURY³, Kevin Bouchard³, Daniel Fulford⁴, Ahmed Jerome ROMAIN¹

¹University of Montreal, ²Université du Québec à Montreal, ³Université du Québec à Chicoutimi, ⁴Boston University

Background: Although physical activity is recommended for people with psychotic disorders, the majority are inactive, and their main barrier is low motivation. Intentions to be physically active is known to influence the level of motivation and physical activity, yet there is a gap between having the intention to be active and the actual practice of physical activity. Also, affect is known to influence motivation and physical activity. However, no studies have examined the relationship and interaction between intention and affect over time. One solution to expose this relationship is to use momentary ecological assessment (real-time data) probed on the participants' cell phones daily.

Methods: Preliminary analysis of a 4-week multicenter intervention study in which participants (aged 18-50) with a diagnosis of psychotic disorder played with an exergame ("Ocean Empire", mobile physical activity application) created to increase physical activity levels in this population. Using momentary Ecological Assessments, participants rated their intentions to be active and their affect twice a day on a 7-point visual analog scale. In the morning survey, participants ranked their intentions to be active during the day and their affect at the time of the survey, while they ranked their intentions to be active the following day and their affect in the evening survey.

Results: 4 adults (3 females, 1 male) with a mean age of 32.5 ± 6.0 years old with a diagnosis of psychotic disorder, with a mean body mass index of $28.23 \pm 6.5 \text{ kg/m}^2$ and they were all full-time workers. The response rate for the daily momentary ecological assessment was 73.43% ($\pm 11.51\%$) corresponding to a total of 181 completed ecological momentary assessment logs. Intention to be physically active on the same day ranked low with a mean range between 1,68 and 3,64 (± 1.61) in the morning, and the intention to be active the next day had a mean range between 2,60 and 3,75 (± 1.85). Three of the participants had slightly higher intention to be active the following day than during the same day (variation mean = 1.88 ± 0.44). Three of the participants ranked their affect as being mainly happy, awake, full of energy and calm both in the morning and evening without specific patterns in daily variation, while the other participant ranked low on all affect both in the morning and evening. No initial associations were found between affect and intentions to be active.

Discussion: Variation in affect and intention to be active varied on an individual level both between days and within the same day emphasizing the need for individualized physical activity approaches which would be time depending. Preliminarily, the relationship between affect and intentions to be active is still unclear in people with psychotic disorder. Time varying

network model and analysis using accelerometry will be performed to further verify the dynamic between affect, intentions to be active and physical activity.

S47. EXAMINING THE JOINT CONTRIBUTION OF TRAUMA AND ADVERSE NEIGHBORHOOD CHARACTERISTICS ON PARANOID IDEATION: A MULTI-METHOD APPROACH IN A TRANSDIAGNOSTIC SAMPLE

Imani Todd*¹, Ryan Orth¹, Laura Hemphill¹, Melanie Bennett², Jack Blanchard¹

¹*University of Maryland - College Park*, ²*University of Maryland School of Medicine*

Background: Paranoid ideation is common in psychosis and is associated with impairment (Fett et al., 2022; Pinkham et al., 2016). Multiple cognitive factors influence paranoid ideation including lack of belief flexibility and hostile attributions (Freeman et al., 2016; Pinkham et al., 2016). Separately, negative affect precedes and maintains later paranoid ideation (Ben-zeev et al., 2011). Research on what provokes these cognitive and affective biases highlights the influence of trauma and environmental stress (Freeman and Garety, 2014).

Traumatic experiences are a reliable risk factor for psychotic disorders and suspiciousness (Moffa et al., 2017). Prior literature examining trauma and paranoid ideation only uses broad indicators of positive symptoms or single-item assessments (Alameda et al., 2021). Additionally, this literature often examines trauma in isolation without regard for environmental-level factors.

Environmental research identifies two major facets that contribute to the development and maintenance of psychotic symptoms: neighborhood deprivation and crime (Wickham et al., 2014; Wilson et al., 2016). Population studies show that individuals who reside in deprived neighborhoods are more likely to experience increased paranoid ideation (Kirkbride et al., 2017; McElroy et al., 2019). Crime may also influence perceptions of threat and hostility and has been related to paranoid ideation (Vargas et al., 2020).

Aside from objective assessments of neighborhood deprivation and crime, neighborhood perceptions also impact paranoid ideation, above and beyond area-level assessments of neighborhood features (Newbury et al., 2017). Although trauma, neighborhood deprivation, and crime have been shown to impact paranoid ideation, few have examined these constructs in tandem. The current study seeks to examine the association between individual-level (i.e., trauma, neighborhood perceptions) and system-level (i.e., neighborhood deprivation and crime) factors and paranoid ideation. We hypothesize that the experience of more traumas, neighborhood perceptions of violence, deprivation, and area-level crime will be related to greater paranoid ideation. Additionally, we hypothesize that trauma history and neighborhood characteristics will jointly contribute to more severe paranoid ideation.

Methods: Data was collected from a transdiagnostic sample of adults with psychotic disorders and non-clinical participants. Paranoid ideation was assessed using the Revised Green Paranoid Thought Scale (Freeman et al., 2021). Trauma was measured using the Trauma History Questionnaire (Hooper et al., 2011). Neighborhood perceptions were measured using the Neighborhood Environmental Scale (Mujahid et al., 2007). The Area Deprivation Index (Kind et al., 2015) was used to assess neighborhood deprivation objectively. To measure area-level crime, CrimeRisk was used (Applied Geographic Solutions, 2020).

Results: Analyses supported our hypothesis that greater paranoid ideation was related to greater traumas ($r = .33$, $p < .01$) and neighborhood perceptions of violence ($r = .33$, $p < .01$), but not to objective indices of neighborhood deprivation or area-level crime. Regression analyses also revealed that both greater trauma ($\beta = .31$, $p < .01$) and neighborhood perceptions of violence ($\beta = -.30$, $p < .01$) predicted greater paranoid ideation above and beyond other demographic factors.

Discussion: Results indicated that trauma and perceived neighborhood violence jointly contributed to paranoid ideation. These results indicate the importance of considering both trauma history and neighborhood factors in understanding paranoid ideation. Additional results and implications will be discussed at the time of presentation.

S48. THE INFLUENCE OF EMOTION-BEHAVIOUR DECOUPLING ON CLINICAL AND FUNCTIONAL OUTCOMES IN PATIENTS WITH SCHIZOPHRENIA: FURTHER EVIDENCE FROM A CLUSTER ANALYSIS FOLLOWING THE RDOC APPROACH

Simon S. Y. LUI^{*1}, Kimberly K Y Yip², Ezmond S. L. Cheung¹, Raisie W K Wong¹, Cherry H. Y. Lam¹, Christy H. Y. Wong¹, Eunice Shing¹, Wing-Chung Chang¹, Eric Y. H. Chen¹, Pak C. Sham¹, Raymond C. K. Chan³

¹The University of Hong Kong, ²Castle Peak Hospital, ³CAS Key Laboratory of Mental Health, Institute of Psychology

Background: Emotion-behaviour decoupling refers to the failure to translate emotion into motivated behaviour. A recent longitudinal cluster analysis showed that emotion-behaviour decoupling and experiential pleasure deficits predicted clinical and functional outcome of schizophrenia. Research Domain Criteria (RDoC) framework advocated multiple measures to characterize schizophrenia patients, but our earlier analysis did not include working memory and clinical symptoms as clustering variables. To extend our earlier findings according to the RDoC perspective, we conducted this study using an independent sample, and adding working memory and clinical symptoms to emotion-behaviour decoupling as clustering variables. We aimed to characterize schizophrenia patients using emotion-behaviour decoupling and other measures, and to compare the difference in clinical and functional outcome between resultant clusters.

Methods: Our cross-sectional sample comprised 132 schizophrenia patients. Participants completed the Temporal Experience of Pleasure Scale (TEPS), Emotional Expressivity Scale (EES), and Clinical Assessment Interview for Negative Symptoms (CAINS). We also administered the Anticipatory and Consummatory Pleasure (ACP) Task and the Letter-Number Span Test (LNT). A two-stage hierarchical cluster analysis was used, with the TEPS, EES, CAINS-MAP, CAINS-EXP, LNT, and emotion-behaviour decoupling as the clustering variables. We validated the resultant clusters by comparing the between-cluster social functioning.

Results: We found a four-cluster solution. Cluster 1 and Cluster 3 both had low CAINS-MAP and EXP factors, but differed in TEPS and EES. Cluster 2 and Cluster 4 both had high CAINS-MAP and EXP factors, but Cluster 4 had the highest CAINS-MAP factor, and lowest TEPS-consummatory pleasure, and Cluster 2 had the weakness emotion-behaviour decoupling during wanting. Working memory was comparable among the four clusters. Upon validations, Cluster 2 and Cluster 3 had significantly lower functioning than the other clusters.

Discussion: Our findings suggested a modest role of emotion-behaviour decoupling in influencing schizophrenia patients' functional outcome. However, our findings supported the feasibility of characterizing schizophrenia patients using multimodal measures of negative symptoms and related constructs.

S49. COGNITIVE DIFFERENCES BETWEEN SCHIZOPHRENIA OFFSPRING WITH ADHD AND ADHD BORN TO HEALTHY PARENTS

Aitana Bigorra^{*1}, Elena De la Serna², Gisela Sugranyes³, Patricia Camprodon-Boadas³, Dolores Moreno⁴, Inmaculada Baeza³, Yamila Tosetti³, Sara Parrilla⁴, Covadonga Diaz-Caneja⁴, Josefina Castro-Fornieles³

¹*Institut Clinic de Neurociències, Hospital Clinic Universitari*, ²*Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)*, ³*Hospital Clínic de Barcelona*, ⁴*Hospital General Universitario Gregorio Marañón*

Background: While there has been wide agreement that schizophrenia is a neurodevelopmental disorder (Weinberger, 1987) the status of cognitive deficits as specific risk markers for schizophrenia remains uncertain (Mohn-Haugen et al., 2022). Given the high heritability of this condition (Rasic et al., 2014), one approach to exploring early markers of vulnerability to psychosis is to assess the first-degree relatives of individuals with schizophrenia.

Children and adolescents who are first-degree relatives of individuals diagnosed with schizophrenia may exhibit neurodevelopmental characteristics similar to those observed in young people diagnosed with attention deficit hyperactivity disorder (ADHD) (Keshavan et al., 2003). In fact, ADHD is the most prevalent form of psychopathology in schizophrenia offspring (SZoff), with rates ranging between 20-46% (De la Serna et al., 2021). Although some studies have described overlap in cognitive difficulties between youth-onset psychosis and ADHD (Karatekin et al., 2008, 2009; Karatekin and Asarnow, 1998), there are very few studies that have investigated the relationship between SZoff and ADHD.

The objective of this study is to compare the cognitive characteristics of a SZoff group with ADHD (SZoff-ADHD) to a group of children and adolescents diagnosed with ADHD (ADHD) but without a history of psychotic disorders in their first-degree relatives.

Methods: The participants comprised 22 SZoff-ADHD and 69 ADHD children and adolescents. The results of the Wechsler Intelligence Scale for Children-IV (WISC-IV) (Wechsler, 2005) and Conners' Performance Test (CPT-II) (Conners, 2000) were compared with mean comparison T-tests, following verification of the conditions for their application.

Results: Compared to the ADHD group, SZoff-ADHD obtained worse results in several subscales of the WISC-IV: Vocabulary ($t=3.25$, $p=0.002$), Block Design ($t=2.38$, $p=0.019$), Similarities ($t=2.30$, $p=0.002$), Digit Span ($t=3.32$, $p=0.001$), Letter-Number Sequencing ($t=2.76$, $p=0.007$), Matrix Reasoning ($t=2.37$, $p=0.02$), as well as in Verbal Comprehension ($t=2.67$, $p=0.009$), Perceptual Reasoning ($t=2.07$, $p=0.041$), Working Memory ($t=3.28$, $p=0.001$), and General Ability indices ($t=3.49$, $p=0.001$). In contrast, the ADHD group obtained worse results in Commissions ($t=3.51$, $p=0.003$) and d' ($t=3.12$, $p=0.005$) of the CPT-II.

Discussion: There are cognitive differences between ADHD and SZoff-ADHD: the SZoff-ADHD group scored lower on general cognitive measures related to abstract reasoning and

working memory, while ADHD individuals showed greater inhibition difficulties. These results suggest that although both groups have similar clinical characteristics (ADHD diagnosis), they likely exhibit specific neurodevelopmental alterations.

S50. OPPOSITE DIRECTION SPATIAL WORKING MEMORY BIASES IN PEOPLE WITH SCHIZOPHRENIA AND HEALTHY CONTROLS

James Gold^{*1}, Sonia Bansal¹, Benjamin Robinson¹, Alan Anticevic², Steven Luck³

¹MPRC, ²Yale University, ³U.C. Davis

Background: Recent research has shown that spatial working memory representations are unconsciously biased by prior trials such that current-trial responses are attracted to previous-trial responses (serial dependence). It is thought that these types of cross-trial biases result from different neural processes than those that mediate performance within a single WM trial. Data from single cell recordings suggest that WM representations are mediated by sustained firing of neurons that represent the to-be-remembered feature, which stops after the response is completed on that trial (1). Across-trial biases are thought to be mediated by short-term synaptic plasticity that can represent information after the cessation of sustained neural activity. The persistence of these synaptic changes from trial N-1 interact with the representation on trial N, causing the latter representation to drift towards the former. This opens a new window to examine how schizophrenia impacts both the sustained neural firing representing the current-trial target and longer-term synaptic plasticity that stores previous-trial information. Serial dependence effects are of special interest because the normal attractive bias is abolished in patients with NMDA receptor encephalitis, suggesting that this system may be implicated in mediating these longer-term cross trial effects.

Methods: 41 clinically stable people with schizophrenia (PSZ) and 32 demographically similar healthy controls (HCS) participated. We examined response accuracy in a single-item spatial working memory test with delay intervals of 0, 2, 4, or 8 seconds. The main question was whether the reported location on a given trial was influenced by the target location on the previous trial. Our main dependent variable was the bias index, which quantifies the extent to which the current-trial responses were biased toward or away from the previous-trial target.

Results: PSZ and HCs showed opposite-direction serial dependence bias effects: the bias became progressively more positive over increasing delays in HCS (attraction) and progressively more negative over increasing delays in PSZ (repulsion). HCS (attraction) and progressively more negative over increasing delays in PSZ (repulsion). A 2-way ANOVA with factors of Group and maintenance period delay yielded a significant Group X maintenance period interaction ($F [2.58, 186.21] = 3.95, p=0.013, \eta^2p=0.05$). The main effect of Group was also significant ($F [1, 72] = 33.22, p \text{ LESS THAN } 0.001, \eta^2p=0.32$). but the main effect of maintenance period was not ($F [2.58, 186.21] = 2.02, p=0.12, \eta^2p=0.27$). Post-hoc between-group comparisons were significant for the 2, 4, and 8 s delays. In PSZ, the magnitude of the repulsion bias correlated negatively with broad measures of cognitive ability and working memory capacity, suggesting that the bias measure is indexing a core process implicated in the broad cognitive impairment seen in schizophrenia.

Discussion: PSZ show a qualitative, opposite-direction alteration in the effects of previous trials on working memory. This stands in contrast to typical evidence of cognitive impairment where PSZ perform more poorly than HCs-- showing a quantitative performance difference. Qualitatively distinct differences in performance are extremely rare in psychopathology and may index a fundamental alteration in neural processing that could serve as a valuable

biomarker for pathophysiology and treatment development research. Such qualitative differences are uniquely important because they cannot be explained by poor attention, reduced motivation, or general intellectual impairments-- factors that complicated the interpretation of most cognitive findings. Importantly, NMDA encephalitis patients fail to show the repulsion bias seen in schizophrenia. Thus it is likely that the findings in PSZ suggest the impact of an additional process beyond reduced short-term synaptic plasticity. The results could be accounted for by a combination of reduced synaptic plasticity accompanied by unopposed long term neuronal adaptation effects that can result in repulsive biases as seen here.

S51. SEX DIFFERENCES IN SOCIAL COGNITION AMONG INDIVIDUALS WITH SCHIZOPHRENIA AND HEALTHY CONTROL PARTICIPANTS

Anja Vaskinn^{*1}, Torill Ueland², Ingrid Melle², Kjetil Sundet³

¹*Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital,*

²*University of Oslo and Oslo Univeristy Hospital,* ³*Univ of Oslo*

Background: There is limited evidence for sex differences in social cognition in schizophrenia, with conducted studies yielding mixed findings. Studies from the general population, however, indicate the possibility for a small female-advantage in social cognition. Since sex differences are present for other characteristics of schizophrenia, it is important to establish whether this is the case also for social cognition as it may serve as a basis for sex-specific treatment.

Methods: The presence of sex differences in social cognition among individuals with schizophrenia (n = 30-91) and in healthy controls (n = 71-185) was examined with five social cognitive tests. Emotion perception was assessed with Pictures of Facial Affect (PFA) and Emotion in Biological Motion (EmoBio). Social perception was measured with the Relationships Across Domains Test (RAD); ToM with the Movie for the Assessment of Social Cognition (MASC) and Hinting Task.

Results: Using two-way analyses of variance, we found a significant effect of group for all tests, in that healthy controls performed better than individuals with schizophrenia. Significant sex effects were present for PFA and Hinting Task, but we did not identify any significant interaction effects. In within-group independent samples follow-up t-tests, the only significant sex difference appeared among healthy controls for PFA.

Discussion: We found very few social cognitive sex differences. Although females had better facial emotion perception than males, this difference was statistically significant only among healthy controls. There were no significant sex differences for other social cognitive domains. The study did not find evidence for a general female advantage in social cognition. The results suggest that there is no need for sex-specific treatment of schizophrenia in terms of social cognition.

S52. FACIAL EXPRESSION AND EMOTION EXPERIENCE IN PATIENTS WITH SCHIZOPHRENIA

Shuaibiao Li^{*1}, Minyi Chu¹, Lingling Wang², Qinyu Lv¹, Simon S. Y. Lui³, Zhenghui Yi¹, Raymond C. K. Chan⁴

¹Shanghai Mental Health Center, ²Shanghai Normal University, ³The University of Hong Kong, ⁴Chinese Academy of Sciences

Background: Patients with schizophrenia (SCZ) usually exhibit blunted affect or disturbance of affect. However, it is still unclear whether these symptoms are caused by the deficits of the emotion experience process or the deficits of the emotion expression process. This study aimed to examine the relationship between emotional experience and emotional expression in patients with SCZ.

Methods: We recruited 28 SCZ patients and 27 healthy controls (HC). All participants watched three types of video clips: positive, neutral, and negative. Self-report measures of valence (unpleasant-pleasant) and arousal (deactivation-activation) were measured before and after viewing each movie clip. Moreover, we also used FaceReader to conduct real-time analysis of participants' facial expression while they were watching the video clips.

Results: Our results showed that there was no significant difference between SCZ and HC in the self-reported emotion valence of different types of video clips. However, SCZ patients' arousal after watching negative video clips was significantly lower than HC. HC also exhibited significantly higher facial expression of sadness while watching negative as compared to positive and neutral video clips. However, SCZ patients exhibited no significant difference among three different types of video clips.

Discussion: Patients with SCZ exhibited reduced emotional arousal and expressed reduced facial expression of sadness after watching negative video clips. These preliminary findings suggest that patients with SCZ may be impaired in the process of emotional expression and emotional experience of negative emotions.

S53. EMOTIONAL CONTAGION AND EMOTIONAL MIMICRY IN INDIVIDUALS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW

Mathilde Parisi*¹, Ludovic Marin², Tifenn Fauviaux², Aigoïn Emilie², Stéphane Raffard³

¹EuroMov Digital Health in Motion, ²EuroMov Digital Health in Motion, Univ Montpellier, IMT Mines Ales, ³Epsilon Laboratory Dynamic of Human Abilities and Health Behaviors, University of Montpellier

Background: Individuals with a diagnosis of schizophrenia were shown to have social interaction deficits. Two emotional processes: emotional contagion (i.e., the transfer of emotion between individuals) and emotional mimicry (i.e., the imitation of emotional expressions) are associated with several social benefits including increased social interaction quality. Therefore, this review aimed to report measures of emotional contagion and emotional mimicry in individuals with a diagnosis of schizophrenia.

Methods: We conducted a Pubmed, Web of Science, and PsycInfo database search. Inclusion and exclusion criteria were determined based on the definition of emotional contagion and emotional mimicry rather than on using specific terminology to consider every field of research. More specially, to be considered in the review, studies must propose an experimental procedure with a human or an avatar stimulus expressing emotions through facial expression, vocalization, posture, or movement. Then, searchers must have measured the emotional state (i.e., through self-reported emotion or psychophysiological reactions) for emotional contagion or the emotional expression (e.g., facial expressions) for emotional mimicry of the participant in response to that stimulus. In addition, participants should be separated into at least two

groups, one group of individuals with a diagnosis of schizophrenia according to the DSM-V and one control group.

Results: Forty-two studies were included in the review, among which six were emotional mimicry studies and thirty-six were emotional contagion studies. The current findings suggested decreased or inappropriate emotional mimicry in individuals with a diagnosis of schizophrenia. Relating to emotional contagion, results showed altered brain and psychophysiological activity in individuals with a diagnosis of schizophrenia whereas self-reported measures indicated no difference between groups. The relationships between emotional contagion, emotional mimicry, and psychotic symptom severity showed variability across studies whereas no association between antipsychotic dosage and both emotional mimicry and emotional contagion were found.

Discussion: This review highlights three major points. First, there are limitations to the existing literature, indeed, there are huge discrepancies in methodologies and results within and across fields of research in the measure of emotional contagion. In addition, there are yet very few emotional mimicry studies in schizophrenia making it difficult to generalize a conclusion. However, the studies included in this review still point out potential emotional contagion and emotional mimicry alterations in schizophrenia. As emphasized previously, emotional contagion and emotional mimicry are associated with many social benefits. However, when these phenomena are decreased or incongruent, which seems to be the case in individuals with a diagnosis of schizophrenia, it not only prevents them from taking advantage of the social benefits but also worsens the quality of the interaction. Consequently, while this review encourages future studies to continue assessing emotional contagion and emotional mimicry in schizophrenia to reinforce the literature, it is also clear that emotional contagion and emotional mimicry training should from now on be incorporated into the social rehabilitation of individuals with a diagnosis of schizophrenia. Guidelines for future studies and clinical implications are discussed.

S54. PROBING VISUAL DISTORTIONS IN THE PSYCHOSIS PRODROME USING VIRTUAL REALITY

William Palmer^{*1}, Fabian Mueller², Nan Wang², Leon Franzen³, Steven Silverstein⁴, Philipp Sterzer², Dominique de Quervain², Tyrone Cannon¹, Albert Powers¹

¹*Yale University*, ²*University of Basel*, ³*University of Lübeck*, ⁴*University of Rochester Medical Center*

Background: There has been a growing recognition for the role of distorted perceptual experiences that do not rise to the level of complex hallucinations during early stages of psychosis. Recent studies have reported that over 60% of patients with schizophrenia endorsed experiencing visual distortions. These distortions have been associated with conversion to full-blown psychosis as well as core clinical features such as delusions and hallucinations. According to the Predictive Coding hypothesis of psychosis, symptoms are the result of aberrant perceptual inference due to imprecise integration of prior expectation and incoming sensory evidence. However, it remains inconclusive whether visual distortions originate from abnormal perceptual sensitivity or heightened sensory expectations. Furthermore, conventional experimental tasks typically fall short of capturing the phenomenology of natural perceptual disturbances, potentially limiting the generalizability of the findings. To address these issues, we have developed two psychometric tasks to disentangle perceptual sensitivity from bias

using immersive virtual reality (VR) videos of commonly endorsed visual distortions in ecologically valid environments. We have also created a Visual Distortion Screener that unlike conventional self-report measures provides video examples of the phenomena of interest to facilitate accurate symptom reporting. The psychometric tasks and clinical measure are currently being tested in an in-person study of clinical high risk (CHR) for psychosis patients and healthy controls as well as an online general population study.

Methods: In an ongoing pilot study, 30 CHR and 30 healthy controls are being recruited from New Haven, Connecticut. All participants first complete a VR task measuring sensitivity and bias to perceiving an unknown visual distortion. Participants are placed in a 360° video scenario and instructed to report when they detect any change in their environment. During the initial 30 seconds of the task, no distortion is presented, allowing for false percepts as a measure of bias. Then, one of the six distortions is gradually faded in over 90 seconds and the first accurate identification is used as a measure of sensitivity. Next, participants are administered our novel Visual Distortion Screener, which presents video examples of the distortions and assesses experiences by examining frequency, duration, perceived control, and distress. Finally, participants complete a two-interval forced choice task that measures participant-specific sensitivity to perceiving a target distortion. Over the course of 60 trials, the distortion intensity will be adapted using the Quest+ algorithm to attain a 75% detection threshold estimate. Following the lab visit, participants complete self-report measures of personality traits, perceptual experiences, and delusional thinking. CHR patients are also followed for one year with the Scale of Psychosis-Risk Symptoms scores recorded at baseline, 6 months, and one year.

In the online study, 100 adult participants are being recruited via Prolific. These participants complete an online version of our screener and additional measures of psychosis symptoms. Data collected from this sample will be used to determine base rates of these distortions in a general sample as well as establish how visual distortions relate to subclinical psychotic-like symptoms.

Results: Data collection and analysis is currently ongoing for the pilot and online study. We plan to present initial findings of the occurrence of visual distortions in a general sample and the relationship between visual distortion intensity and subclinical psychotic-like symptoms. We hypothesize that elevated visual distortion intensity will be associated with higher subclinical psychotic-like symptoms.

Discussion: Our Visual Distortion Screener may improve symptom characterization by circumventing the need for a patient to translate verbal descriptions into mental images by directly providing visual examples. Once validated, our video scenarios and screener will be openly released online. Furthermore, identifying whether visual distortions are rooted in poor bottom-up perceptual sensitivity or strong cognitive bias, could advance our understanding of the underlying mechanisms of visual distortions. Our novel psychometric tasks also lay the groundwork for uncovering brain markers of visual distortions as neural responses to complex, naturalistic stimuli are known to differ from conventional experimental stimuli. Given previous findings that these symptoms emerge early and are hypothesized to contribute to delusion formation, improved symptom identification and mechanistic understanding may provide novel opportunities and targets for prevention.

S55. PSYCHOTIC AND NEURODEVELOPMENTAL DISORDERS: A DIAGNOSTIC ISSUE. VALIDATION OF SPAIDD-P "SYSTEMATIC PSYCHOPATHOLOGICAL ASSESSMENT FOR PERSONS WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES- PSYCHOTIC DISORDERS"

Luciana Forte*¹, Marco Bertelli¹, Felice Iasevoli², Annamaria Bianco¹

¹CREA (Research and Clinical Centre), Fondazione San Sebastiano, Misericordia di Firenze,

²Dipartimento di Neuroscienze e Scienze Riproduttive ed Odontostomatologiche, Università degli Studi di Napoli Federico II

Background: The global prevalence of Intellectual Disabilities (ID) ranges from 1% to 6%. The prevalence of autism spectrum disorder (ASD) reaches 2.8%. Around 35% of people with ID exhibit autistic traits, while up to 60% of those with ASD exhibit some degree of ID. The coexistence of ASD and ID configures the low-functioning ASD (LF-ASD), which increases the likelihood of developing psychiatric disorders in affected individuals by 4-5 times. The prevalence of psychotic disorders (PD) ranges from 3% to 8% and appears to rise with age, peaking between the ages of 33 and 44, although persons with ID can show an earlier onset than the general population. Non-affective psychosis is 10 times more common in individuals with ASD compared to the general population²⁰, with onset occurring in 30-50% of cases during childhood. 30% of persons with ID have an undiagnosed psychiatric disorder²². Distinguishing between ID, ASD, and other psychiatric disorders is challenging, especially for those in the schizophrenia spectrum, due to high co-occurrence rates and potential overlapping symptoms in people with LF-ASD. These disorders share alterations in cognitive functions, brain regions, neurotransmitter systems, and genes. In around half of cases, Problem Behaviours (PBs) represent Behavioral Equivalent (BEs) of psychopathological symptoms or clusters of symptoms. Specialized diagnostic tools can help identify BEs, enhancing knowledge of psychopathological features in people with ID/LF-ASD. The SPAIDD project (Systematic Psychopathological Assessment for people with Intellectual and Developmental Disabilities), is aimed to develop a complex array of psychopathological assessment tools for the diagnosis of major psychiatric disorders in persons with ID, based on behavioural observation, irrespective of the severity of cognitive impairment. The present paper reports the first results of a PhD research aimed at validating the SPAIDD-P, PD version of the SPAIDD battery, as well as evaluating its psychometric characteristics.

Methods: The first two versions of the SPAIDD-P were administered to a consecutive sample of 110 adults with ID and/or LF-ASD, who also underwent a comprehensive clinical and psychopathological assessment. Contemporarily, a systematic literature mapping on the presentation of PD in persons with ID/LF-ASD was carried out to identify possible new BEs to be included in the tool.

Results: Previous versions of SPAIDD-P demonstrated good internal consistency (Cronbach $\alpha \geq .6$) and a significant correlation between clinical diagnoses and the tool diagnostic scores (Pearson's $r = .280$; $p \leq .01$). Three factors, hallucinatory, delusional, and paranoid, explained 50% of the tool score variance, unaffected by gender, age, ID severity, co-occurrence of ASD. These processes allowed to produce a new checklist.

Discussion: SPAIDD-P seems to be a valid tool for assessing psychotic disorders in people with ID / LF-ASD due to its good psychometric features. The revised SPAIDD-P includes 24 items, each corresponding to a symptom or cluster of symptoms for diagnosis according to DSM-5 and ICD-11 criteria. It identifies Delusional Disorder, Brief Psychotic Disorder, Schizophreniform Disorder, Schizophrenia, and Personality Disorders.

S56. SELF-RATED EMPATHY AND COMPASSION IN SCHIZOPHRENIA

Federica Klaus*¹, Rebecca Daly¹, Ellen Lee¹, Lisa Eyster¹

¹*University of California - San Diego*

Background: People with schizophrenia (SZ) experience lower levels of social functioning than people without (HC). Impairments in social functioning cause significant disability, hindering recovery. Most mental health research is focused on deficits, while a strength-based, recovery-oriented approach focusing on positive psychological traits could improve well-being.

Positive psychological traits include compassion, self-compassion and empathy (EC), which can be considered to enhance social functioning. Higher levels of EC are associated with better well-being, more positive affect, less depressive symptoms, and better mental health. In SZ, most studies point to reduced participant-reported aspects of empathy compared to HC; few studies have compared compassion or self-compassion between SZ and HC, with one study observing lower levels of compassion and self-compassion in SZ vs HC. Within SZ, a relationship of more self-compassion with fewer symptoms of SZ and better physical well-being was observed. To our knowledge, the level and correlates of participant-reported compassion, self-compassion and empathy in SZ and how this differs from matched HC have not been elucidated in the same sample. We hypothesized lower levels of self-rated EC in SZ vs HC and that higher EC would be related to higher resilience and happiness and lower depression particularly in the SZ group

Methods: In a cross-diagnostic, observational approach, group differences in participant-reported levels of compassion (Santa Clara Brief Compassion Scale score), self-compassion (Neff Self-Compassion Scale) and empathy (composite of empathy related items from SD-WISE) in a dataset of 201 people (115/86 (HC/SZ, age range 29-73 years, age- and gender-matched)) were compared. Levels of resilience (Connor Davidson Resilience Scale) and depression and happiness (CESD) were correlated with EC measures. Linear mixed models controlled for age and gender. All tests are two-sided with $\alpha=0.05$.

Results: The mean (SD) age of participants was 52.3 (11.6) years, 53% female, and education was 16.6 (2.0)/13.8 (2.4) years. The racial/ethnic distribution was 60% White, 11% Black/African American, 27% Hispanic, 4% Asian, and 3% More than One Race. Partially in line with our hypotheses, levels of self-rated self-compassion ($F(1,164)=10.3$, $p=0.002$) and empathy ($F(1,172)=38.1$, $p < 0.001$) were lower in SZ vs HC, with no differences in compassion towards others ($F(1,174)=1$, $p=0.31$). While significant in both groups, correlates were generally stronger in HC vs SZ, including a stronger positive relationship of resilience and happiness with self-compassion and of resilience with empathy, and a stronger negative relationship of depression with self-compassion.

Discussion: Our hypothesis on differential experiences of EC between groups is supported, while on the direction of significant moderator's influence is not. Potentially the SZ group could benefit from interventions to increase resilience, happiness and reduce depression to boost the experience of positive psychological mechanisms. Understanding subjective perceptions of EC and specifically self-compassion could help to improve social functioning in SZ. Interventions to increase self-compassion might reduce perceptions of low self-efficacy, counter defeatist beliefs about social processes and increase positive affect. Specifically in SZ, reduction in defeatist beliefs have been shown to be linked to improved functioning. Ideally, these findings would advance the existing research on EC as positive psychological traits that foster wellbeing and allow development of novel EC-focused interventions to increase well-being in SZ.

S57. UNDERSTANDING THE DIMENSIONS OF SOCIAL COGNITION IN AUTISM SPECTRUM AND SCHIZOPHRENIA SPECTRUM DISORDERS

Ayesha Rashidi*¹, Lindsay Oliver², Colin Hawco¹, George Foussias¹, Robert Buchanan³, Anil Malhotra⁴, Meng-Chuan Lai², Aristotle Voineskos¹, Stephanie Ameis¹

¹*Centre for Addiction and Mental Health, University of Toronto*, ²*Centre for Addiction and Mental Health*, ³*Maryland Psychiatric Research Center, University of Maryland School of Medicine*, ⁴*Zucker Hillside Hospital, Feinstein Institute for Medical Research*

Background: Individuals with autism spectrum disorder (autism) or schizophrenia spectrum disorders (SSDs) exhibit greater deficits in social cognition compared to those without these conditions (i.e., typically developing controls, TDCs). Studies have shown that these social cognitive deficits severely impair psychosocial functioning and quality of life, however, the underlying mechanism behind this impairment is poorly understood. To better determine the effects of social cognition on mental health symptoms and functioning, we aim to examine the underlying factor structure related to social cognitive performance across a transdiagnostic dataset, including participants with autism and SSDs.

Methods: This study utilizes data from two harmonized NIMH-funded RDoC studies, including n= 100 autism (aged 16-35 years), 276 SSDs, and 209 typically developing controls (TDCs) (SSDs/TDC: aged 18-55 years). All participants completed a variety of validated assessments including social cognitive (e.g., ER-40, TASIT-R, RMET, Empathic Accuracy), neurocognitive (e.g., MCCB), clinical, and functional measures (e.g., Birchwood Social Functioning Scale, BSFS). Initial group-wise comparisons were carried out to examine performance characteristics across groups. Structural equation modeling was then used to test whether social cognitive measures acquired across a transdiagnostic dataset are consistent with a two-factor model including a lower-level and higher-level factor, as found in SSDs/TDCs.

Results: Group-wise comparisons revealed significant between-group differences in social cognitive performance on all tasks (p LESS THAN 0.001). Lower scores were consistently found in SSDs compared to controls (p LESS THAN 0.001), whereas autistic-control differences were limited to those found on TASIT-2 (simple and paradoxical sarcasm) and TASIT-3 Lies subscales (p LESS THAN 0.001), and ER-40 (p LESS THAN 0.01). Notably, autistic individuals outperformed those with SSDs in most tasks (all p LESS THAN 0.001), except ER-40, TASIT-1, TASIT-3-Lies. The hypothesized two-factor social cognition model, comprising a lower-level "simulation" factor (e.g., emotion detection) and higher-level "mentalizing" (e.g., theory of mind) factor exhibited an adequate fit in our transdiagnostic sample ($\chi^2 = 40.53$, $df = 13$, $P \text{ LESS THAN } 0.001$, $CFI = 0.979$, $TLI = 0.966$, $RMSEA = 0.06$, $SRMR = 0.03$).

Discussion: Preliminary findings in this sample reveal a pattern indicating broader impairments across social cognitive tasks in SSDs than autism. Autistic individuals displayed selective impairments, indicating a more circumscribed impairment on low and high-level social cognitive tasks at the group level. Despite disorder-specific patterns, a transdiagnostic two-factor social cognitive model suggests a common structure of social cognition, including separate simulation and mentalizing factors. However, further investigation of the group-specific models and related fit measures is required to fully characterize the complexity and variability of social cognitive processes across groups. The anticipated results of this study will enhance our understanding of the overlapping nature of social cognitive impairments in autism

and SSDs. The study's findings, especially efforts to establish a transdiagnostic social cognition model, serve as an important foundational step to facilitate future research to develop targeted interventions and enhance the quality of life for individuals affected by these disorders.

S58. LONG-TERM COGNITIVE FUNCTION IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: LONGITUDINAL CHANGES 10 TO 20 YEARS AFTER FIRST DIAGNOSIS

Marie Starzer*¹, Helene Gjervig Hansen², Nikolai Albert³, Carsten Hjorthøj⁴, Merete Nordentoft⁵, Louise Birkedal Glenthøj⁶

¹Gentofte University Hospital, University of Copenhagen, ²Copenhagen Research Centre for Mental Health, University of Copenhagen, ³Copenhagen Research Center for Mental Health – CORE, ⁴Copenhagen University Hospital, Mental Health Center Copenhagen, ⁵Mental Health Center Copenhagen, University of Copenhagen, ⁶Copenhagen Research Center for Mental Health (CORE), Mental Health Center Copenhagen, AND University of Copenhagen, Faculty of Social Sciences, Department of Psychology,

Background: Cognitive deficits are a core feature of schizophrenia and are closely associated with poor functional outcomes. While a lot of research has focused on cognitive development, long-term results are scarce, and it remains unclear if cognitive deficits progress over time or remain stable. Determining patients at increased risk of progressive worsening might help targeted neurocognitive remediation approaches.

Methods: This 20-year follow-up study examined the neurocognitive outcomes of 156 participants from the OPUS I trial. Neurocognition was assessed using the brief assessment of cognition in schizophrenia at the 10- and 20-year follow-up, allowing us to examine changes in neurocognition over a 10-year period during the later course of illness.

Results: We found that 30.5% of patients have a declining course of neurocognition, 49.2% have a stable course of neurocognition, and 20.3% experience improvements in neurocognition. Good cognitive functioning at the 20-year follow-up was significantly associated with higher levels of social functioning while increasing experiential negative symptoms were significantly correlated to cognitive worsening. Older age at inclusion and low level of education (below 10 years) predicted declining neurocognition, while cannabis cessation after the 10-year assessment and early remission predicted improved executive functioning.

Discussion: Our findings support the notion of different schizophrenia subtypes with varying trajectories and emphasize the need to examine cognition individually and not as a group mean, because the course differs between patients. Neurocognitive impairment at the 20-year follow-up was associated with other poor outcomes, highlighting the importance of treatments to improve neurocognition in patients with schizophrenia spectrum disorders. Since cognitive remediation therapy has been proven very successful, this treatment should be prioritized for patients at risk of cognitive decline.

S59. IDENTIFYING PROTEIN MARKERS ASSOCIATED WITH ECT IN SCHIZOPHRENIA PATIENTS: A PRELIMINARY STUDY

Sunghyun Park*¹, Minah Kim², Jun Soo Kwon²

¹Seoul National University Hospital, ²Department of Psychiatry, Seoul National University College of Medicine

Background: Electroconvulsive therapy (ECT) is an effective treatment for treatment-resistant schizophrenia, though underused due to social stigma, resource demands, and potential side effects like memory loss. Biomarkers that mediate ECT response could lead to less invasive alternatives and enable more targeted treatments. While biomarker research in depression is well-established, it is limited in schizophrenia.

Serum proteomic analysis is a promising approach due to its accessibility and ability to reflect rapid biological changes from ECT. Prior studies have shown serum BDNF and proBDNF/BDNF ratio changes in schizophrenia patients post-ECT, correlating these with treatment response and brain structural changes.

This study investigates serum proteomic profiles in schizophrenia patients undergoing ECT and pharmacotherapy, versus pharmacotherapy alone, aiming to identify ECT-specific changes. This could enhance our understanding of ECT's mechanisms and support predictive models for treatment response.

Methods: This study, conducted at Seoul National University Hospital between June 2018 and December 2022, involved a total of 65 patients diagnosed with schizophrenia or schizoaffective disorder. The participants were divided into two groups: 34 patients underwent electroconvulsive therapy (ECT) and medication treatment while 31 received medication-only treatment during the same period. The ECT group received bitemporal brief-pulse ECT 2-3 times per week, totaling 8-20 sessions. Psychiatric medications were continued as before, with necessary adjustments made based on clinician's decision. Clinical assessments, including the Positive and Negative Syndrome Scale (PANSS), and blood sampling were conducted before the start and within one week after the end of ECT treatment for the ECT group, and at recruitment and 4 weeks later for the medication-only control group. After removing abundant proteins, label-free quantification was performed using liquid chromatography-tandem mass spectrometry.

Results: A total of 1130 proteins were quantified. Among these, 112 proteins exhibited significant changes in expression levels after ECT in the ECT group. Notably, 106 of these proteins showed changes exclusive to the ECT group, with no corresponding changes observed in the medication control group. Pathway analysis revealed that these proteins were associated with pathways related to the innate immune system, complement cascade, and hemostasis, indicating an overrepresentation of these pathways in the response to ECT. Further analysis showed that among the 106 differentially expressed proteins, changes in three specific proteins – Podocalyxin (PODXL; $r=0.0856$), Insulin-like Growth Factor 2 (IGF-2; $r=0.2032$), and Biglycan (BGN; $r=0.3509$) – were significantly positively correlated with reductions in PANSS (Positive and Negative Syndrome Scale) scores.

Discussion: These results provide insights into the specific protein changes associated with ECT in schizophrenia spectrum disorders, highlighting potential biomarkers and molecular pathways implicated in the therapeutic response to ECT.

S60. CLASSIFYING SCHIZOPHRENIA WITH MACHINE LEARNING ALGORITHMS: A META-ANALYTIC INVESTIGATION OF TASK-BASED NEUROIMAGING DATA

Chao Yan^{*1}, Xuan Wang², Peng-yuan Yang³, Zheng Xia⁴, Xin-lu Cai⁵, Yi Wang², Sze Kwok⁶, Raymond Chan²

¹Key Laboratory of Brain Functional Genomics (MOE and STCSM), Shanghai Changning-ECNU Mental Health Center, School of Psychology and Cognitive Science, East China Normal University, ²Neuropsychology and Applied Cognitive Neuroscience Laboratory; CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, ³Department of Psychology, University of Chinese Academy of Sciences, Beijing, China e Social and Health psychology, Maastricht University, ⁴Key Laboratory of Brain Functional Genomics (MOE and STCSM), Affiliated Mental Health Center (ECNU), School of Psychology and Cognitive Science, East China Normal University, ⁵Institute of Brain Science and Department of Physiology, School of Basic Medical Sciences, Hangzhou Normal University, ⁶Phylo-Cognition Laboratory, Division of Natural and Applied Sciences, Data Science Research Center, Duke Kunshan University, Kunshan

Background: Schizophrenia (SCZ) poses a complex and heterogeneous challenge for researchers seeking reliable biomarkers to enhance diagnostic accuracy. The advent of machine learning (ML) techniques has provided opportunities for discovering biomarkers linked to SCZ through task-related fMRI (t-fMRI) designs. In the present study, we aimed to assess the efficacy of this approach by conducting a meta-analysis of task-related fMRI (t-fMRI) studies utilizing a bivariate model.

Methods: There were 30 papers, encompassing 31 studies, identified. We used the bivariate model proposed by Reitsma to conduct a meta-analysis, assuming that sensitivity and specificity followed a binomial normal distribution. To evaluate the possibility of publication bias, we conducted the Deek's test that examines the significance of funnel plot asymmetry. To investigate the impact of various factors on the chosen classification performance indicators, we conducted moderator analyses on those factors such as neuropsychological domains, demographic factors, ML approach-related factors, classification algorithm used, as well as clinical factors.

Results: We observed a notable overall sensitivity of .83 and specificity of .82 in t-fMRI studies. Notably, the classification performance was influenced by neuropsychological domains, where selective attention exhibited significantly higher specificity compared to working memory ($\beta = 0.98$, $z = 2.11$, $p = .04$). T-fMRI studies on selective attention had higher sensitivity and specificity than sMRI studies (Sensitivity: $\beta = .87$, $z = 3.77$, $p < .001$; Specificity: $\beta = .76$, $z = 3.24$, $p = .001$) and higher specificity than r-fMRI studies ($\beta = .79$, $z = 3.38$, $p = .001$). Moreover, studies involving older, chronic SCZ patients reported higher sensitivity ($p < .015$) and specificity ($p < .001$) than those involving younger, first-episode patients or high-risk individuals for psychosis. Furthermore, we identified a positive association between the severity of negative symptoms and the specificity of the classification model ($\beta = 7.19$, $z = 2.20$, $p = .03$).

Discussion: In summary, these findings underscore the promise of utilizing task-based fMRI data in conjunction with machine learning techniques to pinpoint biomarkers associated with symptom outcomes in SCZ. This presents a hopeful path toward enhancing diagnostic accuracy and treatment efficacy. Future endeavors in ML classification should carefully address considerations such as algorithm selection, data quality and quantity, and issues related to generalization.

S61. THalamo-CORTICAL WHITE MATTER CONNECTIVITY AS AN INDICATOR OF ELECTROCONVULSIVE THERAPY RESPONSE IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDER

Minah Kim^{*1}, Hyungyou Park², Jun Soo Kwon³

¹Seoul National University Hospital, ²Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, ³Department of Psychiatry, Seoul National University College of Medicine, Department of Brain and Cognitive Sciences, Seoul National University,

Background: Electroconvulsive therapy (ECT) is an effective treatment for patients with treatment resistant schizophrenia spectrum disorders (SSD). However, understanding of underlying mechanisms for ECT response has not yet been sufficient in addition to lack of knowledge regarding the target for region specific neuromodulation. Therefore, we investigated thalamo-cortical white matter (WM) connectivity as an indicator of ECT response in patients with SSD.

Methods: A total of 26 SSD patients and age-, sex-matched 28 healthy controls (HCs) underwent diffusion tensor imaging (DTI) to examine the probabilistic tractography of thalamo-cortical WM connectivity. DTI recordings were performed twice before (T1) and after (T2) the course of ECT (i.e., 1-2 months interval) in SSD group, and data were compared across time and groups (i.e., SSD vs. HCs). Relationship of change in thalamo-cortical WM connectivity and symptomatic improvement by ECT was explored in SSD patients.

Results: At T1, SSD patients showed lower thalamo-lateral prefrontal cortex WM connectivity and higher thalamo-parietal cortex (PC) WM connectivity than in HCs. At T2, difference of thalamo-PC WM connectivity shown at T1 was disappeared between SSD patients and HCs. In SSD patients, there was significant decrease of thalamo-PC WM connectivity between T1 and T2. In addition, change in thalamo-PC WM connectivity was significantly associated with improvement in Positive and Negative Syndrome Scale total and Clinical Global Impression-Severity scores in SSD patients.

Discussion: The current study results suggest that decrease in thalamo-PC WM connectivity can be an indicator of ECT response in SSD patients. Furthermore, PC may be a future target for region specific neuromodulation in patients with treatment resistant SSD.

S62. INSULIN RESISTANCE IN SCHIZOPHRENIA: IS IT RELATED TO GUT-BRAIN AXIS?

Manuel Couce-Sánchez^{*1}, Gonzalo Paniagua¹, Leticia González-Blanco¹, Ainoa García-Fernández², Clara Matínez-Cao², Francesco Dal Santo¹, Paula Zurrón¹, Julio Bobes², María Paz García-Portilla¹, Pilar Alejandra Sáiz¹

¹Central University Hospital of Asturias, ²University of Oviedo

Background: Glucose metabolism is impaired in patients with schizophrenia (SZ), even in naïve patients with psychosis (Xiu et al. 2023; Greenhalgh et al. 2017), but the causes remain unclear. As gut dysbiosis (imbalance of intestinal microbiota composition) seems to play a role in the etiopathology of SZ (Shi et al. 2023) and has also been shown in general population with

insulin resistance (Kant et al. 2022), we aim to find out if alterations in gut-brain axis play a role in glucose metabolism in SZ.

Gut dysbiosis can be evaluated indirectly through lipopolisaccharide binding protein (LBP), a plasmatic marker of increased gut permeability and bacterial translocation from gut to blood (Severance et al. 2013).

Methods: Cross-sectional study of 101 patients [mean age = 41.0 ± 12.08 , range = 18-67; males = 62 (61.4%)] with diagnosis (DSM-5) of SZ (without antidiabetics or a diagnosis of diabetes) recruited from their mental health outpatient clinics in Oviedo (Spain).

Assessment:

- Plasmatic glucose (mg/dL), insulin ($\mu\text{U/mL}$), HOMA-IR (Homeostasis model assessment: insulin resistance); insulin resistance = $\text{HOMA-IR} \geq 3.0$.
- Plasmatic LBP ($\mu\text{g/mL}$), C-reactive protein (CRP; mg/dL).
- International Physical Activity Questionnaires (IPAQ: low activity vs moderate/vigorous), Mediterranean Diet Adherence Score (MEDAS), toxic habits (alcohol use/smoking/cannabis).
- CGI, Chlorpromazine equivalent doses (CPZ-ED), body mass index (BMI) (kg/cm^2).

Statistics: Spearman correlation, t Student, χ^2 , stepwise logistic regression.

Results: 54 patients (53.5%) showed insulin resistance, with a mean HOMA-IR = 4.14 ± 3.3 , while 36 people (35.6%) had increased gut permeability (LBP GREATER THAN $15 \mu\text{g/mL}$).

We found relation between HOMA-IR values and BMI ($r = 0.545$, $p \text{ LESS THAN } 0.001$), but not with age, sex, length of illness, CRP, CGI, CPZ-ED and MEDAS. A partial correlation for HOMA-IR and LBP controlled by BMI was near to statistical signification ($r=0.197$, $p=0.060$).

Patients with insulin resistance had higher levels of LBP ($t = 3.754$, $p \text{ LESS THAN } 0.001$) and BMI ($t = 4.570$, $p \text{ LESS THAN } 0.001$). Insulin resistance was more prevalent in people with low physical activity based on IPAQ ($\chi^2 = 7.944$, $p = 0.005$) but no differences were found by other studied variables.

A logistic regression analysis was performed for insulin resistance considering LBP, BMI and IPAQ as independent variables. The overall regression was statistically significant (Cox-Snell $R^2 = 0.352$, $p = 0.01$), including all variables in the model: LBP (OR = 1.25, $p \text{ LESS THAN } 0.001$), BMI (OR = 1.18, $p \text{ LESS THAN } 0.001$) and high/moderate physical activity (OR = 0.24, $p = 0.013$).

Discussion: In our sample of SZ patients there is a high prevalence of increased gut permeability and insulin resistance, as previously described (Xiu et al., 2023; Greenhalgh et al., 2017; Shi et al., 2023), so gut permeability seems to be a risk factor for developing insulin resistance in patients with SZ, as well as BMI and low physical activity.

S63. SPARING OF NATURAL LANGUAGE PROCESSING DEFICITS IN SCHIZOTYPAL PERSONALITY DISORDER COMPARED WITH SCHIZOPHRENIA: NEGATIVE SYMPTOM AND SUPERIOR TEMPORAL GYRUS VOLUME CORRELATES

Erin A. Hazlett^{*1}, Mary Kowalchuk², Alessia McGowan², Sean Hollander², Elen-Sarrah Dolgopolskaia², Katelyn N. Challman¹, Agrima Srivastava², Chi C. Chan², M. Mercedes Perez-Rodriguez², M. Mehmet Haznedar¹, Margaret M. McClure², Stephen Heisig², Kim E. Goldstein², Philip Szeszko¹, Cheryl Corcoran¹

¹*Icahn School of Medicine at Mount Sinai and James J. Peters VA*, ²*Icahn School of Medicine at Mount Sinai*

Background: Thought disorder and disorganized speech occur across the schizophrenia (SZ) spectrum, including deficits in syntactic complexity (e.g., poverty of speech) and semantic coherence (e.g., perseveration, tangentiality, looseness of associations). Traditionally, this has been assessed using clinical assessments. More recently, these metrics are being studied using automated methods of natural language processing (NLP). While previously examined in SZ, clinical high risk (CHR) for psychosis, and psychometric schizotypy, this is the first study to examine: (a) NLP across the SZ spectrum, including healthy controls (HCs), individuals with schizotypal personality disorder (SPD), and recent-onset SZ patients and (b) how NLP is correlated with clinical symptom severity and volume of key language brain regions across the spectrum. The four brain regions were: Pars Opercularis/Brodmann area (BA)44 (language production); Pars Triangularis/BA45 (semantic processing); Pars Orbitalis/BA47 (language processing); and Superior Temporal Gyrus (STG)/BA22 (auditory).

Methods: Participants in this ongoing study were 41 HCs, 26 individuals with SPD, and 26 SZ patients. The participants were rigorously screened and assessments included SCID-5 and SIDP structured diagnostic interviews and the Positive and Negative Syndrome Scale (PANSS).

NLP: Naturalistic speech samples were obtained using an open-ended 45-min narrative research interview identical to our prior SZ and CHR studies. Interviews were then transcribed using a HIPAA-compliant transcription service. Next, the text from the interview was processed following our standard NLP pipeline. Part-of-Speech tags, phrase length, and Bidirectional Encoder Representations from Transformers (BERT) embeddings were generated for analysis of complexity and coherence. Groups were compared using ANCOVA (covarying age/sex) and follow-up Tukey HSD post-hoc tests.

MRI: All participants received a 3T MRI scan (Siemens MAGNETOM). Cortical reconstruction and volumetric segmentation were performed on MP-RAGE using Freesurfer image-analysis software. Bivariate-correlations were calculated to examine associations between NLP, clinical symptom severity, and volume of the four key language brain regions in the left and right hemisphere.

Results: SZ patients showed: a) reduced complexity compared with HC (p LESS THAN 0.08) and SPD (p LESS THAN 0.03) groups, 1-way ANCOVA, p=0.05. Interestingly, across the SPD+SZ groups, reduced complexity was associated with smaller left but not right STG volume (p LESS THAN 0.05). 2) greater coherence, consistent with perseveration, compared with both HC (p LESS THAN 0.001) and SPD (p LESS THAN 0.02) groups (SPD group was intermediate and did not differ from HCs). Importantly, across the SPD+SZ groups, greater coherence was associated with greater negative but not positive symptom severity (p LESS THAN 0.03).

Discussion: This is the first study to show that SZ patients have reduced syntactic complexity compared to individuals with SPD. Prior work has shown SZ patients have reduced complexity compared with HCs. Our finding of reduced complexity being associated with smaller left STG volume across the SZ spectrum is novel and consistent with prior work showing left

hemisphere dominance for language, and SZ-related STG volume deficits which are less marked in SPD. SZ patients also had greater coherence, consistent with perseveration, compared with both HC and SPD groups and this was associated with greater negative (deficit) symptom severity. These findings suggest that in SPD, sparing of language and STG volume deficits may serve as protective factors in mitigating psychosis. Next steps include continuing to grow our sample size, examining prosody (e.g., intonation), and examining whether NLP at baseline predicts functional outcome and changes in brain function/connectivity/volume, and cognition at 18-month follow-up.

S64. ALTERATIONS OF ASTROCYTES IN THE MEDIAL ORBITOFRONTAL CORTEX AND COGNITIVE FUNCTIONS IN PATIENTS WITH SCHIZOPHRENIA

Sunah Choi^{*1}, Minah Kim², Sang Soo Cho¹, Woori Choi¹, Harin Oh¹, Jongrak Kim¹, Jungha Lee¹, Su-Jin An¹, Jun Seo Hwang¹, Yun-Sang Lee², In Chan Song², Sun-Young Moon³, Silvia Kyungjin Lho⁴, Jun Soo Kwon¹

¹Seoul National University College of Natural Sciences, ²Seoul National University College of Medicine, ³Seoul National University Bundang Hospital, ⁴Seoul Metropolitan Government-Seoul National University Boramae Medical Center

Background: The underlying mechanism of cognitive and negative symptoms in schizophrenia remains poorly understood. Studies suggested that changes in the medial orbitofrontal cortex (mOFC) and abnormal astrocytes may contribute to the development of the symptoms. However, there is inconsistency in in vivo findings using previous imaging targets. Reactive astrocytes upregulate monoamine oxidase B (MAO-B) expression, and MAO-B binding positron emission tomography (PET) enables the in vivo imaging of astrocyte reactivity. In this study, we aimed to investigate the relationship between cognitive and negative symptoms and reactive astrocytes in the mOFC in patients with schizophrenia using MAO-B binding PET.

Methods: This study analyzed MAO-B binding [18F]THK5351 PET data from 33 patients with schizophrenia and 35 age- and sex-matched healthy controls (HCs). We tested group differences in standardized uptake value ratio (SUVr) in the mOFC and their association with Wisconsin Card Sorting Test (WCST) performance scores and Positive and Negative Syndrome Scale (PANSS) negative symptom scores.

Results: Schizophrenia patients showed higher SUVr in the bilateral mOFC compared to HCs (left, $t = -2.01$, $p = 0.048$; right, $t = -2.04$, $p = 0.045$). Negative correlations were observed between SUVr and WCST performance scores (left, $r = -0.33$, $p = 0.006$; right, $r = -0.26$, $p = 0.032$). The correlation between SUVr and PANSS negative symptom scores was not statistically significant.

Discussion: These findings provide evidence supporting an association between reactive astrocytes in the mOFC and cognitive functioning including executive function in schizophrenia. Our study suggests a potential biomarker for the neurobiological mechanism underlying cognitive symptoms in schizophrenia.

S65. VALIDATION OF DIAGNOSTIC AND PREDICTIVE FMRI BIOMARKERS IN SCHIZOPHRENIA

Jose Rubio*¹, Todd Lencz², Hengyi Cao³, Elvisha Dhamala⁴, Nina Kraguljac⁵, Juan Gallego², Guillermo Horga⁶, John Kane⁷, Anil Malhotra⁸

¹Northwell Health, ²The Zucker Hillside Hospital, ³Feinstein Institute for Medical Research and Zucker Hillside Hospital, ⁴Feinstein Institutes for Medical Research, ⁵The Ohio State University, ⁶Columbia University and New York State Psychiatric Institute, ⁷The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, ⁸The Feinstein Institutes for Medical Research

Background: fMRI readouts of function in the striatum have emerged as promising diagnostic and predictive biomarkers in schizophrenia. For instance, the Functional Striatal Abnormalities (FSA) score was developed to classify individuals with schizophrenia vs healthy controls using inputs from striatal functional connectivity and striatal fALFF, two measures derived from resting state fMRI. In a rigorous internal validation, the FSA demonstrated high diagnostic accuracy (GREATER THAN 80%) and there were data to suggest that it could predict treatment response. Separately, our team developed another biomarker, the Striatal Connectivity Index (SCI), a measure that summarizes functional striatocortical connections relevant to treatment response. In the initial publication, the SCI was externally validated in a separate cohort of 40 individuals, which yielded classification accuracy of ultimate treatment response of 78%. To bring these biomarkers closer to clinical application, it is critical to demonstrate that they do replicate in unseen data. Here we are presenting replications of the diagnostic and predictive ability of the FSA, and of the predictive performance of the SCI in novel datasets.

Methods: Using the original scripts, we calculated FSA scores in the Human Connectome Project for Early Psychosis dataset, which includes individuals within 5 years of a diagnosis of a psychotic disorder (n=101) and healthy controls (n=51). This dataset has different demographic and MRI acquisition characteristics to the FSA development dataset. Similarly, and also using the original scripts, we calculated SCI values from scans of individuals participating in the Human Connectome Project for Early Psychosis, as well as in a separate cohort of 97 individuals with first episode psychosis who were subsequently treated with risperidone or aripiprazole for 12 weeks, and for whom treatment response could be determined prospectively. We tested classification accuracy for cases vs controls in the Human Connectome Project dataset for the FSA (diagnostic biomarker performance) by the area under the curve (AUC) in receiver operator characteristic (ROC) curves. Similarly, we attempted to replicate the prediction of treatment response by the FSA and SCI in the treatment cohort by calculating AUCs for ROCs that used a categorical definitions of treatment response in agreement with our previous work.

Results: The FSA had good/excellent diagnostic discrimination (AUC=75.4%, 95%CI=67.0%-83.3%; in non-affective psychosis AUC=80.5%, 95%CI=72.1-88.0%, and in affective psychosis AUC=58.7%, 95%CI=44.2-72.0%). However, when tested in the treatment cohort, baseline FSA scores did not classify those who would be responders from non-responders better than chance. Tested in an independent treatment cohort, baseline SCI scores classified responders from non-responders better than chance (AUC=72.1%, 95%CI=65.1%-80.2%).

Discussion: Using independent data, we replicated the individual prediction performance for the indication for which each fMRI biomarkers was originally developed: The FSA for diagnostic classification and the SCI for prediction of treatment response. These data show that fMRI biomarkers are generalizable, a prerequisite for their clinical application. The FSA replication yielded better performance than that of the SCI, which likely reflects the large dataset in which it was originally developed (n=1,100 for the FSA vs n=41 for the SCI). Despite

replication performance was good for the SCI, it falls short of the minimum accuracy of 80% generally recommended for clinical use. Optimization of the SCI using pooled datasets may further improve predictive performance, enough to be used in clinical applications.

S66. CEREBELLAR MORPHOMETRY IN SCHIZOPHRENIA: AN INVESTIGATION ACROSS DIFFERENT ILLNESS STAGES

Neelabja Roy*¹, Rakshathi Basavaraju¹, Urvakhsh Meherwan Mehta¹

¹*National Institute of Mental Health and Neurosciences*

Background: Brain connectivity within the cerebellar-thalamo-cortical circuits has been found to be impaired in schizophrenia (Andrease, Paradiso, and O'Leary., 1998). It is not well established if there are morphometric abnormalities in the individual structures that comprise this critical circuitry. We aim to compare volumetric measures in these brain regions between individuals with schizophrenia (two MRIs acquired 2 years apart) and healthy comparison subjects.

Methods: We recruited three groups of subjects at the National Institute of Mental Health and Neurosciences, Bangalore, India: a clinical group of 54 drug naïve first-episode schizophrenia (FESdn), 22 FES remitted group after 2 years of treatment with risperidone (FESrm) and 43 healthy comparison participants (HC) recruited locally. MRI scans were obtained on a 3-Tesla MRI scanner using a 32-channel head coil to acquire high-resolution structural MRI (T1 MPRAGE sequence; 5m) of 1-mm section with no inter-slice gap. The scans were then subjected to Freesurfer recon-all processes for volumetric morphometry. Post validation of satisfactory segmentation with successful visual inspection, the aseg and aparc volumes of the regions of our interests were derived for all subjects across all groups. Then independent t tests were performed for volumetric differences between HC-FESdn and HC-FESrm.

Results: We found significantly reduced volumes in the right ($p=.001$, Cohen's $d=.667$) and left ($p=.006$, $d=.573$) cerebellar cortices in FESdn compared to HC group. and no difference in either thalamus between HC and FESdn. We also observed significantly reduced volumes in the right ($p \text{ LESS THAN } .001$, $d=.996$) and left ($p=.002$, $d=.818$) cerebellar cortices and the left thalamus ($p=.019$, $d=.625$) in FESrm compared to HC. We also observed significant differences in Left Posterior Cingulate ($p=.007$, $d=.558$), Right Posterior Cingulate ($p=.000$, $d=.743$), Right Rostral Anterior Cingulate ($p=.047$, $d=.410$) between HC and FESdn, and significance in difference in Left Posterior Cingulate ($p=.007$, $d=.558$), Right Posterior Cingulate ($p=.000$, $d=.743$), Right Rostral Anterior Cingulate ($p=.047$, $d=.410$) between HC and FESrm. The cerebellar volume differences in both the patient groups remained significant on FDR corrections.

Discussion: Cerebellar structural deficiencies in terms of volume reductions may play a central role in schizophrenia across stages of illness. Future studies may examine if these structural deficiencies are associated with functional aberrations in the cerebellar-thalamo-cortical circuits in schizophrenia. Lack of follow-up data in the HC group and the lack of randomized treatment allocation limits our inferences on the progressive nature of these aberrations and the potential role medications might play.

S67. INCREASED PLASMA LEVELS OF MATRIX METALLOPROTEINASES IN EARLY PSYCHOSIS, ANXIETY AND DEPRESSION: EVIDENCE FROM THE ALSPAC COHORT.

Lorenzo Ghelfi^{*1}, David Mongan¹, David Cotter¹

¹*Royal College of Surgeons in Ireland*

Background: Converging evidence supports the role of Matrix Metalloproteinases (MMPs) in psychiatric disorders. Originally identified as regulators of the extracellular matrix (ECM), MMPs functions span multiple processes, including inflammation, synaptic plasticity, neuronal migration, and blood-brain barrier maintenance. Tissue Inhibitors of Metalloproteinases (TIMPs) on the other hand are major regulators of MMPs. In the present study we examined the associations of plasma MMPs and TIMPs with mental disorders in young adults aged 24 years in the Avon Longitudinal Study of Parents and Children (ALSPAC).

Methods: The present study comprised 775 participants (of 4019 who attended at age 24 years) who completed psychiatric assessments and provided plasma samples. Of these, 35 met the criteria for psychotic disorder, 201 for mild/moderate depressive disorder, and 266 for generalised anxiety disorder. The remaining 401 participants constituted controls without these disorders. Plasma concentrations of MMP2, MMP3, MMP9, and TIMP-4 were quantified using proximity extension assays. Logistic regression compared standardised MMPs and TIMPs levels in cases and controls. Additionally, negative binomial regression was utilized to measure associations between MMPs and TIMPs levels and psychiatric comorbidities (number of disorders). Models were adjusted for sex, body mass index, and cigarette smoking.

Results: Compared to controls, cases exhibited slightly higher mean BMI and higher proportions of female participants, daily tobacco smokers, regular cannabis users, individuals under medication, and not in employment, education or training (NEET) status.

Limited evidence of an association between TIMP4 and psychotic disorders was observed in unadjusted analysis (Odds Ratio [OR]: 1.79, 95% CI 1.22-2.63). However, this association lost significance after adjustment for multiple comparisons. Evidence supporting an association between TIMP4 and depressive disorders was found in unadjusted analysis (OR: 1.83, 95% CI 1.50-22.39). After adjusting for sex, BMI, and smoking habits, evidence was also found for an association between both MMP3 (OR: 1.35, 95% CI 1.06-1.73) and TIMP4 with depressive disorders (OR: 1.51, 95% CI 1.22-1.87).

Unadjusted logistic regression revealed evidence for an association between MMP3 and anxiety disorders (OR: 0.78, 95% CI 0.66-0.91). Additionally, associations were observed between anxiety disorders and MMP9 (OR: 1.22, 95% CI 1.04-1.43) and TIMP4 (OR: 1.65, 95% CI 1.38-1.97). However, after adjusting for covariates, only evidence for an association between TIMP4 and anxiety persisted (OR: 1.44, 95% CI 1.19-1.73).

Unadjusted negative binomial regression analyses demonstrated an inverse association between MMP3 levels and psychiatric comorbidities (β -0.72, 95% CI -1.28 -0.17, p-value: 0.02). Additionally, positive associations were observed between psychiatric comorbidities and MMP9 levels (β 0.63, 95% CI 0.10 1.16, p-value: 0.025) as well as TIMP4 levels (β 1.89, 95% CI 1.27 2.50, p-value: LESS THAN 0.005). However, upon adjusting for covariates, including BMI, sex, and smoking habits, only the association between TIMP4 levels and psychiatric comorbidities remained significant (β 1.26, 95% CI 0.61 1.92, p-value: LESS THAN 0.005).

Discussion: This study revealed that young adults from the ALSPAC cohort with depressive disorders exhibited elevated plasma concentrations of MMP-3 and TIMP-4 compared to

controls. Additionally, we identified an association between TIMP-4 plasma levels and generalised anxiety disorder. Furthermore, the study suggests the potential role of TIMP-4 as a transdiagnostic marker for mental illness. However, no compelling evidence for an association between plasma metalloproteinases and psychotic disorders was observed. These findings contribute to the growing evidence supporting the involvement of metalloproteinases in mental disorders during early adulthood.

S68. ASSOCIATIONS BETWEEN NEUROMELANIN ACCUMULATION IN PATIENTS WITH SCHIZOPHRENIA AND TREATMENT RESPONSIVENESS: A CROSS-SECTIONAL NM-MRI STUDY

Fumihiko Ueno^{*1}, Yusuke Iwata², Shiori Honda³, Guillermo Horga⁴, Clifford Cassidy⁵, Edgardo Torres-Carmona¹, Jianmeng Song¹, Vincenzo De Luca¹, Sakiko Tsugawa³, Yoshihiro Noda³, Sri Mahavir Agarwal¹, Gary Remington¹, Philip Gerretsen¹, Shinichiro Nakajima³, Ariel Graff-Guerrero¹

¹Centre for Addiction and Mental Health, University of Toronto, ²Department of Neuropsychiatry, University of Yamanashi Faculty of Medicine, ³Department of Neuropsychiatry, Keio University School of Medicine, ⁴Columbia University and New York State Psychiatric Institute, ⁵The Royal's Institute of Mental Health Research Affiliated with the University of Ottawa

Background: Neuromelanin (NM) is a product of monoamine metabolism, including dopamine. NM-sensitive magnetic resonance imaging (NM-MRI) sequences allow in vivo quantification of NM levels in the substantia nigra (SN). NM-MRI signal is believed to serve as a surrogate marker for SN dopamine neuron integrity and, consequently, striatal dopaminergic functioning. Higher striatal dopamine synthesis is associated with first-line antipsychotic responsive (FLR) patients with schizophrenia, while normal striatal dopamine synthesis is linked to the pathophysiology of treatment-resistant schizophrenia (TRS). Clozapine is currently the only antipsychotic approved for TRS. However, no studies have yet investigated the relationship between SN accumulations, as measured by NM-MRI, and clozapine response in patients with TRS.

Methods: This study enrolled patients with TRS who either did not respond to clozapine (ultra-resistant schizophrenia [URS]) or responded to clozapine (non-URS), FLR, and healthy controls (HCs). TRS was defined as resistance to at least two first-line antipsychotics and ongoing clozapine treatment at the time of the study. SN-NM were measured using 3T-MRI. The contrast ratio (CR) was calculated as the relative signal intensity difference between SN and crus-cerebri. SN-CR were compared between the groups, controlling for age and sex. The associations between SN-CR and symptom severity scores were also explored within the patient groups.

Results: A total of 78 participants (URS: n=16; non-URS: n=16; FLR: n=20; HCs: n=26) completed the study. We found the overall group differences in SN-CR values ($F(3,72)=3.80$, $\eta^2=0.21$, $p=0.001$). Specifically, patients with URS (Cohen's $d=0.86$, $p=0.049$) and FLR (Cohen's $d=1.27$, $p < .0001$) exhibited higher SN-CR values compared to HCs. SN-CR values showed no associations with any of the symptom severity scores within each group or the entire patient group.

Discussion: Our study is the first to assess a proxy measure of mesostriatal dopamine function in patients with schizophrenia, stratified according to their treatment responsiveness, using

NM-MRI. We found high SN-NM contrast in patients with URS and FLR compared to HCs, and similar to HCs in non-URS. Longitudinal studies are warranted to establish whether SN-NM levels are suitable as a biomarker to predict treatment response in schizophrenia.

S69. ALTERED CORTICAL GYRIFICATION AS A MARKER OF TREATMENT RESISTANCE IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS

Moonyoung Jang^{*1}, Jun Soo Kwon², Minah Kim³, Inkyung Park⁴, Sunghyun Park⁵

¹*Seoul National University College of Medicine, ²Seoul National University College of Medicine; Seoul National University Hospital; Seoul National University College of Natural Sciences; Institute of Human Behavioral Medicine, SNU-MRC, ³Seoul National University Hospital; Seoul National University College of Medicine, ⁴Seoul National University College of Natural Sciences, ⁵Seoul National University Hospital*

Background: Predicting resistance to drug treatment in the early stages of schizophrenia can improve patient outcomes and ultimately enable more personalized therapies, potentially leading to healthcare cost savings. Currently, there is no biomarker that accurately predicts the prognosis of first-episode psychosis patients. Alterations in gyrification represent abnormal neurodevelopmental processes and have the potential to identify treatment resistance at the onset of the illness. However, only a few studies have explored the gyrification patterns of first-episode psychosis, and none of them suggested alterations in gyrification as a predictive marker of treatment resistance. This study aims to investigate cortical gyrification as a viable biomarker candidate for predicting resistance to drug treatment in the first-episode of schizophrenia.

Methods: A cohort of 101 individuals diagnosed with first-episode psychosis and an equivalent number of age- and sex-matched healthy controls underwent T1-weighted magnetic resonance imaging scans immediately after their initial contact. Patients received treatment in a naturalistic clinical setting, and treatment resistance was assessed at the last follow-up. Treatment resistance was defined as either taking clozapine or exhibiting moderate to severe symptoms despite of taking more than two types of antipsychotics in sufficient amounts and duration at their last follow-up point, based on Treatment Response and Resistance in Psychosis Working Group Consensus criteria. Cortical gyrification was calculated using the local gyrification index in a vertex-wise manner across the entire cortical surface, employing Freesurfer pipeline. Local gyrification indices were compared across treatment-resistant patients, non-treatment-resistant patients, and healthy controls.

Results: Patients with first-episode psychosis exhibited hypogyria compared to healthy controls in three clusters: (1) precuneus, cuneus, and lingual gyrus, (2) precentral and postcentral gyrus, and (3) insula. Patients classified as treatment-resistant showed significant reduction in cortical gyrification compared to healthy controls in a cluster including precuneus, cuneus, and lingual gyri. Meanwhile, patients not categorized as treatment-resistant exhibited significantly reduced cortical gyrification compared to healthy controls in a cluster including precentral and postcentral areas (all clusters significant at $P < 0.05$).

Discussion: The present study revealed that the treatment-resistant group exhibited hypogyria in the parieto-occipital region, consistent with previous findings in patients with first-episode psychosis who showed poor response to initial antipsychotic treatments and in asymptomatic individuals at a genetic high risk for schizophrenia. Conversely, patients not classified as treatment-resistant exhibited hypogyria in the fronto-parietal region, aligning with previous

findings in first-episode psychosis patients. The observed disparities in gyrification patterns between the two groups suggest the presence of discrete neurodevelopmental anomalies underlying these distinct groups. These findings indicate that cortical gyrification may serve as a promising biomarker for early prediction of treatment resistance in conventional antipsychotic interventions within the context of psychotic disorders.

S70. SMOOTH PURSUIT DYSFUNCTION AS A SENSORIMOTOR BIOMARKER FOR PSYCHOSIS – EVIDENCE FROM COMPREHENSIVE EXTERNAL VALIDATION STUDIES

Rebekka Lencer^{*1}, Inga Meyhöfer², Andreas Sprenger³, David Derad³, Dominik Grotegerd², Ramona Leenings², Elisabeth J. Leehr², Fabian Breuer², Marian Surmann², Volker Arolt², Georg Romer², Markus Lappe², Johanna Rehder², Nikolaos Koutsouleris⁴, Stefan Borgwardt³, Frauke Schultze-Lutter⁵, Eva Meisenzahl⁵, Tilo T. Kircher⁶, Sarah S. Keedy⁷, Jeffrey Bishop⁸, Elena Ivleva⁹, Jennifer E. McDowell¹⁰, James L. Reilly¹¹, Kristian S. Hill¹², Godfrey D. Pearlson¹³, Carol A. Tamminga⁹, Matcheri Keshavan¹⁴, Elliot S. Gershon⁷, John A. Sweeney¹⁵, Tim Hahn², Udo Dannlowski², Brett A. Clementz¹⁰

¹University of Lübeck, ²University of Münster, ³University of Lübeck, ⁴Ludwig-Maximilians-University, ⁵University of Düsseldorf, ⁶University of Marburg, ⁷University of Chicago, ⁸University of Minnesota, ⁹UT Southwestern Medical Center, ¹⁰University of Georgia, ¹¹Northwestern University, ¹²Rosalind Franklin University of Medicine and Science, ¹³Yale University, ¹⁴Harvard Medical School, ¹⁵University of Cincinnati College of Medicine

Background: Using neurobiological markers for classifying psychiatric syndromes on an individual level is limited by heterogeneity. Implementing machine learning algorithms for classifications purposes requires comprehensive external validation studies to avoid overestimation of prediction models. Considering this, balanced accuracies (BAC) of 60-70% for the correct identification can be expected. Here, we studied quantifiable measures of different aspects of sensorimotor function derived from smooth pursuit eye movements which are regarded as neurobiological markers for psychosis.

Methods: A multivariate pattern algorithm was trained in a large sample of chronically ill psychosis probands (N=674, mean illness duration 15.4 y) and healthy controls (HC, N=305) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP1) cohort to generate predictions (psychosis proband vs. HC). The derived model was externally validated in three independent large samples with external validation-1 including chronically ill psychosis probands (N=727, mean illness duration 17.9 y) vs. HC (N=292), external validation-2 comprising a sample of bipolar probands with (N=49, mean illness duration 11.9 y) and without (N=36, mean illness duration 9.4 y) psychotic symptoms vs. HC (N=71), and external validation-3, a sample comprising probands with affective disorders without psychotic symptoms (N=119, mean illness duration 7.5 y) and psychosis probands (N=51, mean illness duration 9.6 y) vs. HC (N=72). Following an exploratory approach, the model was further tested using data from a sample of recent-onset psychosis or depression (N=28, mean illness duration 0.7 y) as well as Clinical High Risk (CHR) state for the development of psychosis (N=19) vs. HC (N=16). Statistical inference was examined using permutation distributions created from 1000 random rearrangement of the two group labels (healthy controls vs. psychosis group) to the predictors.

Results: Our model trained in the B-SNIP1 sample was able to discriminate psychosis probands from HC based on sensorimotor function with a BAC of 64%. External validation in independent large samples resulted in a BAC of 65% by external validation-1, a BAC of 66% for the identification of psychotic bipolar disorder by external validation-2, and a BAC of 58% for identifying psychosis patients by external validation-3. Notably, 80% of probands with major depression without psychosis were correctly classified as non-psychotic, i.e. being similar to HC with respect to sensorimotor function. Regarding early disease states, 42% of CHR-participants were classified as psychosis patients but only 18% of recent-onset psychosis probands. Of the probands with recent-onset, non-psychotic depression, 76% were correctly classified as non-psychotic. Associations between eye movement performance and possible confounds, i.e., cognition scores or chlorpromazine equivalents, were negligible.

Discussion: Balanced accuracies of about 65% for the individual prediction of psychosis status based on psychosis-related visual sensorimotor dysfunction are in line with recent results from other large heterogeneous psychiatric samples. Our findings underline the impact of sensorimotor dysfunction in a considerable subgroup of chronically ill psychosis patients, which point to specific, illness-related deficits in the transformation of visual sensory motion signals into motor action being associated with alterations in occipito-parieto-frontal networks. Our exploratory observations from the small recent-onset psychosis group suggest that smooth pursuit eye movement dysfunctions may serve as illness progression markers. Future studies should broaden this biomarker approach by combining multiple significant neurobiological measures, e. g. brain structure indices, that might improve prediction accuracies and help to pave the way to improve the clinical diagnostic process for psychotic disorders.

S71. A PRAGMATIC ANALYSIS OF SCHIZOPHRENIA THROUGH THE COOPERATIVE PRINCIPLE AND GRICE'S MAXIMS

Dalia Elleuch*¹

¹*University of Sfax*

Background: Schizophrenia, a complex neuropsychiatric disorder, has captivated the attention of medical and language experts, yet its multifaceted nature has hindered the quest for definitive answers.

Methods: This study takes a pragmatic approach, employing the Cooperative Principle and Grice's maxims to explore linguistic aspects of the illness. Five interviews with clinically diagnosed Schizophrenia patients form the corpus, transcribed and annotated using the UAM Corpus tool 3.3v. Employing both quantitative and qualitative methods, the research examines the hypothesis that Schizophrenia influences speech with distinct patterns of Gricean maxim non-observance.

Results: Results reveal a consistent pattern of non-observance, particularly in flouting the maxim of quality (hallucinations) and the maxim of relation (derailment and incoherence). Schizophrenia patients exhibit a lack of awareness regarding maxim violations in their speech, exacerbating language deficits and thought disorders.

Discussion: The discussion of the observed inadequacies relating to the cooperative principle, and Grice's maxims suggests the need to observe these principles when interviewing a schizophrenic patient, and to reconsider applying these principles when teaching students with Schizophrenia.

S72. PLASMA COMPLEMENT AND COAGULATION PROTEINS AS PROGNOSTIC FACTORS OF NEGATIVE SYMPTOMS: AN ANALYSIS OF THE NAPLS 2 AND 3 STUDIES

Jonah Byrne^{*1}, Colm Healy², Melanie Föcking², Meike Heurich³, Subash Raj Susai², David Mongan⁴, Kieran Wynne⁵, Eleftheria Kodosaki³, Scott Woods⁶, Barbara Cornblatt⁷, William Stone⁸, Daniel Mathalon⁹, Carrie Bearden¹⁰, Kristin Cadenhead¹¹, Jean Addington¹², Elaine Walker¹³, Tyrone Cannon¹⁴, Mary Cannon², Clark Jeffries¹⁵, Diana Perkins¹⁶, David Cotter²

¹Royal College of Surgeons in Ireland, ²RCSI University of Medicine and Health Sciences, ³Cardiff University, ⁴Centre for Public Health, Queen's University Belfast, United Kingdom and Royal College of Surgeons in Ireland, ⁵Proteome Research Centre, University College Dublin, ⁶Department of Psychiatry, Yale University, ⁷The Zucker Hillside Hospital, Department of Psychiatry Research, ⁸Harvard Medical School / Beth Israel Deaconess Medical Center, ⁹Department of Psychiatry, University of California San Francisco, California, ¹⁰University of California, Los Angeles, ¹¹Department of Psychiatry, University of California, San Diego, ¹²University of Calgary, Department of Psychiatry, ¹³Departments of Psychology and Psychiatry, Emory University, ¹⁴Departments of Psychology and Psychiatry, Yale University, ¹⁵University of North Carolina at Chapel Hill, ¹⁶Department of Psychiatry, University of North Carolina, Chapel Hill

Background: Negative symptoms impact the quality of life of individuals with psychosis and current treatment options for negative symptoms have limited effectiveness. Previous studies have demonstrated that complement and coagulation pathway protein levels are related to later psychotic experiences, psychotic disorder, and functioning. However, the relationship between complement and coagulation proteins and negative symptoms is poorly characterised.

Methods: In the North American Prodrome Longitudinal Studies 2 and 3, negative symptoms in 438 individuals at clinical high-risk for psychosis were measured at multiple visits over 2 years using the Scale of Psychosis-Risk Symptoms. Plasma proteins were quantified at baseline using mass spectrometry. Four factors were derived to represent levels of proteins involved in the activation or regulation of the complement or coagulation systems. Their relationships with serial measurements of negative symptoms over time were modelled using generalised least squares. Analyses were adjusted for baseline candidate prognostic factors: negative symptoms, positive symptoms, functioning, depressive symptoms, suicidal ideation, cannabis use, tobacco use, antipsychotic use, antidepressant use, age, and sex.

Results: Clinical and demographic prognostic factors of follow-up negative symptoms included negative, positive, and depressive symptoms, functioning, and age. Adjusting for all candidate prognostic factors, the complement regulators group and the coagulation regulators group were identified as prognostic factors of follow-up negative symptoms (β : 0.379, 95% CI: 0.121, 0.637; β : 0.345, 95% CI: 0.064, 0.626 respectively). The relationship between complement regulator levels and negative symptoms was also observed in NAPLS2 alone (β : 0.379, 95% CI: -0.028, 0.785) and NAPLS3 alone, additionally adjusting for BMI (β : 0.334, 95% CI: 0.096, 0.573).

Discussion: The results indicate that complement and coagulation regulators are prognostic factors of negative symptoms, beyond clinical and demographic prognostic factors. These results suggest complement and coagulation regulator levels could have utility in informing treatment decisions for negative symptoms in individuals at risk.

S73. MACHINE LEARNING FOR PREDICTION OF SCHIZOPHRENIA USING THE BIOMARKERS IN NIACIN FLUSH PATHWAY

Yu-En Kang*¹

¹*National Cheng Kung University, Tainan*

Background: Abnormal niacin flush response may serve as a stable biomarker of schizophrenia. The abnormality has the potential to affect downstream molecular signaling and lead to anti-inflammatory responses. Previous studies have suggested that the downstream metabolites (e.g., prostaglandins and their receptors) are catabolized by the GPR109A-COX-prostaglandin pathway. The main function of prostaglandins is to mediate inflammation in the surrounding tissues and may cause vasodilation. The underlying pathogenesis and molecular mechanisms of niacin-induced flushing pathway in schizophrenia remain incompletely understood. Therefore, our study aimed to use potential biomarkers in niacin flush pathway to predict schizophrenia by machine learning algorithm.

Methods: The study recruited 150 schizophrenia patients and 100 healthy controls. Initially, niacin responses on subjects' arms were measured using the niacin skin patch test. Next, blood cells isolated within 24 hours were analyzed via flow cytometry for niacin receptor GPR109A and prostaglandin receptor DP1 expressions. Enzyme-linked immunosorbent assays are used to measure the levels of prostaglandins, thromboxanes, and their receptors in plasma. In statistical analysis, we compared the expressions of biomarkers in niacin flush pathway between schizophrenia patients and healthy controls. We employed the ROC curve analysis based on logistic regression and machine learning algorithm to evaluate the discriminative capability of these biomarkers. Finally, the selected biomarkers in niacin flush pathway were combined to construct a discriminant model for predicting schizophrenia.

Results: The results showed that nine biomarkers in niacin flush pathway could differentiate between schizophrenia patients and healthy controls. The AUC values of the nine biomarkers were from 0.62 to 0.80 using ROC curve analysis by logistic regression. We selected the top three biomarkers (flush response and two receptors) that showed good discrimination to establish a risk model for schizophrenia. When we combined the selected biomarkers to assess the discriminant performance by logistic regression, the results showed the AUC was 0.87 and 95% CI was 0.82-0.92 for the prediction of schizophrenia. Further, we performed a supervised machine learning algorithm-Support Vector Machine (SVM) to estimate the discrimination ability of the selected biomarkers for differentiating schizophrenia patients from healthy controls. The results showed AUC was 0.93 and 95% CI was 0.87-0.98 using the combined top three biomarkers in SVM model.

Discussion: In summary, this study focused on exploring the role of niacin and prostaglandin receptors signaling in schizophrenia. Our findings supported the hypothesis that the biomarkers in niacin flush pathway would be abnormally expressed in schizophrenia patients. The findings indicated that the top three biomarkers involved in niacin-related signaling pathway may be considered as useful indicators to discriminate schizophrenia patients from healthy controls. We furthermore used the selected biomarkers to construct a risk prediction model of schizophrenia for clinical practice or research purposes. Through our study, we expect to assist researchers and clinicians in better assessing the risk of schizophrenia.

S74. SCHIZOPHRENIA GENETIC RESILIENCE SCORE MODERATES ENVIRONMENTAL RISK ON WORKING MEMORY CONNECTIVITY

Didenur Sahin Cevik*¹, Hao Yang Tan², Shizong Han², Daniel R. Weinberger³, Timothea Touloupoulou⁴

¹*Bilkent University*, ²*Lieber Institute for Brain Development, Maltz Research Laboratories, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine*, ³*Lieber Institute for Brain Development, Johns Hopkins Medical Campus; Department of Psychiatry, Johns Hopkins University School of Medicine*,; *Department of Neurology, Johns Hopkins University School of Medicine*,; *Department of Neuroscience, Johns Hopkins University School of Medicine*,; *Institute of Genetic Medicine, Johns Hopkins University School of Medicine*, ⁴*Interdisciplinary Neuroscience Program, Bilkent University; National Magnetic Resonance Research Center (UMRAM), Aysel Sabuncu Brain Research Centre (ASBAM), Bilkent University; Department of Psychiatry, National and Kapodistrian University of Athens, Department of Psychiatry, Icahn School of Medicine at Mount Sinai*

Background: Schizophrenia is characterized by abnormalities in the functional integration of working memory (WM) brain networks. Exposure to environmental risks during critical periods of brain development can disrupt the typical trajectory of brain maturation and increase the risk of schizophrenia. Investigating how genetic resilience, defined as a heritable measure of variation that increases resistance to disease by reducing the impact of risk loci, influences this link is critical to understanding the disorder's causal mechanisms.

Methods: 350 individual healthy twins oversampled for familial schizophrenia risk (175 pairs) aged 14-23 provided blood samples and underwent an fMRI scan while performing a WM task. Functional connectivity (FC) indexes were calculated by the Conn toolbox, including seed regions of the paracingulate gyrus (PCG) and precentral area. We examined whether connectivity patterns in these regions were predicted by environmental risks, including discrimination and childhood trauma, and whether the polygenic resilience score influenced this link.

Results: Genetic resilience moderated the relationship between environmental risk and brain connectivity. At lower levels of resilience, childhood trauma significantly reduced connectivity at the precentral right region ($p = 0.012$). Likewise, exposure to higher levels of discrimination significantly reduced PCG connectivity at lower levels of resilience ($p < 0.001$). We did not find significant interaction effects at higher levels of resilience. We did not find significant interaction effects at higher levels of genetic resilience.

Discussion: These findings underscore the interplay between genetics, environmental risk, and the neural mechanism in building resilience to schizophrenia. As PCG and precentral are relevant in schizophrenia, optimal connectivity in these regions may enhance a person's ability to cope with adversity. The moderating role of genetic resilience highlights the importance of gene-environment interactions in investigating neural mechanisms responsible for genetic resilience to adversity.

S75. MACHINE LEARNING METHODS TO CONSTRUCT A RISK PREDICTION MODEL AND IDENTIFY THE PRIMARY AND INTERACTION EFFECTS OF MINOR PHYSICAL ANOMALIES FOR TREATMENT-RESISTANT SCHIZOPHRENIA

Chih-Wei Lin*¹, Jin-Jia Lin², Huai-Hsuan Tseng³, Fong-Lin Jang², Ming-Kun Lu⁴, Po-See Chen⁵, Chih-Chun Huang⁶, Wei-Hung Chang⁷, Hung-Pin Tan⁸, Sheng-Hsiang Lin⁹

¹College of Medicine, National Cheng Kung University, Tainan, ²Chi Mei Medical Center, ³National Cheng Kung University Hospital, ⁴Jianan Mental Hospital, Chia Nan University of Pharmacy and Science, ⁵National Cheng Kung University Hospital, National Cheng Kung University Hospital, Dou-Liou Branch, ⁶National Cheng Kung University Hospital, Dou-Liou Branch, ⁷National Cheng Kung University Hospital, Dou-Liou Branch, ⁸Jianan Mental Hospital, ⁹National Cheng Kung University

Background: Treatment-resistant schizophrenia (TRS) is defined as patients with schizophrenia who despite treatment still have symptoms and poor outcomes. Previous studies showed that neurodevelopmental causes in etiology have a relationship between treatment resistance. In the neurodevelopmental model of schizophrenia, minor physical anomalies (MPAs) were demonstrated as a neurodevelopment marker for schizophrenia. However, the association between MPAs and TRS still needs to be studied. The aim of the study was to use machine learning methods to identify the primary and the interaction effect of MPAs items that can distinguish TRS and non-TRS.

Methods: The study included 87 TRS patients and 97 non-TRS patients. We used two machine learning methods, random forest (RF) and support vector machine (SVM) to build the prediction models and select the important items and the interaction effects of MPAs.

Results: The results showed that the six selected MPAs items of mouth and facial regions using RF and SVM models had the area under the curve (AUC) values of 0.70 and 0.72, respectively. Further ROC analyses of RF and SVM indicated that the AUC values of combining the six selected MPAs and three demographic variables (age, sex, BMI) were both 0.76. Then, we identified the interaction effects in these six MPAs items to find that skull height and outer canthal distance had the strongest interaction.

Discussion: In conclusion, the MPAs can be used as a neurodevelopment marker of treatment resistance in schizophrenia and the machine learning model can have great performance to assess the risk of TRS.

S76. MATERNAL CHILDHOOD TRAUMA PREDICTS ADOLESCENT INFLAMMATORY MARKERS: IS FAMILY SOCIO-ECONOMIC STATUS A MODERATOR OF THIS RELATIONSHIP?

Nare Amasi-Hartoonian*¹, Xuemei Ma¹, Andrew J. Lawrence¹, Rebecca Pollard¹, Pei-Jung Chen¹, Maryam Matter¹, Svenja Kretzer¹, Corentin Vallee¹, Olivia Johnson-Trewick¹, Giulia Giordano¹, Eleni Vargiamidou¹, Sofia Panzeri¹, Craig Morgan¹, Seeromanie Harding², Gunter Schumann¹, Carmine Pariante¹, Mitul Mehta², Giovanni Montana³, Ana Rodriguez-Mateos², Chiara Nosarti¹, Paola Dazzan¹

¹King's College London, Institute of Psychiatry, ²King's College London, ³University of Warwick

Background: Maternal early life adversity can lead to poor psychiatric outcomes in the offspring. However, it remains unclear how maternal early life stress affects the biological systems in the offspring, particularly during a critical developmental period like adolescence. The role of the immune system is particularly interesting, given evidence that immune

activation is associated with mental health problems. Still, studies have mainly investigated the relationship between maternal depressive symptoms and a limited number of immunological markers in adolescents, with conflicting results. Furthermore, postnatal environment and exposure to stressors linked to socio-economic status (SES) can also affect offspring inflammation, and thus may be involved in the pathway leading to poor health in the offspring. In this study, we investigated the relationship between maternal childhood trauma and inflammation in adolescents, also exploring the possible interaction with SES.

Methods: A total of $n=230$ school adolescents aged 11-14 (mean age = 12.9 years (SD 0.94); 44.3% male) participated were included in this study. Maternal childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ) from mothers, and a total CTQ score was obtained by summing the scores of the five subscales. We evaluated CRP and cytokines (TNF- α , IFN- γ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13) from plasma and values were log-transformed. Eligibility for free school meals (FSM) was used as a proxy measure of familial SES. Partial correlation analysis was conducted to identify which immune markers were predicted by maternal CTQ when adjusting for covariates (age, sex, ethnicity, and BMI). We then investigated whether family SES moderated the relationship between maternal CTQ and levels of immune markers in the offspring while controlling for covariates.

Results: Maternal CTQ was only positively correlated with IL-2 ($r=0.304$, $N=80$, $p=0.008$) and IL-10 ($r=0.279$, $N=80$, $p=0.015$). A multiple linear regression analysis was conducted to test for the interaction between maternal CTQ and familial SES. However, the relationship between maternal CTQ and IL-2, as well as with IL-10, was not moderated by family SES. The interaction between maternal CTQ and family SES was not statistically significant for either IL-2 ($R^2=0.25$, $B=-0.013$, $SE=0.008$, $t=-1.671$, $p=0.099$) or for IL-10 ($R^2=0.21$, $B=0.013$, $SE=0.008$, $t=1.582$, $p=0.119$).

Discussion: We found that the experience of childhood trauma in mothers was associated with mild immune activation in adolescents. It is possible that maternal childhood trauma influences the inflammatory fetal biology, thus impacting the offspring's physiological stress systems which are linked to the immune system. Contrary to what was expected, familial SES however, did not moderate this relationship. This suggests that maternal childhood trauma may have an independent rather than a synergistic effect on offspring immune activation. Future research will explore whether the presence of maternal childhood trauma has a persistent and more extensive impact on adolescent inflammation at later time points in development.

S77. THE IMPACT OF DEPRIVATION ON CORTICAL DEVELOPMENT AND PSYCHOTIC SYMPTOMS IN YOUTH

Megan Thomas^{*1}, Sarah Whittle², Vanessa Cropley³

¹Melbourne Neuropsychiatry Centre, ²Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Victoria, Australia, ³The University of Melbourne, Melbourne Neuropsychiatry Centre

Background: People with early experiences of deprivation (e.g., neglect, poverty) are more likely to develop psychotic symptoms, both of clinical and non-clinical severity. Research suggests that disruption to the structural development of the cerebral cortex in childhood and adolescence may play a role in these associations. However, the specific cortical regions involved, the temporal relationship between these factors, and the extent to which potential mechanisms overlap for different forms of deprivation, are not well understood. Investigating

these relationships longitudinally in youth, whilst also considering sex-specific effects, may help to elucidate cortical pathways from deprivation to psychosis.

Methods: For the current study, we utilised data for 6323 youth participating in the Adolescent Brain Cognitive Development study, from two study timepoints, two years apart. The data included several measures of exposure to deprivation, regional cortical volumes derived from T1-weighted imaging, and a measure of sub-clinical psychotic-like experiences (PLEs). Linear mixed models were performed to examine the effects of deprivation at age 9/10 years (measured as one overarching construct, and split into material, interpersonal, cognitive and neighbourhood deprivation), on PLEs at age 11/12 years. Associations between deprivation measures and both cortical volume at baseline and the rate of cortical volume change from baseline to follow-up, were also examined for 34 regions spanning the cortex. Finally, mediation analyses were conducted to investigate whether implicated cortical metrics mediated associations between deprivation measures and later PLEs. Sex-specific effects were explored throughout. To evaluate whether findings were specific to individual deprivation subtypes, analyses were repeated with all subtypes included in models simultaneously.

Results: All deprivation measures were significantly associated with a greater number of PLEs (all $p < 0.001$, standardised- β ranging from 0.15-0.25), and, with the exception of interpersonal deprivation (i.e., caregiver neglect), all had widespread associations with lower baseline cortical volume, and steeper cortical volume decline from baseline to follow-up, with the strongest effects in temporal regions. Mediation analyses revealed small but significant indirect effects of total, material, cognitive and neighbourhood deprivation on greater PLEs via lower baseline cortical volumes; most widespread in parietal areas but with certain temporal and occipital regions yielding some of the strongest effects. While fewer significant mediation effects were found for the rate of cortical volume change from baseline to follow-up, moderated mediation analyses revealed that steeper cortical volume decline in several (most commonly occipital) regions partially mediated associations between total, material, cognitive and neighbourhood deprivation, and greater PLEs, in females but not males. When analyses were repeated with all deprivation subtypes included in models simultaneously, the majority of associations between deprivation subtypes and cortical measures, and indirect effects of deprivation subtypes on PLEs via cortical measures, lost significance. This indicates a substantial level of overlap in the cortical mechanisms linking different forms of deprivation with PLEs.

Discussion: The findings of this study are consistent with a pathway from early experiences of deprivation to psychotic symptoms via disruption to cortical development, that is largely common to several forms of deprivation, and persists into adolescence for certain regions, particularly in females.

S78. GENDER DISPARITIES IN PSYCHOPATHOLOGICAL OUTCOMES ASSOCIATED WITH DIFFERENT DIMENSIONS OF ADVERSITY EXPERIENCE

Rebecca Pollard^{*1}, Pei-Jung Chen¹, Corentin Vallee¹, Andrew J. Lawrence¹, Xuemei Ma², Nare Amasi-Hartoonian¹, Svenja Kretzer³, Craig Morgan⁴, Seeromanie Harding¹, Gunter Schumann¹, Carmine Pariante⁵, Mitul Mehta⁶, Giovanni Montana⁷, Chiara Nosarti⁸, Sylvane Desrivieres¹, Ana Rodriguez-Mateos¹, Paola Dazzan⁹

¹King's College London, Institute of Psychiatry, ²Institute of Psychiatry, King's College,

³King's College London; Agency for Science, Technology and Research (A*STAR), Singapore,

⁴Centre for Society and Mental Health, King's College London, ⁵Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London,

⁶Center for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁷Department of Data Science, University of Warwick, ⁸Department of Psychosis Studies, King's College London, Institute of Psychiatry, Psychology and Neuroscience King's College London, ⁹Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Exposure to early life adversity (ELA) has been shown to be a risk factor for the development of psychopathology during adolescence and adulthood. According to the Dimensional Model of Adversity and Psychopathology (DMAP), there is evidence to suggest that different dimensions of adversity would confer risk for different psychopathological outcomes, and that they are associated with distinct neurobiological mechanisms. There is also evidence for differential effects of adverse experiences in males and females, as well as a between-sex differences in outcomes, with females reporting a significantly higher level of internalising symptoms. It is essential to understand more about the impact and mechanisms of different adversity dimensions on the emergence of psychopathological domains during adolescence to provide rationale for specific evidence-based interventions.

Methods: We included in this study a total of $n=230$ school adolescents, aged 11-14 (mean age = 12.4 years $SD=0.98$, 44.8% males) and $n=185$ returned 1 year later for a follow up (mean age = 14 years, $SD = 0.93$, 47% males). Experiences of adversity were assessed using a semi-structured interview derived from the Brief Adolescent Life Events Checklist. Experiences were categorised into 3 dimensions according to DMAP: Threat, Deprivation and Unpredictability. Experiences of each adverse experience were binarized and the total number of adversities in each subgroup was summed to create a total score for each dimension. Internalizing and externalizing symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ), and psychotic experiences using a questionnaire devised from adolescent psychotic-like symptom screen (APSS).

Univariate analyses were conducted to test for associations between each ELA dimension and psychopathology outcome at both time points. We then used linear regression to investigate whether sex was a significant predictor in the relationship between ELA dimensions and outcomes.

Results: Only Threatening experiences were associated with outcomes at 1-year follow-up (Internalizing symptoms, externalizing symptoms, and psychotic experiences (r ranging 0.23-0.42, p LESS THAN 0.005). There was no significant association between Deprivation and Unpredictable experiences and psychopathology (p GREATER THAN 0.05).

Female participants reported a significantly higher level of internalizing symptoms ($t = -2.6$, $df = 228$, p LESS THAN 0.05) and psychotic experiences ($t = -.27$, $df = 228$, p LESS THAN 0.05), while there was no significant sex difference in externalising symptoms.

In the linear regression, sex, alongside Threat exposure, was a significant predictor of both internalising symptoms ($R^2 = 0.14$, p LESS THAN 0.001) and psychotic experiences ($R^2 = 0.1$, p LESS THAN 0.001), but was not a significant predictor of externalising symptoms.

Discussion: Only threatening experiences were associated with psychopathology outcomes at 1-year follow-up. This could suggest that the effect of threat exposure becomes apparent earlier in life compared to the effects of other adversities. This finding underscores the necessity of using a dimensional approach to adversity research, as different adversity subtypes may increase the risk of distinct outcomes.

Our data suggest that the higher risk for females to develop mental health symptoms during adolescence might be associated with a higher vulnerability to threatening experience exposure.

Future longitudinal work will evaluate the potential mechanisms by which sex differences in vulnerability to threatening experiences occur and elucidate the trajectories of psychopathology emergence following exposure to adversity during adolescence.

S79. THE SOCIAL MISTRUST SCALE – ITALIAN (SMS-I): FACTOR STRUCTURE AND CONVERGENT VALIDITY WITH ANXIETY, DEPRESSION, AND SCHIZOTYPY IN 286 ITALIAN COMMUNITY AND CLINICAL 8- TO 14-YEAR-OLDS

Valerio Zaccaria*¹, Ignazio Ardizzone¹, Susanna Maggi¹, Emiliano Luchetti², Federica Forte², Elvira Piazza², Chiara Rogora², Francesco Pisani¹, Keri Ka-Yee Wong³

¹*Sapienza University of Rome*, ²*ASL Roma 2 TSMREE 6th district, Rome*, ³*University College London*

Background: Paranoia and suspiciousness exist in the adult general population as well as in children and are a key feature of schizotypy and schizophrenia-spectrum disorders. Attempts to develop age-appropriate tools to assess suspiciousness and its associations with common psychopathological disorders is ongoing. The present study explored childhood mistrust and suspiciousness by validating the Italian Social Mistrust Scale (SMS) and its correlations with internalizing and externalizing in community and clinical samples.

Methods: A community (N = 242) and clinical sample with a diagnosis of anxiety and/or mood disorder (N = 44) of 8-to 14-year-olds were recruited from two public schools and from the Child Neuropsychiatry Institute of Policlinico Umberto I and Italian Local Health Unit in Rome respectively. Both samples completed the SMS and other tests of schizotypal traits, anxiety, depression, and internalizing and externalizing problems.

Results: The Total Score of the SMS was positively skewed, with 50% of the children scoring 3 points or less; the top 15% score was 7 points or more. Exploratory and Confirmatory Factor Analysis (EFA/CFA) revealed a three-factor model (i.e., General Mistrust, Home Mistrust, and School Mistrust) as per the English SMS. As expected, in the community sample childhood mistrust was positively correlated with schizotypal traits, anxiety, and depression ($\rho = 0.49, 0.42, \text{ and } 0.54$ respectively). Similar results were observed in the clinical sample, where these correlations were even stronger ($\rho = 0.75, 0.51, \text{ and } 0.85$ respectively). Overall, the SMS has good internal reliability (Total = 0.74, School Mistrust = 0.66, Home Mistrust = 0.49, General Mistrust = 0.62).

Discussion: Replicating previous studies, childhood mistrust exists on a continuum and is measurable in Italian children and is associated with higher levels of childhood psychopathology.

S80. ADDITION OF EVENAMIDE FOR 1-YEAR TO ANTIPSYCHOTICS IN TRS PATIENTS RESULTS IN INCREASING CLINICALLY IMPORTANT BENEFIT TO AN EXTENT THAT A SUBSTANTIAL PROPORTION NO LONGER MEET INTERNATIONAL CRITERIA FOR TREATMENT RESISTANCE

Ravi Anand*¹, Alessio Turolla², Giovanni Chinellato³, Francesca Sansi², Rodolfo Giuliani², Richard Hartman⁴

¹Anand Pharma Consulting, ²Newron Pharmaceuticals SpA, ³Newron pharmaceuticals, ⁴NeurWrite LLC

Background: The combination of first-and-second-generation antipsychotics (APs) in patients with TRS are not being shown to be beneficial, most likely as all result in modulation of dopaminergic and serotonergic transmission (Galling et al., 2017). As treatment resistant schizophrenia is noted in ~30% of patients within 5 years of treatment and results in increased morbidity, suicidality, and mortality, there is a high unfulfilled medical need to find innovative treatments for this population. Findings from neurochemistry, neurometabolism, and functional imaging studies in TRS patients indicate abnormalities in glutamatergic rather than dopaminergic neurotransmission (Moghaddam et al., 2012; Demjaha et al., 2014; Mouchlianitis et al., 2016). Evenamide, a selective inhibitor of voltage-gated sodium channels, is devoid of biological activity at GREATER THAN 130 CNS targets, normalizes glutamate release without affecting basal levels, and demonstrated benefits in animal models of psychosis as monotherapy and as an add on to APs (Anand et al., 2018)

Methods: Study 014/015 was a 1-year, randomized, open-label, rater-blinded, international study in patients with diagnosis of TRS not responding to a therapeutic dose of an AP with an initial assessment at week-6 followed by regular efficacy and safety assessments every 10-12 weeks up to 1-year of treatment. TRS patients were selected based on the following selection severity criteria: PANSS total score of 70-90, moderately to severely ill (CGI-S of 4 to 6), positive symptoms GREATER THAN 20 and at least 2 of the core symptoms of psychosis rated as at least moderate (4 or more). Eligible patients were randomized to three fixed oral doses of evenamide (7.5, 15 and 30 mg bid) to 52 weeks of treatment. Efficacy ratings were performed by a trained psychiatrist blinded to the evenamide dose. Data from all 3 doses pooled were analyzed to assess the responder rate, maintenance of the response up to 1 year and conversion of patients already on an AP from TRS into a responsive state, according to the operational severity selection criteria for TRS. Assessment of efficacy was based on changes on PANSS, CGI-S/C and functioning (Strauss-Carpenter LOF), while tolerability was assessed based on all safety measures.

Results: The 161 TRS patients randomized to treatment tolerated the study medication very well with a high completion rate at 1 year (~75% at 1-year) and low ADO rate (1.9%). During the 1-year treatment period, ~50% of the patients achieved a clinically meaningful benefit (GREATER THAN =20% improvement on PANSS total score): of the patients who achieved this clinically important reduction, ~40% preserved this benefit for at least 12 weeks according to TRRIP criteria. Remarkably, ~50% of the patients no longer met the operational severity criteria used to diagnose TRS at baseline, therefore converting patients into a responsive state. Detailed results from further analyses will be presented at the Congress.

Discussion: The multi-domain benefits of the addition of evenamide to antipsychotics in TRS patients were associated with clinically meaningful improvement in symptoms of psychosis to an extent that over 50% of these patients no longer met the criteria for TRS. These results suggest that the modulation of glutamate with evenamide in TRS patients on an antipsychotic may be a promising advance for their management (Anand et al., 2023)

S81. TOWARDS A PERSONALIZED MEDICINE APPROACH TO PSYCHOLOGICAL TREATMENT FOR PSYCHOSIS

Maria Lamarca*¹, Steffen Moritz², Fabrice Berna³, Lukasz Gaweda⁴, Vanessa Acuña⁵, Caroline König⁶, Susana Ochoa¹

¹*Parc Sanitari Sant Joan de Déu*, ²*University Medical Center Hamburg, Department of Psychiatry*, ³*Inserm*, ⁴*Institute of Psychology, Polish Academy of Science*, ⁵*Universidad de Valparaíso*, ⁶*Universitat Politècnica de Catalunya*

Background: Despite extensive evidence on the efficacy of psychological interventions at improving symptoms in people diagnosed with Schizophrenia, there is a lack of widely available treatments for this population. There is a need for cost- and time-efficient interventions for mental health disorders worldwide. Moreover, there is growing interest on the benefits of personalised medicine, tailoring interventions to individual needs. Metacognitive Training (MCT) is an ideal candidate for personalised treatment due to its proven efficacy in treating Schizophrenia and its content delivery. The aim of PERMEPSY (Personalised Medicine approach to psychological treatment for Psychosis) is to offer personalised delivery of MCT for people with Schizophrenia.

Methods: PERMEPSY is a three-year project composed of 5 clinical partners from 5 different countries (Spain, Germany, France, Poland and Chile) and one technological team (Spain). PERMEPSY members collaborate by reviewing the literature on the variables associated with better treatment response in Schizophrenia and identifying key factors predicting MCT effectiveness. PERMEPSY aims to analyse multimodal retrospective data from previous clinical trials using machine learning (ML) techniques and the variables identified via systematic reviews. The ML algorithm will inform the development of a prototype platform which will be made freely available to clinicians worldwide to aid their clinical decision-making when treating patients with Schizophrenia. The platform will be validated with a pilot clinical trial with two arms, comparing classical MCT to a personalised delivery recommended by the platform, testing its predictive power. Therefore, PERMEPSY has three main aims: (1) identify key sociodemographic, clinical, cognitive and metacognitive variables and biomarkers associated to treatment response in Schizophrenia; (2) demonstrate which variables best improve treatment outcomes using a stratification strategy based on ML applied to multimodal retrospective databases; and (3) develop and validate a platform via a proof-of-concept pilot clinical trial that includes the user's perspective at each stage.

Results: Data from 22 clinical trials has been collected and harmonised yielding a database with over 20 sociodemographic, clinical, cognitive and meta-cognitive variables from over 700 patients. ML experts will analyse the database and extract the variables that best predict MCT efficacy. A predictive platform will be developed from this analysis and a proof-of-concept clinical trial will validate the prototype platform's predictive power. The ML algorithm will dictate which variables will be input to the platform at baseline. The expected outputs for the platform will include predicted changes in positive symptoms, delusions, insight, self-esteem and the probability of treatment adherence for a given patient profile.

Discussion: Reducing the personal, social, and economic burden of Schizophrenia is a vexing need at both the mental and global health levels. Despite decades of research focusing on improving outcomes of psychosis, these remain a clinical challenge. Predictive models of personalised medicine are still in their infancy. This project aims to fill in the gap by providing clinicians with a tool to predict which patients will benefit from receiving MCT, and how to tailor the treatment to maximize its effects. The predictive platform will not only aid in decision-making but will also result in reduced economic and labour costs for clinicians. The novelty of this approach resides in integrating sociodemographic, lifestyle, environmental, clinical, cognitive, and biological data.

S82. TV-44749, A LONG-ACTING SUBCUTANEOUS (SC) INJECTABLE FORMULATION OF OLANZAPINE IS DESIGNED TO PROVIDE SUSTAINED CONTROLLED CONCENTRATIONS AND TO ELIMINATE THE CAUSES OF POST-INJECTION DELIRIUM/SEDATION SYNDROME (PDSS)

Iva Krtalić¹, Marina Juretić¹, Andrea Komlosi², Ivana Šoljić Jerbić¹, Mateja Prpić¹, Tunde Szabo², Biserka Cetina-Čižmek¹, Irina Cherniakov³, Avia Merenlender Wagner³, Kristina Ferderber*¹

¹Teva PLIVA Croatia Ltd, ²Teva Pharmaceutical Industries, Hungary, ³Teva Pharmaceutical Industries, Ltd.

Background: Use of the intramuscular (im) formulation of olanzapine (Zyprexa Relprevv, Inke S.A.) has been limited because of a black-box warning of post-injection delirium sedation syndrome (PDSS) and associated REMS. PDSS has occurred in 0.07% im injections and is thought to be due to the inadvertent intravascular access of olanzapine pamoate during the IM injection process. This results in a fast dissolution of olanzapine pamoate and unexpectedly high olanzapine plasma concentrations related to PDSS.

TV-44749 (Teva) is a long-acting subcutaneous (sc) injectable formulation of olanzapine and is based on a novel copolymer drug delivery technology that forms a depot under the skin that ensures controlled release of olanzapine. TV-44749's sc route of administration and formulation were also designed to eliminate causes of PDSS. Subcutaneous tissue is much less vascularized compared to muscular tissue, therefore inadvertent intravascular access is assumed to be less likely. To explore the risk of PDSS following TV-44749 sc injection, a study of in vitro release (IVR) in human plasma of TV-44749 in comparison to the IM formulation was undertaken. The pharmacokinetic and safety results concerning PDSS are also reported from the first in human phase 1 study of TV-44749.

Methods: The stability and solubility of base crystalline form II (the active pharmaceutical ingredient (API) in TV-44749) and olanzapine pamoate monohydrate (the API in the IM formulation) in commercially available human plasma were tested to implement optimal parameters in the IVR analysis. The depots of TV-44749 at the beginning and end of the IVR analysis in human plasma were characterized; including surface and cross section morphological properties, changes in copolymer molecular weight distribution and drug substance particle size.

In the phase 1 study, participants (n=91) received oral olanzapine doses for 7 days followed by a washout, and then received TV-44749 single sc injection of either 70mg or 105mg for healthy volunteers; single 318mg, 425mg or 531mg, or three q1m sc injections of 283mg or 566mg for patients with schizophrenia. All who were administered TV-44749 remained under clinical observation for at least 3 hours postdose to monitor for any possible symptom suggestive of PDSS occurrence.

Results: The results show that both APIs were stable in human plasma, however, olanzapine base in crystalline form II in TV-44749 showed 1.8 times lower solubility than olanzapine pamoate monohydrate of the IM formulation. For the IM formulation, 39% of olanzapine is released within first 0.5 h with complete release achieved within 24 hours. For TV-44749, only 3% of olanzapine is released within 4 hours and at the end of IVR experiment at 72 hours, only 14% of olanzapine is released. At the end of the IVR analysis after 72 hours, the depots appear slightly swollen and olanzapine particles are smoothly covered by copolymers, which is in

accordance with the IVR results showing that more than 85% of olanzapine still entrapped within. These results are in line with the phase 1 study which found that following TV-44749 administration, the pharmacokinetic profile demonstrated sustained-release attributes and there were no confirmed or suspected PDSS events.

Discussion: The in vitro study demonstrates that upon contact with human plasma, copolymers of TV-44749 instantly form a depot which entraps olanzapine particles preventing their rapid dissolution in plasma. Overall the sc route of administration and formulation characteristics of TV-44749 appear to eliminate the causes of PDSS. These results are further supported by the lack of PDSS events in the phase 1 study.

S83. EFFECTS OF LUMATEPERONE ON PSYCHOSOCIAL FUNCTIONING: POST HOC ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

Suresh Durgam¹, Susan Kozauer¹, Robert E Davis¹, Kimberly E Vanover¹, Jason Huo¹, Tobie Escher*¹, Philip D Harvey²

¹*Intra-Cellular Therapies, Inc.*, ²*Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine and Research Service, Miami VA Healthcare System*

Background: Schizophrenia is associated with social and functional impairment which can be difficult to treat, may not correlate with improvements in psychotic symptoms, and has been associated with poor long-term patient outcomes. Lumateperone is a mechanistically novel, FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. In a Phase 3, randomized, double-blind, placebo-controlled trial (Study 301, NCT02282761), lumateperone 42 mg significantly improved symptoms of schizophrenia compared with placebo and had a favorable safety profile in patients with an acute exacerbation of schizophrenia. This post hoc analysis of Study 301 evaluated the effects of lumateperone 42 mg on social and functional impairment associated with schizophrenia.

Methods: Eligible adults (18-60, inclusive) with schizophrenia who were experiencing an acute exacerbation of psychosis were randomized to 28-day inpatient treatment with lumateperone 42 mg or placebo. Improvements in functioning were assessed by the Personal and Social Performance Scale (PSP); this scale ranges from 1-100 with higher scores representing better function. Analyses were conducted using an analysis of covariance. The percent of patients that met improvement criteria for minimally clinically important differences (MCID) in PSP, defined as a 10-point improvement from baseline, was also assessed. Evaluations were conducted in both the intent-to-treat (ITT) population and in patients with marked or severe dysfunction (baseline PSP score ≤ 50).

Results: The ITT population comprised 289 patients (placebo, n=141; lumateperone 42 mg, n=148), of which 283 had evaluable baseline PSP data (placebo, n=137; lumateperone 42 mg, n=146). Mean baseline PSP total score was 47.7 for patients in the placebo group and 47.8 for the patients in lumateperone 42-mg group. For patients in the ITT population, lumateperone 42 mg treatment significantly improved compared with placebo in the PSP total score at Day 28 (least squares mean change [SE], 11.0 [1.13]; least squares mean difference vs placebo [LSMD], 3.3; P LESS THAN .05). A greater percentage of lumateperone patients (41.1%) than placebo patients (35.0%) met criteria for MCID improvement at Day 28.

At baseline, 59.4% of the patients in the ITT population with PSP data (placebo, n=83; lumateperone 42 mg, n=85) had marked or severe impairment in social and personal function

(PSP score ≤ 50). Mean baseline PSP total scores in this subgroup were 40.2 (lumateperone) and 40.5 (placebo). In patients with baseline PSP total score ≤ 50 , there was significantly greater improvement with lumateperone 42 mg compared with placebo in the PSP total score at Day 28 (least squares mean change [SE], 16.9 [1.63]; LSMD, 5.8; P LESS THAN .05). The percent of patients that met criteria for MCID improvement was greater with lumateperone (50.6%) than with placebo (38.6%) at Day 28.

Discussion: Lumateperone 42 mg treatment was associated with significant and clinically meaningful improvements in social and personal function in patients with an acute exacerbation of schizophrenia. Improvements were greater in those with marked or severe social and functional impairment at baseline. These results suggest that lumateperone benefits schizophrenia symptoms associated with social and personal function.

S84. MAINTAIN THE EFFICACY AND SAFETY IN TREATMENT OF SCHIZOPHRENIA AFTER SWITCHING TO LONG-ACTING INJECTABLE ARIPIRAZOLE FROM ORAL ATYPICAL ANTIPSYCHOTICS (MAESTRO)

Euitae Kim^{*1}, Seoyoung Kim¹, Sung-Wan Kim², Beom-Woo Nam³, Kyoung-Uk Lee⁴, Bong Ju Lee⁵, Seung-Hee Won⁶, Chang Hwa Lee⁷, Christoph Correll⁸, Jun Soo Kwon⁹, MAESTRO study group¹⁰

¹Seoul National University Bundang Hospital, ²Department of Psychiatry, Chonnam National University Medical School, Gwangju Bukgu Community Mental Health Center, Gwangju, Korea, ³Department of Psychiatry, Konkuk University Medical School, ⁴Department of Psychiatry, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, College of Medicine, Uijeongbu, Korea, ⁵Lee Bong Ju Psychiatric Clinic, Republic of Korea, ⁶Department of Psychiatry, Kyungpook National University School of Medicine, Daegu, Republic of Korea, ⁷Department of Psychiatry, Eulji University School of Medicine, Eulji University Hospital, Daejeon, Republic of Korea, ⁸The Zucker Hillside Hospital, ⁹Seoul National University College of Medicine, ¹⁰Republic of Korea

Background: Schizophrenia is a chronic, severe mental illness characterized by psychotic symptoms such as hallucinations and delusions, often coupled with cognitive and social impairments. Although clinical remission is not rare with adequate antipsychotic treatment, most patients experience recurring psychotic relapses along the disease course that result in clinical deterioration and functional impairments. Poor drug adherence is a serious concern in the treatment of schizophrenia since it increases the psychotic relapse risk. Long-acting injectable (LAI) antipsychotic drugs, which ameliorate the daily burden of taking oral medication and prevent psychotic relapse from poor adherence, have been introduced.

Aripiprazole has a unique receptor profile as a dopamine partial agonist and has been demonstrated to be safe and effective in the treatment of schizophrenia. LAI aripiprazole has also proved useful for treating schizophrenia, improving treatment adherence and, ultimately, treatment outcomes. However, some patients treated with aripiprazole did not show a favorable response. Indeed, patients exhibited a diverse clinical response to aripiprazole, including symptomatic aggravations. It could be related to the dopamine partial agonism of aripiprazole, which could affect the treatment outcome more when changing antipsychotic drugs from dopamine antagonists to aripiprazole. The variation in the clinical response when changing

antipsychotic drugs to aripiprazole prompts clinical studies about the efficacy and safety in switching to long-acting injectable aripiprazole.

We conducted a clinical trial to evaluate the efficacy and safety in switching oral atypical antipsychotic drugs to LAI aripiprazole according to the pharmacological characteristics.

Methods: The study was based on an open-label, parallel-group study design. Patients with schizophrenia treated with oral antipsychotic drugs who were clinically stable were enrolled. Their symptomatic changes and treatment-emergent adverse events (TEAEs) were evaluated after switching to LAI aripiprazole.

Results: All the patients showed better responses to LAI aripiprazole in terms of PANSS scores. PANSS scores decreased after switching to LAI aripiprazole. Patients who were previously treated with oral aripiprazole (Group I) showed a larger reduction in PANSS score compared to patients who were previously treated with oral antipsychotic drugs other than aripiprazole (Group II).

In the aspects of TEAE, Group II showed higher incidences of sleep disturbance and psychotic symptoms when switching to LAI aripiprazole. However, the two TEAEs were subsided, comparable to Group I.

Discussion: Switching to LAI aripiprazole did not worsen the psychiatric symptoms in clinically stable patients with schizophrenia, regardless of prior antipsychotic drugs. A strategy for managing temporary sleep disturbance and psychotic symptoms when switching from oral antipsychotic drugs with dopamine antagonism to LAI aripiprazole is required to be developed.

S85. RELATIONSHIPS BETWEEN AKATHISIA AND PSYCHOTIC AGITATION AS EVALUATED BY CONSISTENCY CHECKS FOR THE BARNES AKATHISIA RATING SCALE IN A LARGE CLINICAL TRIALS DATASET

Kazunori Tatsumi*¹, Selam Negash¹, Cong Liu¹, Christopher Poppe¹, Mark Opler¹

¹*WCG Clinical Endpoint Solutions*

Background: Akathisia is one of the most debilitating side effects related to antipsychotic drug use. It is characterized by subjective feelings of inner restlessness and mental distress and objective motor restlessness caused by an urge for continuous movement. Although atypical antipsychotics are less likely to cause akathisia, the propensity of individual atypical agents to cause akathisia varies. Accurate information on the side effect burden of commercially available drugs is important to guide treatment selection and clinical management. Consequently, accurate assessment of akathisia is critically important in clinical trials to ascertain the safety profile of investigational products.

The Barnes Akathisia Rating Scale (BARS) has been commonly used in clinical trials and also in clinical practice. It consists of four items designed to systematically assess both subjective and objective aspects of akathisia. Failure to understand scoring rules and item anchor descriptions may result in misclassification of symptoms. Side effects associated with the atypical antipsychotics often overlap with signs and symptoms of psychiatric illness. In particular, psychosis related psychomotor agitation may resemble the symptoms of akathisia. While consistency checks to improve precision of measurement have recently been developed for psychiatric rating scales (e.g., PANSS), their importance and utility in adverse effect measures have not been explored. In this analysis, we propose consistency checks for the BARS based on the scoring rules, theoretical, and clinical frameworks. The objective of the

current study is to investigate how accurately BARS raters assess akathisia by examining the frequency of flags and to evaluate the correlations between the PANSS Marder excitement factor score and the BARS global total score in a large dataset derived from multiple schizophrenia trials.

Methods: A total of 11,077 BARS assessments were derived from five large multicenter schizophrenia clinical trials investigating the efficacy and safety of atypical antipsychotics. A set of consistency checks developed to monitor data quality for the BARS and PANSS were applied to the data, and flag rates were calculated. The data were stratified into two groups based on the design of study to see if blinding plays a role in the evaluation of the side effect. To examine how well raters are differentiating psychomotor agitation from akathisia, a 2x2 table is presented to demonstrate unlikely rating patterns between the scales, and the Kendall's rank correlation coefficient was calculated to measure the correlations between the PANSS Marder factor scores and the BARS global score.

Results: Concordant with the concept that akathisia occurs less frequently in atypical antipsychotic treatment, a substantial number (GREATER THAN 91%) of BARS global score in studies of atypical drugs and novel agents are rated=0. To address the uneven distribution of scores, assessments in which BARS global score=0 were excluded from the analysis of flag rate. A total of 968 assessments were rated with a global score greater than or equal to 1. In comparing the groups, the open-label group showed a significantly higher overall flag rate (33.7%) compared to the double-blind group (26.7%); $t = -2.06$, $df = 10031$, $p \text{ LESS THAN } 0.05$. The percentage of assessments with at least one flag was also significantly higher for the open-label group (31% vs 19%, $t = -3.87$, $df = 7750$, $p \text{ LESS THAN } 0.0001$), while assessments with two or more flags did not differ between the two groups (3% vs 5%; $t = 1.69$, $df = 11209$, $p = 0.0092$). The flag designed to identify incorrect use of scoring conventions was the most frequently flagged error for both studies. When both the BARS and PANSS were administered together at the same visit, approximately 2.3 – 2.5% of time both akathisia and agitation defined as PANSS-EC GREATER THAN 14 and PANSS-AF GREATER THAN 17 were present. The correlation between the PANSS Marder excitement factor and the BARS global total score was low ($r=0.06$, $p \text{ LESS THAN } 0.01$), and it was almost identical ($r=0.07$, $p \text{ LESS THAN } 0.01$) when BARS=0 was excluded from the correlational analysis.

Discussion: The results suggest that the most common error among BARS raters participating in schizophrenia clinical trials of new generation of antipsychotics is incorrect classification of pseudoakathisia. According to the scale author, a rating of 0 is given for the global item if there is a positive score on objective akathisia but a 0 rating on subjective items. The reason for the rating error may not only stem from the lack of awareness of the scoring rule, but also that raters may be misclassifying psychomotor agitation with akathisia as well. A similar rating error seems to be manifested when examining the relationship between two measures. The correlation between the BARS global score and the PANSS Marder hostility/excitement score was very low. This, in turn, suggests that unexpectedly strong correlations between the two measures could be an indicative of imprecise measurement. Lastly, the open-label study design seems to be more prone to rating errors. While both syndromes theoretically can occur at the same time, application of flags and monitoring of higher correlations of the BARS global score and PANSS factor score may help identify rating errors and misclassification of symptoms.

S86. CLINICAL BENEFIT AND RISK PROFILE OF TV-46000 FOR PATIENTS WITH SCHIZOPHRENIA AS ASSESSED BY NUMBER NEEDED TO TREAT (NNT) AND NUMBER NEEDED TO HARM (NNH)

Leslie Citrome¹, Orna Tohami², Nir Sharon², Ayellet Jehassi², Eran Harary², Mark Suett³, Kelli R. Franzenburg⁴, Christoph U. Correll⁵, Orna Tohami^{*6}

¹New York Medical College, Department of Psychiatry and Behavioral Sciences, ²Teva Pharmaceutical Industries Ltd., ³Teva UK Limited, ⁴Teva Branded Pharmaceutical Products R and D, Inc., ⁵The Zucker Hillside Hospital, Northwell Health, Department of Psychiatry,; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine,; Feinstein Institutes for Medical Research, Institute of Behavioral Science,; Charité – Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, ⁶Teva Pharmaceutical Industries, Ltd.

Background: TV-46000 is a long-acting subcutaneous antipsychotic that combines risperidone and an innovative, copolymer-based drug delivery technology. TV-46000 was approved by the Food and Drug Administration in April 2023 for administration once monthly (q1m) or once every 2 months (q2m) in adult patients with schizophrenia. The Risperidone Subcutaneous Extended-release (RISE; NCT03503318) study was a phase 3, double-blind, placebo-controlled, randomized, relapse prevention study. Compared with placebo, TV-46000 prolonged time to impending relapse (TV-46000 q1m, hazard ratio [HR] 0.200 [95% CI 0.109–0.367], P LESS THAN .0001; TV-46000 q2m, HR 0.375 [0.227–0.618], P LESS THAN .0001). Number needed to treat (NNT) and number needed to harm (NNH) are important metrics that can help healthcare professionals understand the benefits and risks of treatments and thus inform their clinical decision-making.

Methods: NNT estimates versus placebo were calculated for TV-46000 in the treatment of schizophrenia using data from the RISE study. NNH estimates versus placebo were calculated for adverse events of interest based on common second-generation antipsychotic side effects (akathisia, somnolence, weight increased $\geq 7\%$) using safety data from the RISE study.

Results: In the RISE study, 543 patients were evaluated for efficacy (TV-46000 q1m, n=183; TV-46000 q2m, n=179; placebo, n=181) and safety (TV-46000 q1m, n=183; TV-46000 q2m, n=179; placebo, n=179). NNT estimates for impending relapse were 5 (95% CI 3.4–6.9) for TV-46000 q1m and 7 (4.1–12.2) for TV-46000 q2m. NNT estimates for other efficacy endpoints (impending relapse rate at week 24 and proportion of patients who maintained stability) were also robust for TV 46000 q1m (range, 4–5) and TV-46000 q2m (range, 5–6). NNH estimates for akathisia, somnolence, and weight increased $\geq 7\%$ were GREATER THAN 10, indicating a favorable tolerability profile with weight increased $\geq 7\%$ (10 and 16 for TV-46000 q1m and TV-46000 q2m, respectively) having the highest risk, and akathisia (64 and 60) and somnolence (37 and 30) having a lower risk.

Discussion: In the phase 3 RISE study, TV-46000 administered q1m and q2m exhibited a favorable efficacy and safety profile as expressed by NNT and NNH. The robust, single digit number of patients needed to be treated to see a positive effect on risk of impending relapse and symptomatic stability supports the efficacy of TV-46000 in patients with schizophrenia. The high NNHs calculated for selected safety assessments suggest TV-46000 was well tolerated. TV-46000 NNTs and NNHs may provide clinicians with clinically meaningful information when considering the use of long acting injectables for patients with schizophrenia.

S87. SCHIZOPHRENIA PLATFORM FOR IMPROVING RECOVERY WITH INTEGRATED TRIALS (S.P.I.R.I.T.).

Dan Siskind*¹, Urska Arnautovska², Andrea Baker³, Mike Trott², Rebecca Soole², Ravi Iyer⁴, Julia Lappin⁵, Anthony Rodgers⁶

¹*Metro South Addiction and Mental Health Service*, ²*Faculty of Medicine, The University of Queensland*, ³*Queensland Centre for Mental health Research*, ⁴*Swinburne University*, ⁵*University of New South Wales, Sydney, Australia*, ⁶*George Institute, Sydney*

Background: Adaptive platform trials, demonstrated extremely successfully in other health domains like COVID-19, streamline evidence generation by addressing multiple questions rapidly and much more efficiently. Platform trials offer an efficient approach, by using one standardised control arm, while comparing outcomes across multiple parallel treatment arms. Throughout the trial, predefined interim analyses assess the viability of treatment arms, informing whether treatment arms should be terminated early and facilitating enrolment of participants to more promising treatment arms, or to newly added treatment arms. This optimised use of control data reduces the overall sample size required, minimising recruitment time and resource expenditure compared to traditional individual RCTs. This design has promise for trials among people with schizophrenia.

Methods: Rather than ‘intervention focused’, our proposed platform will be ‘schizophrenia focused’ and will use adaptive randomisation techniques to simultaneously evaluate multiple interventions, generate separate effects across subgroups, and minimise trial downtime. In this study, a Master Protocol will be established to guide all trial operations, focusing on four core health domains identified through consumer consultation for treating schizophrenia. Domain-specific primary outcomes are defined: Cardiometabolic (weight), Psychotic symptoms (PANSS), Cognition (BACS), and Social functioning (SF-36). An integrated, cloud-based data management system will be implemented for secure, standardized data collection and automated quality control. A Bayesian statistical framework will be used for data analysis, incorporating prior knowledge for a comprehensive assessment of treatment efficacy. Interim analyses will allow for modifications such as dropping or introducing treatment arms based on predefined criteria.

Results: Our first SPIRIT platform trial randomisation SWiMS (Schizophrenia Weight, Metformin and Semaglutide). This trial will compare semaglutide (2.0mg subcutaneous, weekly) to placebo injections over 52 weeks among 188 people with schizophrenia on antipsychotic medications and obesity. The primary outcome will be change in body weight (percent). Secondary outcomes include changes in metabolic syndrome components, proportion of participants with GREATER THAN 5%, GREATER THAN 10% and GREATER THAN 15% loss of body weight, visceral/hepatic adiposity, cognition, quality of life and psychosis from baseline to 52 weeks. Early stopping will be non-binding, considered only once sufficient data has been accrued, and in consultation with the trial steering committee. Sufficient data will be defined as occurring once 30 participants have been enrolled and adhered to protocol (completed all outcome assessments) for 24 weeks. If one of the arms of this trial meets our predefined futility stopping rules, we will add tirzepatide and a new treatment arm.

Discussion: Through the creation of world’s first schizophrenia platform trial, we will improve the efficiency of clinical trials, with multiple interventions tested simultaneously against a single control group. As ineffective treatments within schizophrenia domains are identified, they can be dropped, and new interventions added without needing to start a new trial. This will lead to immediate consumer benefit, with a higher probability of receiving an effective treatment since there are multiple active treatment arms. Moreover, as ineffective treatments are dropped and effective ones are identified more quickly, patients benefit from better

treatments sooner and more efficient treatment can be more rapidly translated into better health care for this population group.

S88. CANCLOZ: CANNABIDIOL FOR CLOZAPINE RESISTANT SCHIZOPHRENIA - A MULTI-CENTRE RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP TRIAL

Dan Siskind^{*1}, Andrea Baker², Nicola Warren³, Shuichi Suetani², Claudia Bull³, Mike Trott³, Urska Arnautovska³

¹*Metro South Addiction and Mental Health Service*, ²*Queensland Centre for Mental health Research*, ³*Faculty of Medicine, The University of Queensland*

Background: Schizophrenia affects approximately 1% of the global population, with about a third of these individuals having treatment-resistant schizophrenia (TRS). Clozapine is the most effective known antipsychotic for TRS, yet only 40% of TRS patients show adequate response to clozapine. Existing augmentation strategies for clozapine are limited in effectiveness. Cannabidiol (CBD) has shown promise in reducing positive psychotic symptoms in schizophrenia but has not been tested specifically in clozapine-resistant schizophrenia.

Methods: This study is a 12-week randomised, placebo-controlled, double-blind, parallel-group trial. Forty individuals with clozapine-resistant schizophrenia will be randomly assigned to receive either 1,000mg of CBD daily or a placebo. Participants will be aged 18-64, meet DSM-IV criteria for schizophrenia or schizoaffective disorder, have a PANSS score ≥ 60 , and be on a stable dose of clozapine for at least 18 weeks with a blood level of GREATER THAN 350ng/ml. The primary endpoint is the change in total PANSS scores at 12 weeks. Secondary endpoints include measures of depression, anxiety, sleep quality, quality of life, alcohol consumption, weight change, metabolic syndrome components, neurocognitive functions, and safety and tolerability of the treatment.

Results: We will present results regarding any potential significant reduction in total PANSS scores in the CBD group compared to the placebo group at week 12. Secondary outcomes will be presented on changes in sleep quality, anxiety, neurocognitive measures, depression scores, metabolic syndrome components, or alcohol consumption between the CBD and control group. Tolerability of CBD will be reported.

Discussion: The study will explore whether CBD could be an effective and safe adjunctive treatment for individuals with clozapine-resistant schizophrenia. If it shows promise in improving psychotic symptoms it has the potential to be a safe augmentation agent for people with clozapine resistant schizophrenia.

S89. OXIDATIVE STRESS RELATES TO NEGATIVE SYMPTOMS IN A GLUTEN SENSITIVE SCHIZOPHRENIA SUBGROUP

Deanna L. Kelly^{*1}, Eunkyong Kim², Sidney Redwood³, William Eaton⁴, Valerie Harrington⁵, Daniel Roche⁵, Daniela Cihakova⁶, Monica V. Talor⁶, Donna Dadkhoo⁵, Shuo Chen⁵, Matthew Glassman⁵, Stephanie Kulaga⁵, Fang Liu⁵, Bruce Patterson⁷, Gregory F. Payne²

¹*University of Maryland Baltimore, Maryland Psychiatric Research Center*, ²*University of Maryland College Park - Institute for Bioscience and Biotechnology Research*, ³*University of*

Maryland College Park, ⁴Johns Hopkins Bloomberg School of Public Health, Department of Mental Health, ⁵Maryland Psychiatric Research Center, University of Maryland School of Medicine, ⁶Johns Hopkins Bloomberg School of Public Health, Department of Pathology, ⁷Johns Hopkins University

Background: In individuals with schizophrenia-related disorders (SRD), negative symptoms are enduring and persistent, contribute more to loss of function than positive symptoms, and may be the most significant predictor of poor long-term outcomes. Understanding of their pathophysiology and discovery of new treatments have been elusive, as evidenced by the current lack of Food and Drug Administration-approved medications for negative symptoms associated with SRD.

We have identified and characterized a subgroup of people with SRD, representing about 33-38% of all people with SRD, with an immune and inflammatory response to gliadin, a protein found in wheat, barley and rye. Specifically, this subgroup has high antigliadin antibodies (AGA IgG) correlated to peripheral and central markers of inflammation. Notably, we have found negative symptom improvements in this subgroup when on a gluten-free diet compared to a gluten-containing diet (Cohen's D=0.53) in a 5-week randomized, double-blind, inpatient clinical trial (N=16).

Oxidative stress (OxSt), a marker of excess production of reactive oxygen species (ROS) vs. antioxidants, has been linked to negative symptoms and inflammatory markers in SRD. Our group has developed a global peripheral measure of OxSt that we previously found to be increased in SRD. Consumption of gluten by people with gluten sensitivity induces the overproduction of ROS, triggering a cascade of reactions that cause OxSt at both the small intestinal mucosa and the systemic level. Yet, it is unclear how OxSt relates to negative symptoms in this SRD subgroup with elevated AGA IgG.

Methods: We assayed the initial and 5-week end-point serum samples from the 16 participants in the aforementioned gluten-free diet trial. All participants had an SRD diagnosis and AGA IgG GREATER THAN 20 U (i.e., were gluten sensitive). Serum samples were frozen at -80 °C and analyzed for cytokines (IL-23) and a peripheral measure of oxidative stress (OxSt) using an Ir-reducing capacity assay (Ir-RCA). Iridium (Ir) probes "chemical space" for global information of a sample's oxidation levels, is especially sensitive to the oxidation state of sulfur-based metabolites (e.g., glutathione and protein cysteine residues), and yields results in conveniently measurable optical and electrochemical signals. Triplicate measurements of these samples showed an Intraclass Correlation Coefficient (ICC) of 0.84 which indicates good reproducibility. Negative symptoms were measured at baseline and endpoint using the Scale for the Assessment of Negative Symptoms (SANS).

Results: In this small underpowered sample, the gluten free diet, vs. the gluten containing diet, reduced OxSt over 5-weeks of treatment ($\chi^2 = 3.834$, $df=1$, $p=0.050$, $F=9.85$, $df=1,13$, $p=0.10$). (Cohen's D= -0.71). Critically, reductions in OxSt over these 5 weeks were correlated with improved negative symptoms ($r=+0.518$; $p=0.039$) and gastrointestinal (GI) symptoms ($r=+0.642$; $p=0.007$) and trended toward being associated with decreased IL-23 ($p=0.089$).

Discussion: We have identified an SRD subgroup for which a gluten-free diet appears to improve GI and negative symptoms, and these improvements may be related to reductions in OxSt. In this subgroup, a gluten-free diet may attenuate gut permeability by preventing breakdown of the tight junction barriers stimulated by IL-23 and a resultant immune-inflammatory/OxSt response in the gut and possibly the brain. These results extend our previous work showing the Ir-RCA is a sensitive, global measure of OxSt that can objectively characterize differences in psychiatric populations. In gluten sensitive individuals with SRD,

OxSt may serve as an important biomarker and help elucidate the pathophysiologic underpinnings of negative symptom pathology.

Funding Source: This work was funded in part by NIMH 1R01 MH113617-01 and NIMH R34MH100776 (PIs Eaton and Kelly).

S90. DAILY-LIFE STRESS REACTIVITY AND RECOVERY FOLLOWING VIRTUAL-REALITY-BASED COGNITIVE BEHAVIOURAL THERAPY IN PATIENTS WITH A PSYCHOTIC DISORDER

Elise van der Stouwe^{*1}, Sanne Booi², Chris Geraets¹, Roos Pot-Kolder³, Anna Kuranova¹, Mark van der Gaag⁴, Wim Veling¹

¹University Medical Center Groningen, ²Groningen University, ³The University of Melbourne, ⁴VU University Amsterdam

Background: Studies have consistently demonstrated increased stress sensitivity in individuals with psychosis. Since stress sensitivity may play a role in the onset and maintenance of psychosis, this could potentially be a promising target for treatment. The current study was the first to investigate whether reactivity to and recovery from daily-life stressors in psychosis change in response to treatment, namely virtual-reality-based cognitive behavioural therapy (VR-CBT).

Methods: 116 patients were randomized to either VR-CBT or the waiting list control group (WL). Pre-treatment and post-treatment participants completed a diary ten times a day during six to ten days. Multilevel analyses were used to model the time-lagged effects of daily stressful events on negative affect (NA) and paranoia symptoms to examine reactivity and recovery.

Results: There was a significant difference in NA reactivity. VR-CBT showed higher NA at post-treatment compared to pre-treatment than WL (bpre=0.14; bpost=0.19 vs bpre=0.18; bpost=0.14). There was a significant difference in NA recovery and paranoia recovery between the groups at lag 1: VR-CBT showed relatively lower negative affect (bpre=0.07; bpost=-0.06) and paranoia (bpre= 0.08; bpost=-0.10) at post-treatment compared to pre-treatment than WL (bpre=0.08; bpost=0.08; bpre=0.04; bpost=0.03).

Discussion: Negative affect and paranoia recovery improved in response to treatment. Increased NA reactivity may be explained by a decrease in safety behaviour in the VR-CBT group. The discrepancy between reactivity and recovery findings may be explained by the inhibitory learning theory that suggests that an original threat reaction may not erase but can be inhibited as a consequence of exposure therapy.

S91. PHARMACOKINETIC SIMULATIONS OF ARIPIPRAZOLE 2-MONTH READY-TO-USE LONG-ACTING INJECTABLE TO INFORM ADMINISTRATION IN ADULT PATIENTS WITH SCHIZOPHRENIA

Yanlin Wang¹, Matthew Harlin^{*1}, Frank Larsen², Xiaofeng Wang¹, Wansu Park³, Benjamin Rich⁴, Jogarao V. Gobburu⁵, Arash Raoufinia¹

¹Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC), ²H. Lundbeck A/S, ³Alnylam Pharmaceuticals, ⁴InnoMx Inc., ⁵University of Maryland

Background: Ongoing symptom control in patients with schizophrenia relies on long term, consistent antipsychotic treatment. However, a meta-analysis of available data for adherence to oral antipsychotics in patients with schizophrenia suggests that adherence rates are ~70% (range: 50–78%), which is below the 80% threshold widely used to define satisfactory adherence (1). Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a novel long-acting injectable formulation of aripiprazole for gluteal intramuscular administration once every 2 months. Ari 2MRTU 960 was developed to extend exposure to aripiprazole concentrations within the established aripiprazole therapeutic window from 1 month (with aripiprazole once-monthly [AOM]) to 2 months. Extending the dosing interval beyond 1 month may reduce treatment burden for patients and clinicians and improve adherence. A combined population pharmacokinetic (popPK) model for oral aripiprazole, AOM, and Ari 2MRTU was developed. Use of this model to explore dosing with Ari 2MRTU in scenarios relevant to the European clinical context is reported herein.

Methods: Aripiprazole plasma concentration–time profiles were simulated for various Ari 2MRTU initiation and maintenance scenarios. Simulations were performed using Pumas v2.0 in a population of 1,000 virtual patients. Model covariates were assigned to virtual patients by resampling from the total patient population used to develop the popPK model; individual random effects were obtained by resampling from patient subgroups with the most relevant/robust information for each PK parameter of interest. Poor metabolizers of CYP2D6, in whom the PK profile of lower-dose Ari 2MRTU 720 mg was studied, comprised 5% of the virtual population, except for simulations requiring all patients to be normal or poor CYP2D6 metabolizers.

Results: Across multiple simulated initiation scenarios, Ari 2MRTU 960 resulted in aripiprazole concentrations that were comparable to AOM 400, and within the established aripiprazole therapeutic window (95–534 ng/mL) (2,3). This was the case for:

- initiation of Ari 2MRTU 960 after a direct transition from AOM 400
- initiation of Ari 2MRTU 960 plus 14 days of overlapping oral aripiprazole 10 or 20 mg/day following stabilization on oral aripiprazole 10 or 20 mg/day, and
- initiation of Ari 2MRTU 960 on Day 28 after administration of AOM 400 on Day 0 plus 14 days of overlapping oral aripiprazole 20 mg/day following stabilization on oral aripiprazole 20 mg/day.

In maintenance scenarios, median trough concentrations were 191, 144, 110, and 80.1 ng/mL after an Ari 2MRTU 960 dosing delay of 2, 4, 6, and 8 weeks, respectively, increasing in these groups to 231, 217, 205, and 196 ng/mL, respectively, 56 days after Ari 2MRTU 960 was given (plus 14 days of oral aripiprazole 10 mg/day overlap in the last scenario). In CYP2D6 poor metabolizers, Ari 2MRTU 720 mg showed steady-state aripiprazole concentrations comparable to AOM 300 mg. Compared with Ari 2MRTU 960 without a CYP3A4 or CYP2D6 strong inhibitor, aripiprazole concentrations were similar with Ari 2MRTU 720 plus a CYP3A4 strong inhibitor and higher with Ari 2MRTU 720 with a CYP2D6 strong inhibitor.

Discussion: Discussion Model-based simulations across a variety of dosing scenarios relevant to the European clinical context showed that aripiprazole plasma concentrations over the 2-month dosing interval with Ari 2MRTU 960 were comparable to those for AOM 400.

References

1. Yaegashi et al. *CNS Drugs* 2020;34:579–598.
2. Wang et al. *Clin Pharmacol Drug Dev* 2022;11(2):150–164.

S92. OUTCOMES OF THE CLINICAL TRIAL ETRO TO EVALUATE AN SMARTPHONE APP-BASED TREATMENT PROGRAMME FOR ADOLESCENTS AT ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

Nina Traber-Walker*¹, Miriam Gerstenberg², Fabian Probst³, Camille Bertossa³, Claudia Bühlmann³, Lukasz Smigielski⁴, Susanne Walitza², Maurizia Frascini²

¹Psychiatric University Hospital Zurich, ²University of Zurich, Department of Child and Adolescent Psychiatry, ³Psychiatric University Hospital Zurich, Department of Child and Adolescent Psychiatry and Psychotherapy, ⁴University of Zurich, Switzerland

Background: The goal of preventing psychotic disorders has led researchers to focus on the early identification of individuals at clinical high risk (CHR) for psychosis and to treat CHR symptoms. CHR symptoms usually appear during adolescence and young adulthood. This is a very sensitive developmental period and the CHR condition is associated with increasing functional impairment. Age-appropriate treatment approaches are needed that address youth-specific concerns, complex symptomatology, associated distress and functional impairment. However, there is a lack of research on treatment strategies for this vulnerable age group. To address this gap, the combined treatment programme "Robin" (standardised manual and smartphone app) has been developed. The treatment programme targets CHR symptoms, comorbid symptoms as well as improvement of quality of life and daily functioning. The "Robin Z" smartphone app is an additional treatment tool to support patients between the therapy sessions. While a number of studies on smartphone-assisted interventions have shown promising effects in adult psychosis patients, little is known about their use with minor patients. "Robin Z" is one of the first smartphone apps designed for adolescent patients with CHR or full-blown psychotic symptoms.

Methods: The ETRO study is a prospective, naturalistic follow-up study. A total of 40 help-seeking CHR adolescents (65% female, mean age 15.31) were recruited for the intervention group (16 weekly individual sessions + 4 family sessions). For the control condition (treatment as usual TAU), 72 participants (34% female, mean age 15.07) from a previous study have been included. CHR-symptoms, comorbid symptoms, functioning, self-efficacy and quality of life will be monitored at six time points (baseline, during the treatment period, immediately after intervention, and 6, 12 and 24 months later) and compared with the respective measures of the active control group.

Results: The group comparison of the transition rate to psychosis shows (Fisher's exact test, p LESS THAN 0.1) that there are statistically significantly fewer transitions in the intervention group (n=1, 2.5%) than in the control group (n=10, 16.9%).

An initial analysis of the control group showed a significant improvement in global functionality (F=11.88, p=0.001) compared to baseline at one-year follow-up. In terms of self-efficacy, there was a statistical trend towards improvement across the follow-up time points (F=4.02, p=0.053). However, there was no statistically significant improvement in quality of life over time.

The follow-up data of the intervention group are currently being analysed and prepared for the congress in Florence.

Discussion: An initial comparison showed that the rate of transitions to psychosis was significantly lower in the intervention group than in the control group. First evaluations of the data from the control group with treatment as usual already demonstrated treatment effects. We assume that the data from the intervention group will differ from the control group and that even more treatment effects can be expected.

To our knowledge, our clinical trial is the first to evaluate a therapy manual with a smartphone app for adolescents at clinical high risk. The results are therefore of high importance for research in early intervention and smartphone-based treatment programmes.

S93. USING COMPUTATIONAL MODELLING OF P300 RESPONSES TO INVESTIGATE CIRCUIT CHANGE IN CLINICAL HIGH-RISK FOR PSYCHOSIS: INSIGHTS FROM THE NAPLS-2 SAMPLE

Julia Rodriguez-Sanchez^{*1}, Daniel J. Hauke¹, Rick Adams¹, Catalina Mourgues-Codern², Tyrone Cannon², Daniel Mathalon³, Albert Powers²

¹University College London, ²Yale University, ³University of California, San Francisco

Background: Hallucinations and delusions have been primarily studied in the context of fully-formed psychosis. However, the neurobiological mechanisms underlying the development of these symptoms remain unclear. Recent evidence suggests that the majority of patients experience delusions prior to hallucinations. Understanding the circuit changes that accompany the onset of different symptoms like hallucinations and delusions is crucial for identifying targeted preventative strategies. We investigated effective connectivity in young individuals meeting clinical high-risk criteria for psychosis (CHR-P) with dynamic causal modelling (DCM) of electroencephalography (EEG) recorded during an auditory oddball paradigm. Notably, individuals at CHR-P have been shown to exhibit diminished P300 responses to oddball stimuli (Hamilton et al., 2019, JAMA Psychiatry), an effect which is also observed in patients with schizophrenia and has been linked to clinical outcomes.

Methods: Baseline data from 571 CHR-P participants, including 77 participants who converted to psychosis during the 24-month follow-up, and 241 healthy controls were collected as part of the North American Prodrome Longitudinal Study (NAPLS-2). We defined five different subgroups among CHR-P participants based on symptom onset: 130 with only delusions at baseline, 28 with only hallucinations, 219 with both delusions and hallucinations, 131 with both delusions and hallucinations who developed delusions first, and 63 with both delusions and hallucinations who developed hallucinations first. We modelled EEG responses to standard and target tones in the superior temporal gyrus (STG)-auditory frontoparietal network. Each region comprised superficial and deep pyramidal cells, spiny stellate cells and inhibitory interneurons. Additionally, we explored a longitudinal subsample of 20 CHR-P participants who presented with only delusions at baseline, including 10 participants who developed hallucinations during the follow-up period and 10 matched controls.

Results: Reduced P300 amplitude in CHR-P was explained by increased superficial pyramidal cell self-inhibition (decreased synaptic gain) in the STG (posterior probability $P > 0.95$). Converters, but not non-converters, showed increased self-inhibition across the STG-auditory frontoparietal network, as well as increased forward connectivity from the STG and superior parietal cortex compared with controls ($P > 0.95$). Among CHR-P subgroups, participants with both hallucinations and delusions ($p = .01$, $d = 0.24$) and participants who developed delusions before hallucinations ($p < .001$, $d = 0.41$)

had significantly reduced P300 amplitudes compared with controls, while baseline P300 responses in participants with only delusions were similar to those of controls. Consistent with this, longitudinal data from CHR-P participants who presented with only delusions at baseline showed P300 amplitude reductions following the onset of hallucinations ($p = .02$). Self-inhibition within the STG ($P > 0.95$) and backward connectivity from the superior frontal cortex ($P > 0.99$) were both increased at 12 months relative to baseline in this group.

Discussion: Our findings reveal widespread circuit abnormalities in CHR-P individuals who later convert to psychosis and provide preliminary evidence for changes in bottom-up and top-down connectivity as hallucinations develop. They also highlight alterations in cortical excitability in CHR-P, aligning with aetiological theories of schizophrenia that implicate disturbances in excitatory/inhibitory balance (Krystal et al., 2017, *Biol Psychiatry*). This approach holds promising potential for investigating circuit changes in emerging psychosis non-invasively and may aid in identifying specific mechanisms associated with primary versus secondary symptoms of schizophrenia, ultimately improving clinical outcomes.

S94. CONVERGING EVIDENCE FOR INCREASED PRIOR WEIGHTING IN PSYCHOSIS RISK AND EARLY PSYCHOSIS

David Benrimoh^{*1}, Catalina Mourgues², Jai Shah³, Al Powers⁴

¹*McGill University*, ²*Yale University School of Medicine*, ³*Department of Psychiatry – McGill University – Montreal – Canada*, ⁴*Yale University*

Background: There is increasing empirical evidence for the finding that psychotic symptoms in schizophrenia, such as hallucinations, are driven by a hyper-precision of prior beliefs compared to incoming sensory evidence. However, it remains unclear whether this increased prior precision is a secondary or compensatory process, or if it is a primary process which drives the development of psychotic symptoms. This distinction is relevant as there may be different neural processes involved depending on the sequence of information processing changes, suggesting different potentially effective intervention strategies. In addition, understanding the timing of computational changes will be important if they are to be useful for generating novel staging methods in early psychosis and psychosis risk.

Methods: I will examine evidence from two recent studies which suggest that increased prior weighting may be present early in psychosis. In the first study, we studied responses to a linguistic version of the conditioned hallucinations (CH) task in an online sample of 88 participants from the general population without psychosis diagnoses. In a separate dataset of 695 patients with first episode psychosis who retrospectively reported their prodromal symptoms from PEPP-Montreal, we examined whether hallucinations or delusions were more likely to be reported as first symptoms, and determined which symptom type was more persistent over time.

Results: In the online CH study, higher CH rates were observed both in those with recent hallucinatory experiences as well as participants with high hallucination proneness; CH rates were positively correlated with increased prior weighting; and increased prior weighting was related to hallucination severity. Participants with recent hallucinatory experiences as well as those with higher hallucination-proneness had higher stimulus thresholds, lower sensitivity to stimuli presented at the highest threshold, and had lower response confidence, consistent with lower precision of sensory evidence. In the PEPP dataset, most patients reported delusion-

spectrum rather than hallucination-spectrum symptoms as their first prodromal symptom (22% vs. 7%) and their first psychotic symptom: (62% vs. 22%). In addition, after psychosis and treatment onset, delusions tended to persist at a higher level than hallucination symptoms.

Discussion: It has often been hypothesized that altered perceptual experiences are the first symptoms in incipient psychosis, with delusions forming as compensatory beliefs to explain away these experiences. These results suggest that if this occurs, it is in a minority of patients, with delusions-type symptoms usually being the first psychotic symptoms and remaining present at threshold for longer, potentially serving as priors which help to drive hallucinatory experiences. These two different studies help to establish the likely important role of altered priors in the generation of psychotic experiences early in the illness, while at the same time continuing to highlight the importance of altered sensory precision. Further longitudinal studies are needed in order to determine the precise sequence of information processing changes which lead to psychosis, and to identify potential subgroups within the psychosis risk population which may experience different trajectories- and therefore may have different underlying neurobiology and treatment considerations.

S95. CHANGES IN THE USE OF PRIOR SEMANTIC KNOWLEDGE RELATIVE TO SENSORY INFORMATION IN PATIENTS IN ACUTE PSYCHOSIS AND PSYCHOTIC REMISSION AND THE LINK TO HALLUCINATIONS: A LONGITUDINAL APPROACH

Franziska Knolle*¹

¹*Technical University of Munich*

Background: Schizophrenia is associated with a wide range of language alterations. Interestingly, the recent predictive coding account does not only provide a testable theory for the explanation of positive symptoms in schizophrenia, but is also one of the most promising theories of language processing. Experimental evidence of the predictive coding account of psychosis suggests that an overweighing of sensory likelihood may occur at lower levels (e.g., early sensory processing areas) due to increased dopamine activity causing aberrant salience and leading to delusions, while an overweighting of prior beliefs at higher levels, potentially caused by altered glutamatergic receptor signalling, may cause hallucinations. The interplay of prior information and sensory likelihood can be tested efficiently during language processing, due to its predictive nature. This study therefore investigates (1) how the use of prior knowledge relative to sensory information in a predictive language task changes when patients with schizophrenia transition from acute psychosis to psychotic remission, and (2) whether an overreliance on prior semantic knowledge induces conditioned hallucinations in a state of acute psychosis, but not in a state of psychotic remission.

Methods: Using a longitudinal approach, we assessed 20 patients with schizophrenia first during a state of active psychosis and then, after approximately three months, in a state of psychotic remission. Controls were assessed at two similarly delayed time points. All participants completed a predictive language paradigm in which they listened to sentences of varying predictability (e.g., high predictability: “Goethe was a famous German ... poet”; low predictability: “Next to the window was a ... hole”). The final word of each sentence (e.g., “poet” or “hole”) was degraded in clarity using a noise vocoding algorithm; degradations were available in four levels from fully unintelligible to fully intelligible. After listening to the full sentence, participants were asked to report the word they perceived, assessing conditioned hallucinations. We fitted a linear Bayesian regression model to estimate the prior weight which

presents the relative strength of the prior over the sensory input. Using a repeated measurement model, we compared prior weights and conditioned hallucinations across time points and groups. Furthermore, we correlated those with positive symptoms at both time points.

Results: The modelling results revealed that prior knowledge relative to sensory information was overweighed in patients compared to controls, but especially during the first time point, when patients were in a state of acute psychosis. The same relationship was detected for conditioned hallucinations. Furthermore, patients with stronger psychotic symptoms perceived more conditioned hallucinations, but this positive correlation was only present during the acute psychotic state and absent during the state of remission.

Discussion: This study shows that prior knowledge was overweighted during a language perception task in schizophrenia patients during an acute state of psychosis, and less so during psychotic remission. Importantly, overweighting prior knowledge and stronger psychotic symptoms were linked to experiencing more conditioned hallucinations. Taken together, this study provides novel evidence of how alterations in predictive language processing change when schizophrenia patients change from an acute to a remitted state of psychosis and how this contributes to the formation of hallucinations.

S96. NARRATIVE COMPLEXITY INDEX AS A SCREENING TOOL FOR SOCIAL COGNITION LOSS IN THE CONTEXT OF PSYCHOSIS

Bárbara Malcorra^{*1}, Marina Ribeiro², Tamara Meletti¹, Luísa Jensen¹, Natália Mota³

¹*Mobile Brain*, ²*Mobile Brain*; *Universidade Federal do Rio Grande do Norte (UFRN)*,

³*Mobile Brain*; *Universidade Federal do Rio de Janeiro (UFRJ)*

Background: Schizophrenia patients present a range of functional and social impairments that affect their daily performance and impair their quality of life. Among the possible contributing factors to this drop in patients' functional performance are impairments in social cognition. However, such social deficits still need to be well established. Based on this, the present study aims to investigate the application of narrative complexity (a measure based on word-recurrence graphs weighted by years of education and compared to a normative curve) as an indicator of loss of social cognition in adults' speech compared with their educational path, considering the importance of seeing the deterioration of this population's communication skills.

Methods: Narratives from 232 Brazilian Portuguese-speaking individuals were collected. One hundred sixty-seven (167) typical subjects and 65 patients with psychotic symptoms (age from 2 to 60; years of education from none to 20 years of education) were requested to produce emotional narratives (such as dream reports and stories based on affective pictures chosen from the IAPS database). The narratives were then represented as word-recurrence graphs, in which a node represents each word, and the sequence between them is represented by edges (directed arrows). We used sliding windows of 30 words to control for verbosity differences, with a 50% overlap between windows. We then calculated the number of Nodes (proxy to lexical diversity), repeated edges – RE (or short-range recurrence), nodes inside the largest strongly connected component – LSC (connectedness or long-range recurrence), and average shortest path – ASP (graph size). A multilinear correlation between word-recurrence graph attributes and years of formal education defined narrative complexity (NC). The combination of graph attributes linked to the individual's level of education makes up the narrative complexity index. We then produced a normative curve for each year of education and calculated the values of the narrative complexity index and its respective percentile.

Results: The multilinear correlation between word-recurrence graph attributes and years of education was significant and explained 36% of data variance ($R^2 = 0.36$, $p < 0.001$). We compared the mean and standard error of the two measures (narrative complexity index and its percentile) between the typical and atypical groups. The results demonstrate that the raw values of narrative complexity do not differ between the two groups (typical group: mean = 5.24, standard error = 0.18; atypical group: mean = 5.22, standard error = 0.29; $p = 0.5846$). However, when adopting the percentile perspective, the loss related to education can be seen (typical group: mean = 68.65, standard error = 2.24; atypical group: mean = 50.14, standard error = 4.81; $p = 0.0015$).

Discussion: These results demonstrate the potential relevance of narrative complexity to discriminating between controls and psychosis patients, pointing to the tool's effectiveness when considering the percentile values of the participants' narrative complexity index. Therefore, it can be applied as an initial step to screening the risk of loss of social cognition in the context of schizophrenia.

S97. BRAIN GROWTH CHARTS: A NORMATIVE MODELLING APPROACH TO INVESTIGATE BRAIN DEVIATIONS IN PATIENTS WITH SCHIZOPHRENIA AND FIRST-DEGREE RELATIVES

Francesco Massari^{*1}, Thomas Wolfers², Gabriele De Agazio¹, Annalisa Lella¹, Roberta Passiatore¹, Giuseppe Blasi³, Aaron Goldman⁴, Teresa Popolizio⁵, Antonio Rampino¹, William Ulrich⁴, Daniel R. Weinberger⁴, Alessandro Bertolino⁶, Giulio Pergola⁷, Pierluigi Selvaggi⁸

¹Università degli Studi di Bari "Aldo Moro", ²University of Tübingen, ³Università degli Studi di Bari Aldo Moro; Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, ⁴Lieber Institute for Brain Development - Johns Hopkins Medical Campus, ⁵IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, ⁶Università degli Studi di Bari "Aldo Moro"; Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, ⁷Università degli Studi di Bari "Aldo Moro", Lieber Institute for Brain Development - Johns Hopkins Medical Campus, ⁸Università degli Studi di Bari "Aldo Moro"; Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Case-control studies have shown structural and functional brain alterations in patients with Schizophrenia (SCZ) and familiar high-risk individuals (FHR) who share part of the genetic risk. However, this approach carries the risk of settling an artificial symmetry between Healthy Controls (HC) and patients, which might not reflect the heterogeneous biology of the disease. Recently, the Normative Modelling (NM) approach has been proposed to parse neurobiological heterogeneity in psychiatric disorders by estimating individual deviations from the normative population through covariate distribution (i.e. age, gender). Previous NM studies in SCZ showed a pattern of heterogeneous increased negative deviations from the norm with respect to HC. To date, it is still unclear to what extent brain deviations identified with NM are linked to genetic risk or to disease-state factors. To fill this gap of knowledge we used NM to investigate deviations in brain structural metrics in SCZ, FHR, and HC. We hypothesized that FHR share a pattern of deviations with SCZ. We also investigated the association between genetic risk and brain deviations through the Polygenic Risk Score for Schizophrenia (PRS) in areas suggestive of an intermediate phenotype.

Methods: We applied a validated normative model based on a large set of structural Magnetic Resonance Imaging (MRI) data (N= 58,836, Age range= 2-100 years) to predict brain features in our test sample (HC= 834, FHR= 166, SCZ= 255) obtained merging 2 datasets (i.e., University of Bari and Lieber Institute for Brain Development). FHR group included unrelated and unaffected siblings and parents of SCZ. We processed T1-weighted MRI images using the FreeSurfer recon all command, extracting brain structural metrics by applying the Destrieux atlas for cortical regions and Fischl atlas for subcortical areas. The segmentation resulted in 150 Regions of Interest (ROI) of cortical thickness, cortical surface, and 14 ROIs of subcortical volumes. We marginalized the site effect through an adaptation sample (HC= 100). Quality check through Euler number was performed to remove artifact images (N= 27). Consistently with previous studies in patients with SCZ, we focused on negative deviations only. We computed Z-scores that quantitatively assessed brain feature differences between the estimated normative trajectory and each subject's true measure. We computed extreme deviations (Z-score LESS THAN -2.6) for each subject and ROI and we counted how many subjects extremely deviated from the norm. Then we normalized the count to the group size, obtaining the percentage of extremely deviating subjects per ROI. We performed permutation-based ANOVA and post-hoc t-tests for extreme and mean Z-scores between-group comparisons. We tested the association between Z-scores and PRS through ANCOVA. False Discovery Rate (FDR) and Bonferroni method were used to correct for multiple comparisons where needed.

Results: SCZ showed a higher number of extreme deviations in cortical thickness and subcortical volumes than FHR (pBONF FHRvsSCZ= 0.0033, pBONF FHRvsSCZ= 0.0049, respectively) and HC (pBONF HCvsSCZ = 0.0001, pBONF HCvsSCZ= 0.008, respectively). Descriptively, FHR showed a higher number of extreme deviations as compared with HC but differences were not significant (pBONF HCvsFHR GREATER THAN 0.085). We found an overlapping percentage of extreme deviations in brain regions in SCZ around 4-6%. FHR had a significantly higher mean of negative Z-scores than HC in the surface of the right middle frontal sulcus (pBONF= 0.0024) and in the thickness of the whole right hemisphere cortex (pBONF= 0.0034), left fusiform gyrus (pBONF= 0.0037), right lingual gyrus (pBONF= 0.0086) and right anterior collateral transverse sulcus (pBONF= 0.0022). SCZ showed higher negative deviations than HC in the same regions, without significant FHR/SCZ differences. Higher PRS5 negatively correlated with right hemisphere thickness Z-scores in the whole group (Pearson's $r = -0.108$, pFDR= 0.037). No significant PRS by group interaction was found ($F = 0.096$, $p = 0.9$). No significant main effect of PRS or PRS by group interactions on Z-scores from other ROIs were found (all pFDR GREATER THAN 0.174).

Discussion: Our findings suggest that part of the heterogeneity in brain structural metrics, evaluated as deviations from the normative distribution, is shared between SCZ and FHR. However, the small effect sizes detected in the FHR-HC comparison and in the association with PRS suggest that heterogeneity in brain structural metrics is only modestly explained by variability in genetic risk. Future studies should investigate the impact of state-dependent variables (e.g. treatment effects, disease severity) on brain morphology heterogeneity in SCZ.

S98. SEMANTIC SPACE CONTRACTS IN PSYCHOSIS AND REVEALS NEUROFUNCTIONAL CHANGES IN THE HIERARCHICAL ORGANIZATION OF COGNITION

Rui He^{*1}, Claudio Palominos-Flores¹, Han Zhang¹, María Francisca Alonso², Lena Palaniyappan³, Wolfram Hinzen¹

Background: Atypical forms of discourse in psychosis were conceptualized early on as revealing ‘loosening of associations’, quantified as the decrease in semantic similarity between consecutive word pairs using embeddings from large language models. Recent studies have contradicted this, revealing a contraction of the semantic space as indexed by higher semantic similarity. In this presentation, we give a comprehensive view of the alterations in the structure of meaning, using different language models in a hypothesis-driven way, and across multiple metrics and languages, followed by correlations with neurofunctional changes measured using 7T resting-state fMRI.

Methods: Analyses were performed on picture descriptions from twenty-nine untreated first-episodic psychosis (FEP) patients, matched to twenty-nine healthy controls (HC) on age, gender, and education. Firstly, five language models, FastText, Infsent, BERT, SBERT, and CLIP, which differ in their sensitivity to context and grammar, were used to quantify semantic distances crossed between successive tokens/utterances, and semantic perplexity indicating unexpectedness in continuations. Finally, we explored the structure of meaning as graphs, using thresholded semantic affinity matrices from similarities between lexical entities and utterances. These semantic and syntactic measures were correlated with a functional gradient across the whole cortex and within a semantic network comprising the left default mode and limbic regions. Parts of these analyses were replicated in datasets in other languages, including Chilean Spanish, Taiwan Mandarin, and German.

Results: FEP showed higher mean semantic similarity as computed from FastText, Infsent, and SBERT, but lower from BERT. Their descriptions showed lower similarities to the picture stimuli as quantified with CLIP, as well as being more perplexing (higher entropy). Semantic graphs, from both lexical categories and utterances, highlighted higher centrality and lower small-worldness coefficients in FEP. Such shrinking of the semantic space was also observed in free speech samples from chronic schizophrenia in Chilean Spanish, and picture descriptions in both Taiwanese Mandarin and German. These semantic measures predicted the dispersion between the visual and default mode networks in the first cortical gradient. FEP patients also exhibited alterations in the argument structure, with fewer and simpler noun phrases, but more and longer verb phrases.

Discussion: These results reveal that the traditional intuition of a ‘looser’ semantic space is not born out by crosslinguistic data using a variety of lexically-oriented language models, while metrics of perplexity at the grammatical level do vindicate this intuition. Alternations of the semantic space may act as a promising read-out of neuropathological changes in the hierarchical organization of cognition in the brain.

S99. SPEECH AND LANGUAGE MODELS PERFORM BETTER IN WOMEN WITH A SCHIZOPHRENIA SPECTRUM DISORDER THAN IN MEN

Janna de Boer¹, Alban Voppel², Silvia Ciampelli¹, Hugo Corona Hernández¹, Sanne Schuite-Koops¹, Iris Sommer¹, Silvia Ciampelli*³

¹University Medical Center Groningen, ²McGill University, Department of Psychiatry,

³University of Groningen, University Medical Center Groningen

Background: Natural language processing (NLP) and speech processing techniques have proven effective in a range of applications in psychosis. However, recent studies suggest that these models may depend largely on demographic and social characteristics, rather than providing a reflection of symptoms. An obvious source of variation in language analyses is sex. A men's voice is for example much lower in pitch than the voice of a women, but also semantic sex differences have been reported. Recent work from our group suggests that syntactic language analyses are different for men and women with a schizophrenia spectrum disorder (SSD). More specifically, women with SSD had lowest syntactic scores, while female controls had highest scores, compared to men with and without SSD. This resulted in higher diagnostic classification accuracy in women compared to men. The aim of the current study is to analyze whether this sex-specific pattern also applies to other forms of language and speech processing techniques.

Methods: The current study reused data from two previously published studies by our group. In both studies, voice recordings were made via a semi-structured interview lasting at least five minutes. Part 1 included 142 patients with SSD and 142 healthy controls (HC) matched for age, sex and parental education. Acoustic parameters were extracted from the audio recordings with OpenSMILE, using the extended Geneva Acoustic Minimalistic Parameter Set (eGeMAPS), which includes standardized analyses of pitch (F0), speech quality and pauses. Part 2 included 94 patients with SSD and 73 HC matched in age, sex and parental education. The voice recordings were manually transcribed and used to calculate semantic word similarity using word2vec. In both parts, random forest classifiers were trained separately on the women and the men. Because the accuracy generally increases in a smaller sample due to overfitting, the analyses were repeated in non sex-specific samples of the same size. 10-fold cross-validation was used for each model.

Results: In part 1, the original classifier had an accuracy of 86.1% in distinguishing between patients with SSD of both sexes and healthy controls. When the classifier was trained only on the female sample, the accuracy increased to 89.6% (n = 48 SSD and n = 47 healthy controls) while in the males it reduced to 83.5% (n = 94 SSD and n = 93 healthy controls). In the non sex-specific subsamples the respective accuracy rates were 87.4% (n = 95) and 89.8% (n = 187). In part 2, the original diagnostic accuracy in the full sample was 80.0%. In the female sample the accuracy increased to 87.2% (n = 26 SSD and n = 24 healthy controls), while in the males it reduced to 77.8% (n = 68 SSD and n = 49 healthy controls). In the non sex-specific subsamples these were 81.5% (n = 50) and 83.3% (n = 117).

Discussion: Our results indicate that there are substantial differences in language-based classification performance between men and women. Sex-specific classifiers based on speech and language processing perform better in women than in men, because the differences between controls and patients with schizophrenia spectrum disorder are greater in women than in men. These findings confirm and extend previous research by our group by showing that this applies to a range of speech and language processing techniques (i.e., syntactic analyses, acoustic analyses and word2vec analyses). The results also show that the performance improves in smaller samples, as expected, most likely due to overfitting. Future studies should incorporate sex in NLP classifiers, either by training separate classifiers or by including sex as a confounder in the model.

S100. TRANSPROGNOSTIC PREDICTION MODELS IN CHRONIC SCHIZOPHRENIA

Fiona Coutts*¹, Christoph Correll², Paris Lalouis¹, Nikolaos Koutsouleris³

¹King's College London, Institute of Psychiatry, ²Charité - Universitätsmedizin Berlin,

³Ludwig-Maximilian-University, KCL

Background: Individuals with psychotic disorders have highly heterogeneous clinical and functional outcomes. There is large body of research in early psychosis populations dedicated to understanding this heterogeneity and predicting individual outcomes in order to target those with the highest risk with early interventions. Far less research has focused on outcome prediction in chronic schizophrenia, even though knowing a patient's future response to medication, long-term functioning, or relapse risk could guide decisions relating to the type of care they require. The aim of my research is to develop accurate models predicting symptomatic outcomes in chronic schizophrenia, and to see if these models are influenced by how far into the future we wish to predict.

Methods: The sample consists of 680 individuals with chronic schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) clinical trial, split into a discovery sample (596 individuals from 48 sites) and a validation sample (84 individuals from the remaining 7 sites). Participants were included in the study if they were between 18 and 65 years of age, did not have major contraindication to any of the study drugs, had more than one episode of psychosis and more than two years since their first psychotic episode.

In the discovery sample, machine learning models using baseline clinical, sociodemographic, and cognitive variables will predict symptom severity, defined as the Positive and Negative Syndrome Scale (PANSS) total score at 3 months and 12 months after baseline, and a binary measure of symptomatic remission defined by the Remission in Schizophrenia Working Group criteria. Any models above 65% will be replicated in the validation cohort. Machine learning analyses will be performed in Neurominer 1.2: all models will have a 10-by-10 nested cross-validation structure. Support vector regressions will be used for the continuous symptom severity outcomes, and support vector machines will be used for the binary symptomatic remission outcomes. Model performances will be assessed by Pearson's r for linear models, and Balanced Accuracy for classification models.

Results: The discovery sample had a mean age of 41.3 years, 72.8% of the sample were male, and the mean PANSS score at baseline is 75.6. The mean age of the validation sample was 41.8, 86.9% of this sample were male, and the mean PANSS total score at baseline was 69.1. Gender and PANSS total scores were significantly different between the discovery and validation samples ($p < 0.05$).

In the discovery sample, at 3 months after baseline the mean PANSS total score was 67.4, and 69.6% of the sample were in non-remission. At 12 months the mean PANSS total score was 65.3, and 65.6% of the sample were in non-remission. In the validation sample, at 3 months after the mean PANSS total score was 64.3, and 69% of the sample were in non-remission. At 12 months the mean PANSS total score was 62.1 and 59.5% were in non-remission. The 12-month PANSS total score was significantly lower in the discovery sample ($p=0.049$), but there were no significant differences in the other outcomes.

Preliminary results using a subset of the final feature space show that symptom severity at 12 months can be predicted by baseline quality of life, years in education, functioning, depressive symptoms, and risperidone use ($r=0.53$, $p=1.39 \times 10^{-55}$). The PANSS positive ($r=0.34$, $p=1.7 \times 10^{-22}$), PANSS negative ($r=0.48$, $p=2.1 \times 10^{-45}$), and PANSS general ($r=0.49$, $p=1.8 \times 10^{-47}$) subscales were also significantly predicted.

Discussion: These initial results suggest continuous symptomatic outcomes can be well-predicted in chronic schizophrenia patients. Further analyses will determine whether this prediction is affected by the time that the outcome was measured.

S101. EXPLORATORY NETWORK ANALYSIS OF INDIVIDUAL AND GROUP-LEVEL SOCIAL PROCESSES IN SCHIZOPHRENIA USING INTENSIVE LONGITUDINAL DATA

Joseph Maimone^{*1}, Gil Grunfeld¹, Jasmine Mote¹, Kim Mueser¹, David Gard², Daniel Fulford¹

¹*Boston University*, ²*San Francisco State University*

Background: People with schizophrenia (SZ) can experience acute social deprivation, resulting in severe impacts on mental and physical well-being. Interventions designed to improve social connection in this population have limited efficacy, possibly due to observations that mechanisms supporting social connection are heterogeneous and idiosyncratic. We propose that rigorous understanding of individual patterns of social processes in SZ may set the stage for more targeted treatment approaches.

Methods: In this study, 31 individuals (median age = 48 years, range 22 to 65; 52% male; 55% non-White) diagnosed with schizophrenia or schizoaffective disorder completed an eight-week intervention designed to enhance social goal attainment through smartphone-delivered social skills and motivation training. The app prompted them twice a day to engage with tailored training content, and to complete a brief ecological momentary assessment (EMA) battery about their social motivation (e.g., “How much would you like to talk to or interact with someone right now?”), appraisals of recent social interactions (e.g., “How well do you think you communicated in those conversations”), and affect (e.g., “How [happy, sad, excited, calm, anxious, angry] did those conversations make you feel?”). In the current analysis, we seek participant-specific patterns between social motivation, social appraisals, and affective states to study individual differences in social connection. We use group-iterative multiple model estimation (GIMME) to achieve this goal. GIMME produces directed network plots for each individual, which show whether a relationship between any two nodes exists, as well as the relationship’s magnitude, sign, and direction. An advantage of this approach is that it also produces a group-level network plot by selecting those relationships that are significant and present for a majority (at least 75%) of the sample. This approach enables comparison between individual and group-level patterns to see (1) what node-to-node relationships the sample has in common and (2) how individual processes differ from one individual to the next above and beyond the group relationships.

Results: GIMME requires at least 60 observations per individual to produce reliable results; 16 individuals (median age = 48 years, range 22 to 65; 44% male; 63% non-White) met this threshold (mean observations = 95; range: 64-115) and are included in this analysis. Inspection of variances demonstrated sufficient variability within each individual across all variables for GIMME analysis. Some participants showed inter-item correlations ≥ 0.90 , primarily within positive affect variables or negative affect variables, suggesting a single positive affect node and single negative affect node will be appropriate for network analysis. Final data preparation is under way; once ready, the results will characterize individual- and group-level networks of social processes, providing insights into the presence, direction, and strength of relationships among social motivation, appraisals, and affect in those with SZ over time.

Discussion: Intensive longitudinal data that shed light on idiographic associations between momentary measures of social processes and affect could be useful for approaches to individualized interventions to improve social connection in SZ. For example, models may show that for one participant, positive affect is strongly tied to social motivation; another individual's model may show that social appraisals play a more central role. Differences such as these might suggest different and potentially more effective targets for treatment for each individual. Final results will allow for a comprehensive description of these possibilities and implications for intervention will be discussed.

S102. DOPAMINE 1 RECEPTOR (D1R) MECHANISMS FOR HALLUCINATIONS AND WORKING MEMORY DEFICITS IN SCHIZOPHRENIA: A PRELIMINARY COMPUTATIONAL MODELLING STUDY OF DLPFC

Tsvetoslav Ivanov^{*1}, Mark Slifstein², Jared Van Snellenberg², Rahul Gupta¹, Matt Jones¹, Anissa Abi-Dargham², Sean Froudish-Walsh¹

¹University of Bristol, ²Stony Brook University

Background: Current medications mainly treat positive symptoms of schizophrenia (SZ), like hallucinations. However, patients remain impaired by cognitive symptoms, e.g., working memory (WM) deficits, thought to have a separate cause. Identifying shared mechanisms for hallucinations and WM deficits may lead to drugs that promote full remission in patients showing both symptoms.

Notably, SZ patients exhibit lower than typical dopamine (DA) release in the dorsolateral prefrontal cortex (dlPFC) (Slifstein et al., 2015), which may counterbalance the higher than typical dlPFC D1R expression reported in unmedicated SZ patients (Abi-Dargham et al., 2012). These landmark findings suggest that dysregulation of D1R activation in dlPFC is one common factor underlying hallucinations and WM deficits.

Crucially, dlPFC D1R activation forms an inverted U-shaped relationship with the maintenance of persistent activity during the delay period of WM tasks. Optimal D1R activation enables distractor-resistant persistent activity, while too low or too high D1R activation causes transient, non-persistent activity, only during stimulus presentation.

Likely, the increased dlPFC D1R expression in SZ shifts the inverted U to lower levels of D1R occupancy (i.e., the fraction of active, DA-bound D1Rs). Thus, assuming dlPFC DA release varies in time, albeit around a lower mean, SZ patients should still experience episodes of optimal D1R activation and good WM but also too low D1R activation and poor WM. Too high D1R activation may cause hallucinations. Specifically, this upregulation of D1R activation may be overcompensating for the widely reported downregulation of the inhibitory output of parvalbumin (PV) cells and the excitatory output of pyramidal (E) cells in dlPFC (Dienel and Lewis, 2019).

Methods: To link microcircuit physiology and SZ symptoms, we designed a spiking network model of a visuospatial WM task where we first present a brief target stimulus and later a brief distractor stimulus at a different location (Compte et al., 2000). The model featured E cells and two functional PV cell types – PV_NEAR and PV_OPP – with near- and opposite-feature selectivity (Kuan et al., 2022). E cells are arranged uniformly on a ring according to the angle

of the stimuli for which they fire the most. PV cells are also arranged uniformly based on the angle of the E cells from which they receive the strongest excitation. The microcircuit has E-E, E-PV, PV-E, and PV-PV synapses. E cells send their strongest glutamatergic projections to cells at the same angle. PV_NEAR cells send their strongest GABAergic projections to cells also at the same angle, while PV_OPP cells – to cells located 180° away on the ring.

We studied the propensity of cell type-specific D1R expression profiles to induce pathology in three networks where E cells and, respectively, PV_NEAR (Net.1), PV_OPP (Net.2), or both PV_NEAR and PV_OPP (Net.3) expressed D1Rs. D1R activation modulated G_NMDA and G_AMPA conductances and the firing thresholds of D1R+ PV cells (Durstewitz et al., 2000; Kröner et al., 2007). In particular, across networks, from low to optimal D1R activation, we (1) fitted a 40% increase in G_NMDA for synapses with D1R+ target cells and a 20%, synapse-unspecific, decrease in G_AMPA, and (2) decreased the thresholds of D1R+ PV cells, to facilitate a transition from non-persistent to noise- and distractor-resistant persistent activity regime, thus simulating the inverted U's increasing phase and peak. The G_NMDA value for low D1R activation was the highest G_NMDA that did not support persistent activity. Towards high D1R activation, the thresholds of D1R+ PV cells continued to decrease to simulate the inverted-U's decreasing phase until the model reached a non-persistent activity regime. For sub-optimal D1R activation, the magnitudes of the G_NMDA, G_AMPA, and threshold modulations were intermediate, relative to the low and optimal D1R activations. For supra-optimal D1R activation, the magnitudes of the modulations were also intermediate, but relative to the optimal and high D1R activations.

Results: When PV_OPP cells express D1Rs (i.e., in Net.2 and Net.3), as expected, low and high D1R activation cause non-persistent activity, while optimal D1R activation enables noise- and distractor-resistant persistent activity. The sub-optimal D1R activation elicits distractible persistent activity (i.e., the model holds target stimuli in WM after they disappear, but the persistent activity trace jumps to the location of the distractor when it appears). The supra-optimal D1R activation elicits a hallucinatory persistent activity regime where noise-driven activations occur at non-stimulus locations but still give rise to persistent activity traces with coherent structure. On the other hand, grid searches over the D1R-mediated modulations of the G_NMDA's, G_AMPA's, and the D1R+ PV thresholds revealed no parameter sets in Net.1 that elicit hallucinations, suggesting that its D1R expression profile is closest to biology in health.

Discussion: Our model links cellular, molecular, and microcircuit changes in SZ with hallucinations and WM deficits and suggests mechanistically targeted treatments for the disorder, e.g., partial D1R antagonists that reduce the effects of DA binding on D1Rs.

S103. REFINING THE PHENOTYPE OF MENSTRUAL PSYCHOSIS: SYSTEMATIC REVIEW OF CASE REPORTS

Thomas Reilly*¹, An Hsu², Adam Al-Diwani³, George Gifford⁴, Philip McGuire³, Ian Brockington⁵

¹*Institute of Psychiatry, King's College*, ²*Royal College of Surgeons of Ireland*, ³*University of Oxford*, ⁴*Department of Psychiatry, University of Oxford*, ⁵*University of Birmingham*

Background: Psychotic episodes linked to the menstrual cycle have been described for over 200 years. A proposed definition of 'menstrual psychosis' classifies it as: (i) acute onset; (ii)

episodes of psychosis, mania, catatonia or confusion; (iii) in synchrony with the menstrual cycle; (iv) with complete recovery within two weeks. There have been many cases reports describing this phenomenon, but these have never been systematically reviewed and quantitatively analysed.

Methods: A search of electronic databases was conducted using MEDLINE, Embase and PsycINFO. Search terms were [psychosis OR psychotic OR schizoaffective OR bipolar affective OR bipolar disorder OR mania OR manic OR catatoni*] AND [menstrua* OR catamenia* OR monthly OR cyclic OR menses OR menarche]. This was supplemented with historical case reports and unpublished cases. Cases were included if they described brief episodes of psychosis, mania, or catatonia, synchronised with the menstrual cycle, with complete recovery between episodes. Reports of menstrual exacerbation of chronic mental disorders were excluded. Demographic and clinical characteristics were extracted. The AMDP system was used to extract individual symptoms from case reports. The study was pre-registered with PROSPERO: CRD42023408345.

Results: A total of 10,558 records were retrieved from the electronic database search. After assessing 149 full texts for eligibility, 82 studies were included, consisting of 112 individual patients. An additional 218 published cases (including historical cases) were identified from previous reviews, as well as 100 anonymised unpublished cases. The total number of cases for analysis is 418. Most episodes had onset in the premenstrual (55.9%) or menstrual (22.3%) phase. The most common clinical diagnosis reported was bipolar disorder (40%), followed by schizophrenia spectrum disorder (18.9%). The modal age of onset was 14, and the median was 19 (interquartile range 15-26). Of all cases, 71 experienced episodes during the postpartum period, with 50 of these being the index episode. Four cases were associated with termination of pregnancy or miscarriage, and three cases were associated with weaning. Menarche was the other reproductive event associated with cases, with 59 cases having onset at this time. The most common individual symptom was depressed mood (36.0%), followed by motor restlessness (32.0%), auditory hallucinations (28.1%), euphoria (25.7%), clouded consciousness (25.4%). The most common symptom domain was disturbance of affect (69.3%), followed by disorders of drive and psychomotor activity (58.3%), disorders of consciousness (33.6%), disorders of perception (33.6%), and delusions (30.7%).

Discussion: This study is the first systematic review of menstrual psychosis and the largest analysis to date. Menstrual psychosis is predominately a disorder of adolescence, with a modal and median onset before the age of 20. Indeed, 59 cases were associated with menarche, suggesting this time of hormonal fluctuation confers higher risk of psychotic episodes. The phase of onset of episodes was either premenstrual or menstrual in most cases, which is similar to the time of increased risk of psychosis relapse. The psychopathology of menstrual psychosis suggests a strong affective component, with the most reported symptom domain being disturbance of affect while the most common individual symptom was depressed mood. In keeping with this, the most common clinical diagnosis in cases was bipolar disorder. A link is suggested with postpartum psychosis, which is also characterised by affective symptoms, sudden onset, and subsequent development of bipolar disorder. Postpartum psychosis is a more widely recognised, but similarly rare condition. It is therefore striking that one in six cases of menstrual psychosis also experienced episodes during the postpartum period.

S104. 49 SYMPTOMS OF PSYCHOTIC-LIKE EXPERIENCES: ESTIMATING OVERLAP BETWEEN PSYCHOTIC-LIKE EXPERIENCES MEASURES

Mariia Goncharova^{*1}, Clement Donde¹, Hans Ijzerman¹, Catherine Botolon¹

Background: Psychosis is characterized by hallucinatory and delusional experiences. Conventionally, it was mostly considered to be present among clinical populations. However, attenuated variations of psychosis can be found in the general population and are referred to as psychotic-like experiences (PLEs) (Kelleher and Cannon, 2011). Limited reviews currently exist on the quality of the assessment methods designed to evaluate psychotic-like experiences in the general population (Lee et al., 2016). None of them assessed whether the existing instruments measure the same construct and, consequently, neglected problems associated with the "jingle-jangle fallacy" (Weidman et al., 2017; Flake and Fried, 2020). This fallacy might account for contradictions in the literature, as well as, issues with generalizability of the results. Thus, the goal of our study is to better understand the agreement between different instruments assessing psychotic-like experiences by calculating item overlap (Fried et al., 2017).

Methods: We conducted a systematic search of the scales assessing psychotic-like experiences and schizotypy personality traits among the general population (i.e., hallucinations, magical thinking, and delusions), excluding negative symptoms. Labels for the different psychotic experiences were created based on their definition in literature by the first authors and subsequently revised by another researcher. Different experts provided feedback on these labels and definitions. Two researchers coded each item independently of each other. A third researcher then revised the items that were disagreed upon. Further adjustments were made after discussion. We then estimated to which extent any item overlaps with any item from the other scale included in the analysis. Finally, we used Jaccard index to assess similarities between sets (from 0 with no overlap among scales) to 1 (complete overlap). The analysis was done in R and Excel.

Results: For 12 scales of psychosis proneness, 49 labels were identified with a mean overlap of 0.14. We used network analysis to visualize the data. The most commonly mentioned items for the psychosis scales were paranormal (mentioned in 9 scales) depersonalization (7 scales), suspiciousness, visual hallucinations, and grandeur (each in 6 scales). There were 16 idiosyncratic items. The highest overlap between scales measuring psychosis were SPQ and Prodromal questionnaire-brief (0.34). Lowest mean overlap — BQSPS (0.03), which only had four items, which led to 2 labels.

Discussion: The results demonstrate a poor overlap between the scales. CAPE scale stands out as one having the most overlap with other scales (0.19), which is consistent with previous results (Bernardin et al., 2023). Even though these scales were supposed to measure psychotic symptoms, they might be tapping different, although related, phenomena or, at least, different ways of conceptualizing psychotic experiences (and PLE). Thus, future studies need to acknowledge the issue of defining PLE and be transparent about what is considered a PLE in any study. Our results also point to the lack of content validation during scale development. Future studies should include both bottom-up (e.g., qualitative studies) and top-down (e.g., theory based) strategies for scale development.

S105. DISTINCT CHARACTERISTICS OF RECENT-ONSET PSYCHOSIS WITH AUTISTIC SYMPTOMS

Kyuyoung Lee^{*1}, Jae Hoon Jeong²

¹*Nowon Eulji University Hospital*, ²*Department of Psychiatry, Eulji University Eulji Hospital*

Background: Although autism and schizophrenia have been classified as distinct illnesses, a number of studies have investigated the similarities between them. Patients with psychosis with prominent autistic symptoms were known to generally have lower cognitive and functional level of life. We intended to investigate the differences in clinical, cognitive, and functional characteristics according to the severity of autistic symptoms in recent-onset psychosis.

Methods: The participants were 671 patients with recent-onset psychosis enrolled in the Korean Early Psychosis Cohort Study (KEPS). To evaluate the severity of autism symptoms, PANSS Autism Severity Score (PAUSS) was used, dividing the subjects into three different groups: “Autistic group” (PAUSS $\geq$ 30), “Non-autistic group” (PAUSS $\leq$ 10) and “Moderate group” (10 LESS THAN PAUSS LESS THAN 30). The baseline sociodemographic and clinical characteristics, cognitive functions and emotional recognition were compared by group.

Results: The rate of diagnosis of schizophrenia was highest in autistic group and found to be a significant predictor of autistic group. Regarding the presence of comorbid psychiatric disorders, lowest incidence was shown in autistic group. In the group with more severe autistic symptoms, non-autistic symptoms and functional outcomes measured by PANSSminusPAUSS and SOFAS were also worsened. These two measures also significantly predicted the autistic group. In cognitive functions and emotional recognition, the more severe the autistic symptoms, the more severe the impairments.

Discussion: Autistic symptoms have a significant impact on overall symptoms and functions on patients with recent-onset psychosis. There seems to be an overlap between psychosis and autism.

S106. INTERACTION OF BDNF WITH IL-18 IS ASSOCIATED WITH COGNITIVE DEFICITS IN CHRONIC SCHIZOPHRENIA

Dongmei Wang*¹

¹*Institute of Psychology, Chinese Academy of Science*

Background: The interaction between cytokines and neurotrophic factors may contribute to the etiology and psychopathology of schizophrenia. Accumulating evidence suggests that both BDNF and IL-18, an important and pleiotropic cytokine modulator of immune responses may be involved in the psychopathological symptoms and cognitive deficits of schizophrenia. However, the possible interaction between BDNF and IL-18 has not been examined.

Methods: We recruited 40 chronic schizophrenic patients and 38 healthy control subjects and examined the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as well as serum BDNF and IL-18 levels in both groups. Schizophrenic symptoms were assessed using the Positive and Negative Syndrome Scale.

Results: Compared to the control group, the patients exhibited a significant decrease in BDNF levels, but a significant increase in IL-18 levels. In patients, but not in controls, we observed a significant negative correlation between BDNF and IL-18. Furthermore, the interaction between BDNF and IL-18 was associated with immediate memory, delayed memory and RBANS total scores.

Discussion: Our results suggest that both altered BDNF and IL-18 levels may be implicated in the pathophysiology of chronic schizophrenia. Their inverse association only in the schizophrenia group may reflect a pathological mechanism involving an interaction of immune

response and neurotrophin dysfunction. Moreover, IL-18 may interact with the BDNF system to influence the clinical symptoms and cognitive impairment in schizophrenia, which is line with the neurodevelopmental hypothesis of schizophrenia.

S107. CONNECTION AND CREATION OF SHARED MEANING IN SCHIZOPHRENIA: A QUALITATIVE INVESTIGATION OF THE PSYCHIATRIST-PATIENT RELATIONSHIP

Melissa Uehling*¹

¹*Emory University School of Medicine*

Background: For individuals experiencing schizophrenia, various facets of engaging with the psychiatric system may be a source of trauma. Experiences such as involuntary hospitalization, loss of autonomy, and paternalistic doctor-patient relationships may limit the effectiveness of psychiatric treatment and may cause further harm. Emerging work in the area of intersubjectivity may offer the potential to re-imagine the psychiatric system as a place that is more consistently centered on meaningful understanding and valuation of the patient perspective. Specifically, theorists have presented the idea of developing an intersubjective understanding between provider and patient, through creation of a shared understanding of the patient's illness experience. Forging a shared understanding and co-creating a path forward departs from the authoritarian psychiatric modality of imposing an external explanation upon the patient based upon the psychiatrist's own conception of reality. Concerns about authoritarianism in medical treatment are particularly relevant for patients with schizophrenia spectrum disorders, as psychiatrists may be less likely to create a shared understanding with patients or attempt to enter patients' psychological framing, which may be assessed as inaccessible and separate from a shared reality.

Methods: Despite the potential utility of intersubjective approaches in psychiatric treatment, limited work has assessed provider perspectives on how shared meaning and relationship development unfolds in psychiatric spaces. Accordingly, this study seeks to characterize the process of how psychiatrists develop shared meaning and connection with patients with schizophrenia spectrum disorders. This study involved open-ended interviews with 24 U.S.-based psychiatrists who currently treat patients with schizophrenia spectrum disorders. Interviews lasted roughly 60 minutes, and interview questions focused on if and how psychiatrists develop shared understandings and connection with their patients, the values and beliefs affecting these relationships, as well as situational characteristics that facilitate or inhibit such processes. I conducted thematic analysis on the data and employed the analytic method of abductive analysis to perform thematic coding and theoretical development throughout the research process.

Results: Interviews revealed that respondents varied greatly in their perspectives on creating shared understandings with patients with psychosis. When discussing what defines a shared understanding, three main modalities emerged across interviews, including: 1) patient and physician joining in an understanding of symptoms and diagnostic information; 2) creating functionality-oriented, shared goals for treatment and life; and 3) creating a shared understanding of the patient's subjective perspective or narrative of their illness. Virtually all psychiatrists interviewed engaged in each method of shared understanding during different circumstances and time points, with the majority of participants aligning most closely with one approach overall.

Many participants reported grappling with balancing their own expertise with centering the patient's perspective, regardless of the approach taken to creating shared understandings. Some clinicians reported using their own perspective as a benchmark for developing a shared understanding, thus prioritizing the clinician's view or opinion. In contrast, some physicians described an approach that attempted to balance both psychiatrist and patient perspectives during clinical practice, with a flexibility to modify the participant's own desired approach or viewpoint in order to engage more effectively with the patient's view.

Furthermore, virtually all psychiatrists interviewed acknowledged the existence of power imbalances with regards to whose expertise or viewpoint is prioritized within these relationships. However, a minority of respondents discussed making a conscious effort to address the imbalances and could name practical approaches to addressing them. Among those who struggled to name concrete, explicit steps they take to minimize power imbalances, they reported facing challenges with knowing exactly how to navigate inequities in clinical spaces. Furthermore, clinicians reported several barriers to developing shared understandings and connecting with patients effectively, including inadequate formal medical training, the pressures of managed care constraints, and lack of trust due to the ubiquity of involuntary hospitalization and coercive treatment in the medical system.

Discussion: Overall, these findings highlight the complexity in the ways in which psychiatrists approach connection and shared meaning when treating individuals with schizophrenia spectrum disorders. Characterizing the process of intersubjectivity may be a path to understanding aspects of the psychiatrist-patient relationship in the context of psychosis, its intersection with multi-level factors, and the associated impacts on treatment. This study provides a basis for developing further understandings of how to build relationships and more thoroughly understand clinicians' perspectives during psychiatric treatment.

S108. PHENOMENOLOGY OF SOCIAL NEEDS AND EXPERIENCES IN PSYCHOSIS: AN EXPLORATORY MIXED-METHODS APPROACH

Gil Grunfeld*¹, Joseph Maimone¹, Jasmine Mote², David Gard³, Kim Mueser⁴, Daniel Fulford¹

¹*Boston University*, ²*Boston University, College of Health and Rehabilitation Sciences*, ³*San Francisco State University*, ⁴*Center for Psychiatric Rehab, Boston University*

Background: Individuals with psychotic disorder often report difficulties with social functioning, ranging from social cognition, to communication, to maintenance of existing relationships. Dissatisfaction with one's social life — especially perceived deficits in connection — can exacerbate psychosis symptoms and potentially delay recovery in functioning. While a host of laboratory methods have been employed to study social processes in psychosis, little naturalistic data exists attending to the social needs of those with lived experience.

Methods: Using a mixed-methods approach, we examined both ambulatory self-report (i.e., Ecological Momentary Assessment [EMA]) and qualitative interview data from adults with a schizophrenia spectrum disorder (median age = 48, range = 22-65; 48% female; 55% non-White). EMA questions were prompted twice a day over an eight-week period to evaluate social goals as well as to collect information on affect following engagement with others ("happy," "sad," "excited," "calm," "anxious," "angry"). Narrative data about self-described

social needs was collected pre-intervention, which we will code and analyze to a sample size of thematic saturation.

Results: Through longitudinal analysis of ecological momentary assessment (EMA) data, we will explore affect experience in the context of social goal-pursuit over the eight-week intervention period. We will also highlight a range of subjective social goals and motivations through thematic analysis of pre-treatment interviews.

Discussion: Tying together longitudinal EMA data to our granular qualitative findings, our work will provide insights on the affective qualities of social goal formation and attainment in psychosis, as well as broadly pointing to methodological implications for idiographic, phenomenological approaches to studying social dynamics in psychosis.

S109. INTRODUCING TWO ADAPTATIONS OF THE PSYCHOTIC SYMPTOM RATING SCALES (PSYRATS): THE ADAPTED RESPONSE SCALE – PSYRATS AND OTHER MODALITIES HALLUCINATIONS - PSYRATS

Wai Fung Tsang¹, Nadine Keen², Emmanuelle Peters*¹, STAR (Study of Trauma And Recovery) Research group³

¹Institute of Psychiatry, Psychology and Neuroscience, King's College London, ²South London and Maudsley NHS Foundation Trust, ³London, Manchester, Newcastle, Oxford and Sussex

Background: The Psychotic Symptom Rating Scales (PSYRATS) are the most widely validated and internationally translated multidimensional assessment of positive psychotic symptoms, including two assessor-rated subscales for auditory verbal hallucinations and delusions. Over time potential areas for refinement have been identified, particularly the discrete descriptions anchoring its five-point severity scale leading to a floor effect for some items, and others lacking sufficient sensitivity for detecting clinical change. There is also growing evidence of the high prevalence of hallucinations in other modalities in psychosis and other populations such as complex post-traumatic stress disorder (PTSD), which are not captured by the current subscales. The present study aimed to validate (i) an Adapted Response Scale - PSYRATS (ARS-PSYRATS), which uses a 0-10 analogue thermometer rating scale; (ii) an adaptation of the auditory hallucinations subscale to assess hallucinations in other modalities, including multimodal hallucinations.

Methods: The study utilized baseline data (N=305) from a randomized controlled trial evaluating an integrated Trauma-Focused Cognitive Behaviour Therapy for Psychosis, the Study of Trauma and Recovery (STAR trial). Participants met criteria for ICD-10 schizophrenia-spectrum disorder (F20-29) and DSM-V PTSD and presented with distressing hallucinations and/or delusions. The construct validity, internal consistency, and concurrent validity of ARS-PSYRATS subscales, including Hallucinations in Other Modalities-PSYRATS, with the original delusions and auditory hallucinations PSYRATS, were assessed.

Results: Principal Components Analysis identified a two-factor structure for the delusion subscale (Emotional, Physical), and a three-factor structure across the two hallucination subscales (Emotional, Physical, Cognitive), replicating a number of previous studies. Cronbach's alpha for total subscales indicated good internal consistency. Correlations showed good concurrent validity with the original scales. Together, psychometric properties were better for the delusion than for the hallucination subscales but were acceptable overall. The hallucinations in other modalities subscale were a highly useful addition, with 80% of the sample reporting such experiences.

Discussion: The ARS-PSYRATS, including the adapted Hallucinations in Other Modalities, are valid and reliable measures and may be particularly useful for future studies or clinical services wanting to assess clinical change over time. The high prevalence of other modalities hallucinations underscores the importance of assessing such experiences.

S110. MEASURING SOCIAL FUNCTIONING IN PEOPLE WITH SMI: A SYSTEMATIC REVIEW

Bouwina Sportel*¹, Elise Bennik², Emke Lantink³, Hettie Aardema⁴, Nynke Boonstra⁵

¹GGZ Drenthe Mental Health Institute, ²University of Groningen, Department of Clinical Psychology and Experimental Psychopathology, / GGZ Drenthe Mental Health Institute, Department of Psychotic Disorders, ³University of Groningen, Department of Clinical Psychology, ⁴GGZ Drenthe Mental Health Institute, Department of Psychotic Disorders, ⁵NHL Stenden University of Applied Science, / UMC Utrecht

Background: Approximately 281,000 people in the Netherlands have a serious mental illness (SMI; Delespaul, 2013). People with SMI experience major problems in their daily lives, including limited social functioning (Howell et al., 2023).

Research shows that people with SMI often suffer from reduced social functioning: experiencing loneliness, social isolation, smaller social network, less social connection and lower social relationship satisfaction. The relationship between social functioning and personal recovery is receiving increasing attention. Social network size and satisfaction with social support are positively related to self-reported recovery (Thomas et al., 2016), and interpersonal functioning is positively related to personal recovery (Watanabe et al., 2021). Social functioning appears to play a mediating role between psychiatric symptoms and personal recovery (Howell et al., 2023). Therefore, improving social functioning is an important goal of treatment and recovery-oriented care for people with SMI. However, to gain more insight into one's social functioning, accurate measuring is crucial. The aim of our systematic review is to map the available patient reported outcome measures (PROMs) for social functioning in people with SMI and their psychometric qualities, resulting in an advise for clinical practice and research on best fitting instruments.

Methods: We systematically searched Embase, PsycInfo and Epub Ahead of Print using the following terms (used synonyms not included): rating scales AND psychometric properties AND social functioning AND serious mental illness. Included articles contained a target population of people with SMI, psychometric properties of instruments, and at least 3 out of 5 domains of social functioning (work/daily activities, living, relationships, recreation, self-care). After several rounds of screening 70 articles on 24 PROMs were included. COSMIN methodology for systematic review of PROMs was then used to further assess the quality of the PROMs.

Results: Several instruments were included, amongst them BSFQ, ICF-Mental-A and P, WHODAS, CAN, SOFI and SIS. Quality of the included instruments varies between low and high, with a large range of present psychometric properties and a large variation in scores on the properties.

Discussion: Advise for clinical practice and research will be presented.

S111. SEX DIFFERENCES IN SYMPTOMS OF PSYCHOSIS: A META-ANALYSIS ACROSS STAGES

Marta Ferrer-Quintero*¹, Clara Serra-Arumí², Ana Echevarría-Bruno¹, Marina Verdaguer-Rodríguez², Renée Douven³, Mia Plenkovic⁴, Susana Ochoa², Covadonga M Díaz-Caneja¹

¹*Institute of Psychiatry and Mental Health Gregorio Marañón*, ²*Parc Sanitari Sant Joan de Déu*, ³*Maastricht University*, ⁴*Sveučiliste u Splitu Medicinski Fakultet*

Background: There is evidence of clinically relevant differences between women and men with psychosis with potential treatment implications. However, sex differences in clinical presentation are still controversial.

In this work, we aim to assess differences in clinical presentation between males and females at different stages of schizophrenia and other psychotic disorders (ultra-high-risk mental state (UHR), first-episode psychosis (FEP), and established illness (EI)).

Methods: Methods of this meta-analysis adhere to the PRISMA guidelines and are registered in the PROSPERO database under the number CRD42021264942. We retrieved published literature from Web of Science, PubMed, SCOPUS, PsychInfo, and Dialnet databases until 2021, with an update in July 2023. Studies were included if reporting results of male and female individuals aged 16–65 years with a diagnosis of schizophrenia or other psychotic disorder (e.g., schizophreniform, schizoaffective disorder, delusional disorder, brief psychotic disorder, recent-onset psychosis, ultra-high risk for psychosis), irrespective of the diagnostic criteria used. We collected positive, negative, general, depressive, or anxiety symptoms measured with a validated scale. Data were analyzed using a random-effects model. The effect size was computed using Hedges g.

Results: Our search strategy identified 36,147 eligible articles. After abstract screening and full-text review, 532 articles were included for data extraction. The search was updated in 2023, identifying 2,897 articles, of which 80 were finally included. This section presents preliminary findings from an analysis of 182 studies, including 4,277 observations of UHR participants, 9,580 observations of FEP participants, and 15,457 observations of EI participants.

In positive symptoms, the meta-analysis did not find significant differences between females and males in UHR (SMD= -0.0166, 95%-CI [-0.1242; 0.0909], p=0.7528), FEP (SMD= -0.0408, 95%-CI [-0.1119; 0.0303], p=0.2549), nor EI (SMD= -0.0317, 95%-CI [-0.1162; 0.0528], p=0.4579).

In contrast, we found that males present more severity of negative symptoms than females at the UHR (SMD= -0.3522, 95%-CI [-0.4523; -0.2521], p LESS THAN 0.0001), FEP (SMD= -0.2362, 95%-CI [-0.2993; -0.1732], p LESS THAN 0.0001), and EI (SMD= -0.2362, 95%-CI [-0.3187; -0.1537], p LESS THAN 0.0001) stages. Heterogeneity was significant and high in UHR ($I^2 = 64.8\%$ [48.4%; 75.9%], $Q = 85.11$, p LESS THAN 0.0001) and EI ($I^2 = 73.5\%$ [67.4%; 78.5%], $Q = 328.54$, p LESS THAN 0.0001).

Discussion: Preliminary meta-analytic results suggest that men with psychosis tend to exhibit more severe negative symptoms than women across all the illness stages. Given the pervasive nature of negative symptoms and limited effectiveness of available treatments to address them, it is likely that men with or at high risk of psychosis need earlier and more comprehensive support to prevent the loss of functionality and autonomy. These findings underscore the importance of sex-sensitive interventions in the management of negative symptoms among individuals with psychosis.

S112. MINOR PHYSICAL ANOMALIES IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ekin Sut^{*1}, Özge Akgül², Emre Bora¹

¹Dokuz Eylul University, ²İzmir Democracy University Karabaglar,

Background: Minor physical anomalies (MPAs) are subtle physical abnormalities that manifest early in the first or second trimester of fetal development and endure throughout an individual's life. Extensive research has explored the connection between MPAs and neurodevelopmental disorders, predominantly focusing on schizophrenia patients and their relatives. Most studies have examined total MPA scores or anatomical region scores, there is a need for a deeper understanding of the frequency of specific anatomical regions or individual MPA items associated with schizophrenia. This study aims to shed light on potential endophenotypic markers by providing an updated meta-analysis of the relationship between MPAs and schizophrenia. Thus, further studies specifically examining MPAs associated with schizophrenia and the gestational period in which they occur may provide information about the neurodevelopmental pathogenesis of schizophrenia.

Methods: A literature search was conducted using the databases Pubmed and Web of Science to identify the relevant studies (January 1980 to August 2023) using the keywords as follows: ("schizophrenia" OR psychosis OR psycho*) AND ("minor physical anomalies" OR MPA). Statistical analyses were performed using JAMOVI (Version 2.3.26). Homogeneity of the distribution of weighted effect sizes was assessed by Q test and I²; and publication bias was assessed by Egger's test for funnel plot asymmetry.

Results: In this comprehensive meta-analysis, we incorporated 47 studies comparing Minor Physical Anomalies (MPAs) scores between individuals with schizophrenia and healthy controls. Among these, 43 studies, involving 3780 schizophrenia cases and 3871 controls, provided data on total MPA scores. The observed difference between patients and controls was medium-large ($g=0.78$ [0.63-0.93], p LESS THAN 0.001), accompanied by significant heterogeneity in the distribution of effect sizes ($I^2= 88.62\%$). In our regional MPA meta-analyses, effect sizes ranged from 0.56 to 0.78, with the most substantial difference identified in the area of the mouth ($g=0.78$, CI [0.62-0.94]). This meta-analysis also delved into the investigation of differences in the frequencies of specific MPA scale items between patients and controls. Aligning with the outcomes of regional MPA analyses, the highest rates were observed in palate and tongue anomalies. Notably, items such as fine electric hair (OR=2.22 [1.31-3.77]), hair whorls (OR=2.44 [1.27-4.70]), epicanthus (OR=2.35 [1.36-4.04]), malformed ears (OR=3.71 [2.16-6.36]), low seated ear (OR=2.65 [1.73-4.06]), lower edges backward/upward (OR=3.06 [1.28-7.35]), furrowed tongue (OR=2.73 [1.77-4.22]), tongue with spots (OR=5.63 [1.72-18.37]), high palate mild (OR=2.73 [1.50-4.95]), high palate severe (OR=5.27 [2.74-10.12]), single palmar crease (OR=2.75 [1.41-5.38]), gap between 1st-2nd finger (OR=3.24 [1.88-5.56]), curved 5th finger (OR=2.02 [1.38-2.96]), syndactilia (OR=2.19 [1.22-3.94]) were identified as the most significant.

Discussion: The frequency of MPA is increased in schizophrenia patients compared to healthy controls. Exploring the prevalence of specific minor physical anomalies in particular anatomical regions can provide valuable insights into the timing of dysmorphology and the neurodevelopmental phases in which developmental pathology occurs. In our study, it is observed that frequency of midline anomalies such as high palate, fine electric hair and hair whorls has increased. Evaluating these anomalies provides useful information for comprehending the neurodevelopmental pathology of schizophrenia. These findings

underscore the importance of not only quantifying total MPA scores but also identifying specific anatomical anomalies. In this way, the neurodevelopmental aspect of schizophrenia can be better understood. Additionally, clarifying the specific and characteristic differences for MPAs may point the way for their use as endophenotypic markers. We recommend that future research delve deeper into the biological mechanisms underlying these abnormalities and their connection to schizophrenia.

S113. DYSEXECUTIVE BEHAVIOR IN FIRST-EPISODE SCHIZOPHRENIA

Gricel Orellana Vidal*¹, Andrea Slachevsky¹, Fernando Henriquez¹

¹*University of Chile*

Background: Dysexecutive syndrome is a prominent and functionally significant cognitive feature of schizophrenia. This research studies dysexecutive behaviors in first episode of schizophrenia (FES) patients.

Methods: We evaluated 22 FES patients, from 17 to 29 years of age with a recent history of a single psychotic outbreak only treated with atypical neuroleptics. We also evaluated twenty healthy persons matched by sex, age and educational level with FES patients as a control group. Executive function using Modified Wisconsin Card Sorting Test (MWCST) and Frontal Assessment Battery (FAB) and dysexecutive conducts applying the questionnaires Dysexecutive Index (DEX) and Behavioral Dysexecutive Syndrome Inventory (BDSI) in both groups. This study marks the first application of the BDSI in a sample of FES patients. DEX scores are DEX self-rating (DEX-S), "significant other" (DEX-SO) and the difference between DEX-S and DEX-SO scores reflects awareness of the deficit (DEX-A). The FAB consists of 6 subtests of frontal- lobe functions: (1) Conceptualization and Abstract Reasoning (similarities); (2) Mental Flexibility (verbal fluency); (3) Motor Programming and Executive Control of Action (Luria motor sequences); (4) Resistance to Interference (conflicting instructions); (5) inhibitory control (go/no-go test); and (6) Environmental Autonomy (prehension behavior). Each subtest is scored from 3 (better score) to 0, for a maximum score of 18. [21]. this study marks the first application of the FAB in a FES sample.

Results: We found that FES patients had marked executive function impairments and dysexecutive behavior as compared to controls (table 1, 2).

FAB: Total, Conceptualization, Motor Programming, Resistance to Interference, and Inhibitory Control scores were significantly lower in FES patients than controls (Table 1).

The t-tests showed significant differences between the FES and control participants for BDSI, DEX-SO, and DEX-S total scores. There were no significant differences in DEX-A scores between groups (Table 2).

Discussion: Dysexecutive behavior is common during FES and may be a primary impairment throughout disease progression. The present results could help clinical practice by providing information on some specific characteristics of dysexecutive behavior in FES. Understanding the associations between executive function and dysexecutive behavior helps to explain the social adjustment disorders associated with schizophrenia. This knowledge may be used to improve diagnostic and therapeutic tools; for example, clarifying the implications of specific DEX and BDSI dimensions could increase the efficacy of individual or family psychotherapy interventions.

S114. BEYOND THE VEIL: UNVEILING SEX DIFFERENCES IN PSYCHOSIS PRONENESS MEASURED BY DELTA INVENTORY AMONG NON-CLINICAL INDIVIDUALS

Nadja Maric^{*1}, Goran Knezevic², CoV2Soul.rs Study Group³

¹*Institute of Mental Health, Faculty of Medicine, University of Belgrade*, ²*Faculty of Philosophy, Department of Psychology, University of Belgrade*³*Serbia*

Background: There have been several studies that have shown differences between men and women in a non-clinical population about their Schizotypy, which was assessed using the Schizotypal Personality Questionnaire, or their psychosis symptoms, which are evaluated through a structured psychiatric interview. Recently, Knezevic et al. proposed that proneness to psychotic-like experiences and behaviours can be redefined as a personality trait known as Disintegration (D), which can be measured using the DELTA inventory. This trait indicates a predisposition to perceive, comprehend, and feel connections among factually unrelated phenomena, which can lead to illusory pattern perception (apophenia or false positive detection errors). The concept of D as a personality trait aims to account for individual differences observed in both clinical and non-clinical populations.

The primary objective of this study was to investigate whether there are sex differences in Disintegration within a nonclinical, nationally representative adult sample, using a 20-item version of the DELTA inventory. We hypothesised that women would show more "positive" features, such as magical thinking or mania/depression, while men would exhibit more "negative" features, such as flattened affect.

Methods: The present study was part of a larger cross-sectional observational epidemiological survey, CoV2Soul.rs (registration number NCT04896983), which employed multistage household probabilistic sampling to recruit a representative adult sample (age 18-65) from Serbia (N=1203; mean age 43.7 years (SD = 13.6)). Around 48.7% were male. We calculated the total DELTA score and nine lower-level traits: General Cognitive/Executive Impairment, Perceptual Distortions, Enhanced Awareness, Apathy/Depression, Paranoia, Mania, Flattened Affect, Somatic Dysregulations, and Magical Thinking. The Total D score, along with the scores for the nine subdimensions, was measured using a 20-item Likert-type scale, ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). To test the difference between females and males on DELTA scores, a t-test for independent samples was used. To predict the probability of a binary outcome (female/male) based on all nine Disintegration subdimensions, logistic regression was used.

Results: There were no statistically significant differences between females and males in age (M_{age}=44.30, SD_{age}=13.52; M_{age}=43.08, SD_{age}=13.60; $t(1201)=1.55$, $p = .121$) and education (M_{educ}=3.30, SD_{educ}=1.38; M_{educ}=3.24, SD_{educ}=1.39; $t(1201)=0.78$, $p = .435$). Female participants had a slightly higher total DELTA score than males (M_f=1.56, SD_f=.66; M_m=1.46, SD_m=.60; $t(1198.86)=2.88$, $p < .001$, $\eta^2 = .007$). The DELTA subscales contributing to this difference were General Cognitive/Executive impairments (M_f=1.73, SD_f=.90; M_m=1.53, SD_m=.77, $t(1189.10)=4.03$, $p < .001$), Somatoform Dysregulations (M_f=1.42, SD_f=.80; M_m=1.28, SD_m=.66, $t(1174.31)=3.43$, $p < .001$), and Apathy/Depression (M_f=1.35, SD_f=.74; M_m=1.24, SD_m=.60, $t(1176.86)=2.80$, $p=.005$). A composite (logistic regression), based on the DELTA subscales revealed that for each point increase in General Cognitive/Executive impairments and Somatoform dysregulation scores, there were the odds of 1.46, $p < .001$ and 1.30,

$p = .034$, respectively, of being a female. For each point increase in Flattened Affect and Paranoia, there were the odds of .77, $p = .003$, and .83, $p = .037$, respectively, of not being a female.

Discussion: Acknowledging gender differences in schizophrenia spectrum disorders and schizotypy is crucial for gaining valuable insights into sex-specific aspects of psychosis risk, clinical manifestations, and the potential for delivering gender-tailored treatments and care to patients. The disparities observed in the Disintegration subdimensions are consistent with established findings in various aspects of schizotypy, revealing some innovative perspectives. The current findings are interpreted as providing support for the validity of the newly introduced 20-item DELTA scale.

This work was supported by the Science Fund of the Republic of Serbia, grant number #7528289. The special research program on COVID-19 is financed by a World Bank loan through Serbia Accelerating Innovation and Entrepreneurship Project – SAIGE.

S115. SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDERS IN INTRAFAMILIAL HOMICIDE

Dominique Bourget^{*1}, Jiyoung Hwang¹, Shuying Zheng², Pierre Gagné³, Alain Labelle⁴

¹Royal Ottawa Mental Health Hospital, ²University of Ottawa, ³Université de Sherbrooke,

⁴Schizophrenia Program, The Royal Ottawa Mental Health Centre

Background: The homicide of another person due to psychotic symptoms is an uncommon but severe and unfortunate complication of psychotic illness. Psychotic individuals will most often target acquaintances or individuals with whom they interact the most. In this context, close family relatives are more at risk than the general population.

This poster presentation will review and analyse the results of an original study comprising over one-thousand consecutive cases of intrafamilial homicide coroner cases, collected over a period of 32-years in the province of Quebec, Canada, with respect to the impact and role of psychosis in intrafamilial homicide.

Methods: The data presented in this paper is extracted from the Quebec Study, a longitudinal study of domestic homicide from 1991 to the present. The study received approval from an institutional Ethics Board. The coroners' files contain data on both victims and offenders, their main characteristics, the circumstances and manner of death, the spatial location of the homicide, the type of weapon used in each case, the coroner's findings, the police report, the autopsy report, and toxicology report. In addition to the coroners' files, the authors reviewed any other available examination, including expert opinions and legal outcomes, when available. For the purpose of this presentation, we considered the following variables: type of intrafamilial homicide (e.g. filicide, parricide...), gender and age of offender, the number, gender and age of victims, method used, diagnosis of the offender and substance use, and known risk factors.

Results: The presence of a psychotic disorder was identified in a significant number of cases, and particularly in the categories of parricide (the killing of a parent), fratricide (the killing of a sibling) and filicide. In the sample of parricide, two-thirds of offenders were found to suffer from severe psychosis. Their actions were particularly violent and motivated by delusions against one or two parents. The presence of Capgras syndrome was noted in some cases. In the

category of fratricide, substance-induced psychotic disorder was prevalent. In the category of filicide, the presence of a psychotic diagnosis was high when it came to an offender killing several family victims. Risk factors showed the presence of pre-existing pathology and recent deterioration of behaviour, as well as recent psychosocial stressors. Specific numbers will be provided in table form in the poster.

Discussion: This study examines the prevalence and impact of psychosis, including schizophrenia, in intrafamilial homicides in a province of Canada. As forensic psychiatrists, we are often called upon to assess the offenders after the fact. The findings from this study and our own clinical experience reveal that indicators of a potential increased risk of violence in predisposed individuals do exist. Such risk factors include specific delusions, persecutory beliefs, behavioural and mental disorganization, and other clinical characteristics including worsening of psychosis. In an era where access to assessment and treatment are jeopardized by the insufficiency of resources in place, it is imperative, as a society, to reflect on better prevention and protective remedies.

S116. RELATIONSHIPS BETWEEN CHILDHOOD TRAUMA AND PSYCHOPATHOLOGY: A TRANSDIAGNOSTIC NETWORK ANALYSIS

Yi-hang Huang^{*1}, Chao Liu², Jian-biao Zhang², Shuai-biao Li³, Ling-ling Wang⁴, Hu Hui-xin⁵, Min-yi Chu³, Yi Wang⁶, Qin-yu Lv⁷, Simon S. Y. LUI⁸, Zheng-hui Yi⁷, Li Hui⁹, Raymond C.K. Chan¹⁰

¹Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, ²Nantong Fourth People's Hospital, ³Translational Neuropsychology and Applied Cognitive Neuroscience Laboratory, Shanghai Mental Health Centre, Shanghai Jiao Tong University School of Medicine, ⁴Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology; Department of Psychology, University of Chinese Academy of Sciences, ⁵Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; Department of Psychology, the University of Chinese Academy of Sciences, ⁶Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, ⁷Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, ⁸The University of Hong Kong, ⁹Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University, ¹⁰Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences

Background: Empirical evidence suggests that childhood trauma is a significant risk factor for various psychiatric disorders and is associated with a range of psychopathological symptoms. However, the specific mechanism linking childhood trauma to psychopathology remains unclear. There is a lack of transdiagnostic comparisons among different psychiatric disorders. This study adopted network analysis to examine a large cross-sectional transdiagnostic sample of patients with schizophrenia, bipolar disorder and major depressive disorder to investigate such a link utilising network analysis.

Methods: We administered the Positive and Negative Syndrome Scale (PANSS), the Clinical Assessment Interview for Negative Symptoms (CAINS), the Childhood Trauma Questionnaire

- Short Form (CTQ-SF), and the Clinical Global Impression - Severity of Illness (CGI-S) to 318 patients with schizophrenia, 163 bipolar disorder, and 194 major depressive disorder. We constructed a regularized partial correlation network of childhood trauma and psychopathological symptoms at both the dimension and the item levels. Network Comparison Tests (NCTs) were also used to investigate the differences among diagnoses, gender-stratified groups, and patients with and without childhood trauma.

Results: Our results showed that (1) childhood trauma is closely connected with psychopathological symptoms, after controlling for the inter-relationships between all nodes in the network. Different subscales of childhood trauma were distinctly linked to specific dimensions and/or items of psychopathology; (2) Emotional abuse of the CTQ-SF and motivation and pleasure deficits factor of the CAINS showed high expected influence and strength, while emotional abuse and depressive symptom of the PANSS showed high closeness and betweenness in centrality estimation. (3) NCTs revealed that patients who had suffering ed childhood trauma had exhibited greater network connections than those who did not. Schizophrenia patients also exhibited stronger network connections than both bipolar disorder and major depressive disorder patients. However, we did not find any there was no gender impact difference was upon the network structure across the transdiagnostic groups.

Discussion: In summary, this study utilized network analysis to reveal examine the existence of differential subtype effects of childhood trauma types on psychotic symptoms dimensions psychopathologies across a transdiagnostic sample. Notably, our findings underscored the central role of childhood trauma in shaping motivation and pleasure deficits, making them crucial targets for intervention. Additionally, Moreover, our results highlight emotional abuse as the key childhood trauma subtype influencing psychopathology development in patients with schizophrenia, bipolar disorder and major depressive disorder.

S117. IS THERE ANY TRIGGER FOR THE ONSET OF OBSESSIVE-COMPULSIVE SYMPTOMS IN SCHIZOPHRENIC PATIENTS?

Yasushi Okamura*¹, Hirohiko Harima¹, Masafumi Mizuno¹

¹*Tokyo Metropolitan Matsuzawa Hospital*

Background: Previously, it was generally held to be difficult to understand the developmental basis of symptoms and patterns in psychosis. However, psychogenic factors are known to play a prominent role in the development of neuroses. Thus, the two disorders, psychosis and neurosis, were recognized as etiologically disparate groups of diseases. Obsessive-compulsive disorder (OCD) was thought to originate in obsessive-compulsive neurosis, and it is sometimes still suggested that life events may be deeply involved in the onset of typical OCD. In clinical practice, however, schizophrenia and OCD co-occur in many patients. Indeed, Schneider, K. has remarked that obsessive-compulsive symptoms can occur in the early stages of schizophrenia. Recent epidemiological studies describing cases of comorbidity of OCD and schizophrenia have reported that a diagnosis of OCD increases the risk of later schizophrenia development. However, few psychopathological studies have examined whether obsessive-compulsive symptoms in patients with schizophrenia and OCD differ etiologically from those in patients with OCD without psychosis. With the removal of the requirement that patients acknowledge the irrationality of their obsessions or compulsions (i.e., insight) from the DSM-5 diagnostic criteria for OCD, the definition of OCD was broadened to include new forms characterized by delusional insight. The line of demarcation between schizophrenia and OCD increasingly deserves closer, clinical scrutiny.

Methods: This is a secondary analysis of our previously reported study (Okamura et al., 2022) in which some of the patients analyzed in the study are consistent with those analyzed in this presentation and only new psychopathological findings on the onset trigger are described here. The present study aimed to investigate whether there is any difference in the onset of obsessive-compulsive symptoms between patients with schizophrenia and OCD and those with OCD without a psychotic disorder. Between April 2015 and April 2022, 83 patients with OCD at the Department of Psychiatry at Tokyo Metropolitan Matsuzawa Hospital were divided into a group of 25 patients with OCD with a psychotic disorder (schizophrenia) (the OCD+PD group) and a group of 58 patients without any psychotic disorders (the OCD-PD group) based on the Mini International Neuropsychiatric Interview, Japanese version 5.0.0 2003 (M.I.N.I.) (Sheehan et al., 1997; Lecrubier et al., 1997; Amorim et al., 1998; Sheehan et al., 1998; Otsubo et al., 2005; Sheehan et al., 2010) and ICD-10 (World Health Organization, 2005) for cross-sectional comparison.

Results: The OCD+PD group was significantly less likely to have an onset trigger. Thirty-four patients with any trigger were classified and quantified in terms of the causes and severity of stress using the Social Readjustment Rating Scale (Holmes and Rahe, 1967). The causes of stress were Begin or end school (n=5), Change in working hours or conditions (n=5), Personal injury or illness (n=4), Change in health of family member (n=3), Sex difficulties (n=3), Change to a different line of work (n=3), and unclassifiable (n=21). The severity of stress was significantly higher in the OCD-PD group, and female patients were significantly more likely to have illness onset after some life event, especially if it was acute rather than enduring.

Discussion: The fact that the development of obsessive-compulsive symptoms was associated with significantly fewer triggers and a lower severity of stress in the OCD+PD group than in the OCD-PD group might be considered difficult to understand from the developmental perspective as expressed in the term, *genetisches Verstehen*. However, the present study did not use a life event rating scale nor fully examine the possible role of predisposing factors and the child-rearing environment in OCD onset in addition to environmental changes and events. To overcome these limitations, future studies might re-examine the definition of trigger and employ an objective life event scale while also taking into account personality traits, child-rearing environment, and gender differences.

S118. RESISTING INTERNALIZED STIGMA (RIS): ACCEPTABILITY AND FEASIBILITY OF A COGNITIVE BEHAVIORAL BASED STIGMA REDUCTION INTERVENTION FOR EARLY PSYCHOSIS

Francesca Crump^{*1}, Tom Dinzeo², Monica E. Calkins³, Christian Kohler³, Arielle Ered⁴, Kathryn Coniglio³, Riley Capizzi⁵, Bridgette Patton³, Alicia Lucksted⁶, Lawrence Yang⁷

¹Cambridge Health Alliance, ²Rowan University, ³Department of Psychiatry, University of Pennsylvania, ⁴Perelman School of Medicine University of Pennsylvania, ⁵Temple University, ⁶VA VISN 5 MIRECC, VA Maryland Health Care System, ⁷New York University

Background: The clinical high-risk for psychosis (CHR-p) designation was created to identify individuals exhibiting attenuated psychotic symptoms early to improve course of illness. Although there are invaluable benefits to entering specialized treatment programs for early psychosis, CHR-p individuals are likely to experience increased stigma due to the public's perception of receiving mental health treatment. Similarly, those diagnosed with their first episode of psychosis (FEP) are exposed to similar experiences of stigma and discrimination.

Currently, the only stigma reduction strategies implemented in early psychosis treatment contain psychoeducational elements. This study sought to pilot a manualized, cognitive behavioral therapy (CBT)-based stigma intervention for individuals identified as CHR-p and FEP in an early psychosis clinic.

Methods: This study piloted an 8-week, virtual group stigma intervention (RIS) that contained psychoeducation, CBT techniques to challenge stigmatizing thoughts, and anti-bullying strategies to diffuse confrontations. This study took place at the University of Pennsylvania's Psychosis Evaluation and Recovery Center (PERC) and a total of 9 individuals identified as CHR-p and FEP participated in two mixed groups. Qualitative interviews, psychosocial and functional outcomes were administered at baseline and follow-up. Pearson correlations and Wilcoxon Signed Rank Tests were performed.

Results: Overall, acceptability and feasibility of the intervention was established (attendance M=74.5%). Qualitative interviews indicated improvements in sense of purpose, perspectives on taking psychiatric medication, and increased family support. At baseline, correlations were associated with shame. Higher shame was linked to increased depression ($p=0.013$), worse psychological health ($p=0.001$), poor nutrition ($p=0.019$), low sense of purpose ($p=0.001$), and decreased self-esteem ($p=0.002$). At follow-up, most of the associations with shame became non-significant. Instead, most correlations were associated with positive emotions. Specifically, increased positive emotions were related to better emotion identification ($p=0.026$), quality of life for physical health ($p=0.042$), self-esteem ($p=0.006$), and role functioning ($p=0.005$). Wilcoxon Signed-Rank Tests demonstrated a decrease in stigma ($p=0.044$), an increase in positive emotions related to symptoms ($p=0.038$), and an elevation in sense of purpose ($p=0.024$). Furthermore, trend findings indicated increased self-esteem ($p=0.072$) and improved Theory of Mind performance ($p=0.074$) from baseline to follow-up.

Discussion: This is the first CBT-based stigma intervention to be piloted with CHR-p participants and demonstrated appropriate acceptability and feasibility for early psychosis groups. Participants endorsed uptake of CBT techniques to challenge stigmatizing thoughts, which led to increases in positive emotions, sense of purpose, and decreases in stigma. As specialized programs for early psychosis adopt recovery-oriented models, group stigma interventions, such as RIS, could be incorporated into their treatment offerings to improve outlook on course of illness and increase sense of purpose.

S119. RELATIONSHIP BETWEEN BRAIN STRUCTURE AND NEUROMETABOLITES IN THE EARLY STAGES OF PSYCHOSIS

María Ortuño^{*1}, Adriana Fortea¹, Irene Martínez¹, María Muriel¹, Patricia Camprodon¹, Elena De la Serna², Roger Borràs³, Mireia Masias⁴, Daniel Ilzarbe¹, Inmaculada Baeza⁵, Josefina Castro-Fornieles⁵, Gisela Sugranyes¹

¹Fundació Clínic Recerca Biomèdica - Institut d'Investigacions Biomèdiques August Pi i Sunyer, Clinical and Experimental Neuroscience, ²Centro de Investigación Biomédica En Red de Salud Mental CIBERSAM, Child and Adolescent Psychiatry, ³Department of Child and Adolescent Psychiatry, Institute of Neurosciences, University of Barcelona, ⁴BCN-MedTech, Universitat Pompeu Fabra, ⁵Department of Child and Adolescent Psychiatry, Institute of Neurosciences, University of Barcelona

Background: Patients at high risk for psychosis who develop the disorder have been found to present less gray matter volume and cortical surface area in the temporal and anterior cingulate

cortex compared to those who do not transition to psychosis suggesting that changes in brain structure precede the onset of the disorder. Nevertheless, the neurobiological mechanisms underlying these morphological changes are still not fully understood. Adolescence is an important neurodevelopmental period which is thought to be especially informative for understanding deviation in brain metrics associated with disease. The present study aimed to understand the relationship between levels of glutamatergic metabolites and measures of brain structure in adolescent patients with first episode of psychosis (FPE) or with familial high-risk for schizophrenia or bipolar disorder (HR), and controls.

Methods: 34 FPE (mean age 15.21 [7-18], 35% females), 44 HR (offspring of patients with schizophrenia or bipolar, none of whom meeting criteria for these disorders; mean age 14.06 [7-18], 70% females) and 76 healthy subjects (mean age 14.45 [7-18], 55% females) were recruited in the Hospital Clinic of Barcelona and assessed with clinical and brain imaging measures. All participants underwent the acquisition of two magnetic resonance imaging (MRI) sequences on a 3T scanner: a T1-weighted sequence and a magnetic resonance spectroscopy sequence (MRS) in volumes of interest (VOIs) located in the lateral prefrontal cortex (PFC) (2x2x2cm³) and the medial temporal lobe (mTL, 3x2x2cm³). MRS data was processed employing LCModel in order to obtain the creatinine-corrected ratios of glutamate and glutamate + glutamine (Glx). Moreover, the T1-weighted images were processed with Freesurfer (version 7.1) to retrieve cortical thickness, surface area and gray matter volume from frontal and medial temporal regions. Linear models were conducted in R to study the group by age effect on metabolite levels and the group by metabolite effects on structural measures.

Results: In the mTL we found differences between groups in Glx, specifically between FPE and controls ($t = 2.05$, $p = 0.042$) and HR ($t = 1.86$, $p = 0.065$), at a trend level, whereby Glx levels had a negative relationship with age in FPE, which was absent in the other groups. Moreover, we found a positive relationship between the gray matter volume of the left frontal pole and the values of glutamate ($p = .0011$) and Glx ($p = .016$) measured in the prefrontal VOI in all three groups. No associations were found between measures of brain structure at the hippocampal level and neurometabolites measured in this brain region nor metabolite by group effects in structural measures of any of the VOIs.

Discussion: These findings highlight the complex interplay between glutamatergic metabolite changes with age and brain structure in the early stages of psychosis during adolescence. Further studies characterizing high-risk youth according to their outcome and genetic background will provide a greater understanding of the biological changes that precede the emergence of psychosis or protect towards its development.

This study was funded by Instituto de Salud Carlos III co-funded by the EU (PI1800976, PI2100330, PI2100519), and by the EU grant (101057529), TV3_SalutMental_21 (202232-30), Alicia Koplowitz Foundation, CIBERSAM and 2021 SGR 01319.

S120. WHY HOW WE GOT HERE MATTERS: A QUALITATIVE STUDY OF THE IMPACT OF REFERRAL EXPERIENCE TO EARLY INTERVENTION SERVICES ON PERCEPTIONS OF CARE AND ENGAGEMENT IN TREATMENT

Brannon Senger^{*1}, Quinn MacDonald¹, Candice Crocker¹, Alissa Pencer¹, Jean Hughes¹, Philip Tibbo¹

¹Dalhousie University

Background: Background: Most young adults experiencing psychosis enter early intervention services (EIS) via inpatient services and emergency departments. Referral in this manner is often highly distressing for service users, especially considering the high likelihood of involuntary hospitalization and law enforcement involvement during these interactions. These experiences are suggested to impact young adults' trust and confidence in health services as well as their engagement in subsequent treatment, namely EIS. However, limited research has empirically examined the impact of young adults' referral and helpseeking experiences on these outcomes. This study aimed to explore the referral experiences of young adults enrolled in EIS and assess the impact of these on their current views towards healthcare services/providers and engagement in treatment.

Methods: 12 young adults (mean age = 24.83) within 3-12 months following their acceptance to EIS, were engaged in semi-structured qualitative interviews. Interviews were conducted and analyzed using an interpretative phenomenological analysis approach, which emphasizes the importance of understanding individuals' subjective experiences of an event and explores how this subjectivity influences their sense-making. Interview transcripts were analyzed to identify emergent themes in participants' accounts of their experiences. Two researchers independently analyzed interview transcripts to limit the risk of bias in identified themes.

Results: 3 superordinate themes emerged from participants' accounts of their experiences: (1) Navigating the Maze of Healthcare (2) Dignity and (3) Impact of Referral Experiences. Participants with referral pathways involving urgent care services, particularly through involuntary hospitalization described more adversity during their referral pathway and were more likely to

endorse help-seeking experiences as contributing to negative views towards EIS and diminished engagement in treatment.

Discussion: The impact of early negative experiences with healthcare on views towards EIS and engagement is evident in participants' accounts. Participants' perspectives were further contextualized by their illness insight, degree of recovery, and social support throughout their experiences. Participants with negative views towards EIS often described experiencing increased treatment delay, decreased awareness of the illness, residual psychotic symptoms, and decreased social support in addition to their adverse experiences with healthcare. Themes identified in qualitative analysis indicate specific features of treatment experiences predicting negative views that could be potential targets for improvement in health service delivery. Results highlight the need for psychiatric services to emphasize service users' dignity. Providing opportunities for patients enrolled in EIS to discuss and process past negative healthcare experiences may challenge existing negative beliefs about treatment and strengthen engagement in services.

S121. COMPARING THE IMPACT OF DUP ON 6 AND 12-MONTH OUTCOMES IN A PROSPECTIVE COHORT OF FEP CASES ACROSS TWO SITES

Hadar Hazan^{*1}, Bin Zhou², Fangyong Li², Toni Gibbs-Dean², Sumeyra Tayfur², Sneha Karmani², Emily Kline³, Maria Ferrara⁴, Sarah Riley², John Cahill², Cenk Tek², Matcheri Keshavan⁵, Vinod Srihari²

¹Yale Medical School, ²Yale Center for Analytical Sciences, ³Boston University, ⁴Yale Medical School; University of Ferrara, ⁵Harvard Medical School

Background: This study examined the correlation between Duration of Untreated Psychosis (DUP) and treatment outcomes in two Coordinated Specialty Care (CSC) clinics. One clinic implemented Early Detection (ED) strategies (STEP, n = 147), and the other used standard detection methods (PREP, n = 75).

Methods: We examined the correlation of DUP with treatment outcomes across the entire sample (median DUP = 228 days), and within the ED site, where the median DUP was reduced during the ED campaign (median DUP = 169 days). We used repeated measures of ANOVA and logistic regression to test the change in continuous (functioning, symptom severity, quality of life) and binary outcomes (employment status), respectively. The Difference-in-differences method was used to estimate the causal effect of low DUP on the outcome.

Results: In both samples, patients with a lower DUP showed better odds of employment, schooling, or job-seeking activities than those with a higher DUP at both the 6-month and 12-month intervals. In both samples, individuals with a lower vs. high DUP exhibited better global assessment of functioning (GAF) at the 6-month follow-up. However, this improvement was not maintained at the 12-month follow-up in either sample. Across sites, the low DUP group demonstrated a significantly greater improvement in quality of life (QoL) compared to the high DUP group at the 6-month and 12-month follow-ups. The same trend was evident in the ED sample, although it did not reach statistical significance.

Discussion: Despite the notably shorter DUP at the ED site, both samples exhibited similar trends. Functional outcomes appeared to be most consistently associated with DUP in this observational study. We did not find evidence supporting an association between DUP and symptom severity or GF: role and social scores. Individuals with a high DUP in CSC show improvement over time, although their progress seems to be slower.

S122. SEX DIFFERENCES IN PREVALENCE OF STRESSFUL LIFE EVENTS AND RELATION WITH SYMPTOMATOLOGY IN FIRST EPISODE PSYCHOSIS

Alicia Colomer-Salvans^{*1}, Regina Vila-Badia¹, Clara Serra-Arumi¹, Anna Butjosa², Nuria Del Cacho¹, Helena Escobedo-Pareras¹, Judith Usall¹

¹Parc Sanitari Sant Joan de Déu, ²Hospital Sant Joan de Déu

Background: It is described that there is a high incidence of Stressful Life Events (SLEs) in people with psychosis and that they are three times more likely to experience SLEs before the onset (Beards et al., 2013). There are few studies focused on sex differences of SLEs in First Episode Psychosis (FEP) and on the relationship between SLEs and clinical variables such as psychotic and maniac symptoms. However, the literature suggest some differences in women and men (Mansueto and Faravelli, 2022) and some associations with SLEs and symptomatology (Butjosa et al., 2016). The aims of the study are: 1) to study the prevalence and types of SLEs in FEP women and men, 2) to know the relationship between SLEs and symptomatology in FEP women and men.

Methods: This research is part of a longitudinal observational study called 'PROFEP Group' in Catalonia. The patients belong to Mental Health Parc Sanitari Sant Joan de Déu, Hospital Sant Joan de Déu and Hospital Germans Tias i Pujol health care sector. Participants included are 86 FEP patients (26♀; 60♂) and 87 HC (32♀; 55♂). The Stressful Life Events

Questionnaire (QSLE, Butjosa et al., 2017) was used to assess the total of SLE experimented during life and categorize SLE in nine areas: education, work, partner, family, home, legal, finances, social and health. The U Mann-Whitney test was used to evaluate differences in the prevalence of SLE between FEP women and HC women. Additionally, the T Student test assessed differences in the prevalence of SLE between FEP men and HC men. Finally, Spearman correlation and Pearson correlation tests examined associations between SLE and symptomatology in FEP women and men, respectively.

Results: Comparing with healthy controls (HC), FEP women present more SLEs in education ($U=186.500$; $p=.004$) and health ($U=286.000$; $p=.042$) categories, while FEP men experience more SLEs in total SLEs ($t=5.894$; $p < .001$), education ($t=7.083$; $p < .001$), work ($t=4.346$; $p < .001$), family ($t=3.205$; $p=.002$), home ($t=2.723$; $p=.008$), legal ($t=3.068$; $p=.003$), finances ($t=2.190$; $p=.031$), social ($t=3.810$; $p < .001$) and health ($t=4.841$; $p < .001$).

Regarding the relationship between SLEs and symptomatology, women with FEP who reported more SLEs related to health presented greater positive symptoms ($r=.455$; $p=.022$). In contrast, men with FEP who reported more total SLEs experienced more positive symptoms ($r=.400$; $p=.010$), and those who present more SLEs in the legal and social categories presented more positive ($r=.297$; $p=.021$, $r=.307$; $p=.019$, respectively) and excited ($r=.266$; $p=.040$, $r=.276$; $p=.036$, respectively) symptoms.

Discussion: Both FEP women and men experienced more SLEs than the HC, implying a potential association between experimenting SLEs and the onset of FEP.

Sex differences were observed in the relation between symptomatology and SLEs among individuals with FEP. This highlights the importance of incorporating a gender perspective in studies focusing on SLEs and FEP.

It is important to detect SLEs and provide good support, to reduce the stress and discomfort they can generate and the likelihood of developing a FEP.

Detecting SLEs and providing adequate support is crucial for mitigating the stress and discomfort they can generate, thereby reducing the likelihood of developing FEP.

S123. YOUTH MED.INFO - CO-DESIGN OF MENTAL HEALTH MEDICINES INFORMATION RESOURCES FOR YOUTH

Caroline Hynes^{*1}, Ian Kelleher², Sophie Kathryn³, Izzie X³, Charlie X³, Joseph Morning³, Stephen McWilliams⁴, Maria Migone⁵, David Columb⁵, Sarah Donnelly⁵, John Hayden⁶, Judith Strawbridge⁶, Nimantha Gamage⁷, Dolores Keating⁷

¹*Saint John of God Hospital*, ²*University of Edinburgh*, ³*SpunOut*, ⁴*St. John of God Hospital*, ⁵*Lucena Clinic, Child and Adolescent Mental Health Services*, ⁶*RCSI University of Medicine and Health Sciences, Dublin, Ireland*, ⁷*Saint John of God Hospital Ltd*,

Background: Mental health medicines information resources for youth in Ireland and globally are inadequate. Young people and their parents find existing mental health medicines information difficult to navigate as there are few reliable resources available. They also report lack of access to information on mental health medicines as a barrier to treatment adherence. Between 95-100% of those aged 12-17 report owning or having access to a personal smart device, and YouTube, TikTok and Instagram are the most commonly used platforms by this

age group. They are increasingly used by young people as search tools for queries about mental health diagnoses. However, as health information videos on these platforms are not peer-reviewed or aligned to any specific quality standards, search results may often return misleading or incorrect information. Those with content knowledge, are unlikely to possess skills, time or funding to produce high-quality video resources for youth. We aimed therefore to overcome this barrier by bringing clinicians and young people together to co-design a suite of accurate and accessible medicines information videos for use on YouTube, TikTok and Instagram.

Methods: Using an online design platform (www.canva.com) we produced three pilot videos on fluoxetine, olanzapine and methylphenidate. We then engaged in an iterative review process with a panel of expert collaborators including two specialist mental health pharmacists, two academic pharmacists, four consultant child and adolescent psychiatrists, a consultant adult psychiatrist, a child and adolescent psychiatric nurse and a focus group of young people. The clinical information in the videos was sourced from the manufacturers' summary of product characteristics and adapted in line with the experience of the clinical collaborators. In an effort to be inclusive and accessible, we considered racial and ethnic diversity, the needs of neurodivergent young people and those in LGBTQ+ community in the development process. To promote transparency and ensure that viewers are aware that the information is accurate and reliable, we developed a brand – Youth Med.Info with a logo and website: www.youthmed.info and a short trailer video.

Results: Having refined the three pilot videos, we then produced another five videos under the same medicine categories – sertraline, venlafaxine, risperidone, aripiprazole and lisdexamfetamine. These videos underwent the same rigorous review process as the initial three. The final eight videos were then uploaded to YouTube (@YouthMedInfo), TikTok (@YouthMed.Info) and Instagram (@Youth.Med.Info). The videos are also hosted on the website – www.youthmed.info – where there are links to more information resources as well as details of those involved in the co-design project. We then went on to develop another eight videos on mirtazapine, quetiapine, clozapine, guanfacine, atomoxetine, melatonin, promethazine and lorazepam all of which are undergoing the same review process.

Discussion: The format, language and overall accessibility of mental health medicines information resources for the youth of today is not suitable to their needs. Young people find the current information difficult to navigate and want to relate the use of the medicines to their everyday experiences. As the voice of young people matters most in their own mental healthcare, engaging with them as well as the clinicians who care for them when developing medicines information resources is crucial.

Given the growing popularity of social media platforms such as YouTube, TikTok and Instagram as search engines amongst young people, accessible and reliable mental health medicines information resources should be compatible with them. While there is a wealth of content on mental health medicines on these platforms presently, its accuracy is unclear. To our knowledge, our videos are the only mental health medicines information resources produced by young people and mental healthcare professionals working with young people.

S124. CEREBELLAR TRIPLE NETWORK DYSCONNECTIVITY WITH CORTICAL AND THALAMIC NETWORKS ACROSS DIFFERENT RISKS AND EARLY STAGE OF PSYCHOSIS

Minji Ha^{*1}, Inkyung Park¹, Taekwan Kim², Wu Jeong Hwang¹, Sunghyun Park³, Minah Kim³, Jun Soo Kwon³

Background: Cerebellar dysconnectivity is consistently linked to psychosis, alongside disruptions in the thalamus and cortical regions. Interestingly, these disruptions align with the triple network model, explaining psychopathological phenomena through abnormal interactions within the salience network (SAL), default mode network (DMN), and executive central network (ECN). However, the specific pattern of cerebellar functional network interactions with cortical and thalamic networks across different stages of psychosis risk within the triple network model remains largely unknown.

Methods: Resting-state fMRI data from 241 participants, including 37 first-episode psychosis (FEP), 63 clinical high-risk (CHR), 41 unaffected relatives (URs), and 100 healthy controls (HCs), were used. To capture the network properties of the thalamus and cerebellum, we generated parcellated thalamic and cerebellar maps reflecting their functional connectivity (FC) to associated cortical networks. FC between cerebellar and cortical networks, as well as between cerebellar and thalamic networks, was computed across the groups.

Results: Compared to the HCs, FEP showed more widespread network dysconnectivity across different regions, while CHR showed dysconnectivity primarily between the networks within the same region. This pattern of widespread dysconnectivity was more pronounced in FEP group than in CHR group. Also, URs did not show significantly different FC from the HCs.

Discussion: The expansion of the classical triple network model to incorporate cerebellar and thalamic networks, along with their distinct FC patterns, holds potential significance in contributing to early psychosis pathophysiology. Furthermore, it can be inferred that dysfunctional interactions within cerebellar, thalamic, and cortical triple networks may manifest as impaired prediction- and error-based learning and inappropriate information updating.

S125. COGNITIVE FUNCTION AT FIRST EPISODE IN PATIENTS SUBSEQUENTLY DEVELOPING TREATMENT-RESISTANT SCHIZOPHRENIA

Juan Aguirre¹, Camila Diaz², Javiera Vásquez Núñez³, Juan Pablo Ramirez-Mahaluf⁴, Daniella Barbagelata¹, Ángeles Tepper³, Cristian Mena², Ruben Nachar², David Aceituno⁵, Alfonso González-Valderrama⁶, Nicolás Crossley⁷, Nicolas Crossley*⁸

¹Department of Psychiatry, Pontificia Universidad Católica de Chile, Santiago, Chile., ²Early Intervention Program, J. Horwitz Psychiatric Institute, ³Pontificia Universidad Católica de Chile, ⁴Facultad de Medicina, P. Universidad Católica de Chile, ⁵Department of Psychiatry, School of Medicine, Pontificia Universidad Católica de Chile, Chile. King's College London, Institute of Psychology, Psychiatry, and Neuroscience, Department of Health Service and Population Research, ⁶Instituto Psiquiátrico Dr. José Horwitz Barak, Santiago, Chile., ⁷Pontificia Universidad Católica, ⁸Facultad de Medicina, P. Universidad Católica de Chile

Background: This study addresses cognitive differences between treatment-responsive (TRESP) and treatment-resistant (TRESIST) schizophrenia patients when they first become unwell (in their first episode of psychosis). Previous research has predominantly focused on chronic patients, making it challenging to distinguish inherent neuropsychological deficits in TRESIST from those influenced by chronicity, antipsychotic exposure and overall deleterious

illness progression. Exploring whether these cognitive differences emerge early in the course of the illness or evolve progressively, could offer insights into the nature of cognitive performance in Treatment-resistant schizophrenia and be used as potential early markers of treatment resistance.

Methods: Cohort study of eighty-one first-episode schizophrenia patients aged 18-65 from Santiago, Chile. Patients were followed-up (mean = 64.03 weeks; median = 10.14) and were classified as treatment resistant if fulfilling TRRIP criteria on clinical assessment or if they were prescribed clozapine at any point by their treating psychiatrist. Cognitive performance was assessed using the Matrices Consensus Cognitive Battery (MCCB). A multivariable model was used to compare cognitive performance between groups.

Results: 51 (63 %) patients were allocated to the treatment-responsive group (TRESP) and 30 (37 %) to the treatment-resistant (TRESIST) sample. Groups did not differ significantly in age, sex, antipsychotic dose, duration of illness in treatment or duration of untreated psychosis (p GREATER THAN 0.05). However, TRESIST cases scored significantly higher in symptom severity (PANSS total score, $p = 0.002$).

A multivariable model controlling for age and sex, revealed that TRESIST at their first episode patients exhibited worse performance than their TRESP counterparts in speed of processing tasks (BACS, $p = 0.002$; TMT-A, $p = 0.004$), verbal fluency ($p = 0.03$), attention/vigilance (CPT-IP, $p = 0.048$), and working memory (WMS-III, $p = 0.045$), with medium to large effect sizes (Cohen's d GREATER THAN 0.5). After correction for multiple comparisons (Bonferroni), only speed of processing tasks (Symbol Coding; TMT-A) remained statistically significant. When accounting for symptom severity, duration of untreated psychosis, and antipsychotic dose, TRESIST subjects still exhibited a significantly lower performance in the two speed of processing task (BACS, $p = 0.036$; TMT-A, $p = 0.027$), which was not significant after correcting for multiple comparisons.

Discussion: Treatment-resistant schizophrenia patients exhibit impairment in speed of processing compared to treatment-responsive patients during the first episode, although this result is partly driven by other known factors of cognitive performance such as symptom severity, antipsychotic dose, and duration of untreated psychosis.

Speed of processing appears as an early deficit that could help the timely identification of patients presenting a disease trajectory towards treatment-resistance and facilitate the prompt implementation of known effective treatments such as clozapine. Our results are similar to previous studies with similar design (Kravariti et al., 2019; Millgate et al., 2023). This combined evidence highlights the existence of some cognitive differences at illness onset in TRESIST patients, which are in stark contrast to the severe impairment seen later in their illness (Millgate et al., 2022). It is unclear whether this deterioration is secondary to the high doses of antipsychotic medication these patients are exposed to, the environment changes associated to being severely unwell, or associated with a particularly damaging illness progression. Such deteriorating course sets aside TRESIST cases from TRESP.

The relatively small sample size emphasizes the need for larger and more diverse samples in future research to bolster the robustness of the findings. This consideration underscores the cautious interpretation of the results and emphasizes the preliminary nature of the current findings.

S126. AVOLITION IN EARLY PSYCHOSIS: INTERNAL EXPERIENCE AND RELATIONSHIPS WITH SOCIO-DEMOGRAPHIC FACTORS

Sylvia Romanowska*¹, Michael Best¹

¹*University of Toronto Scarborough*

Background: Negative symptoms, prominent in schizophrenia-spectrum disorders, are notably difficult to treat. Thus, a better understanding of mechanisms underlying this class of symptoms is needed. Avolition, or lack of motivation, has been hypothesized to be the primary negative symptom construct, with other domains representing phenotypic expressions of an overall loss of motivation. Avolition has the most direct effect on psychosocial functional decline and has been demonstrated to be the single most important domain to target for global treatment of negative symptoms. The present study examined internal factors related to avolition in the daily lives of young people with psychosis and its associations with goal-directed behaviour in order to uncover how motivation is translated into action. The specific aims were to investigate whether young people with psychosis differ from community controls (CCs) on, (a) quantity and diversity of activities of daily living, (b) intensity and variability of motivation for different types of goal-directed activities.

Methods: This study included one week of ecological momentary assessment (EMA) to assess engagement in goal-directed activities, the internal experience of avolition, and social networks, followed by a remote assessment of demographics, symptoms, and psychosocial functioning. Thirty-eight participants with early psychosis and 51 community controls between the ages of 18-36 were recruited. All participants were prompted to respond to 5 survey notifications per day for the one-week study period. Summary-level data was compared between psychosis and control groups using two-tailed t-tests. The effect size (Cohen's d) and confidence intervals (95%) were calculated to estimate and compare group differences.

Results: Participants with psychosis had reduced overall levels of motivation for current activities, as well as motivation to persist during activities, relative to CCs. However, participants with psychosis did not rate their current activities as being more effortful relative to CCs. Regarding motivation for specific goal-directed activities, participants with psychosis reported less motivation to engage in (or search for) work/school but had similar levels of motivation to engage in social and recreational activities. Participants with psychosis engaged in fewer different categories of goal-directed activities, more often endorsing engaging in "Nothing" or a passive activity and had smaller social networks relative to CCs.

Discussion: The present data demonstrate the importance of assessing motivation for different categories of goal-directed activities rather than approaching motivation as a unitary construct. Standard assessments of motivation overlook potentially intact areas of motivation, such as social motivation, which may be leveraged in treatment. Moreover, although motivation for certain pleasurable activities (e.g., hobbies; socialization) was intact, participants with psychosis still engaged in fewer different types of activities. Awareness that avolition itself may not be the source of lower activity engagement in young people with psychosis may prompt exploration into alternate roadblocks to engagement in such activities.

S127. THE RELATIONSHIP BETWEEN HDL CHOLESTEROL AND COGNITIVE RESERVE IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS: A TWO-STUDY ANALYSIS

Barbora Keřková*¹, Karolína Knížková¹, Mabel Rodriguez¹

¹*National Institute of Mental Health, Klecany, Czech Republic*

Background: Markers of cardiovascular disease risk can predict cognitive performance, leading to their consideration as components of the so-called cognitive reserve (CR), a hypothetical buffer against psychopathology. Initial evidence suggests that in first-episode schizophrenia spectrum disorders (FES), reduced levels of high-density lipoprotein (HDL) cholesterol may be uniquely related to poorer CR, with this relationship being particularly evident for certain CR proxies, such as years of education. We tested this suggestion in two samples of FES individuals, for whom CR was computed as either a conventional composite score of demographic and cognitive scale proxies, or comprehensively assessed within the Cognitive Reserve Assessment in Health (CRASH) interview.

Methods: Study 1 included a previously described sample of 137 FES individuals (66.4% males, aged 25.93 ± 6.47 years). CR was the regression component score of: years of education, premorbid IQ, and socioeconomic status. For Study 2, we recruited an additional 45 FES individuals (64.4% males, aged 28.53 ± 8.61 years) who completed the CRASH interview, generating a global CR score as well as educational, occupational, and leisure activity subscores. In both studies, we assessed Pearson's correlations between CR and fasting plasma HDL cholesterol levels. Considering the sex differences in HDL cholesterol's predictive value for cardiovascular risk, the data were also reanalyzed after stratifying by biological sex.

Results: Study 1 showed no significant correlations between HDL cholesterol and the CR composite or component scores ($r_s = -.056-.080$, p s GREATER THAN .05). In Study 2, we found a marginal association between HDL cholesterol and the global CR score ($r = .292$, $p = .051$), which reached significance for the educational subscore ($r = .369$, $p = .013$). After sex stratification, these relationships remained significant only in males.

Discussion: HDL cholesterol can correlate with CR and some of its components, provided that these are assessed comprehensively, rather than solely through demographic and cognitive scale proxies. In particular, the link between HDL cholesterol and educational CR might only transpire once educational attainment is considered together with other factors, such as parental education, school performance, or language ability. Additionally, the relationships between HDL cholesterol and CR might be influenced by biological sex. Overall, the specificity and weak-to-moderate strength of the observed relationships are likely to limit the usefulness of HDL cholesterol as a universal component of CR. Further research could investigate whether the effects of HDL cholesterol and CR on cognitive performance in FES are independent or interchangeable.

S128. ASSOCIATIONS BETWEEN ANTIPSYCHOTIC MEDICATION AND DAILY-LIFE EXPERIENCE OF PSYCHOLOGICAL ADVERSE EFFECTS AFTER FIRST EPISODE PSYCHOSIS - A HAMLETT ECOLOGICAL MOMENTARY ASSESSMENT STUDY

Matej Djordjevic^{*1}, Martijn Kikkert², Shiral Gangadin¹, Lieuwe de Haan³, Priscilla Oomen¹, Claudia Simons⁴, Machteld Marcelis⁵, Mark Nijland⁶, Marieke Begemann¹, Hannah Jongsma¹, Wim Veling¹

¹University Medical Center Groningen, ²Arkin Mental Health Care Amsterdam, ³Academic Medical Center, University of Amsterdam, ⁴GGzE, ⁵Maastricht University Medical Center, ⁶Rob Giel Onderzoekscentrum

Background: Pharmaceutical agents acting on dopamine-2 (D2) receptors (i.e., “antipsychotics”) are a cornerstone of the current treatment for psychotic disorders. However, their adverse effects (AE) can pose a significant subjective burden on patients, though evidence from people’s daily-life is scarce.

This study aimed

1.)To investigate the distribution of momentary indicators of psychological AE (i.e., blunted emotional experience, reduced initiative of social contact, avolition, tiredness and difficulty concentrating, and anhedonia) in 56 people in remission of First Episode Psychosis (FEP).

2.)To investigate whether type, dosage or estimated D2 receptor-occupancy of antipsychotic medication are associated with momentary psychological AE throughout the day.

Methods: The current Ecological Momentary Assessment (EMA) study was conducted in 56 people in remission of FEP, as part of the HAMLETT (Handling Antipsychotic Medication: Long-term Evaluation of Targeted Treatment) trial. At baseline, participants were prompted to report on momentary indicators of psychological AE 10x/day for eight consecutive days. Data on the type and dosage of antipsychotic medication were retrieved from the Dutch Foundation for Pharmaceutical Statistics. We grouped the medications based on D2 receptor-affinity, mechanism of action (D2 antagonism versus partial agonism) and H1 receptor antagonism. We performed stepwise multilevel mixed-effects linear regression analyses to investigate average cross-sectional associations between the type and dosage of antipsychotic medication as well as estimated D2 receptor-occupancy and momentary indicators of psychological AE throughout the day, i.e., overall as well as separately in the mornings (first 3 prompts per day), daytime (prompts 4-7) and evenings (last 3 prompts per day). All models were adjusted for fixed effects of age, gender, tobacco and cannabis use in the past month and symptom severity during FEP.

Results: Analyses of 3,005 questionnaires showed that a higher dosage of antipsychotic medication was associated with increased momentary variability in positive affect ($B = 0.23$ [95% CI: 0.04; 0.42]) and with increased levels of momentary anhedonia ($B = -1.12$ [95% CI: -1.99; -0.25]). Moreover, as compared with dopamine antagonists with high D2 affinity (K_i LESS THAN 20), the use of dopamine antagonists with low D2 affinity (K_i GREATER THAN 20) and the use of partial dopamine agonists were associated with decreased levels of anhedonia ($B = 10.68$ [95% CI: 1.23; 20.14] and $B = 13.40$ [95% CI: 2.95; 23.86], respectively). Estimated D2 receptor-occupancy was not associated with psychological AE overall, though higher D2 receptor-occupancy was associated with increased tiredness and difficulty concentrating in the mornings ($B = 0.29$ [95% CI: 0.10; 0.48]) and in the evenings ($B = 0.23$ [95% CI: 0.02; 0.44]).

Discussion: Type, dosage and D2 receptor-occupancy of antipsychotic medication can be associated with daily-life experience of anhedonia, positive affect variability as well as tiredness and difficulty concentrating. More research into underlying mechanisms and consequences for clinical treatment recommendations after FEP is warranted.

S129. LONGITUDINAL TRAJECTORIES OF PLASMA POLYUNSATURATED FATTY ACIDS AND ASSOCIATIONS WITH PSYCHOSIS-SPECTRUM OUTCOMES IN EARLY ADULTHOOD

David Mongan^{*1}, Benjamin Perry², Colm Healy³, Subash Raj Susai⁴, Stan Zammit⁵, Mary Cannon⁴, David Cotter⁴

¹Queen's University Belfast and Royal College of Surgeons in Ireland, ²University of Cambridge, ³Royal college of Surgeons in Ireland, ⁴Royal College of Surgeons in Ireland, ⁵University of Bristol

Background: There is evidence for associations between polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and psychosis risk, including Mendelian randomisation analyses that support a causal effect for long-chain PUFAs in reducing risk of schizophrenia. However, most population studies have used single PUFA measurements at one point in time, which may overlook dynamic patterns of temporal variability. Longitudinal plasma PUFA trajectories have not been previously characterised in the general population, and associations between such trajectories and psychosis-spectrum outcomes in early adulthood are thus unknown.

The aims of this study were: 1) To characterise, for the first time, longitudinal trajectories of plasma omega-6:omega-3 (n-6:n-3) PUFA ratio and DHA levels in a large general population sample; and 2) To evaluate associations between these trajectories and psychosis-spectrum outcomes in early adulthood.

We focused on n-6:n-3 ratio and DHA because these measures have been associated with psychosis risk in previous studies. We hypothesised that trajectories characterised by higher n-6:n-3 ratio and lower DHA levels would be associated with increased odds of psychosis-spectrum outcomes.

Methods: We examined a cohort of participants in the UK-based Avon Longitudinal Study of Parents and Children who completed psychiatric assessments at age 24 years (n=3635, of whom 2247 [61.8%] were female). Participants provided plasma samples at four timepoints when aged 7 (n=2268), 15 (n=1896), 17 (n=1933) and 24 years (n=3163). Plasma n-6:n-3 ratio and DHA levels (expressed as % total fatty acids) were measured using nuclear magnetic spectroscopy, then standardised by sex.

We examined five psychosis-spectrum outcomes at age 24 years. Presence/absence of psychotic experiences (PEs), At-Risk Mental State status and psychotic disorder were assessed using the Psychosis-Like Symptoms interview, as was the total number of PEs (range 0 to 11). Negative symptoms score (range 0 to 10) was measured using the Community Assessment of Psychic Experiences.

Curvilinear growth mixture modelling was used to derive longitudinal trajectories of plasma n-6:n-3 ratio and DHA levels. Models were adjusted contemporaneously for body mass index at each timepoint. Associations between trajectory membership and binary outcomes (any PEs, At-Risk Mental State status and psychotic disorder), number of PEs and negative symptoms score were evaluated using logistic, negative binomial and linear regression respectively, before and after adjusting for sex, ethnicity, parental socioeconomic class, smoking and alcohol use. Multiple imputation using Bayesian analysis was used to impute missing exposure and covariate data across 10 imputed datasets.

Results: At 24 years, 116 (3.2%) met criteria for PEs; 23 (0.6%) for At Risk Mental State; and 46 (1.3%) for psychotic disorder.

A three-trajectory solution was optimal for n-6:n-3 ratio (stable average, n=3282 [90.3%]; slightly above average, n=61 [1.7%]; and persistently high, n=292 [8.0%]) and DHA (stable average, n=2739 [75.4%]; persistently high, n=245 [6.7%]; and persistently low, n=651 [17.9%]).

Relative to stable average, the persistently high plasma n-6:n-3 ratio and persistently low DHA trajectories were associated with increased odds of PEs and psychotic disorder in unadjusted analyses, but these associations attenuated on adjustment for covariates. There was little evidence for associations with At Risk Mental State status. Conversely, the persistently high n-6:n-3 ratio trajectory was associated with increased number of PEs (adjusted β 0.41, 95% confidence interval [CI] 0.05 - 0.78, $p=0.026$) and negative symptoms score (adjusted β 0.43, 95% CI 0.14 - 0.72, $p=0.004$). Similarly, the persistently low DHA trajectory was associated with increased number of PEs (adjusted β 0.45, 95%CI 0.14 - 0.76, $p=0.004$) and negative symptoms score (adjusted β 0.35, 95%CI 0.12 - 0.58, $p=0.003$).

Discussion: In this first characterisation of longitudinal plasma PUFA trajectories in a large general population cohort, we found evidence for three broad trajectories of n-6:n-3 ratio and DHA levels across childhood, adolescence and early adulthood. Trajectories characterised by persistently high plasma n-6:n-3 ratio and persistently low plasma DHA levels were associated with psychosis-spectrum outcomes in early adulthood, and in the case of number of PEs and negative symptoms, not fully explained by included covariates. Strengths of this analysis include the use of objective plasma PUFA markers in a large, well-characterised cohort with multiple repeated measures over time. However, the relatively small number of individuals who met criteria for At Risk Mental State and psychotic disorder in this general population study may have limited statistical power. Residual confounding is possible, for example, due to other dietary factors. Compared to erythrocyte membrane measures, plasma PUFA levels reflect a shorter timeframe of 1-2 weeks due to higher metabolic turnover. Despite these limitations, these novel findings suggest that optimisation of PUFA status during development warrants further investigation in relation to psychosis-spectrum symptoms in early adulthood.

S130. TARGETING STIGMA IN FIRST EPISODE PSYCHOSIS: SELF-STIGMA AND CORRELATES

Evan Myers^{*1}, Daniel R. Samost², Sheharyar Hussain², Bethany L. Leonhardt³, Philip T. Yanos²

¹Indiana University - Purdue University Indianapolis, ²John Jay College Of Criminal Justice, City University of New York, ³Department of Psychiatry, Indiana University School of Medicine

Background: Self-stigma affects many people with severe mental illness. Research has shown that self-stigma is negatively linked to treatment engagement and both objective and subjective aspects of recovery in adults. Less is known about self-stigma in youth experiencing first episode psychosis. Adolescence and young adulthood are crucial periods of identity formation, which the onset of psychosis can disrupt, and therefore critical times to address self-stigma. In this study, we aimed to identify correlates of self-stigma in youth with psychosis. These correlates may be important to consider in interventions targeting self-stigma in this population and more generally in clinical care.

Methods: Participants were recruited from a first episode psychosis clinic as part of the development of an exploratory group-based intervention to address self-stigma (NIMH grant: #R34MH122500). Prior to enrollment, potential participants completed a screening of self-stigma (Internalized Stigma of Mental Illness Inventory) and were included in the study if they showed elevated self-stigma. Enrolled participants then completed measures of self-esteem

(Rosenberg Self-Esteem Scale), hopelessness (Beck Hopelessness Scale), recovery style (Recovery Style Questionnaire), and symptoms (Positive and Negative Syndrome Scale).

Results: Data collection is ongoing (target $n = 40$), and initial data ($n = 6$) show that self-stigma is positively related to an integrated recovery style ($r = .81$). Results also show self-stigma is negatively related to self-esteem ($r = -.89$) but not hopelessness ($r = .51$). Subscale analyses reveal that recovery style is specifically related to perceived discrimination ($r = .84$) and self-esteem is inversely related to social withdrawal ($r = -.97$). Correlations between self-stigma and symptom dimensions were not significant.

Discussion: Results provide preliminary evidence that among care-seeking youth with first episode psychosis, self-stigma is related to recovery style. That is, people who tend to “seal over” have less self-stigma. Another preliminary finding is that self-stigma is related to self-esteem but not hope. This may suggest that self-stigma may not immediately impact hope, and that youth with psychosis show resilience in this respect. Therefore, it may be important to consider youths’ recovery style when delivering self-stigma interventions and provide opportunities for them to discuss how stigma relates to self-esteem.

S131. INDIVIDUAL DATA QUANTITY HAS A STRONG IMPACT ON THE PREDICTION OF PSYCHOSIS DISTRESS FROM FUNCTION CONNECTIVITY IN THE ABCD STUDY

Alexis Porter^{*1}, Katherine Damme¹, Vijay Mittal¹, Caterina Gratton²

¹Northwestern University, ²Florida State University

Background: Psychosis spectrum disorders typically manifest in adulthood, following prodromal periods in adolescence (Walker et al., 2007). The severity of psychotic-like experiences (PLE) during adolescence may predict the onset of psychosis (Cowan and Mittal, 2020). This developmental phase provides a unique opportunity to pinpoint neural biomarkers and mechanisms associated with emerging PLEs. Adolescence is characterized by the dynamic formation of large-scale functional networks, and machine learning techniques can detect subtle disruptions in these networks that are linked to adult symptoms and deficits. Recent methodological advancements in accounting for individual differences in functional network organization have significantly improved model predictions in clinical populations (Fan et al., 2021). In our study, we aimed to improve machine learning classification through two methods. First, we assessed whether constructing functional connectivity (FC) using more individual-level data (35-50 minutes) enhanced accuracy in predicting symptom course compared to FC matrices built with less data (10-20 minutes). Next, we employed a parcellation method designed to consider individual differences in brain network topography (Kong et al., 2021) and compared its performance with parcellation methods relying on group average approaches. Collectively, these approaches may enable improved precision in identification of relevant mechanisms for emerging PLEs.

Methods: We analyzed a subset of the ABCD Study ($N=1,320$). In the ABCD, participants underwent up to 50 minutes of task and resting state scans during the initial visit, along with annual behavioral assessments of distress related to PLEs. Participants were included in the study if they had at least 35 minutes of combined time series data after standard motion scrubbing procedures (Power et al., 2014). In this study, we investigated whether a machine learning model based on baseline fMRI data could distinguish between high and low PLE distress scores across five different points in time. We developed models using FC derived from task or resting state data (10 minutes) and compared performance to models constructed

using a concatenation of all task and resting state data (35-50 minutes). To assess the impact of parcellation approaches on identifying individual differences in brain networks, we compared FC derived from individualized parcels (Kong et al., 2021) to standard group atlases.

Results: 30-minute models exhibited significantly higher performance at predicting PLE distress than 10-minute models. Through permutation testing, we determined that models based on extended amounts of data could predict PLE distress above chance from the initial year of collection up to two years later. Additionally, we observed that models using individualized parcels showed a small but significant improvement in performance compared to the other three group atlas methods for predicting the initial year of psychosis distress.

Discussion: These findings suggest that emerging differences in FC relate to PLE distress. However, best performance was seen when larger amounts of data were used for FC estimation, likely due to significant improvements in the underlying reliability of FC estimates (Gordon et al., 2017). The use of an individualized parcellation approach also significantly improves the prediction of psychosis distress within the initial year of data collection, but to a smaller degree. This work underscores the importance of collecting larger amounts of data and deep phenotyping at the individual level to extract meaningful biomarkers and mechanisms for early identification of psychosis risk and relevant treatment targets for early intervention.

S132. TRAJECTORIES OF SUICIDAL BEHAVIOR AND THEIR CLINICAL CORRELATES IN THE EARLY PHASES OF SCHIZOPHRENIA SPECTRUM DISORDERS

Amalie Solberg*¹, Akiah Ottesen², Elisabeth Ann Barrett³, Ingrid Kristiansen⁴, Kristin Lie Romm³, Erlend Mork³, Ping Qin⁵, Ingrid Melle⁶

¹*Oslo University Hospital - Psychosis Research Unit*, ²*Norwegian Centre for Violence and Traumatic Stress Studies*, ³*Early Intervention in Psychosis Advisory Unit for South East Norway, Division of Mental Health and Addiction, Oslo University Hospital*, ⁴*Oslo University Hospital - Psychosis Research unit*, ⁵*Natinal Centre for Suicide Research and Prevention*, ⁶*University of Oslo, Norwegian Centre for Mental Disorders Research*

Background: The risk of suicide in schizophrenia spectrum disorders (SSD) is highest in the first treatment years; suicidal behaviors (SB) are also often the trigger of the first treatment contact, and some die by suicide before treatment is initiated. Still, the trajectories of SB have only been investigated from the first treatment contact onwards while many risk factors for SB in SSD (e.g. earlier suicidal attempts, comorbid depression, substance use, low self-esteem, and experience of childhood trauma) may be present before the onset of psychosis. A better understanding of the development of SB and risk factors for early SB trajectories can help to understand the early high risk of SB and aid early interventions. Our aim is to investigate i) different trajectories of suicidal ideation and behavior from the premorbid period until first treatment, and ii) the relationship between early risk factors for SB and different SB trajectories.

Methods: A total of 223 patients with DSM-IV first-episode SSDs were recruited close to treatment start from departments in the Oslo areas. They underwent a structured and comprehensive clinical examination including the Birchwood Insight Scale (subscales awareness of illness and need for treatment), the Childhood Trauma Questionnaire, and the Rosenberg Self-Esteem Scale. We collected retrospective reports of the number of depressive episodes, weeks of untreated psychosis, and the severity of SB in three time periods: Premorbid

(before the onset of psychosis), post-onset (in the period of untreated psychosis), and at/after treatment start. We used K-mean cluster analyses to identify different trajectories of SB over these time points. SB severity was assessed as 0= no SB, 1=suicidal ideation, 2=suicide plans, and 3=suicide attempts (1=mild SB, 2 or 3=severe SB). The highest score for the period was used in the analyses.

Results: We identified four trajectories of SB. Group A (50,2%), consisted of patients with no SB, SB only premorbid or mild SB in untreated psychosis. Group B (23,8%), had mild persistent SB throughout or initially mild but increasing towards the start of treatment. Group C (14,3%), had severe SB during the period of untreated psychosis. Group D (11,7%), had severe SB premorbid and in one or both of the post-onset periods. Compared to group A, group C had statistically significantly more depressive episodes, longer duration of untreated psychosis (DUP), lower self-esteem, and higher awareness of illness; group B had significantly higher awareness of illness and insight into the need for treatment; group D had significantly higher exposure to emotional abuse, more depressive episodes, lower self-esteem, higher awareness of illness, and insight into the need for treatment. There was also a statistically significant difference between groups B and C, with higher DUP and lower insight into the need for treatment in group C. Group B reported significantly lower exposure to emotional abuse than group D.

Discussion: This study shows significant differences in clinical characteristics between different trajectories of SB in SSD. All groups reported higher awareness of illness than group A. The groups with more severe SB (post-onset and severe persistent) had an accumulation of risk factors but with significant differences. Longer DUP was only associated with the post-onset group C, indicating a role of psychotic symptoms for SB. The severe persistent group D reported more exposure to emotional abuse than all the other groups, underlining the role of childhood trauma in the severity of SB and the development of SB before psychosis onset.

S133. EARLY LIFE STRESS AND FUNCTIONAL CONNECTIVITY IN ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

Hillary Patton*¹, Jose Maximo¹, Adrienne Lahti¹

¹*The University of Alabama at Birmingham*

Background: Childhood trauma (CT) occurs at a much higher frequency in psychosis spectrum disorders as compared to the general population. Evidence suggests that CT is a risk factor for psychosis spectrum disorders but the neural mechanisms underlying this association remains unclear. Previous work has identified associations between CT and altered fronto-limbic functional connectivity in psychosis patients, but the research is limited. The objective of this study is to examine the relationship between childhood trauma and functional connectivity in a large sample of antipsychotic-naïve patients with first episode psychosis (FEP).

Methods: Resting state fMRI data from 105 FEP patients and 123 healthy controls (HC) were used. Our regions of interest included bilateral hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC). Childhood Trauma Questionnaire (CTQ) total and subscale scores (physical and emotional abuse/neglect and sexual abuse) were correlated with the resting state functional connectivity (rsFC) data.

Results: Compared to HC, patients had significantly higher CTQ total and subscale scores and significantly reduced rsFC in L/R hippocampus – vmPFC (p LESS THAN .05) and L/R amygdala –vmPFC (p LESS THAN .05). Partial correlation analyses accounting for age, sex,

and framewise displacement indicated that higher CTQ sexual abuse subscale scores in FEP patients were associated with increased left amygdala—vmPFC rsFC ($r(59) = .27$, $p < .05$) and higher CTQ emotional neglect subscale scores in FEP patients were also associated with increased left hippocampus—vmPFC rsFC ($r(59) = .27$, $p < .05$). Follow-up analysis showed a significant interaction effect of group (FEP and HC) and CTQ score (sexual abuse subscale) on left amygdala—vmPFC rsFC ($\beta = .014$, $p < .05$). Simple slopes analyses showed that higher CTQ sexual abuse subscale scores were associated with increased rsFC in FEP patients ($\beta = .56$, $p < .001$) but decreased rsFC in healthy controls ($\beta = -.56$, $p < .001$).

Discussion: The findings show evidence that the impact of childhood trauma on brain mechanism patterns differ significantly between the general population and individuals with psychosis spectrum disorders. The results also provide support for the long-term differential impact of trauma subtypes on the human brain. Increased connectivity in FEP individuals in response to greater childhood trauma may reflect a compensatory mechanism or neural adaptation in response to early life stress. Overall, the results contribute to the understanding of the neural mechanisms underlying the association between childhood trauma and psychosis spectrum disorders.

S134. COST AND UTILIZATION OF EARLY PSYCHOSIS SERVICES IN CALIFORNIA

Sophie McMullen^{*1}, Merissa Kado-Walton², Heather Garman³, Yi Zhang⁴, Amanda McNamara², Valerie Tryon⁵, Andrew J. Padovani⁶, Sabrina Lourerio⁶, Joy Melnikow⁶, Tara A. Niendam⁷, Todd P. Gilmer², Rachel Loewy⁸

¹University of California - San Francisco, ²Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, ³Department of Psychiatry, Weill Institute for Neuroscience, University of California San Francisco, ⁴University of California Davis, ⁵Department of Psychiatry, University of California, Davis, School of Medicine, ⁶Center for Healthcare Policy and Research, University of California-Davis, ⁷Department of Psychiatry and Behavioral Sciences, University of California, Davis, School of Medicine, ⁸Department of Psychiatry, Weill Institute for Neurosciences, University of California - San Francisco

Background: Although untreated mental illness can be devastating, an individual typically does not qualify for treatment until their symptoms are severe enough to adversely impact their life. In California, specialized early psychosis (EP) programs targeting youth were implemented to attempt to reduce the negative outcomes related to untreated mental illness. Prior research suggests that EP programs are associated with reduced hospitalization costs, emergency department visits, and improvements in quality of life. However, such research is not specific to California and does not consider potential impacts on the counties where the programs are implemented.

Methods: Using administrative data from an electronic health record, we identified youth aged 12-26 who (1) were enrolled in an EP program from January 2017 to July 2022 and (2) received a first diagnosis of psychosis within one year prior to enrollment. We identified a comparison group (CG) of youth with a first diagnosis of psychosis who received at least one outpatient service during the study period, also within one year of receiving their diagnosis. We calculated

the annual number of mental health outpatient visits and inpatient admissions in the one and two years prior, as well as one and two years post-first diagnosis of psychosis. We used regression analysis to examine the relationship between the number of outpatient visits and the probability of having an inpatient admission, controlling for age, gender, and location of initial diagnosis.

Results: We identified 171 youth who enrolled in EP programs and 2,031 CG youth with a first episode of psychosis who received usual care. The mean age was 21 (SD=3.3) and 62% were

male. EP youth were most likely to receive their first diagnosis of psychosis in an outpatient clinic setting: 49% vs. 17% of CG youth. CG youth were most likely to receive their first diagnosis in an emergency or crisis stabilization unit: 41% vs 15% for EP youth.

We found that 2 years prior to first diagnosis, youth averaged 1.8 outpatient visits per year and the probability of inpatient admission was 1.4%; there was no statistically significant difference between groups. In the year prior to diagnosis, the number of outpatient services increased to 6.8 among youth who eventually enrolled in EP programs compared to 1.3 visits among CG youth in usual care (P LESS THAN .001). The probability of inpatient admission is also higher among youth who eventually enrolled in an EP program: 17.9% vs. 4.4%. In the year following diagnosis, the number of outpatient services increased to 61.3 among EP

youth compared to 19.9 among CG youth (P LESS THAN .001); there was no significant difference in inpatient admission. In the second year after diagnosis, both the number of outpatient services

(38.7 vs 11.1, P LESS THAN .001) and the probability of inpatient admission (20.2 vs. 12.7, P LESS THAN .001) remained higher among EP youth.

Discussion: Youth who enroll in EP programs are more likely than youth in usual care to receive their first diagnosis of psychosis in an outpatient program. They also receive more outpatient and inpatient care in the year prior to enrolling in the program, along with significantly more

outpatient care in the first and second years after enrollment. Additional work should examine whether referrals to EP should be increased from emergency settings.

S135. NAVIGATING ADVERSITY: EXAMINING THE INTERPLAY OF ETHNORACIAL DISCRIMINATION, FAMILY SUPPORT, AND PSYCHOTIC SYMPTOM SEVERITY IN LATINXS WITH FIRST EPISODE PSYCHOSIS

Vanessa Calderon*¹, Mirian Vasquez², Carmen Uribe³, Carrie Bearden⁴, Steven Lopez⁵

¹*Semel Institute for Neuroscience and Human Behavior at UCLA*, ²*Children's Hospital Los Angeles*, ³*California State University, San Bernardino*, ⁴*University of California, Los Angeles*, ⁵*University of Southern California*

Background: Discrimination is associated with an increased risk for psychotic symptoms (Bardol et al., 2020). However, limited prior research has focused on the effects of discrimination among clinical populations with psychotic illness. Even less is known about sociocultural protective factors, particularly among U.S. Latinxs with psychotic illness, a population vulnerable to diagnostic and service use disparities (Schwartz and Blankenship,

2014; van der Ven et al., 2020). The present study assessed the relationship between perceived ethnic/racial discrimination and psychotic symptom severity among U.S. Latinxs with first episode psychosis (FEP), along with the moderating effect of family support.

Methods: Individuals with a psychotic illness diagnosis were recruited from an inpatient or outpatient public mental health center as part of a larger study evaluating a psychosis communication campaign (Lopez et al., 2022). They completed a modified version of the Everyday Discrimination Scale (Williams et al., 1997), including 9-items inquiring about the frequency of different types of discriminatory experiences. Participants were also asked to indicate the main reason(s) for those experiences via a checklist of potential attributions, from which a dichotomous score capturing endorsement of racial and/or ancestry-based discrimination was created (i.e., ethnic/racial discrimination). Clinical interviewers administered the Positive and Negative Symptom Scale (Kay et al., 1987) 30-item measure of psychotic symptom severity. Participants completed a qualitative interview from which family support quality was coded on a 4-point scale using concept-driven methods (Miles et al., 2013). Four independent raters achieved good reliability (ICCs ranging from .77 to .89). Measures were administered in English or Spanish depending on participant preference.

Results: Our analysis included 43 participants (mean age 23.47 years; SD = 6.60), with 11.87 (SD = 1.92) years of education. A majority identified as male (69.8%), Latinx (92.3%), U.S.-born (65.1%) and primarily English-speaking (79.1%). Participants reported an average total PANSS score of 2.77 (SD = 0.64), on a 7-point scale. The mean discrimination frequency score was 1.52 (SD = 1.00) on a 6-point scale. Over half (61.9%) endorsed ethnic/racial discrimination. Discrimination frequency was not associated with PANSS symptom severity, $r(43) = .14, p = 0.37$.

A linear regression model with total PANSS symptoms as the dependent variable was statistically significant [$F(1, 33) = 5.27, p < .05$], with significant main effects of ethnic/racial discrimination [$b = 50.21, t(33) = 3.05, p < .05$] and significant interaction effects (discrimination X support quality) $b = -23.69, t(33) = -2.80, p < .05$. All effects remained consistent after adding covariates (i.e., age, sex, education, medication adherence) to the model.

Discussion: More than half of Latinxs with FEP (62%) report ethnic/racial discrimination “a few times per year” or more often. Furthermore, ethnic/racial discrimination endorsement, but not frequency of discrimination, is associated with greater psychotic symptom severity among a clinical U.S. Latinx population. As hypothesized, family support buffers the relationship between ethnic/racial discrimination and psychotic symptoms among those who endorse discrimination; however, an opposite effect was found for those who do not endorse discrimination, such that greater support quality is associated with greater symptom severity. These findings suggest that family support may be protective in the context of ethnic/racial stressors (i.e., discrimination); however outside of the presence of these sociocultural stressors, an excessive amount of family support may be indicative of high emotional overinvolvement, and low caregiver perceived efficacy, which is a risk factor for relapse among Latinxs with psychotic illness (Breitborde et al., 2013). Findings are limited by cross-sectional data; future studies should assess these relationships longitudinally. Clinical and research practice should inquire about perceived ethnic/racial discrimination among marginalized populations with psychotic illness and incorporate family support interventions to cope with social stressors.

S136. SOCIODEMOGRAPHIC AND CLINICAL CORRELATES OF HALLUCINATIONS IN PATIENTS ENTERING AN EARLY INTERVENTION PROGRAM FOR FIRST EPISODE PSYCHOSIS

Samantha Aversa*¹, Joseph Ghanem², Gil Grunfeld², Ann-Catherine Lemonde², Ashok Malla², Srividya Iyer³, Ridha Joobar², Martin Lepage², Jai Shah²

¹Douglas Mental Health Research Institute, ²McGill University, ³McGill University and Douglas Hospital Research Institute

Background: Hallucinations are a core feature of psychosis, and their severity during the acute phase of illness is associated with a range of poor outcomes. Various clinical and sociodemographic factors may predict hallucinations and other positive psychotic symptoms in first episode psychosis (FEP). Despite this, the precise factors associated with hallucinations at first presentation to an early intervention service have not been extensively researched.

Methods: Through detailed interviews and chart reviews, we investigated sociodemographic and clinical predictors in 636 minimally-medicated patients who entered PEPP-Montréal, an early intervention service for FEP, between 2003-2018. Hallucinations were measured using the Scale for the Assessment of Positive Symptoms (SAPS), while negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms. Depressive symptoms were evaluated through the Calgary Depression Scale for Schizophrenia, and anxiety symptoms via the Hamilton Rating Scale for Anxiety. Groups were categorized according to the presence or absence of clinically significant hallucinations, determined by the SAPS global hallucination rating (LESS THAN 3 considered not clinically significant; ≥ 3 regarded as clinically significant). These groups were then compared on relevant sociodemographic and clinical variables using t-tests or nonparametric tests as appropriate, and significant variables were later entered in a logistic regression model.

Results: A majority (n = 381, 59.9%) of the sample presented with clinically significant hallucinations at program entry. These patients had an earlier age at onset, fewer years of education, and a higher severity of delusions, depression and negative symptoms than those without clinical-level hallucinations.

Discussion: These results suggest that individuals with clinically significant hallucinations at admission tend to be younger and have a greater overall symptom burden. This, along with dynamic changes in the prevalence of hallucinations during the first few months of treatment, makes it especially important to monitor this symptom alongside delusions, depression and negative symptoms in order to identify who might benefit from differential targeted interventions. The implications of these findings for early intervention and person-centered care are discussed.

S137. OPEN BOARD

S138. DO NEUROCOGNITION OR SOCIAL COGNITION PREDICT NEED FOR PSYCHIATRIC CARE IN THE YEARS FOLLOWING FIRST PSYCHOTIC EPISODE?

Maija Lindgren*¹, Sebastian Therman¹, Saskia Stigzelius¹, Marjut Grainger¹, Jaana Suvisaari¹

¹Finnish Institute for Health and Welfare

Background: More severe cognitive deficits at psychotic illness onset are linked with a more severe clinical picture and poorer outcomes. Social cognition affects daily functioning and has found to have even larger effects on outcome than neurocognition. Whereas there usually seems to be no further decline in neurocognitive performance after the illness onset, few longitudinal studies have investigated the trajectory of development of social cognition. We therefore wanted to investigate whether social cognitive performance at the time of entering treatment changed during the following years. Secondly, the predictive value of baseline neurocognition and social cognition were studied in terms of intensity of care during the following years.

Methods: A first-episode psychosis (FEP) group, consisting of adults making their first psychiatric treatment contact for psychosis (n=66), as well as matched controls (n=62), were recruited to the Helsinki Early Psychosis Study. Cognitive assessment, including the Hinting Task to measure the theory of mind domain of social cognition, was administered at study entry, and a subgroup (17 FEP, 23 controls) was tested again 6–11 years later (mean follow-up time 9 years). We investigated whether social cognition performance changed between the assessments. Secondly, using data from the Care Register for Health Care, we investigated whether baseline composite neurocognitive factor and social cognition factor predicted 5-year outcomes of outpatient psychiatry visits and psychiatric hospital treatments (n=65 FEP, of which 39 males) before and after controlling for baseline clinical symptoms (BPRS positive and negative symptom sums).

Results: In the FEP group, the Hinting Task raw score was 16.0 ± 3.0 at baseline and 16.0 ± 1.8 at follow-up assessment. Among the controls, the score also remained from 17.4 ± 1.6 to 16.9 ± 1.6 . Spearman correlations between the task raw scores at the two timepoints was .55 in FEP ($p=.022$). The mean number of outpatient visits during the 5-year register follow-up was 98.9 ± 61.3 , with females having more visits than males. On average there were 2.1 ± 2.2 hospital stays and 87.9 ± 204.3 hospital days during the follow-up. None of the register outcomes were predicted by baseline social cognition. Poorer neurocognitive functioning at baseline correlated with higher number of hospitalizations ($r -0.42$, p LESS THAN .001) and number of hospital days ($r -0.31$, $p=.011$) during follow-up. Number of outpatient visit was not associated with baseline cognition. In regression models, controlling for sociodemographic variables and baseline symptom levels, baseline neurocognition was no longer a significant predictor of the clinical outcomes.

Discussion: Hinting Task performance remained unchanged after 9 years, suggesting neither progression nor recovery of social cognitive deficits in the course of the illness at group level. The sex differences and the state/trait nature of social cognition in terms of symptom fluctuations will be more closely inspected.

Social cognition assessment at the beginning of treatment did not provide information on the clinical outcome in FEP. Baseline neurocognitive deficits were associated with hospitalizations during the following five years, indicating more severe symptomatology and possible relapses. However, cognitive testing at baseline did not provide information on the outcomes independently of baseline clinical symptoms. These results add to our knowledge on neurocognitive and social cognitive deficits at illness onset, seen as prognostic markers. The implications to targeting early cognitive deficiencies with interventions will be discussed.

S139. TREATMENT FOR INDIVIDUALS WITH EARLY PSYCHOSIS AND COMORBID CANNABIS USE: A SYSTEMATIC REVIEW OF LITERATURE

Christina Loisel*¹, Carlos Rocha¹, Sarah Btsh¹, Tamare Piersant, PsyD¹

¹*Albizu University*

Background: Cannabis is one of the most commonly used substances for individuals with psychosis (Barrowclough et al., 2014; Johnson et al., 2016). While there seems to be a link between psychosis and cannabis use, there is very little information that exists on the interventions used to help these individuals (Petros et al., 2022; Van der Steur et al., 2020).

Methods: The present systematic review investigated the effects of individual, group, and combined psychotherapy in the treatment of those with early psychosis and comorbid cannabis use. Published studies were identified through a search of electronic databases. Inclusion criteria included peer-reviewed articles since 2010. Studies were considered if they provided data on individuals with early psychosis and the outcome of treatment. Exclusion criteria were articles about individuals younger than adults, those with comorbid psychiatric diagnoses, and articles mainly focusing on either pharmacological treatment or genetics.

Results: Early intervention services are critically important for individuals who have comorbid cannabis use and early psychosis. Interventions include motivational interviewing (MI), cannabis use cessation, cognitive-behavioral therapy (CBT), family therapy, harm reduction, and contingency management (CM) (Kelly et al., 2012). However, there has been a reduction in treatment-seeking rates. Services are impacted by the individuals' frequency of use, stage of change, amount of cannabis used, age of onset of use, and overall history of use (González-Ortega, et al., 2022). Individual psychotherapy based on cannabis cessation has been found to reduce cannabis use severity (Bucci et al., 2010; González-Ortega, et al., 2022). Group psychotherapy did not have the same desired effect that individual psychotherapy had (Madigan et al., 2012). Combining interventions to account for these variables is the most effective for the comorbidity of cannabis use and psychosis (Kelly et al., 2012).

Discussion: The use of cannabis after the onset of early psychosis can have negative consequences, which include higher relapse rates, more prolonged hospital admissions, and increased severity of symptoms (Fusar-Poli et al., 2017; Hammond et al., 2020; Leeson et al., 2012). While there is room for improvement, these findings indicate that a combination of psychotherapies and techniques is essential for the cessation of cannabis use. More research is needed to understand better the interventions that work for these individuals as well as the link between cannabis and psychosis.

S140. VALIDATING COGNITIVE SCREENING FOR FIRST-EPISODE PSYCHOSIS: THE “COGSCREEN” PROTOCOL

Kelly Allott*¹, Alexandra Stainton¹, Shayden Bryce¹, Isabel Zbukvic¹

¹*Orygen and Centre for Youth Mental Health, The University of Melbourne*

Background: Cognitive impairment is common for young people experiencing First-Episode Psychosis (FEP) and can impact everyday functioning. However, clinicians currently have no fast and effective method for determining which of their patients are experiencing cognitive impairments. The “CogScreen” study is a hybrid effectiveness-implementation study which aims to 1) validate a cognitive screening tool for this population from two leading candidates (Screen for Cognitive Impairment in Psychiatry, “SCIP”; and Montreal Cognitive Assessment; “MoCA”) and 2) conduct a comprehensive implementation evaluation to explore the

acceptability, feasibility, barriers and facilitators of adopting cognitive screening into routine treatment for FEP.

Methods: First, CogScreen will use gold-standard classification accuracy methodology to assess the accuracy of the SCIP and MoCA, relative to comprehensive cognitive assessment. Participants will be 350 young people (age 12-25) being treated for FEP across 7 Australian early psychosis services, who will complete a cross-sectional assessment including the cognitive tests and measures of psychopathology and functioning. A subset of participants (n=120) will repeat the screening measures after two weeks to examine test-retest reliability. Second, in the implementation evaluation we will gather both quantitative and qualitative data from key stakeholder groups who are engaged in early psychosis services (young people with FEP, carers or parents, clinicians or service leaders).

Results: Ethics approval has been received and CogScreen started participant recruitment in August 2023. Recruitment will continue for the next 2 years.

Discussion: At the end of this study, we will provide early psychosis services with a valid cognitive screening tool in addition to both general, and local, guidelines for implementing cognitive screening into their routine care for FEP.

S141. TOPUS - A QUASI EXPERIMENTAL TRIAL TO REDUCE DUP

Nikolai Albert^{*1}, Rie Louise Dyhr¹, Stephen Austin², Lene Halling Hastrup³, Carsten Hjorthøj⁴, Marlene Buch Pedersen⁵, Merete Nordentoft⁶, Vinod Srihari⁷, Wenche ten Velden Hegelstad⁸, Erik Simonsen⁹

¹*Copenhagen Research Center for Mental Health – CORE*, ²*Psychiatric Research Unit, Region Zealand, Denmark*, ³*Psychiatric Research Unit, Region Zealand, Slagelse, Denmark*, ⁴*Copenhagen University Hospital, Mental Health Center Copenhagen*, ⁵*Early Psychosis Intervention Centre, Psychiatry East, Region Zealand, Denmark*, ⁶*Mental Health Centre Copenhagen*, ⁷*Yale University*, ⁸*TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital*, ⁹*Psychiatric Research Unit, Zealand Region, Psychiatry East, Denmark*

Background: The association between duration of untreated psychosis (DUP) and later outcome in schizophrenia is well established and have been investigated in several meta-analyses. The latest meta-analysis (Howes et. a 2021) found DUP to be associated with a range of psychopathological and functional outcomes. The nature of the association is still not understood. The TIPS study has found evidence of a causal relationship between DUP and functional outcomes up to ten years after initiation of treatment, but else the evidence of causality is scarce. Further, even if there is no causal relationship the suffering of patients with psychotic symptoms makes it an imperative in itself to reduce the DUP, but there are few trials who successfully have been able to accomplish this.

Methods: Region Zealand in Denmark has implemented an early detection of psychosis team. The team uses widespread information campaigns and consists of specifically trained nurses and clinical psychologist, who responds to a hotline that is open to patients, relatives, teachers etc, without the need of a referral from a GP or other professionals. The team do not provide treatment, but can makes referrals, and thereby quickly identifying patients suffering from psychosis and can reduce the time to initiation of treatment. No other region in Denmark has implemented a similar model. The TOPUS study is designed as a quasi-experimental study including 125 patients for Region Zealand (the intervention region) and 125 patients from the Capital Region (the control region) with non-affective psychosis. Patients will be included from

Early Intervention Services in both regions. The DUP of the participants will be assessed using the Nottingham Onset Schedule (NOS). Duration of untreated psychosis at baseline is a continuous variable which in all prior studies have been found to have a skewed distribution. The variable will be logarithmically transformed and analyzed using linear regression with known confounders included as covariates. After inclusion in the study participants will be reassessed at 3, 9 and 20 months after the baseline assessment.

Results: Inclusion will begin early 2024 and will be completed in 2026. The trial aims to investigate whether a widespread information campaign in combination with a well-established early detection team is effective in reducing the DUP, and if so, if this reduction is associated with the clinical and functional outcomes. When concluded the trial will provide new insights into the relationship between DUP and outcome.

Discussion: The presentation will give an overview of the trial and discuss limitations and strengths.

S142. LONGITUDINAL EVALUATION ON NEGATIVE SYMPTOMS IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS: A 2-YEAR FOLLOW-UP INVESTIGATION IN A REAL-WORLD CLINICAL SETTING.

Lorenzo Pelizza*¹, Alessandro Di Lisi¹, Emanuela Leuci², Emanuela Quattrone², Marco Menchetti¹

¹Bologna University, ²AUSL di Parma

Background: Negative Symptoms (NS) severely affect real-world functioning in young individuals at Clinical High Risk for Psychosis (CHR-P), already before their first access to specialized mental healthcare services. However, longitudinal studies on beneficial effects of specialized intervention on NS in CHR-P people is still poor and inconclusive, especially in real-world clinical settings. The aims of the present investigation were: (1) to evaluate longitudinal stability of NS in young CHR-P individuals treated within a specialized “Early Intervention in Psychosis” (EIP) program along a 2-year follow-up period, and (2) to examine any relevant association of NS longitudinal change with the specific intervention components (i.e., antipsychotic medication, individual psychotherapy, family psychoeducation, case management) offered within the EIP program.

Methods: One hundred UHR individuals (aged 12–25 years) completed the Positive And Negative Syndrome Scale (PANSS). The PANSS 5-item “Negative Symptoms” factor score proposed by Galderisi et al. (2021) was used because of its better fitting into our CHR-P sample. The Wilcoxon test for repeated measure was performed to evaluate statistically relevant longitudinal change in NS severity levels. A multiple linear regression analysis was also conducted to examine significant associations between longitudinal change in NS severity and EIP treatment components.

Results: Across the 2-year follow-up period, a significant decrease in NS severity was found. This reduction was associated with the intensity of individual psychotherapy sessions offered in the first year of treatment, a shorter duration of untreated illness (DUI) at baseline, and the 2-year longitudinal decrease in positive symptom levels. Our regression analysis result explained 44.6% variance of the explored model. However, at the end of the follow-up, improvement in NS severity levels was predicted exclusively by the longitudinal decrease in positive symptom scores.

Discussion: NS are clinically relevant at the onset of psychosis. The findings of this investigation showed that longitudinal improvement in NS is positively associated with the intensity of individual psychotherapy sessions provided to young CHR-P individuals during the first year of treatment, together with a shorter DUI at presentation and the longitudinal improvement in positive symptom scores. Specific targeted psychosocial interventions on NS in people at CHR-P are thus recommended and to be routinely implemented. Moreover, maintaining an optimal intensity of individual psychotherapy for at least 2 years within specialized EIP programs could further match a more decisive, stable and prolonged over time improvement in NS levels, consequently favoring better long-term outcomes and a fuller personal, functional and social recovery in this young at-risk population.

S143. THE ASSOCIATION OF ANTERIOR CINGULATE CORTEX GLUTAMATE AND CLOZAPINE ELIGIBILITY IN AN EARLY PSYCHOSIS SAMPLE

Kara Dempster^{*1}, Temi Toba-Oluboka², Candice Crocker², Philip Tibbo²

¹*Queen Elizabeth II Health Sciences Center*, ²*Dalhousie University*

Background: The ability to identify patients who may benefit from clozapine at the earliest opportunity is important for maximizing long-term outcomes in schizophrenia and may facilitate stratification of treatment based on neurobiology. Approximately one third of individuals with schizophrenia do not respond appreciably to first-line pharmacological treatment options and meet criteria for treatment resistant schizophrenia (TRS), the majority of whom demonstrate poor response from the first episode of psychosis (FEP). Given first line dopamine blocking medications are essentially ineffective in this subgroup, it has been hypothesized that alternative neural pathways may be implicated. Glutamate, an excitatory neurotransmitter, has been shown to be elevated in individuals with FEP who do not respond to dopamine blocking antipsychotic medications. Despite the considerable evidence of superiority for clozapine in TRS, its use is frequently delayed. There are currently no objective biomarkers available to support clinicians in identifying individuals who may benefit from a clozapine trial. Given the response to clozapine is more robust if used earlier in the illness, there is an urgent need to characterize the neurobiological underpinnings of clozapine eligibility. To date, no studies have investigated the association of elevated glutamate with clozapine-eligibility in a FEP sample, a group in which clozapine initiation may have the most profound impact on long-term outcomes. We hypothesized that elevated glutamate in the Anterior Cingulate Cortex (ACC) would be associated with clozapine-eligibility in an early psychosis sample.

Methods: Clozapine eligible (CE) individuals and treatment responders (TR) with non-affective psychotic disorders from the Nova Scotia Early Psychosis Program (within the first five years of illness onset) underwent magnetic resonance spectroscopy (1H-MRS) to measure glutamate in the bilateral dorsal ACC. 1H-MRS acquisitions were performed using Point RESsolved Spectroscopy (TE=40ms, TR=2000ms; 128 averages). CE individuals continued to have moderate psychotic symptoms on the PANSS, an illness severity of moderate on the CGI-S, and moderate functional impairment, and had undergone at least two trials of non-clozapine antipsychotic medications. The TR group had no more than mild symptoms on all PANSS items and were taking a single antipsychotic medication.

Results: While data collection is ongoing, to date, 37 individuals have completed the study (TR = 20, CE = 17). The TR group (15 males, 5 females) did not differ from the CE group (14 males, 3 females) in terms of mean age (26 for both groups). The CE group had higher PANSS

scores ($M = 69.47$) and a longer duration of untreated psychosis (DUP) ($M = 25$ weeks) than the TR group ($M = 36.70$ for the PANSS and mean DUP of 12 weeks). To date, glutamate levels in the ACC are not significantly different between the CE ($M = 10.05$, $SD = .84$) and TR ($M = 10.47$, $SD = 1.14$) groups ($t = -1.311(35)$, $p = .199$). Up to date results will be presented at the conference with an anticipated final sample size of 50 (25 per group).

Discussion: While elevated ACC glutamate has been associated with poor response to antipsychotic medications in early psychosis samples, this is the first study to examine the association with clozapine-eligibility. The ability to triage clozapine eligibility based on objective neurobiological findings could revolutionize early psychosis care in that some individuals may be offered clozapine after a single failed trial. Contrary to our hypothesis, ACC glutamate was not higher in the CE group. This suggests that while elevated ACC glutamate may be associated with short-term measures of response at discrete intervals, it may not be predictive of long-term treatment resistance. Limitations include the fact that antipsychotic treatment was not standardized, serum levels of antipsychotic medications were not obtained to confirm adherence, and we did not obtain drug tests at the time of glutamate measurement. Further studies are warranted to explore the association of elevated ACC glutamate at baseline and eventual CE in early psychosis samples.

S144. WOMEN ADVANTAGE IN VERBAL MEMORY ASSOCIATED TO RS9896243: A PSYCHOSIS FAMILY-BASED DESIGN STUDY

Rosa Ayesa-Arriola^{*1}, Noelia Rodríguez-Pérez², Víctor Ortíz-García de la Foz¹, Nancy Murillo-García¹, Sergi Papiol³

¹Valdecilla Biomedical Research Institute IDIVAL Research Group on Mental Illness, Marqués de Valdecilla University Hospital, University of Cantabria, ²Grupo de Genómica Evolutiva, Instituto de Biología Evolutiva (IBE), Universidad Pompeu Fabra, ³Max Planck Institute of Psychiatry

Background: There is a growing recognition of sex differences in Schizophrenia Spectrum Disorders. Verbal memory impairment is one of the most prominent cognitive deficits in first episode of psychosis (FEP) patients, but women show an advantage over men on tests that assess this cognitive domain. A previous human genome-wide association study found that one SNP (rs9896243), located in the intron of the NSF gene in chromosome 17, was associated with verbal memory. Exploring this association in a psychosis family-based design study may shed light on the genetic basis of verbal memory and on sex differences.

Methods: Subjects (112 FEP patients, 119 parents, 86 siblings and 169 healthy controls) were participants of the PAFIP-FAMILIES study in Santander (Spain). Verbal memory was assessed by the Rey Auditory Verbal Learning Test, which included measures of immediate recall, short-delay recall, long-delay recall and recognition. DNA genotyping was conducted by CEGEN and mixed-models approaches were performed as a joint GWAS of all participants, adjusting for ancestral background and familial relatedness. A series of one-way analyses of covariance (ANCOVAs), for sex and including age and years of education as covariates, were used to examine differences between the four groups of participants.

Results: The CC genotype was associated with better immediate recall ($F = 7.9$; $p < 0.001$), short-delay recall ($F = 4.92$; $p = 0.03$), long-delay recall ($F = 3.94$; $p = 0.01$) in female controls and sisters than in female FEP patients. No significant differences were found in men. The CG genotype was associated with better immediate recall ($F = 2.95$; $p = 0.037$), short-delay

recall ($F=4.34$; $p=0.007$), long-delay recall ($F=6.54$; $p < 0.001$) in sisters than in FEP patients among women, and on short-delay recall ($F=3.86$; $p=0.031$), long-delay recall ($F=4.5$; $p=0.005$) in controls than in FEP patients among men. Any of the comparisons on GG genotype showed significant differences.

Discussion: The results suggest sex-specific effects of allele C of rs9896243 genotype on verbal memory and provide further evidence of verbal memory genetically relation with schizophrenia. Further discussion is guaranteed. Our findings are excellent basis for further discussion.

S145. ASSESSING SHARED VULNERABILITY AND SEX DIFFERENCES IN PSYCHOTIC DISORDERS USING POLYGENIC SCORING

Marina Mitjans¹, Sergi Papiol², Mar Fatjo-Vilas³, Javier González-Peñas⁴, Miriam Acosta⁵, Marina Zafrilla⁵, Javier Costas⁶, Celso Arango⁷, Elisabet Vilella⁸, Lourdes Martorell⁹, M. Dolores Moltó¹⁰, Julio Bobes¹¹, Benedicto Crespo-Facorro¹², Ana Gonzalez-Pinto¹³, Lourdes Fañanas¹⁴, Araceli Rosa¹⁵, Barbara Arias^{*16}

¹University of Barcelona, CIBERSAM, ²Max Planck Institute of Psychiatry, ³University of FIDMAG Sisters Hospitaliers Research Foundation, CIBERSAM, Biomedical Research Network in Mental Health, Instituto de Salud Carlos III, ⁴Hospital General Universitario Gregorio Marañón, ⁵University of Barcelona, ⁶Instituto de Investigación Sanitaria de Santiago de Compostela-SERGAS, ⁷Hospital General Universitario Gregorio Marañón, ⁸Hospital Univeristari Institut Pere Mata; IISP; Universitat Rovira i Virgili; CIBERSAM, ⁹University Hospital Institut Pere Mata, Pere Virgili Health Research Institute, Universitat Rovira i Virgili, CIBERSAM., ¹⁰INCLIVA Biomedical Research Institute, ¹¹Universidad de Oviedo, ¹²HU Virgen del Rocío, University of Sevilla, CIBERSAM, IBI, ¹³Hospital Universitario Araba, Universidad del País Vasco. CIBERSAM. ¹⁴Departament de Biologia Animal, Facultat de Biologia, Universitat de Barcelona; Institut de Biomedicina de la Universitat de Barcelona (IBUB); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), ¹⁵Secció de Zoologia i Antropologia Biològica, Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Universitat de Barcelona, Institut de Biomedicina de la Universitat de Barcelona, Centre for Biomedical Research Network on Mental Health (CIBERSAM), Instituto de Salud Carlos III, ¹⁶Facultat de Biologia, IBUB, University of Barcelona, CIBERSAM

Background: There is increasing evidence for shared genetic susceptibility between psychiatric disorders. The PGC cross-disorder group has provided molecular evidence for this common genetic architecture clustering schizophrenia (SZ), bipolar disorder (BD) and major depression (MD) in the mood and psychotic disorders group (Lee et al. 2021).

However, although sex differences have been described in relation to clinical features and outcome in psychotic disorders (Riecher-Rössler et al. 2018), sex differences at the genetic level have been so far under-explored.

The aims of this study were: i) to evaluate the association of polygenic scores (PGSs) for SZ, BD and MD with disorders of the psychotic spectrum in a sample of patients with broadly defined psychosis and ii) to test whether sex differences exist in those associations.

Methods: Our study included 1826 patients (33.2% females) with a range of psychotic disorders (DSM-IV criteria) and 1372 healthy controls (45.8% females) from the Spanish

population (CIBERSAM cohort). Samples were genotyped with the Infinium PsychArray (Illumina) and imputation was conducted in the Michigan Imputation Server. PGSs were calculated using PRS-CS tool (Ge et al. 2019) and PLINK 1.9 (Chang et al. 2015) based on the following GWAS: SZ (Trubetskoy et al. 2022), BD (Mullins et al. 2021) and MD (Wray et al. 2018).

Logistic regression models were used to study the association between psychotic disorder diagnosis and the PGSs, including sex and the first ten ancestry principal components as covariates. To quantify the increased risk, the sample was divided into quartiles based on SZ-PGS, BD-PGS and MD-PGS and the odds ratios (ORs) were calculated for affected status in each quartile using the first quartile as reference. Secondary analyses were run stratified by sex. Analyses were run in R v.4.0.4.

Results: We found association between all PGSs and broadly defined psychosis. SZ-PGS explained the highest percentage of the variance of psychotic disorders in the liability scale ($R^2=11.01\%$; $p < 2 \times 10^{-16}$) followed by BD-PGS ($R^2=2.95\%$; $p < 2 \times 10^{-16}$) and MD-PGS ($R^2=0.26\%$; $p=2.73 \times 10^{-4}$).

We observed an increase in the case-control ratio in progressively higher quartile categories using all PGSs. Compared with individuals in the first quartile, those at the highest quartile had an OR for psychotic disorder risk of 7.95 (95% CI:6.34-9.97) for SZ-PGS, 2.67 (95% CI:2.18–3.28) for BD-PGS and 1.36 (95% CI:1.12–1.67) for MD-PGS.

We assessed PGS contribution to psychotic disorders risk stratified by sex and statistically compared prediction in males and females using a bootstrap resampling approach. SZ-PGS and MD-PGS, but not BD-PGS, explained significantly more variance in males than in females (p -values $< 2 \times 10^{-16}$).

Discussion: The association of the PGSs (SZ, BD and MD) with broadly defined psychosis emphasize the reported shared genetic architecture among these psychiatric disorders (Calafato et al 2018; Lee et al. 2021). The sex-stratified results are in line with recent findings suggesting that sex differences in the genetic architecture of neuropsychiatric and behavioural traits exist but are small and polygenic (Martin et al. 2021; Blokland et al. 2022).

The use of transdiagnostic approaches recognises the multidimensionality of psychopathology and enable the investigation of shared genetic risk factors. Moreover, understanding the genetic basis of sex differences in psychiatric disorders, is crucial for developing sex-stratified diagnostics and therapeutics and for paving the way for precision medicine.

Funding PI17/01122, PI22/01048, PI22/00431, LaMaratóTV3-202203-30-31-32, 2021SGR01093, 2021SGR00706, 2021SGR01358, RYC2021-033573-I, PID2022-139740OA-I00

S146. UNRAVELLING THE POLYGENIC BURDEN OF TRANSCRIPTION FACTORS IN SCHIZOPHRENIA: THE IMPORTANCE OF THE PRENATAL TRANSCRIPTOME

Gemma Riquelme¹, Maria Guardiola-Ripoll², Carmen Almodóvar-Payá³, Mariona Latorre-Guardia³, Edith Pomarol-Clotet⁴, Belén Ramos⁵, Mar Fatjó-Vilas^{*4}

Background: Schizophrenia (SZ) is a severe psychiatric disorder with a strong genetic component (heritability of about 80%) and a polygenic architecture. Genome-Wide

Association Studies (GWAS) have placed gene expression regulation factors as key pathophysiological elements in SZ, particularly focusing on transcription factors (TF). Several studies have examined genetic variants and expression changes of specific TF genes; however, little is known about the polygenic burden of the TF machinery on the SZ etiological roots. From the neurodevelopmental hypothesis framework, we investigated whether the TF polygenic load influences the risk of SZ, while considering the time of expression of the TF (prenatally or postnatally).

Methods: Our case-control sample consisted of 318 individuals: 193 patients diagnosed with chronic SZ (age 42.9 ± 11.4 ; 73.6% males) and 125 healthy controls (age 38.3 ± 11.7 ; 52.0% males). First, using the available data at the BrainSpan Atlas of the Developing Human Brain (www.brainspan.org), we selected all the TF expressed in the brain across the lifespan (1,954 genes) and selected those differentially expressed prenatally (866 genes) and postnatally (194 genes). Second, based on the most recent GWAS on SZ, we calculated for each individual in our sample three polygenic risk scores (PRSs, following the C+T method): one summarizing the polygenic load of all brain-expressed TF (All-TF-PRSsz, based on 57,596 SNPs) and two others corresponding to the prenatally and postnatally differentially expressed TF (PreN-TF-PRSsz, based on 21,129 SNPs; and PostN-TF-PRSsz, based on 7,640 SNPs). Third, we assessed the risk variance explained by these three PRSs in our sample (logistic regression controlled by sex, age and ancestry).

Results: We observed an association of the All-TF-PRSsz with the risk for SZ ($p=1.30 \times 10^{-5}$, $R^2=9.87$). The PreN-TF-PRSsz also showed an effect on SZ ($p=3.07 \times 10^{-3}$, $R^2=5.62$). No role of the PostN-TF-PRSsz was detected. For all PRSs, patients presented higher scores than healthy controls.

Discussion: We conclude that the genetic variants of the TF-encoding genes show an effect on risk and might contribute to the assessment of SZ susceptibility. Our data also suggest the importance of considering different developmentally informed periods to understand better the disorder's aetiology and to implement genetically driven diagnostic approaches in the future.

Acknowledgements: Instituto de Salud Carlos III through the projects PI18/1535 and PI18/00213, and the contract CP20/00072 to MF-V (co-funded by European Regional Development Fund (ERDF)/European Social Fund "Investing in your future").

S147. EXAMINING THE INTERPLAY BETWEEN GENETIC LOAD FOR NEURODEVELOPMENTAL DISORDERS AND FOR SLEEP ABNORMALITIES AND HEAVY CANNABIS USE ON THE RISK FOR PSYCHOSIS

Edoardo Spinazzola^{*1}, Isabelle Austin-Zimmerman¹, Giulia Trotta¹, Diego Quattrone¹, Robin Murray¹, Marta Di Forti¹

¹*King's College London, IoPPN,*

Background: Heavy cannabis use is consistently reported as a risk factor for psychosis, but the role played by the underlying genetic factors remains complex. Twin studies have shown that there is genetic susceptibility to lifetime cannabis use, cannabis use disorder, and schizophrenia. Genome-wide association studies (GWAS) have uncovered genetic overlap between cannabis use and schizophrenia, as well as other phenotypes like developmental disorders and sleep abnormalities. Mendelian Randomisation (MR) studies have used GWAS data to investigate the direction of causality between schizophrenia and cannabis use. However,

findings have been contradictory and most of these studies have limitations that warrant caution when interpreting their results.

Therefore, we aim to explore whether the genetic liability for neurodevelopmental disorders and sleep disorders might increase the risk of a) heavy pattern of cannabis use and b) psychosis onset among cannabis users.

Methods: Utilising data derived from the EUGEI multi-centre case-control study, we calculated PRSs for all participants with PRS-CSx and Plink 2.0. Data on cannabis use was derived from the modified version of the Cannabis Experience Questionnaire (CEQEUGEI-mv). We examined the association between a newly developed Neurodevelopmental PRSs and a short (≤ 5 hours) and long sleep (≥ 10 hours) PRSs and 1) age at first cannabis use, 2) pattern of use (frequency/potency), and 3) psychosis case-control status. Interaction effects between these traits were also tested.

Results: We included 693 first-episode psychosis patients and 405 controls from the EUGEI study. Ordinal logistic regression models, adjusted for age, gender, site, and ten principal components, showed that neurodevelopmental PRS was not associated with a composite measure of frequency-potency of cannabis use. Conversely, we found that higher levels of Sleep PRS were associated with heavy cannabis use, with potential interaction observed between cannabis use patterns and sleep PRS (OR 1.11, 95% CI 1.01 – 1.23). Neither Sleep PRS nor Neurodevelopmental PRS were associated with case-control status. However, adding these measures to the pattern of cannabis use increased the variance explained for psychosis onset. A multiplicative interaction model, testing the interaction between Sleep PRS and frequency-potency of cannabis use on psychosis case-control outcome did not yield significant results.

Notably, high Sleep PRS appears to have a protective effect against psychosis in daily users of high-potency cannabis.

Discussion: This data highlights the influence of genetic load for neurodevelopmental disorders on individual susceptibility to develop psychosis. Conversely, Sleep PRS is associated with the opposite effect, increasing the risk of developing psychosis in non-users, while potentially reducing the risk in cannabis users. These findings suggest that distinct genetic factors may impact psychosis risk through independent and non-pleiotropic mechanisms not directly associated with psychosis, but influencing environmental factors, such as cannabis use.

S148. DNA METHYLATION PATTERNS AND EPIGENETIC AGING IN BIPOLAR PATIENTS WITH CHILDHOOD MALTREATMENT

Miriam Acosta-Díez^{*1}, Mireia Prat-Esquerdo¹, Marina Zafrilla², Anna Giménez-Palomo³, Pilar Alejandra Saiz⁴, Carme Barrot⁵, Esther Jiménez⁶, Sergi Papiol⁷, Victoria Ruiz⁸, Patricia Gavín⁸, Maria Paz García-Portilla⁴, Leticia González-Blanco⁴, Julio Bobes⁴, Thomas G Schulze⁹, Eduard Vieta¹⁰, Antoni Benabarre¹¹, Bárbara Arias¹², Marina Mitjans¹³

¹Universitat de Barcelona, ²Universitat de Barcelona. Biomedicine Institute of the University of Barcelona (IBUB), ³Clinical Institute of Neuroscience, Hospital Clínic de Barcelona. Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ⁴CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto de Neurociencias del Principado de Asturias (INEUROPA), Servicio de Salud del Principado de Asturias (SESPA), ⁵Forensic

Genetic Laboratory, University of Barcelona, ⁶CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Clinical Institute of Neuroscience, Hospital Clinic de Barcelona. Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ⁷CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich. Max Plank Institute of Psychiatry, ⁸Clinical Institute of Neuroscience, Hospital Clinic de Barcelona, ⁹Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich. SUNY Upstate Medical University. Johns Hopkins University School of Medicine, ¹⁰CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Clinical Institute of Neuroscience, Hospital Clinic de Barcelona. Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ¹¹CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Clinical Institute of Neuroscience, Hospital Clinic de Barcelona. Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), ¹²Universitat de Barcelona. Biomedicine Institute of the University of Barcelona (IBUB). CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, ¹³Universitat de Barcelona. Biomedicine Institute of the University of Barcelona (IBUB). CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III. Institut de Recerca Sant Joan de Déu (IRSJD)

Background: Childhood maltreatment (CM), generally defined as parental neglect and childhood physical, sexual, or emotional abuse, is a risk factor for bipolar disorder (BD) that affects around 50% of patients (Garino et al., 2005). CM has been linked with features related to poorer outcomes in BD such as severe and more frequent mood episodes, higher rates of suicide attempts, earlier onset, and comorbid substance misuse (Rowland and Marwaha, 2018). To date, several studies have pointed to the important role of epigenetics, specifically DNA methylation (DNAm) in CM (Rubens et al., 2023). In addition, signs of accelerated aging in BD have been associated with telomere length, increased oxidative stress, and more recently, accelerated epigenetic aging (EA) (Salarda et al., 2021) though, few EA-related studies have focused on CM (Palma-Gudiel et al., 2021).

Thus, this study aims to investigate DNAm patterns and EA in a sample of patients with BD assessed for CM to detect new epigenetic factors associated to CM.

Methods: A sample of 82 bipolar type I (BD-I) and type II (BD-II) patients answered the Childhood Trauma Questionnaire (Bernstein et al., 2003). This retrospective screening self-assessment questionnaire classifies CM into 5 categories: (i) physical abuse, (ii) emotional abuse, (iii) sexual abuse, (iv) emotional neglect, and (v) physical neglect. A total CTQ score, including the punctuation obtained in all five categories, was used as an outcome measure in our association analyses.

Genome-wide DNAm from peripheral blood samples was assessed using the InfiniumMethylationEPICBeadChip (Illumina). Raw DNAm data were processed with ChAMP (Tian et al., 2017). The association between individual CpGs and regions and total CTQ score was tested with a linear regression model adjusted for blood cell counts, sex, age, and smoking score (Bollepalli et al., 2019) by using Limma and DMRcate (Ritchie et al., 2015; Peters et al., 2015). Gene-set enrichment analysis using FUMA (<https://fuma.ctglab.nl>) was conducted for all genes mapped to CM-associated positions and regions, and the BECon web tool (<https://redgar598.shinyapps.io/BECon>) was used to infer blood-brain correlation of significant CpGs. Lastly, EA was estimated using Horvath's calculator (<https://dnamage.clockfoundation.org/>) and Dunedin clock pipeline (Belsky et al., 2022). The

association between EA and total CTQ score was tested for all studied clocks after adjusting for all covariates. For all analyses, Benjamini-Hochberg was used to correct the false discovery rate (FDR), and a p-value of 0.05 was considered for significance.

Results: A total of 28 positions and 2 regions were associated with the total CTQ score (FDR adjusted p-value LESS THAN 0.05), with 20 positions mapped to 24 genes and 1 region to 3 genes. Gene-set enrichment analyses of all mapped genes revealed non-significant results (FDR adjusted p-value GREATER THAN 0.05). Out of all positions, 17 were present in BECon and 3 of them showed strong positive correlations (r GREATER THAN 0.50). As for EA, no statistically significant association was observed (FDR adjusted p-value GREATER THAN 0.05).

Discussion: These findings suggest association between DNAm patterns and CM in BD, with HOXA-AS3 gene having been linked to sexual and physical abuse in a previous epigenome-wide association study (Dunn et al., 2019). Moreover, SAMD12 gene was previously found upregulated in individuals with CM (Cattaneo et al., 2018) and SLC12A2 gene differentially regulated in mice model with postnatal stress (Dayananda et al., 2023). Still, results should be further studied for a better understanding of CM.

Funding PI17/01122, PI22/01048, PI22/00431, LaMarató TV3 (202203-30-31-32), 2021SGR01093; 2021SGR00706; 2021SGR01358, and RYC2021-033573-I, PID2022-139740OA-I00

S149. EPIGENETIC CHARACTERIZATION OF OFFSPRING AT HIGH FAMILIAL RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Alex Segura^{*1}, Elena De la Serna², Irene Martínez-Serrano², Gisela Sugranyes², Immaculada Baeza², Isabel Valli², Covadonga Díaz-Caneja³, Nuria Martín³, Dolores M Moreno³, Patricia Gassó¹, Natalia Rodríguez¹, Sergi Mas¹, Josefina Castro-Fornieles²

¹University of Barcelona, ²Hospital Clínic of Barcelona, ³Hospital General Universitario Gregorio Marañón

Background: Subclinical features of schizophrenia and bipolar disorder can be identified before illness onset, often manifesting from a very young age. Their severity and duration are associated with the manifestation of acute symptoms in later life stages (van Os, Linscott, Myin-Germeys, Delespaul, and Krabbendam, 2009). Genetic and environmental factors may act synergically, modulating the pathogenesis of severe mental disorders and leaving characteristic biological marks (Butera et al., 2023). Epigenome-wide association studies (EWAS) have described some of these biological marks as changes in the methylation pattern of CpG dinucleotides, which modulate gene expression, cell senescence and functionality (Brunet and Rando, 2017).

Schizophrenia and bipolar disorder are associated with a shorter lifespan, linked to age-related biomarkers and physiological conditions (Higgins-Chen, Boks, Vinkers, Kahn, and Levine, 2020; Kirkpatrick and Kennedy, 2018), suggesting that patients suffer from the effects of accelerated biological aging. Epigenetic clocks are calculated to assess putative biological aging asynchronicities with chronological age, based on time-dependent methylation changes. Furthermore, EWAS results reporting the association of specific CpGs with exposure to certain external stressors can be used to estimate epigenetic scores, which summarize the overall biological impact of an external stressor.

Methods: For the present study, offspring aged 6 to 17 years of patients with schizophrenia (n=52) and bipolar disorder (n=178), as well as of community controls (n=113) were recruited from two hospitals in Spain. Biological samples were used to obtain the genome-wide methylation levels, and combined with EWAS summary statistics we constructed a) epigenetic clocks to estimate biological age acceleration and b) epigenetic scores reflecting the impact of stressful pre-conception and gestational conditions. Sociodemographic, cognitive, clinical and functioning data was assessed. Our aim was to characterize the epigenetic patterns, in terms of biological age acceleration and epigenetic impact, of the offspring at familial high risk and the controls. Subsequently, we aimed to assess the role of epigenetic clocks and scores on the cognitive, clinical and functioning scales.

Results: The offspring schizophrenia and bipolar disorder patients reported a biological deceleration on one of the assessed epigenetic clocks. Epigenetic scores were increased in the offspring at familial high risk. Biological age acceleration and epigenetic scores were associated with impaired cognition, more severe subclinical symptoms and worse functioning. Stratified analyses revealed that these associations were more prominent in the offspring of schizophrenia and bipolar disorder patients.

Discussion: The assessment of the biological impact of external stressful conditions presents several methodological limitations. However, the quantification of methylation patterns stands out as a promising approach to accurately summarize the impact of environmental stressors at different life stages. The biological consequences of abnormal methylation patterns can thus be studied, examining their effect on the subclinical and clinical status. In this context, the epigenetic constructs estimated with CpG methylation data characterized the biological marks of children at high familial risk for schizophrenia and bipolar disorder and were associated with worse clinical outcomes.

S150. A POPULATION-DRIVEN FAMILY-BASED GENETIC STUDY OF SCHIZOPHRENIA

Nicole Simons^{*1}, Mafalda Barbosa¹, Gavin Hynes¹, Esther Cheng¹, Katherine Keller¹, Janice Morinigo¹, Vibhuti Patel¹, Rachel Jackson¹, Earnest Chen¹, Alice Hashemi¹, Anina Lund¹, Simon Lee¹, Alexander Charney¹, Rene Kahn¹

¹*Icahn School of Medicine at Mount Sinai*

Background: Two landmark genetic studies of SCZ, the severe and highly heritable psychotic illness, recently established that some SCZ cases are caused by a rare protein-truncating variant (PTV) in one of 12 genes including GRIA3, an X chromosome gene that codes for an AMPA glutamate receptor component. Presented here is a process developed to identify individuals affected by rare PTVs in these 12 genes, followed by a case series of a family with seven members affected by a rare PTV in GRIA3.

Methods: Carriers of rare PTVs in the 12 known causal SCZ genes were identified by mining whole-exome sequencing data from the diverse population of New York City. Identified carriers were re-contacted to undergo comprehensive neuropsychiatric assessments and biospecimen collection. Seven members of this family were enrolled in the study.

Results: Six affected family members are carriers of the rare PTV, and 1 unaffected family member is a non-carrier. No affected non-carriers have been identified. The primary psychiatric diagnoses for the carriers were SCZ and neurodevelopmental disorder (NDD). Affected males

in the family exhibited more severe forms of illness than affected females in the family, but having two X chromosomes was not entirely protective.

Discussion: An X-linked pattern of inheritance was identified between the rare PTV and severe neuropsychiatric diseases, providing evidence for causality. Population-driven family-based genetic studies such as the one presented here are a new way to investigate the mechanisms of disease in individual patients, and lead to the development of novel gene-based therapeutics.

S151. GENOME-WIDE DNA METHYLATION RISK SCORES FOR SCHIZOPHRENIA DERIVED FROM BLOOD AND BRAIN TISSUES FURTHER EXPLAIN THE GENETIC RISK IN PATIENTS STRATIFIED BY POLYGENIC RISK SCORES FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Kazutaka Ohi^{*1}, Mihoko Shimada², Midori Soda³, Daisuke Nishizawa⁴, Daisuke Fujikane¹, Kentaro Takai¹, Ayumi Kuramitsu¹, Yukimasa Muto¹, Shunsuke Sugiyama¹, Junko Hasegawa⁴, Kiyoyuki Kitaichi³, Kazutaka Ikeda⁴, Toshiaki Shioiri¹

¹Gifu University Graduate School of Medicine, ²National Center for Global Health and Medicine (NCGM), ³Gifu Pharmaceutical University, ⁴Tokyo Metropolitan Institute of Medical Science

Background: Genetic and environmental factors contribute to the pathogenesis of schizophrenia (SZ) and bipolar disorder (BD). Among genetic risk groups stratified by combinations of polygenic risk score (PRS) deciles for SZ, BD, and SZ vs. BD, genetic SZ risk groups had high SZ risk and prominent cognitive impairments. Furthermore, epigenetic alterations are implicated in these disorders. However, it was unclear whether DNA methylation risk scores (MRSs) for SZ risk derived from blood and brain tissues were associated with SZ risk, particularly the PRS-stratified genetic SZ risk group.

Methods: Epigenome-wide association studies (EWASs) of SZ risk in whole blood were preliminarily conducted between 66 SZ patients and 30 healthy controls (HCs) and among genetic risk groups [individuals with low genetic risk for SZ and BD in HCs (n=30) and in SZ patients (n=11), genetic BD risk in SZ patients (n=25), and genetic SZ risk in SZ patients (n=30)] stratified by combinations of PRSs for SZ, BD, and SZ vs. BD. Next, differences in MRSs based on independent EWASs of SZ risk in whole blood, postmortem frontal cortex (FC), and superior temporal gyrus (STG) were investigated among our case-control and PRS-stratified genetic risk status groups.

Results: Among case-control and genetic risk status groups, 33 and 351 genome-wide significant differentially methylated positions (DMPs) associated with SZ were identified, respectively, many of which were hypermethylated. Compared with the low genetic risk in HCs group, the genetic SZ risk in SZ group had 39 genome-wide significant DMPs, while the genetic BD risk in SZ group had only six genome-wide significant DMPs. The MRSs for SZ risk derived from whole blood, FC, and STG were higher in our SZ patients than in HCs in whole blood and were particularly higher in the genetic SZ risk in SZ group than in the low genetic risk in HCs and genetic BD risk in SZ groups. Conversely, the MRSs for SZ risk based on our whole-blood EWASs among genetic risk groups were also associated with SZ in the FC and STG. There were no correlations between the MRSs and PRSs.

Discussion: These findings suggest that the MRS is a potential genetic marker in understanding SZ, particularly in patients with a genetic SZ risk.

S152. CLINICAL CHARACTERISTICS OF PATIENTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

Theresa Cassidy*¹, Kira Griffiths², Min Min Chan², Mayowa Oyesanya², Rifqi Alkhatib², Suzanne St Rose³, Rashmi Patel⁴

¹Boehringer Ingelheim Pharmaceuticals, Inc., ²Holmusk Technologies Inc, ³Boehringer Ingelheim, ⁴King's College London, Institute of Psychiatry, Psychology and Neuroscience

Background: Schizophrenia is a severe psychiatric illness characterized by positive, negative and cognitive symptoms. Evidence suggests cognitive impairment (CI) in schizophrenia is common, with nearly all patients having some CI and up to 98.1% falling below premorbid estimates of cognitive performance. Cognitive deficits vary across schizophrenia patients and its domains affecting executive function, attention, reasoning, and social cognition. Despite being a main feature of schizophrenia, no specific diagnostic code or established treatment for CI in schizophrenia exists. Real-world data (RWD) can extend our understanding of CI including clinical presentation and symptom burden within routine mental healthcare.

Methods: Analysis of electronic health records (EHR) examined CI among 8,355 schizophrenia patients using the Holmusk NeuroBlu Database (Version 22R3), a longitudinal behavioral health real-world database containing de-identified, patient-level, clinical data from 25 mental health providers in 15 states in the US. Patients aged ≥ 18 years diagnosed with schizophrenia from 1999 to 2021 were included. Features of cognitive dysfunction recorded within ± 14 days of the first recorded schizophrenia diagnosis (index) were derived from free-text documented during the mental status examination (MSE) and extracted using natural language processing (NLP) models. The NLP models identified specific text strings that are mapped to clinical features in the MSE and social factors. For example, indications of CI included text strings like "poor concentration", "difficulty with attention/focus", "limited reasoning ability". The index was defined as the first-recorded schizophrenia diagnosis and demographic and clinical features were extracted at index ± 14 days (the baseline period). Baseline clinical features including psychiatric comorbidities, treatment patterns, disease severity, functioning and social factors were compared for those with and without at least one recorded MSE clinical feature indicative of CI.

Results: The mean age of patients was 41.6 years (SD=14.8), and the majority were male (63.3%). CI was less frequently documented (27.9%) at first recorded schizophrenia diagnosis than positive (68.0%) and negative symptoms (61.7%). Those with and without documented CI had a similar demographic profile but differences in clinical features were noted between these two. Patients with CI were more likely treated with mood stabilizers (8.5% vs. 6.6%, $p=0.003$) or an analgesic (6.7% vs. 4.7%, $p < 0.001$) compared to those without documented CI. Conversely, those with CI were prescribed a first-generation antipsychotic less often than those with no documented CI (10.7% vs. 12.5%, $p=0.024$). No significant difference was observed when comparing patients with and without CI who received a second-generation antipsychotic (42.8% vs. 44.1%) or an antidepressant (21.0% vs. 21.3%). Also, schizophrenia patients with CI were less likely to receive psychotherapy (15.7% vs. 21.2%, $p < 0.001$). A comorbid diagnosis of substance use disorder, schizoaffective disorder, PTSD, OCD, and ADHD were more likely for those with CI. Patients with documented CI had higher baseline illness severity and lower functioning (based on CGI-S and GAF scores) and were more frequently seen in emergency departments (26.3% vs. 18.8%, $p < 0.001$) and inpatient settings (45.3% vs 27.7%, $p < 0.001$) compared to those without CI. Further, patients with CI were more likely to experience negative social factors in all categories

including family, financial, housing, legal, occupational and academic functioning. Across 18 months post-index, CI was associated with an increased risk of psychiatric hospitalization, significantly higher inpatient visits and total number of inpatient days compared to those without CI.

Discussion: Results show that schizophrenia patients with CI are more unwell, have a higher burden of functional deficits and are more likely to experience negative social factors. Presence of CI was associated with meaningful differences in clinical presentation and other outcomes, providing evidence to support associations between CI and higher illness burden. Higher prescribing of mood stabilizers and analgesic medications for patients with CI suggest additional illness-related features or physical comorbidities among these patients. Yet, while CI is recognized as almost universal in schizophrenia, its recording in this real-world dataset largely underestimated the CI prevalence versus those found in clinical trial studies and prospective research. This is likely due to limited therapeutic treatment options for CI but suggests an opportunity to improve detection of CI through clinician education or digital approaches and therapeutics.

Funding: Funding for the studies presented was provided by Boehringer Ingelheim.

S153. THE BIDIRECTIONAL ASSOCIATION BETWEEN SCHIZOPHRENIA SPECTRUM DISORDER AND SHELTERED HOMELESSNESS

Sandra Nilsson*¹, Theresa Wimberley², Helene Speyer³, Carsten Hjorthøj⁴, Seena Fazel⁵, Merete Nordentoft⁶, Thomas Munk Laursen⁷

¹Copenhagen Research Center for Mental Health - CORE, ²Center for Register-Based Research, Aarhus University, Aarhus, Denmark, ³Copenhagen Research Center for Mental Health-CORE; Mental Health Center Copenhagen, Copenhagen University Hospital, Denmark, ⁴Copenhagen University Hospital, Mental Health Center Copenhagen, ⁵University of Oxford, Department of Psychiatry, ⁶Mental Health Centre Copenhagen, ⁷Aarhus University

Background: Psychiatric disorders and homelessness are related, but temporal associations are unclear. We aimed to explore the overlap between hospital-based psychiatric disorders, focusing on schizophrenia spectrum disorder, and sheltered homelessness.

Methods: This population-based cohort study was conducted using the Danish registers e.g., the Danish Homeless Register and the Danish National Patient Register. The study cohort included all individuals aged 15 years or older, living in Denmark at least one day during 2002-2021 (born 1984-2006). First psychiatric diagnosis was used to define psychiatric disorders and first homeless shelter contact to define homelessness. Adjusted incidence rate ratios (IRRs) and cumulative incidences according to any psychiatric disorder were estimated.

Results: Among 1,530,325 individuals accounting for 16,787,562 person-years at risk aged 15-38 years, 11,433 (0.8%) had at least one homeless shelter contact. Among 1,406,410 individuals accounting for 14,131,060 person-years at risk, 210,730 had at least one psychiatric disorder (IRR 9.2, 95% CI 8.8-9.6 adjusted for sex, age, calendar year, and country of origin). Drug use disorder (IRR 20.6, 95% CI 19.7-21.4) and schizophrenia spectrum disorder (IRR 10.2, 95% CI 9.6-10.8) were associated with highest risk of sheltered homelessness compared with not having these disorders. Ten years after first psychiatric disorder, 3.0% (95% CI, 2.9-3.1) had at least one homeless shelter contact. Individuals experiencing homelessness had increased risk of any psychiatric disorder compared to individuals with no homeless shelter contact (IRR 7.0, 95% CI 6.7-7.4). Especially high risk was found for drug use disorder (IRR

15.3, 95% CI 14.6-16.1) and schizophrenia spectrum disorder (IRR 12.2, 95% CI 11.5-13.0) in individuals experiencing homelessness compared with no history of homelessness. Ten years after first homeless shelter contact, 47.1% (45.3-48.0) had received a hospital-based psychiatric diagnosis. Highest risk of both outcomes was found the year after first schizophrenia spectrum diagnosis or first homeless shelter contact.

Discussion: Strong bidirectional associations between psychiatric disorders and homelessness were identified with highest risk estimates found for drug use disorder and schizophrenia spectrum disorder. Health and social care professionals should be aware of and address these high risks of accumulated psychiatric and social problems.

S154. PROBLEM GAMBLING AMONG PEOPLE WITH PSYCHOTIC DISORDERS: A META-ANALYSIS OF PREVALENCE

Olivier Corbeil^{*1}, Elizabeth Anderson², Maxime Huot-Lavoie³, Charles Desmeules², Lauryann Bachand², Laurent Béchar⁴, Sébastien Brodeur³, Christian Jacques², Isabelle Giroux², Pierre-Hugues Carmichael⁵, Marco Solmi⁶, Michel Dorval⁴, Marc-André Roy³, Marie-France Demers⁴

¹Laval University, ²School of Psychology, Université Laval, ³Faculty of Medicine, Université Laval, ⁴Faculty of Pharmacy, Université Laval, ⁵Center of Excellence on Aging in Quebec, ⁶Department of Psychiatry, University of Ottawa

Background: Psychiatric comorbidities, notably substance use disorders, are prevalent among individuals with psychotic disorders, significantly hindering their recovery. The reclassification of gambling disorder as a behavioral addiction in the DSM-5 underscored its parallels with substance use disorders. Both gambling disorder and problem gambling (PBG) result in adverse financial, social, and psychological outcomes, including an increased risk of suicide. Global prevalence estimates for gambling disorder and PBG vary due to diverse screening tools and methodologies. Despite higher prevalence rates among individuals with mental health disorders, research on PBG among those with psychotic disorders remains limited. This systematic review aimed to determine the prevalence of PBG in individuals with psychotic disorders and investigate how assessment methods and clinical settings influence this prevalence.

Methods: A comprehensive search strategy was conducted in Medline (using Ovid), EMBASE, PsycINFO (using Ovid), CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and ProQuest Dissertation and Thesis. Peer-reviewed studies encompassing both correlational and experimental designs involving a representative sample of individuals spanning all age groups, diagnosed with either schizophrenia spectrum or affective psychotic disorders and providing the prevalence data of PBG were included. There was no language restriction applied. The evaluation of the included studies' risk of bias was carried out using the Joanna Briggs Institute (JBI) critical appraisal checklist for systematic reviews of prevalence data. The overall pooled prevalence estimate of PBG was calculated using the Generalized Linear Mixed Model. The presence of heterogeneity was evaluated using a χ^2 test and the I^2 statistic. All statistical analyses were conducted with R software, version 4.3.0 (R Project for Statistical Computing), using the meta and metafor packages.

Results: The systematic review encompassed 14 non-overlapping studies, out of which 12 studies contributed to the meta-analysis. The pooled prevalence of PBG was calculated at 5.15% (95% CI 3.16 - 7.46), with substantial heterogeneity ($I^2 = 74\%$). Notably, among the

factors analyzed, only the risk of bias within the included studies showed a significant association with the observed heterogeneity.

Discussion: Compared to the general population, individuals with psychotic disorders exhibit a significantly higher prevalence of PBG, estimated to be 5 to 10 times more prevalent. However, due to inconsistencies in PBG assessment methodologies across studies and the absence of screening instruments tailored to this specific population, a more precise estimation of the prevalence of this comorbidity remains challenging. Notably, the presence of PBG among individuals with psychotic disorders may potentially worsen psychosis symptoms and hinder the recovery process. Consequently, integrating routine clinical care with screening measures and providing appropriate treatment for PBG in this demographic is crucial to mitigate its adverse impact on their condition and overall well-being.

S155. AN INVESTIGATION OF RECORDED PHYSICAL, DOMESTIC, AND SEXUAL VICTIMISATION AS RISK FACTORS FOR ADVERSE CLINICAL OUTCOMES IN SERIOUS MENTAL ILLNESS: A LONGITUDINAL STUDY

Ava Mason^{*1}, Jyoti Sanyal², David Chandran³, Angus Roberts⁴, Robert Stewart⁵

¹University College London, ²South London and Maudsley NHS Foundation Trust, ³King's College London, ⁴King's College London, Biostatistics and Health Informatics, School of Mental Health and Psychological Sciences, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Associations have been described between childhood victimisation and psychosis, psychotic symptom severity, and global functioning. However, few studies have examined the effect of other forms of victimisation on clinical outcomes relating to disease burden and treatment adherence. Large data resources are accruing from electronic healthcare records, but these have been under-used for research into the impact of violence experiences because these exposures are traditionally recorded in text rather than pre-structured fields. Taking advantage of recently developed and applied natural language processing algorithms for violence ascertainment, we investigated associations of violence victimisation with clinical outcomes in a large clinical population.

Methods: Clinical records of 16,372 patients receiving care from a large South London (UK) mental health service (SLaM) between January 2007 to October 2022 with a primary serious mental illness (SMI) diagnosis (ICD-10; F2*, F31 or F30) were included in this study. Patients were categorised into those with or without at least one general, physical, domestic, and sexual victimisation mention around the first clinical contact using natural language processing algorithms. Logistic and Cox regressions were used to investigate the association between victimisation and the severity of clinical outcomes in the subsequent three months. Outcomes included the number of prescribed antipsychotics, emergency care (A and E and crisis care), psychiatric inpatient care, compulsory detention and mortality. All regressions controlled for age, sex, ethnicity, neighbourhood deprivation, primary F* diagnosis, secondary diagnosis (substance misuse, intellectual disability, personality disorder), symptom severity (positive, negative, manic, disorganised, catatonic symptoms), antidepressant and mood stabiliser prescriptions, prior inpatient care, and prior emergency care.

Results: Adjusting for all covariates, general, physical, domestic, and sexual victimisation were associated (all p LESS THAN .01) with increased likelihood of patients visiting A and E

(HR range=1.20-1.34) and compulsory detention (HR range =1.52-2.03). General, domestic, and sexual victimisation significantly predicted increased number of antipsychotics prescribed ($B=0.05-0.06$, all $p < .01$). Domestic and sexual victimisation increased the likelihood of having an inpatient admission (HR range=1.37-1.71, all $p < .01$). No type of victimisation affected the likelihood of having an emergency visit by the crisis team or mortality rate (all $p > 0.50$).

Discussion: We believe this is the first longitudinal study to examine the relationship between victimisation types and clinical outcomes in patients with SMI using clinical health record data. When adjusting for multiple sociodemographic and clinical variables, general, sexual, and domestic victimisation significantly predicted multiple adverse clinical outcomes.

S156. PATIENT AND CAREGIVER EXPERIENCES WITH TARDIVE DYSKINESIA: EMOTIONS, CHALLENGES, AND UNMET NEEDS IN THE PATIENT JOURNEY

Aviva Levin^{*1}, Erika Kinjo², Rinat Chaijale³, Nayla Chaijale⁴, Ayelet Yaari⁵

¹Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs, ²Teva Farmacêutica Ltda, Medical Affairs, São Paulo, Brazil, ³Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research, Tel Aviv, Israel, ⁴Teva Branded Pharmaceutical Products R and D, Inc., ⁵Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs,

Background: Tardive dyskinesia (TD) is a drug induced hyperkinetic movement disorder with multidimensional impact on quality of life and functionality. This study aimed to describe the patients' emotional journey from symptom onset to current state and to identify challenges and unmet needs.

Methods: Qualitative interviews were conducted with participants living with TD and caregivers of patients with TD (unconnected to each other) in Brazil, Israel, and China. Web-assisted telephone interviews were based on a pre-defined discussion guide, and TD diagnosis was based on self-report. Questions assessed awareness of TD as a condition, patient journey from onset of symptoms to diagnosis, impact on daily life, treatment, and long-term management. A Blob Tree© (Pip Wilson and Ian Long, 1980) projective exercise that visually portrayed 21 emotions using “blob people” was used to encourage discussion.

Results: Interviews were conducted with 17 respondents (8 patients, 9 caregivers). Mean age at TD diagnosis had a range of 44–48 years. Respondents tended to choose similar “blob people” (ie, emotions) at different points in the patient journey. Many reported feeling alone when symptoms started, as well as confused and powerless. While all had prior antipsychotic treatment (most for 2–3 years before TD onset), none reported having any awareness of TD before diagnosis or knew their risk of developing it; symptoms were often misattributed and multiple consultations were required to receive a diagnosis. At diagnosis, respondents most often reported feelings of sadness and frustration. Diagnosis came as a shock to all respondents, but some were happy to have a diagnosis after living with unexplained symptoms. Upon symptom worsening, hopeless feelings predominated; some respondents reported feeling supported amidst feeling scared and alone. Patients reported feelings of loneliness and isolation in their current state; however, some expressed hope for a useful future treatment.

Respondents reported that onset of symptoms had an immediate impact on activities of daily living, resulting in anger, stress, and withdrawal. Most patients ultimately gave up working and symptoms eventually impacted basic tasks such as walking, eating, and personal hygiene,

leading many to need 24-hour support. TD negatively impacted social interactions and most patients noticed a decline in mental health with feelings of anxiety, depression, embarrassment, and loss of interest in hobbies and social life. Most patients continued taking antipsychotics (often at a reduced dosage) and started TD treatments. Although no specific treatment was mentioned, respondents reported dissatisfaction with available options, and all reported high treatment adherence and satisfaction with information provided for their current treatment. Most respondents received key information from psychologists, psychiatrists, or other physicians. However, some respondents felt there are a lack of resources about TD and would like more official organizations to provide directions to patients to information and support groups. Most patients lived with family members and felt they had a good level of support from close family and friends and mental health professionals.

Discussion: In this international study of the TD patient journey using qualitative interviews, patients and caregivers alike reported substantial impact on patient quality of life and feelings of loneliness, confusion, sadness, frustration, and hopelessness. While many patients had good support systems, there is a need for greater awareness of TD, more accessible information, and more efficient diagnosis routines.

S157. SCHIZOPHRENIA AS A RISK FACTOR FOR CARDIOVASCULAR AND METABOLIC HEALTH OUTCOMES: A COMPARATIVE RISK ASSESSMENT

Suhailah Ali^{*1}, Damian F. Santomauro¹, Alize J. Ferrari¹, Fiona Charlson¹

¹*The University of Queensland*

Background: Cardiometabolic diseases are responsible for the majority of premature deaths in people with schizophrenia. This study aimed to quantify the fatal burden of ischaemic heart disease (IHD), stroke and diabetes attributable to schizophrenia.

Methods: Comparative Risk Assessment methodology from the Global Burden of Disease (GBD) study was used to calculate attributable burden; pooled relative risks (RRs) for IHD, stroke and diabetes were estimated via meta-regression, which were combined with GBD schizophrenia prevalence estimates to calculate the deaths and years of life lost (YLLs) caused by these health outcomes that were attributable to schizophrenia. The proportion of explained all-cause fatal burden and corresponding unexplained burden was also calculated.

Results: The pooled RRs for IHD, stroke and diabetes mortality were 2.36 [95% uncertainty interval (UI) 1.77 to 3.14], 1.86 (95% UI 1.36 to 2.54) and 4.08 (95% UI 3.80 to 4.38) respectively. Schizophrenia was responsible for around 50,000 deaths and almost 1.5 million YLLs globally in 2019 from these health outcomes combined. IHD, stroke and diabetes together explained around 13% of all deaths and almost 11% of all YLLs attributable to schizophrenia, resulting in 320,660 (95% UI 288,299 to 356,517) unexplained deaths and 12,258,690 (95% UI 10,925,426 to 13,713,646) unexplained YLLs.

Discussion: Quantifying the physical disease burden attributable to schizophrenia provides a means of capturing the substantial excess mortality associated with this disorder within the GBD framework, contributing to an important evidence base for healthcare planning and practice.

S158. EXPLORING THE CAUSAL ASSOCIATIONS OF SELF-HARM AND ITS PERSISTENCE WITH PSYCHOTIC EXPERIENCES: A POPULATION-BASED ADOLESCENT COHORT STUDY UTILIZING A MARGINAL STRUCTURAL MODEL

Satoshi Yamaguchi^{*1}, Syudo Yamasaki¹, Mitsuhiro Miyashita¹, Kaori Baba¹, Junko Niimura¹, Naomi Nakajima¹, Shuntaro Ando², Atsushi Nishida¹

¹Tokyo Metropolitan Institute of Medical Science, ²The University of Tokyo

Background: Longitudinal associations between antecedent psychotic experiences (PEs) and subsequent self-harm are well-established. However, recent studies using data from the nationwide registry observed strong relationships between antecedent hospital presentations for self-harm and subsequent psychotic disorder. These findings highlight an urgent need to examine the effects of self-harm on PEs in the general population. This is the first study aiming to explore the causal associations of antecedent self-harm and its persistence with subsequent PEs in a population-based adolescent cohort.

Methods: Data was obtained from a population-based birth cohort (Tokyo Teen Cohort; N = 3,171), consisting of random sampling of adolescents born between 2002 and 2004. A marginal structural model with inverse probability weighting was utilized to examine the association of self-harm at 12y and 14y with PEs at 16y as well as PEs with general psychological distress (GPD), accounting for time-fixed and time-varying confounders. The association of PEs at 12y and 14y with self-harm at 16y was also examined.

Results: Persistent self-harm at 12y and 14y was significantly associated with PEs at 16y (Odds ratio (OR) = 7.28, 95% confidence interval (CI) = 1.34–39.5) and PEs with GPD (OR = 10.1, 95% CI = 1.84–55.8). These associations were stronger than the association of persistent PEs at 12y and 14y with self-harm at 16y (OR = 2.49, 95% CI = 1.30–4.74).

Discussion: Persistent self-harm was strongly associated with subsequent PEs, and especially with PEs with GPD, a more severe phenotype of PEs, suggesting that preventive intervention for persistent self-harm is essential for reducing future psychosis risk.

S159. INVESTIGATING THE INFLUENCE OF PERSONALITY AND COGNITIVE BIASES ON PERCEPTIVE AND NON-PERCEPTIVE CLINICAL HIGH-RISK (CHR) SYMPTOMS FOR PSYCHOSIS IN THE COMMUNITY

Giulia Rinaldi^{*1}, Stefan Lerch¹, Frauke Schultze-Lutter², Stefanie J. Schmidt¹, Marialuisa Cavelti¹, Michael Kaess³, Chantal Michel¹

¹University of Bern, ²Heinrich-Heine University Düsseldorf, ³University of Bern, Airlangga University, ³University of Bern, University Hospital Heidelberg

Background: Beyond their role in predicting psychotic disorders, CHR symptoms influence mental health quality via their associations with psychopathology and impairments in psychosocial and personality functioning. Cognitive biases (e.g., dichotomous thinking, emotion-based reasoning) are also involved in the development of psychosis, and linked to general psychopathology and personality functioning, but their role in the context of CHR is underexplored. Therefore, we investigated the impact of personality functioning,

psychopathology and cognitive biases on CHR symptoms overall, as well as perceptive (P-CHR) and non-perceptive (NP-CHR) CHR symptoms independently, in a community sample. **Methods:** The final sample comprised 444 participants assessed via telephone using clinical interviews and via online questionnaires as part of a larger study. As expected in a community sample, a high proportion of participants had no CHR symptoms, and therefore, we used zero-inflated Poisson (ZIP) models to analyze (i) which factors influenced the likelihood of showing no CHR symptoms versus at least one, (ii) which factors influenced the count and severity of CHR symptoms. To this end, we calculated a CHR, a P-CHR and a NP-CHR sum-score, each representing the outcome variable in a separate ZIP model. In all models, the sum-scores of instruments measuring psychopathology, personality functioning, and cognitive biases were included as predictors, with age, sex and educational level as covariates.

Results: A higher sum-score in cognitive biases and higher impairments in personality functioning correlated with a lower likelihood of having no CHR symptoms. The likelihood of having no P-CHR symptoms also decreased with higher sum-scores in cognitive biases, while the chances of showing no NP-CHR symptoms were lower in women and when impairments in personality functioning were higher. A higher psychopathology sum-score was associated with a smaller probability of having no CHR, P-CHR and NP-CHR symptoms. For CHR symptoms, a higher count and severity correlated with a higher sum-score in cognitive biases, younger age and female sex. In younger participants, P-CHR symptoms' count and severity also tended to be higher. For NP-CHR symptoms, a higher count and severity was associated with a higher sum-score in cognitive biases.

Discussion: Our findings suggest that cognitive biases and personality functioning play a role in the presence, count and severity of CHR symptoms in non-help-seeking populations, influencing their expression and resulting in different patterns of both P-CHR and NP-CHR symptoms. To better understand their impact on CHR and ultimately inform mental health promotion, dedicated prevention, and treatment, future studies should investigate specific cognitive biases and facets of personality functioning individually. Further, our results support existing literature on the association of CHR symptoms with psychopathology, on the influence of age on CHR symptoms and on its differential effect on P-CHR and NP-CHR symptoms. To understand the role of age in CHR in more detail, future research should analyze its interactions with other factors, such as sex. In conclusion, our study highlights the complex interactions of CHR symptoms with other areas of mental health and sociodemographic variables, calling for their further exploration and emphasizing their clinical relevance.

S160. SYSTEMATIC INVESTIGATION OF SHARED AND EXCLUSIVE ASSOCIATIONS OF NON-GENETIC FACTORS WITH INDIVIDUAL PSYCHOTIC EXPERIENCES: EXPOSOME-WIDE ASSOCIATION STUDY IN THE UK BIOBANK

Angelo Arias-Magnasco¹, Bochao D. Lin², Lotta-Katrin Pries², Sinan Guloksuz*¹

¹Maastricht University, ²Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands

Background: By applying exposome-wide analysis (ExWAS) and Mendelian Randomization analysis to investigate a range of nongenetic factors associated with any psychotic experiences (PE) in the UK Biobank, we have previously shown that ever having experienced sexual assault might be a potential causal risk factor for PE but experiencing a physically violent crime and cannabis use rather appeared to be possible aftereffects of having PE. In this study, we aim to

enhance our understanding of the complex web of non-genetic factors through systematic investigation of individual PE items to reveal shared and exclusive non-genetic factors across PE domains.

Methods: This study analyzed the Mental Health Survey data of the UK Biobank (UKB project number: 55392) to investigate individual items of PE as the outcomes. These four individual items of self-reported PE were: ever believing in an unreal conspiracy against self, ever believing in unreal communications or signs, ever hearing an unreal voice, and ever seeing an unreal vision. Following the quality control, 315 variables were included as predictors in the analyses conducted in two sequential main steps. First, ExWAS of each PE item were conducted in two equally split discovery and replication datasets (Bonferroni corrected $P < 1.59 \times 10^{-4}$). In the second step, variables associated with each of the PE item in the ExWAS were tested by applying a multivariable logistic regression model per PE item.

Results: The study population comprised 155,247 participants (57% females; mean age 55.94 years). Several significant associations were identified across PE items in the discovery dataset. Belief in unreal personal conspiracies was associated with 107 variables (34%). Belief in unreal communications or signs was associated with 66 variables (21%). Auditory hallucinations, such as hearing an unreal voice, were associated with 128 variables (41%), while visual hallucinations were associated with 137 variables (43%). The replication dataset confirmed these associations with high replication rates: 89% for unreal conspiracies, 82% for unreal communications, 78% for unreal voices, and 88% for unreal visions.

The subsequent multivariable models per each PE item demonstrated significant independent associations of 27 variables with unreal conspiracies, 19 with unreal communications, 39 with unreal voices, and 45 with unreal visions. In the final multivariable models, several of these predictors were shared across PE items, whereas others were exclusive to specific PE items. Most remarkably, each of the PE item was associated with both childhood and adulthood traumatic experiences across different domains (e.g. felt hated by family member as a child, victim of sexual assault, belittlement by partner as an adult). Cannabis use was also associated with all PE items but belief in unreal communications or signs.

Discussion: Our study paves the way for a systematically constructed map of nongenetic factors associated with psychopathology dimensions to guide the future work that would also include non-psychotic dimensions and apply up-to-date Mendelian Randomization methods.

S161. IMPLEMENTING VIRTUAL REALITY IN SPECIALIZED MENTAL HEALTH CARE FROM LEADERS' PERSPECTIVES

Trine Sandal¹, **Helen Bull**², **Jan Ivar Røssberg**³, **June Lystad**⁴, **Andreas Seierstad**⁵, **Olivia Schjøtt-Pedersen**⁴, **Alexandra Søhoel**⁴, **Helge Skirbekk**⁶

¹University of Oslo, Ulleral Hospital, Department of Psychiatry, ²Oslo Metropolitan University, ³Institute of Clinical Medicine, University of Oslo, Norway. Division of Mental Health and Addiction, Oslo University Hospital, Norway, ⁴Oslo University Hospital, ⁵Oslo University Hospital, Section for Early Psychosis Intervention, ⁶University of Oslo

Background:

Innovation is an essential part of future mental health care. In line with national and international regulations, health services are instructed to invest in and implement technological solutions in care delivery to better manage sparse clinical resources. Technology in general and Virtual Reality (VR) in particular, has the potential to play a key role in bridging

the gap between demand and supply in specialized psychosis treatment as patients and clinicians call for a more specific focus on functional outcome and social inclusion. Consequently, the healthcare system needs to both explore new avenues for treatment. Experiences however indicate that many innovation projects end up in the “pilot graveyard”. gameChange, developed at the University of Oxford, is a VR application for individuals with psychosis experiencing agoraphobic anxiety and avoidance. It has been validated in a large randomized controlled trial in the UK and has recently been piloted in Norway in the VROslo study, mixed methods feasibility study across seven psychosis treatment units at Oslo University hospital (OUH). Twenty-seven individuals with psychosis have tested the gameChange application. All participants, VR therapists and managers of participating hospital units were interviewed. The aim of the current study was to explore and describe challenges and advantages that managers have experienced during the implementation of VR therapy within specialized mental health services.

Methods: Qualitative semi-structured interviews were carried out, gathering data from seven managers. Interviews were recorded, transcribed, and analyzed using inductive thematic analysis. **Results:** On the basis of the seven interviews, four main themes were identified; preparation for change in work methodology, recruiting staff, prioritizing tasks, and the patient as a catalyst for change. Preparing the organization in terms of presenting the project and providing sufficient information was considered important. Different strategies were applied by managers to recruit resource persons and help them adapt to their project roles, varying from adjusting rotation plans to limiting other clinical tasks. Managers described different approaches to prioritizing the implementation of VR therapy underlining the balancing act between day-to-day clinical tasks and innovation. Divergent views regarding the patient group also emerged with some managers considering individuals with psychosis too ill to receive, adhere to or profit from VR therapy.

Discussion: The findings of the current study highlight that the successful implementation of VR therapy in specialized mental health care requires specific factors at the organizational, individual and leadership level. Analyses of patient and (VR-) therapist perspectives may shed further light on unique barriers and facilitators related to the implementation of VR treatment in mental health services.

S162. POLYGENIC RISK OF SOCIAL ISOLATION BEHAVIOR AND ITS INFLUENCE ON PSYCHOPATHOLOGY AND PERSONALITY

Adam Socrates^{*1}, Niamh Mullins², Ruben Gur³, Raquel Gur³, Eli Stahl², Paul O' Reilly², Avi Reichenberg², Hannah Jones⁴, Stanley Zammit⁴, Eva Velthorst⁵

¹*Icahn School of Medicine At Mount Sinai*, ²*Icahn School of Medicine at Mount Sinai*, ³*Penn Medicine and Children's Hospital of Philadelphia*, ⁴*University of Bristol*, ⁵*Mental Health Organization “GGZ Noord-Holland-Noord”*

Background: Loneliness has been described as an epidemic on par with obesity and tobacco use, linked to a range of psychiatric issues, but the behavioral component that drives social isolation is not well understood. Most genetic studies focus on the subjective aspects of isolation i.e. loneliness and social anxiety as opposed to the behavioral manifestations that lead to objective isolation as a measurable construct. Here, a genome-wide associations study (GWAS) was carried out to identify genetic variants that contribute specifically to social

isolation behavior (SIB) in order to investigate the relationship between genetic predisposition to actual social isolation, and psychosis and other psychopathologies and personality traits.

Methods: An SIB phenotype was devised with 4 traits from the UK Biobank, and a GWAS carried out to identify SNPs which contribute to this trait in up to 449,609 participants from the UK Biobank. Using this social isolation GWAS, polygenic risk scores (PRS) were derived in ALSPAC, an independent, developmental cohort, and used to test for association with friendship quality and social traits. Linkage disequilibrium (LD) score regression using the SIB GWAS was used to test for genetic correlation with schizophrenia and other psychiatric disorders. Mendelian randomization was used to test for causal relationships between social isolation and these psychiatric disorders. Finally, Genomic SEM was applied to investigate relationships between social isolation and psychosis, personality, and psychiatric domains.

Results: 17 loci were identified at genome-wide significance, contributing to a 4% SNP-based heritability estimate. At age 18, friendship scores were associated with the SIB PRS, demonstrating that the genetic factors can predict related social traits in late adolescence. LD score correlation using the SIB GWAS demonstrated genetic correlations with schizophrenia, autism spectrum disorder (ASD), major depressive disorder (MDD), educational attainment, extraversion, and loneliness. Genomic Structural Equation Modeling (SEM) revealed a common personality factor contributing to SIB, neuroticism, loneliness, MDD, and ASD, weakly correlated with a second common factor that contributes to psychiatric and psychotic traits.

Discussion: Our results show that SIB contributes a small heritable component, which is associated genetically with reduced social outcomes such as friendship and extraversion, as well as psychiatric disorders including schizophrenia.

S163. POSTMORTEM STUDY OF BCAS1-IMMUNOREACTIVE OLIGODENDROCYTES IN THE POSTERIOR HIPPOCAMPUS: IMPAIRED OLIGODENDROCYTE REGENERATION AS A BIOLOGICAL UNDERPINNING OF SCHIZOPHRENIA?

Johann Steiner^{*1}, Peter Falkai², Anna Kessel¹, Thomas Schneider-Axmann³, Andrea Schmitt⁴

¹University of Magdeburg, Dpt. of Psychiatry, ²Department of Psychiatry, LMU ³Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University Munich, ⁴Department of Psychiatry, LMU

Background: Structural and functional deficits in oligodendrocytes and impaired myelin integrity have been described in schizophrenia and may disrupt connectivity between disease-relevant brain regions. Notably, a population of breast carcinoma amplified sequence 1 (BCAS1)-expressing oligodendrocytes has been discovered as an important player in the remyelination of brain lesions, for example in multiple sclerosis. The hypothesis of our study was that the population of regenerating BCAS1-positive oligodendrocytes is reduced in schizophrenia as a possible cause of disease-related impairments in cerebral wiring and connectivity.

Methods: Numbers and numerical densities of BCAS1-immunostained oligodendrocytes were determined in the hippocampal subregions CA1, CA2/3, CA4, dentate gyrus and subiculum in postmortem brains from ten patients with schizophrenia and ten matched controls. We examined the same brains as previously, where we had found a reduction in total oligodendrocyte numbers in CA4 in a stereological study of Nissl-stained sections.

Results: Compared with controls, patients with schizophrenia showed a significant decrease in the mean number of BCAS1-immunoreactive oligodendrocytes in CA2/3 and CA4, which was associated with a reduction in the total number of oligodendrocytes in these hippocampal subregions.

Discussion: The observed reduction in BCAS1-immunoreactive remyelinating oligodendrocytes suggests that impaired oligodendrocyte regeneration may be involved in schizophrenia, ultimately leading to reduced total oligodendrocyte densities (Nissl staining) previously described in CA2/3 and CA4. Further insights into the underlying mechanisms may lead to new gliotrophic therapeutic approaches.

S164. MITOCHONDRIAL FUNCTION AND WORKING MEMORY IN SCHIZOPHRENIA: A PET AND TASK-FMRI STUDY

Atheeshaan Arumuham*¹, Ekaterina Shatalina², Thomas Whitehurst², Ellis Chika Onwordi³, Alexander Whittington⁴, Ayla Mansur⁴, Roger Gunn⁴, Sridhar Natesan¹, Matthew Nour⁵, Matthew Wall⁶, Eugenii Rabiner⁶, Oliver D. Howes¹

¹Institute of Psychiatry, Psychology and Neuroscience, King's College London, ²Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, ³Bart's and The London School of Medicine, Queen Mary University of London, ⁴Division of Brain Sciences, Imperial College London, ⁵University of Oxford, ⁶Invicro

Background: Cognitive impairment is a core feature of schizophrenia affecting multiple domains, including working memory (WM). The aetiology of this impairment has been associated with genetic, environmental, neurochemical and structural brain abnormalities. Mitochondria are essential for cellular energy metabolism, and their dysfunction can have profound effects on brain function and cognition, with multiple lines of evidence suggesting a relationship between mitochondrial dysfunction and schizophrenia. Postmortem brain tissue from patients with schizophrenia have found significant abnormalities in mitochondrial complex 1 (MC1) expression in the dorsolateral prefrontal cortex (DLPFC), a region strongly implicated with WM function, but MC1 expression and its relationship with WM has not been examined in vivo. To address this, we investigate MC1 availability in patients with schizophrenia and examined the relationship with neural correlates of WM function.

Methods: A total of n=59 volunteers took part in the study (36 patients with schizophrenia and 23 matched controls). They received a dynamic, continuous 90-minute PET acquisition using [18F]-BCPP-EF, a selective radioligand for MC1, and determined the volume of distribution (Vt). Following this, participants underwent a functional MRI scan utilising an established WM task, the n-back, to measure task-evoked blood-oxygen level dependent (BOLD) activation. The DLPFC, anterior cingulate cortex (ACC) and hippocampus were defined as a priori regions of interest (ROIs) based on existing literature. Exploratory cluster-based extraction of Vt was performed according to significantly activated clusters identified during fMRI voxel wise analysis.

Results: For the PET data, we found a significant ROI x Group interaction ($F_{1,57}=10.0$, $p=0.002$), with post hoc testing finding significant reduction in mean patient Vt in the ACC ($t_{58}=-2.70$, $p=0.01$), DLPFC ($t_{58}=-2.69$, $p=0.01$), and hippocampus ($t_{58}=-2.26$, $p=0.03$). During ROI analysis of fMRI data, we did not find a significant difference between groups in BOLD activation during the 1 and 2back GREATER THAN 0back task condition, quantified as parameter estimates. Voxel-wise analysis found a cluster that had significantly higher

activation in patients compared to controls for the same task condition, with the local maxima being located within the left hippocampus ($Z=3.78$, $p=0.02$, MNI co-ordinates: $x=-36$, $y=-10$, $z=-18$). ROI correlation analysis did not find a significant relationship between V_t and task-evoked BOLD activation.

Discussion: We found significantly lower [18F]-BCPP-EF mean V_t in patients with schizophrenia compared to healthy controls, which supports existing postmortem literature. Previous studies have found [18F]-BCPP-EF uptake correlates positively with markers of metabolic activity, such as oxygen and [18F]-FDG uptake. Taken together, our findings of reduced MC1 binding in patients with schizophrenia indicates deficits in MC1 may underlie hypometabolism seen in schizophrenia. Furthermore, voxel-wise analysis of WM-evoked activation, found increased activation in patients compared to controls, in a cluster that partially included the left hippocampus. fMRI studies employing the n-back task have found hippocampal activation is associated with higher WM load and plays a vital role in encoding and retrieval during the WM task. Nevertheless, we did not find a significant correlation between tracer uptake and task-evoked BOLD activation in these ROIs. Although there is some evidence of frontal metabolism being correlated with WM impairments, we did not identify this relationship between MC1 and WM-evoked BOLD activations. Methylene blue is a compound that bypasses the rate limiting role of MC1 in mitochondrial respiration. Given the reduced expression of MC1 in patients with schizophrenia, and its potential effect on hypometabolism seen in schizophrenia, methylene blue could be utilised as a pharmacological challenge to elucidate the relationship between MC1 and WM. These findings build on existing literature suggesting the role of mitochondrial abnormalities in the aetiology of schizophrenia, although further studies are required to determine a causal relationship between MC1 and WM.

S165. MOLECULAR MECHANISMS UNDERLYING EXCITATION/INHIBITION BALANCE DEFICITS FOLLOWING MATERNAL IMMUNE ACTIVATION

Francesca McEwan^{*1}, Chiho Kambara¹, James Dal Santo¹, Jarred Lorusso¹, Jocelyn Glazier¹, Michael Harte¹, Reinmar Hager¹

¹*University of Manchester*

Background: Exposure to maternal immune activation (MIA) has been associated with increased risk for neurodevelopmental disorders such as schizophrenia. To establish the mechanistic pathways underlying this link, animal models recapitulate MIA through mid-gestational administration of the viral mimetic poly(I:C), which stimulates an increased cytokine response in the maternal plasma. Offspring exposed to MIA show behavioural changes, which are often translatable to symptoms in patients with schizophrenia. However, the neurodevelopmental mechanisms underlying such symptoms remain poorly understood. The aims of this study were to determine how MIA affects the expression of schizophrenia linked targets essential for the maintenance of excitatory/inhibitory balance (E/I).

Methods: In this study, pregnant rats were injected with poly(I:C) on gestational day (GD) 15 and plasma cytokines were measured 3 h following injection to confirm MIA. Offspring behaviour was assessed at postnatal day (PD) 100 in novel object recognition (NOR) tasks, with a short (2 min; NOR-S) and long (1 hour; NOR-L) inter-trial interval and anxiety behaviour was measured in the open-field task (OFT). All molecular analyses were conducted on the GD21 hippocampus and PD14, 42 and 98 dorsal hippocampus, including the expression

of schizophrenia linked genes (Nrg1, ErbB4, Dtnbp1, Slc12a2) and corresponding proteins, as well as oxidative stress markers MDA and SOD, and global histone modifications.

Results: Molecular dysregulation in the poly(I:C) dorsal hippocampus was predominantly found at the pre-weaning time point (PD14), including changes to oxidative stress markers such as increased MDA activity in poly(I:C) offspring, and increased SOD in poly(I:C) females. There was also a dysregulation of global histone modifications at PD14 such as increased H3k27ac expression in poly(I:C) offspring and decreased H3k27me3 in female poly(I:C) offspring. This coincided with increased expression of GABAergic targets at PD14 including a main effect of poly(I:C) on Dtnbp1 and Slc12a2 mRNA expression and DTNBP1A and DTNBP1C protein expression. There was also increased ErbB4 mRNA and protein expression and NRG1 protein expression in poly(I:C) females. Molecular changes preceded behavioural deficits in poly(I:C) offspring such as decreased performance in NOR-L and reduced exploration during OFT. Offspring could be clustered based on behavioural phenotype, resulting in significantly more poly(I:C) offspring in deficit cluster in contrast to typical cluster. Although there were no changes significant changes to mRNA expression in poly(I:C) offspring at adulthood, when assessed according to cluster, the deficit cluster displayed increased expression of ErbB4 and Dtnbp1.

Discussion: We propose that MIA results in oxidative stress during the pre-weaning time point affecting mitochondrial function, which provides key metabolites required for epigenetic function and hence, results in global changes to histone modifications. This coincides with increased mRNA or protein expression of Nrg1, ErbB4, Dtnbp1 and Slc12a2, which are implicated in E/I balance through GABAergic synapse development. Future work is required to assess synaptic density within the MIA hippocampus. The use of unbiased clustering methods in this study allowed us to assess the molecular phenotype of offspring susceptible to poly(I:C) deficits, with deficit offspring exhibiting dysregulated mRNA expression, reminiscent to that observed in poly(I:C) offspring at PD14. Future research into the molecular mechanisms underlying resilience and susceptibility to MIA are important in the understanding of schizophrenia aetiology and in the identification of preventative targets.

S166. INTERPLAY BETWEEN EXCITATION-INHIBITION BALANCE, RANGE ADAPTATION AND AMOTIVATION SYMPTOMS IN SCHIZOPHRENIA: A COMBINED 1H-MRS, RESTING-STATE AND TASK-BASED FMRI STUDY

Lingling Wang^{*1}, Hui-xin Hu², Yi Wang³, Huang Jia², Huang Yi-hang², Xuan Wang³, Zhen-hua Zhu⁴, Hong-yan Sun⁴, Yuan Cai⁴, Wen-long Hou⁴, Gang Ye⁴, Zhao-peng Kang⁴, Simon S. Y. LUI⁵, Li Hui⁴, Raymond C. K. Chan³

¹Shanghai Normal University, ²Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; Department of Psychology, The University of Chinese Academy of Sciences, ³Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, ⁴Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University, ⁵The University of Hong Kong

Background: Excitation-inhibition (E/I) imbalance plays an important role in schizophrenia (SCZ) patients' amotivation symptoms. The specific pathway that links E/I imbalance with amotivation symptoms is yet fully clear. Range adaptation refers to representing a stimulus value as its relative place. It is associated with amotivation symptoms and correlated with E/I

imbalance. Range adaptation may underlie the relationship between E/I imbalance and amotivation symptoms. This study examined the interplay between excitation-inhibition balance, range adaptation related brain activity and amotivation symptoms in schizophrenia patients.

Methods: A total of forty-six SCZ patients and 37 healthy controls (HC) were recruited to undertake the resting-state brain scans to examine the range adaptation related ventral prefrontal cortex (vPFC) resting-state functional connectivity. A subgroup of 32 SCZ patients and 36 HC further undertook magnetic resonance spectroscopy (MRS) to measure E/I imbalance and another subgroup of 38 SCZ patients and 33 HC further underwent the Monetary Incentive Delay task-Adaptive version fMRI task.

Results: SCZ patients exhibited reduced E/I balance as compared to HCs. The vPFC connectivities were comparable between the two groups. However, during adaptation to expected value of reward, SCZ patients exhibited hypo-activation in the putamen and insula. Regarding the adaptation to expected value of loss, SCZ patients showed hyper-activation in the caudate. They also exhibited hypo-activation in the inferior frontal gyrus during adaptation to outcome value of reward. E/I balance was correlated with resting-state vPFC connectivity. Moreover, the vPFC connectivity and task-based brain activations were associated with amotivation symptoms in SCZ patients.

Discussion: Our results suggest that SCZ patients exhibit E/I imbalance. Range adaptation may link the E/I imbalance with amotivation symptoms in SCZ patients.

S167. A COMPARISON OF AUDITORY AND VISUAL EVENT-RELATED POTENTIALS IN TREATMENT RESISTANT AND ULTRA-TREATMENT RESISTANT SCHIZOPHRENIA

Andor Bodnár^{*1}, Yifan Mo², Claire McCaulley², Arlene Cuerdo², Lilian Zhong², Chloe Bethany², Malaka Harper², Jay Leonard², Frederick Nucifora², Christopher Ross², Russell Margolis²

¹*Johns Hopkins University School of Medicine*, ²*Department of Psychiatry, Johns Hopkins University School of Medicine*

Background: Approximately 30% of patients with schizophrenia do not respond to standard antipsychotic medicines (treatment-resistant schizophrenia, TRS), and of these, 30% or more do not respond to clozapine (ultra-treatment-resistant schizophrenia, UTRS). We hypothesize that UTRS patients will have diminished event-related potentials (ERPs) across multiple sensory modalities, reflecting sensory gating and attentional control deficits. We conducted electroencephalographic recordings to explore potential neural correlates distinguishing these patient categories.

Methods: To preliminarily test this hypothesis, task-induced changes in ERPs of UTRS (N = 7) and TRS (N = 11) patients, ascertained as part of a comprehensive phenotypic investigation of treatment responsiveness in schizophrenia, were measured using frequency and spatial auditory oddball and visual Stroop protocols. 32 electrodes were mounted in a fitted cap with a standard 10-20 layout. Electrodes on the cap were referenced to the electrode at the vertex (FCz). Average electrode impedance was LESS THAN 20 kΩ. The electroencephalography (EEG) data were sampled at 1000 Hz. In EEG preprocessing steps, electrodes were average referenced, and spherical interpolation was limited to 10-15% of electrodes. After epoch rejection, high (0.5 Hz) and low (60Hz) pass filtering was applied to the EEG data.

Results: In the frequency auditory oddball task, P200 (140-180ms) amplitude at central-parietal electrodes was diminished in UTRS compared to TRS, and negatively correlated with PANSS scores. In the spatial auditory oddball task, reorientation negativity response was significantly diminished in UTRS at left frontal electrodes. In the visual Stroop experiment, P300 amplitudes were reduced at central-parietal electrodes for both congruent and incongruent trials and were inversely correlated to PANSS scores.

Discussion: Taken together, these preliminary ERP findings suggest that deficits in sensory gating attention control, and attention reorientation may distinguish UTRS from TRS. The replicability of this result, and the extent to which the findings reflect the presence of symptoms or an underlying neurophysiologic difference between TRS and UTRS, remain to be determined.

This work was funded by T32MH015330, the Abramson Fund, and ABCD Charitable Trust.

S168. CLOZAPINE-INDUCED ALTERATIONS IN BRAIN STRUCTURE AND CONNECTIVITY IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA AND THEIR IMPACTS ON CLINICAL AND FUNCTIONAL OUTCOMES

Hyejin Sim^{*1}, Seoyoung Kim², Wi Hoon Jung³, Euitae Kim²

¹*Seoul National University*, ²*Seoul National University Bundang Hospital*, ³*Gachon University*

Background: Clozapine stands out as the sole effective antipsychotic for patients displaying inadequate response to treatment, suggesting its distinctive mechanism and different pathophysiology. In those with treatment-resistant schizophrenia (TRS) taking clozapine, volume reduction and disruption in functional connectivity have been reported. This study aims to investigate the longitudinal effects of clozapine treatment on brain structure and connectivity, exploring potential associations with various clinical and functional variables.

Methods: Patients diagnosed with schizophrenia who planned to start clozapine were recruited, and non-treatment-resistant schizophrenia (NTRS) were recruited as the control group. and they are prospectively investigated. T1-weighted and resting-state functional MRI data were obtained both before initiation and 18-weeks after the clozapine treatment. Longitudinal changes in gray matter and functional connectivity were evaluated. Measurement included serum levels of clozapine and nor-clozapine, concomitant antipsychotic doses, and assessments of clinical symptoms and cognitive performances pre- and post-clozapine treatment.

Results: Baseline comparisons between the treatment TRS and NTRS group, compared to treatment responders, showed altered striatal-cortico connectivity at baseline (before the clozapine treatment). After switching to clozapine, patients with treatment-resistant schizophrenia presented gray matter reductions in bilateral frontotemporal gyrus, and limbic areas (insula, putamen, caudate, cingulate gyrus) while no such changes were observed in the control group. Decreased functional connectivity was observed between the frontal gyrus and superior temporal gyrus (Heschl's gyrus, planum temporale) with no such changes observed in the control group.

Discussion: Clozapine treatment is associated with cortical/subcortical volume reductions, particularly affecting the mesolimbic dopamine pathway and its downstream regions, aligning with the dopamine hypothesis of schizophrenia. Additionally, group differences in connectivity alterations shows the effect of clozapine. decreased frontal functional connectivity to superior

temporal gyrus, crucial for auditory perception and language processing, potentially explain the observed diminished hallucination and/or language disruptions.

S169. TEMPORAL POLE, 'IMPENDING UNDERSTANDING' ASPECT OF ABERRANT SALIENCE, AND PSYCHOPATHOLOGY

Jun Miyata*¹, Yukako Nakagami², Shuraku Son², Yujiro Yoshihara², Toshiya Murai², Hidehiko Takahashi³

¹*Aichi Medical University*, ²*Kyoto University*, ³*Department of Psychiatry and Behavioral Sciences, Tokyo Medical and Dental University*

Background: The aberrant salience hypothesis (Kapur, 2003) postulates that a hyper-dopaminergic state in the midbrain-striatum causes heightened attribution of salience to ordinary stimuli, leading to the formation of delusion and hallucination. However, the exact neurobiological mechanisms of aberrant salience and delusion are unclear. Using resting-state functional magnetic resonance imaging (MRI) and the Aberrant Salience Inventory (ASI, Cicero et al., 2010), our previous study revealed region-specific functional connectivity between abnormal salience and the brain (manuscript in preparation by Nakagami et al.). In this study, we investigated the structural connectivity between gray matter and aberrant salience and its relevance to psychopathology.

Methods: We recruited 41 patients with schizophrenia and 67 healthy controls. We measured the intensity of subjective aberrant salience experience by using ASI, which consists of 29 items, and calculated scores of five subscales (increased significance, senses sharpening, impending understanding, heightened emotionality, and heightened cognition). We also rated psychopathology using the Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987) and calculated the negative, positive, excited, depressive, and cognitive factors (Lancon et al, 1998). T1-weighted MRI imaging data were acquired on a 3T scanner and were processed using a voxel-based morphometry pipeline, including segmentation, standardization, nonlinear-only Jacobian correction, and smoothing. Independent component analysis was applied to the resulting gray matter segment images, identifying 10 structural covariance networks (SCN) and calculating each subject's loading on these networks. Using these loadings as dependent variables, we performed multiple regression analyses with diagnosis, age, gender, and five subscales of ASI as explanatory variables, testing 1) the interaction between diagnosis and ASI and 2) the main effect of ASI. The significance level was set at $p < 0.05$ (FWE-corrected for network number, contrast number, and subscale number). When we found significant results, we then explored their correlation with the PANSS five factor scores. This study received approval from the Kyoto University Medical Ethics Committee, and participants provided written and verbal consent after receiving an explanation of the research.

Results: We observed a significant interaction between diagnosis and the "Impending Understanding" subscale of ASI for an SCN involving bilateral temporal poles, amygdala, and hippocampus ($p < 0.018$, FWE). Post-hoc analysis revealed a negative slope in healthy controls and a positive slope in patients. This subscale was correlated with the PANSS positive ($r=0.349$, $p=0.029$) and cognitive ($r=0.335$, $p=0.037$) factor scores.

Discussion: The association between the "Impending Understanding" subscale, which reflects a sense of profound meaning in familiar things, and the temporal pole, a neural correlate of semantic representation, supports the region-specificity of abnormal salience experiences. This association may also indicate the importance of aberrant salience for psychotic symptoms.

S170. DEVELOPING DANTE-PRESS, A SINGLE-SHOT MULTI-METABOLITE-SELECTIVE ¹H-MRS SEQUENCE, TO ACQUIRE ENDOGENOUS MEASUREMENTS OF GLU, GABA, GSH, AND NAA SIMULTANEOUSLY AT 7T

Kesavi Kanagasabai*¹, Lena Palaniyappan², Jean Théberge³

¹University of Western Ontario, ²McGill University, Douglas Mental Health University Institute; Western University, Robarts Research Institute, ³Lawson Health Research Institute, Department of Medical Biophysics, Western University, Robarts Research Institute

Background: Schizophrenia is described to be a complex network of abnormal concentrations of neurotransmitters such as gamma-aminobutyric acid (GABA), glutathione (GSH), and glutamate (GLU). Proton magnetic resonance spectroscopy (¹H-MRS), a non-invasive imaging modality, can quantify the chemical composition of a volume of interest in a living human brain to study metabolite levels. To date, no single-shot metabolite-selective ¹H-MRS pulse sequence has provided high-quality measurements of GLU, GABA, and GSH simultaneously. Currently, metabolite-selectivity is achieved by spectral editing or optimizing acquisition parameters. Both lead to 1) complex spectral modeling, 2) interference from neighboring metabolites, 3) reduced signal-to-noise ratio, 4) face a precision trade-off and 5) increased sensitivity to motion. Therefore, there is an unmet need to implement an effective technique to quantify GLU, GABA, GSH, and NAA precisely and simultaneously to properly investigate the pathophysiology of schizophrenia. One promising technique involves the use of an advanced ¹H-MRS pulse sequence known as Delays Alternating Nutation Tailored Excitation Point RESolved Spectroscopy (DANTE-PRESS). DANTE-PRESS uses a narrow-band radiofrequency pulse to selectively isolate the signal of a molecule of interest in the human brain spectrum. The use of a higher field strength scanner will increase the sensitivity of the measurements of all four neurotransmitters. The objective is to develop, test and validate DANTE-PRESS at 7 Tesla to isolate GLU, GABA, GSH, and NAA in a human brain.

Methods: To complete this, DANTE-PRESS was programmed within the software environment of the 7 Tesla MR scanner at Robarts Research Institute at Western University. An interactive user interface was created to allow users to adjust bandwidth, amplitude modulation, and other features of the pulse sequence in real time to isolate metabolites of interest. An inline display of adjustment loops, to generate accurate frequency profiles to avoid magnetization transfer between metabolites, is a work in progress. Phantoms and healthy volunteers have been scanned to refine scanning protocol for the novel sequence and assess qualitative performance of sequence – isolate metabolite(s) of interest and suppress unwanted signals.

Results: Since this is a novel sequence, there will be echo time phase and magnitude evolution of GLU, GABA, and GSH from 50-150ms. Qualitatively, double DANTE-PRESS was able to isolate metabolites of interest such as NAA, GSH, GABA, and GLU while suppressing unwanted signals in a multi-metabolite phantom and in vivo. To assess within session variability using the GLU-only phantom, GABA-only phantom, and NAA from a multi-metabolite phantom, the mean Cramer Lower Bounds (CRLB) were 0.012, 0.024, and 0.04 respectively. The mean %CRLB were 7.71%, 11.21% and 10.28% respectively. The % coefficient of variance were 18.08%, 9.49%, and 10.29% respectively. We were able to isolate GLU and NAA simultaneously using a multi-metabolite phantom where the mean CRLB, mean % CRLB, and the %CV were 0.04, 10.28%, and 10.29% respectively. Furthermore, DANTE-PRESS can effectively suppress remaining water signal such that water suppression is not required.

Discussion: DANTE-PRESS could provide precise measurements of GLU, GABA, GSH, and NAA to assess disorders affecting excitation/inhibition balance and oxidative stress. Future work involves performing test-retest data in humans. This can be used towards planning a cross-sectional study in schizophrenia.

S171. EXPLORING THE LINK BETWEEN RESTING-STATE FUNCTIONAL CONNECTIVITY AND HEART RATE VARIABILITY IN SCHIZOPHRENIA AND HEALTHY CONTROLS: A COMPARATIVE ANALYSIS

Harsh Pathak*¹, Srinivas Balachander¹, Vanteemar S Sreeraj¹, Swarna Buddha Nayok¹, Bridgit Kaniparambil¹, Chithra Uppinkudru¹, Ketaki Maity¹, Kiran Bagali¹, Makarand Pantoji¹, Nathiya Ezhumalai¹, Rajkumar Krishnamoorthy¹, Rujuta Parlikar¹, Sachin Reddy¹, Saranya Haribabu¹, Vyoma Shah¹, Ashok Jammigumpula², Jithin T Joseph², Manul Das³, Subham Samantaray³, Abhiram Narasimhan purohith², Chandramouli Roy³, Sonia Shenoy², Umesh Shreekantiah³, Samir kumar Praharaj², Nishant Goyal³, Urvakhsh M Mehta¹, Muralidharan Kesavan¹, Jagadisha Thirthalli¹, Ganesan Venkatasubramanian¹

¹National Institute of Mental Health and Neurosciences (NIMHANS), ²Kasturba Medical College (KMC), ³Central Institute of Psychiatry (CIP)

Background: Individuals diagnosed with schizophrenia (SCZ) exhibit symptoms that are associated with aberrant autonomic functioning. Recently, it has been proposed that these dysfunctions play a role in both the onset and exacerbation of auditory verbal hallucinations (AVH). The posterior insula is a key region involved in the processing of interoceptive signals received from autonomic afferents via the posterolateral thalamus. The interoceptive inference theory proposes that the emergence of AVH is linked with prediction error in interoceptive signals, which results in a consistently low-grade arousal state. Studies have shown that a transient increase in arousal state, indicated by reduced RMSSD (root mean square of successive differences between normal beats), is linked with exacerbation of AVH. Other studies have found activation of the insula just before and during AVH. Thus, the dysfunction of the Insula, along with the left temporoparietal junction (TPJ), is implicated in AVH. This association underscores the intricate link between irregularities in autonomic functioning, such as abnormality in heart rate variability (HRV), and the emergence of auditory verbal hallucinations in SCZ. We aim to examine the relationship between the association of HRV measures with the resting state functional brain connectivity between the left TPJ and the insular cortex in SCZ with persistent AVH and healthy controls (HC).

Methods: We analyzed 70 subjects (SCZ - 43, HC - 27, age and gender-matched) for whom HRV data was available. Resting-state functional magnetic resonance imaging (rs-fMRI) was available for 63 subjects (SCZ- 37, HC- 26). rs-fMRI data was pre-processed using fMRIPrep; motion correction was done using aCompCor, and atlas-based connectivity matrices for the Brainnetome regions were derived using ENIGMA-HALFPipe. Our regions of interest included the left TPJ (A41/42), and six sub-regions within the left insular gyrus (dorsal agranular insula, dorsal dysgranular insula, dorsal granular insula, hypergranular insula, ventral granular insula, dorsal agranular insula and ventral granular insula). A 12-minute resting electrocardiogram (ECG) was performed, with the outcome measure for heart rate variability (HRV) being the (RMSSD), calculated through the LabChart software. Regression models were used to examine the relationship between the connectivity of the TPJ with each insular sub-regions, adjusting for age, gender, and diagnosis.

Results: RMSSD was significantly lower in the SCZ group as compared to HC ($d=-0.53$, $p=0.05$). Functional connectivity (FC) of left TPJ was found to be significantly lower with the left hypergranular insula (HI) ($d=-0.17$, $p_{\text{FWE}}= \text{LESS THAN } 0.001$) and the left dorsal granular insula (DGI) ($d= -0.12$, $p_{\text{FWE}}=0.03$). The interaction of FC between the left TPJ and the left DGI and group was significantly associated with the RMSSD ($F=4.592$, $p=0.037$), though the effect of the group alone was not significant.

Discussion: We demonstrate a significant difference in RMSSD and functional connectivity of the left TPJ with left posterior insular subregions in SCZ compared to HC. Moreover, it also highlights the relationship between resting state connectivity of the left TPJ with left posterior insular subregions and the measure of autonomic tone (i.e., HRV). Further studies with a larger sample size may be needed to understand the relationship between the functional connectivity of Left TPJ with the left posterior insula and HRV measures in SCZ. Exploring these may reveal the abnormalities in interoception and enhance our understanding of the underlying mechanisms in the pathophysiology of AVH in SCZ.

S172. MISMATCH NEGATIVITY INDICES AS A PROGNOSTIC FACTOR FOR REMISSION IN SCHIZOPHRENIA

Young-Joon Kwon^{*1}, Won-Myong Bahk², Bo-Hyun Yoon³, Kwanghun Lee⁴, Moon Doo Kim⁵

¹Soonchunhyang University Chunan Hospital, ²Yeouido St. Mary's Hospital, The Catholic University of Korea, ³Naju National Hospital, ⁴Department of Psychiatry, College of Medicine, Dongguk University, ⁵School of Medicine, Jeju National University

Background: Mismatch negativity (MMN) is known to be associated with neuro-social cognition and functional outcomes. Remission and recovery rates are related to the neuro-social cognition of patients with schizophrenia. The present study explored the relationship of MMN with remission in patients with schizophrenia.

Methods: Forty patients with schizophrenia were recruited and divided into two groups, with or without remission, according to the Remission in Schizophrenia Working Group criteria (RSWGcr). Symptom severity (PANSS), cognitive function, functional outcome, and MMN of the patients were evaluated. A regression analysis was used to identify the factors that significantly predicted symptom improvement and remission including MMN at frontal site assessed at baseline, and anticipated clinical variables as predictive factors.

Results: MMN amplitudes in frontal sites were further decreased in the groups without remission compared to the groups with remission. MMN amplitude was significantly correlated with measures of symptom change and functional outcome measurements in patients with schizophrenia. Regression analysis revealed that symptom severity and MMN significantly predicted remission in patients with schizophrenia. Symptom improvement significantly predicted PANSS at baseline, illness duration, and antipsychotic dose, as did MMN amplitude at frontal site.

Discussion: Our results suggest that MMN reflected symptom improvement and remission in patients with schizophrenia. MMN indices appear to be promising candidates as predictive factors for schizophrenia remission.

S173. STRIATAL-CEREBELLAR FUNCTIONAL CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

Xuan Wang^{*1}, Xiao-dong Guo², Xin-lu Cai³, Yi-jing Zhang⁴, Bing-jie Huang⁵, Yi Wang⁶, Cheng-cheng Pu⁵, Xin YU⁷, Raymond C.K. Chan⁸

¹University of Chinese Academy of Sciences, ²Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; University of Chinese Academy of Sciences, ³Institute of Psychology, Chinese Academy of Sciences; Sino-Danish College, University of Chinese Academy of Sciences, ⁴Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; Department of Psychology, the University of Chinese Academy of Sciences, ⁵Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, China, ⁶Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, ⁷Institute of Mental Health, Peking University, ⁸Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences

Background: Impairment of motivation is one of the core negative symptoms of schizophrenia (SCZ). The Cortico-Cerebellar-Thalamic-Cortical (CCTC) Circuit model posits that dysconnectivity between the cerebellar and cerebral regions may underlie the manifestation of amotivation symptoms. However, there is a dearth of studies to support such a claim. This study aimed to test this model through resting-state functional connectivity. We hypothesized that patients with SCZ would show reduced functional connectivity between cerebellar regions and cerebral reward regions compared to healthy controls (HC), and this impairment would be associated with amotivation symptoms in SCZ.

Methods: Sixty-two patients with SCZ meeting the DSM-IV criteria were recruited from Peking University Sixth Hospital and 61 age- and gender-matched HC were recruited from the nearby community. Negative symptoms of patients were assessed using the Scale for the Assessment of Negative Symptoms (SANS). All the participants undertook resting-state fMRI (rsfMRI) scan inside a 3T GE Medical Systems scanner. The rsfMRI data was preprocessed using fMRIPrep, and denoised with CONN. Both theory-driven and data-driven functional connectivity analyses were performed: (1) Driven by CCTC model, cerebral reward regions (i.e., bilateral ventral striatum, caudate, putamen, orbitofrontal cortex, dorsal lateral prefrontal cortex, anterior cingulate cortex), transit regions (i.e., bilateral thalamus and ventral tegmental area), and Buckner's cerebellar 7 networks were taken as regions of interest (ROIs). Group comparisons and symptom-related analyses were performed on ROI-to-ROI functional connectivity. (2) The data-driven analyses were performed based on intrinsic network. Intrinsic network represents a measure of whole-brain centrality at each voxel, defined as the root mean square of correlation coefficients between each individual voxel and all of the voxels in the brain. By applying a general linear model on intrinsic networks, we identified regions whose whole-brain centrality was significantly associated with symptoms. These regions were then used for subsequent ROI-to-voxel connectivity analysis.

Results: Based on the theory-driven analyses, we identified significant decreases in connectivity between the left attention network of the cerebellum and the bilateral putamen in SCZ patients after FDR correction. Besides, SCZ patients also exhibited lower functional

connectivity between the thalamus and caudate. Regarding the data-driven analysis of intrinsic networks, we found that the severity of avolition of SCZ could negatively predict the global centrality of the cerebellar vermis VII region. After extracting the whole-brain connectivity maps of vermis VII, significant between-group differences were observed in bilateral putamen. Moreover, the connectivity between the left putamen and vermis VII was found to be negatively correlated with avolition symptoms in patients with SCZ.

Discussion: Convergent findings from both theory-based and data-driven analyses suggest a reduced dorsal striatal-cerebellar functional connectivity in SCZ. The connection between vermis VII and left putamen was negatively associated with amotivation symptoms in SCZ. These findings support the CCTC model and shed light onto the neural pathophysiology underpinning amotivation in SCZ, and pave way towards improving clinical diagnosis and treatment of related symptoms.

S174. BRAIN-BEHAVIOR PARTICIPANT SIMILARITY NETWORKS AMONG YOUTH AND ADULTS WITH SCHIZOPHRENIA SPECTRUM, AUTISM SPECTRUM, OR TYPICALLY DEVELOPING CONTROLS

Maria Secara*¹, Prashanth Velayudhan², Lauren Lauren Erdman², Lindsay Oliver³, Ju-Chi Yu³, George Foussias³, Erin Dickie¹, Meng-Chaun Lai⁴, Anil Malhotra⁵, Robert W. Buchanan⁶, Aristotle N. Voineskos¹, Stephanie H. Ameis³, Colin Hawco¹

¹*Centre for Addiction and Mental Health, University of Toronto*, ²*Hospital for Sick Children*, ³*Centre for Addiction and Mental Health*, ⁴*Centre for Addiction and Mental Health*, ⁵*Zucker Hillside Hospital*, ⁶*Maryland Psychiatric Research Center, University of Maryland School of Medicine*

Background: Autism spectrum disorder (ASD) and schizophrenia spectrum disorder (SSD) display heterogeneity in brain function and exhibit social cognitive deficits which strongly predict functional outcomes. The objective of the present study was to integrate multiple brain imaging phenotypes and behavioral measures to identify new brain-behavior subgroups across these disorders.

Methods: Multi modal structural MRI, functional MRI, social cognitive and neurocognitive data from 106 SSD, 59 ASD, and 118 controls were examined using meta-similarity network fusion (metaSNF). Meta SNF identifies common patterns of similarity across data types and applies spectral clustering to identify biotypes, iterating models with differing parameters (e.g. including different data types). Left-out Birchwood Social Functioning Scale (BSFS) and Interpersonal Reactivity Index (IRI) were used to identify biotypes with clinically meaningful differences in social function and outcomes.

Results: The top clustering solution identified four transdiagnostic data-driven groups, with between-cluster separation on both BSFS ($p=0.00165$) and IRI ($p=0.00643$), driven by social cognition and cortical surface area. Social cognitive scores and surface area (precuneus, superior frontal, insula, superior temporal, and medial orbitofrontal) comprised the top ten contributing model features driving participant similarity and differences between the groups. A post-hoc analysis revealed between-network resting-state functional connectivity differences in the default mode, dorsal attention, somatomotor, salience, limbic, and visual networks.

Discussion: Our findings open the possibility of studying new data-driven groups that represent individuals with SSD and ASD more similar to each other than compared to traditional diagnostic groups. This has the potential to progress disease subtyping to target

specific neural circuitry among participant subgroups for treatment innovation and support current efforts which aim to expand beyond DSM-based diagnostic groups into transdiagnostic biologically based diagnoses.

S175. CONSTRUCTING THE METABOLIC CONNECTOME BASED ON HIGH-RESOLUTION SPECTROSCOPIC IMAGING TO IMPROVE EARLY DETECTION OF YOUTH AT CLINICAL HIGH RISK

Federico Lucchetti*¹, Edgar Céléreau¹, Martine Cleusix¹, Alessandra Solida², Jean-Baptiste Ledoux¹, Luis Alameda¹, Marco Armando¹, Kerstin von Plessen¹, Philippe Conus¹, Patric Hagmann¹, Paul Klauser¹

¹Lausanne University Hospital and University of Lausanne, ²Centre Neuchâtelois de Psychiatrie

Background: Only a minority of youth identified with a clinical high risk (CHR) state will experience a first psychotic episode and potentially develop schizophrenia (i.e., approximately 20% over two years). Moreover, non-transition to psychosis does not equate to recovery, as less than half of CHR individuals fully recover (i.e., 40% over two years), with many developing other mental disorders like mood disorders. The challenge for clinicians and researchers lies in accurately identifying CHR individuals truly at risk of psychosis or other mental disorders, a crucial step in enhancing early detection and tailoring interventions for youths seeking mental health care. In the pursuit of biomarkers for CHR, neuroimaging studies, while significant, have faced challenges likely due to the subtle and diverse nature of cerebral alterations in the early stages of psychosis. Recent advancements in whole-brain MR spectroscopic imaging (MRSI) offer a solution to address those challenges. Despite facing issues such as limited spatial resolution, suboptimal signal quality for myo-inositol, and extended acquisition times, the latest developments have facilitated the use of 3D high-resolution MRSI techniques whereby enabling comprehensive mapping of brain metabolites with an isotropic resolution of 5mm across the entire brain. The overarching goal of the project is to create a "metabolic connectome" for each individual's brain, based on inter-regional metabolic concentration similarities derived from MRSI. The hypothesis is that brain network analysis (connectomics) of this metabolic connectome will unveil new biomarkers associated with early and subtle changes in CHR. This approach is promising as it takes into account network effects and considers the relationships between brain regions rather than focusing solely on local alterations, which can be highly heterogeneous across individuals and scanning sites.

Methods: In this longitudinal study, MRI brain scans and clinical data have been collected from 42 CHR individuals and 20 matched healthy controls (HC) since 2018 in Lausanne. The MRI protocol included structural, diffusion resting-state functional MRI and MRSI. Metabolite concentrations (i.e. N-acetylaspartate + N-acetyl aspartylglutamate (tNAA), creatine + phosphocreatine (tCre), choline moiety metabolites (Cho), myo-inositol (Ins), and glutamate + glutamine (Glx)) in each voxel were estimated using LCModel with water signal as reference. We relied on pertinent network-based metrics encompassing the pair-wise connectivity matrix based on the Pearson Correlation Index.

Results: First, we show the feasibility of generating stable metabolic similarity matrices from MRSI data in CHR and HC. For each individual, we generated a pair-wise connectivity matrix based on Pearson correlations of metabolites between brain regions. Then, we tested the stability of the generated connectivity matrices. Last, we demonstrate the feasibility of generating a metabolic connectome from the metabolic similarity matrices. We described the topological properties of the metabolic connectome and compared them with natural networks.

Discussion: We present here the first steps of the construction of a metabolic connectome using whole-brain high-resolution MRSI data. From a technical perspective, this project is pioneering, utilizing MRSI data to establish a metabolic connectome. From a neuroscience standpoint, the sensitivity afforded by mapping brain metabolites, coupled with the inter-regional similarity approach, is expected to identify early and subtle brain alterations in CHR. If successful, this method may aid in identifying youths who stand to benefit the most from early intervention.

S176. SYNAPTIC TERMINAL DENSITY AND AMPLITUDE OF LOW FREQUENCY FLUCTUATIONS IN SCHIZOPHRENIA: A RESTING STATE FMRI AND [11C]UCB-J PET STUDY

Ekaterina Shatalina^{*1}, Ellis Chika Onwordi², Thomas Whitehurst³, Alexander Whittington⁴, Ayla Mansur⁴, Atheeshaan Arumham⁵, Tiago Reis Marques⁵, Roger Gunn⁴, Sridhar Natesan⁵, Matthew Nour⁶, Eugenii Rabiner⁴, Matthew Wall⁴, Oliver Howes⁵

¹King's College London, Institute of Psychiatry, ²Bart's and The London School of Medicine, Queen Mary University of London, ³MRC London Institute of Medical Sciences, Imperial College London, ⁴Invicro, ⁵Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁶Max Planck University College London Centre for Computational Psychiatry and Ageing Research, University College London; Department of Psychiatry, Oxford University

Background: Amplitude of Low Frequency Fluctuations (ALFF) measured during resting state functional Magnetic Resonance Imaging (fMRI) is significantly altered in schizophrenia. Previous work showed that fractional ALFF is related to synaptic terminal density, as measured by [11C]UCB-J Positron Emission Tomography (PET) in healthy controls and that schizophrenia is associated with lower [11C]UCB-J binding. Given that Blood Oxygen Level Dependent (BOLD) contrast measured during fMRI has a synaptic origin, we set out to explore if aberrant ALFF in schizophrenia may be related to differences in synaptic terminal density.

Methods: 22 participants with schizophrenia (unmedicated, mean age $\pm$ SEM 26.65 $\pm$ 1.59 years, mean age of symptom onset 23.8 $\pm$ 1.87 years) and 15 healthy control subjects (mean age $\pm$ SEM 34.87 $\pm$ 3.40 years) underwent a [11C]UCB-J PET scan and an 8-minute resting state fMRI scan. Voxel-wise kinetic modelling of [11C]UCB-J was carried out using the 1-tissue compartment model to produce volume of distribution values, with the centrum semiovale then used as a reference region to produce distribution volume ratios (DVRs). FMRI data were pre-processed using standard methods. ALFF measures were derived using the AFNI 3dRSFC module from data in the 0.01-0.1Hz frequency range and normalized to Z-scores. Second-level analyses compared ALFF between groups at the whole-brain level and were carried out using the FSL FLAME-1 module (Z GREATER THAN 2.3, cluster threshold of p LESS THAN 0.05).

Group differences in ALFF were used as regions of interest (ROIs) to extract ALFF Z-scores and [11C]UCB-J DVRcs values for each subject. Pearson's correlations were used to test relationships between the ALFF Z-scores and [11C]UCB-J DVRcs in each group. Exploratory analyses included whole-brain voxel-wise Pearson's correlations in each group, where resultant r-coefficients were transformed to z-scores and thresholded at Z GREATER THAN 2.3 and cluster threshold of p LESS THAN 0.05 to identify significant correlation clusters in the data.

Results: Compared to controls, the schizophrenia group had significantly higher ALFF in frontal cortical regions, the anterior cingulate and the caudate (Z GREATER THAN 2.3, cluster p LESS THAN 0.05). In this ROI, [11C]UCB-J DVRcs was comparable between the groups and there were no significant associations between ALFF Z-statistics and [11C]UCB-J DVRCS in either group (schizophrenia $r=0.179$, $p=0.425$; controls $r=0.309$, $p=0.244$). Exploratory analyses showed significant correlations between ALFF and [11C]UCB-J DVRcs in the control group in regions spanning the putamen, insular cortex, precentral gyrus, angular gyrus, cerebellum and occipital cortex. In schizophrenia significant correlations were seen in the bilateral dorsolateral prefrontal cortex. Whole-brain comparison of correlation-coefficients showed significant differences in r-values between groups across all brain regions.

Discussion: We report a group difference in ALFF in schizophrenia that is in line with published meta-analyses. Our data suggests these differences in ALFF are not related to synaptic terminal density. Exploratory analyses suggest the relationship between resting state brain function and synaptic terminal density is complex and altered in schizophrenia. Further work should focus on testing whether excitation-inhibition imbalance may be contributing to aberrant ALFF in schizophrenia.

S177. COGNITIVE DEFICIT IN PSYCHOSIS: LINKS TO HIPPOCAMPAL SUBFIELDS AND PREFRONTAL SUBREGION VOLUMES

Simon Evans^{*1}, Erkan Alkan², Veena Kumari³

¹University of Surrey, ²University of Surrey, ³Brunel University

Background: Cognitive impairments undermine functional capacity for most patients with schizophrenia, they are persistent and largely unresponsive to treatment. Thus, understanding their neural substrates is important but the literature is inconsistent. Here, we focus on elucidating the role of hippocampal subfields (in relation to memory task performance), and the role of prefrontal subregions (in relation to executive function) so as to provide more detailed insights into structure-function relationships as compared to previous work. A well-matched control group allowed us to determine whether these relationships are unique to patients.

Methods: The sample included 57 SZH and 32 age and gender-matched healthy controls. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) and all participants underwent a T1 MRI scan. Various standard memory and executive (Stroop, Wisconsin Card Sorting Test (WCST)) were administered. Brain volumes were derived using Freesurfer and a region of interest analysis (encompassing hippocampal subfields and prefrontal subregions) was conducted to assess correlations with the relevant cognitive performance measures, and PANSS scores.

Results: Reduced brain volumes were observed in the SZH group, for most of the regions under study. In SZH, after FDR correction, volumes in middle frontal regions showed a

relationship with WCST category and non-perseverative errors. Stroop performance correlated with superior frontal, middle frontal, anterior cingulate and certain ventrolateral prefrontal subregion volumes. Memory task performance was seen to correlate with volumes within specific hippocampal subfields. These relationships were only seen in SZH, not the control group. No correlations with symptom severity were observed within any of the regions of interest.

Discussion: Results point to links between specific prefrontal subregions (particularly middle frontal and superior frontal) and executive function in SZH, as well as the role of specific hippocampal subfields in relation to memory performance. These were not observed in controls, suggesting they are unique to patients. Further, no correlations were observed in relation to symptoms, suggesting they reflect mechanisms at least somewhat independent of general disease severity. These results provide important novel insights and adds detail to the literature, as it is the first investigation into the role of prefrontal subregions and hippocampal subfields, based on a single sample with a well-matched control group, using a comprehensive battery of cognitive tasks.

S178. EXPLORING MYO-INOSITOL DISTRIBUTION AS A BIOMARKER OF ASTROCYTIC ACTIVATION IN PATIENTS AT RISK FOR PSYCHOSIS: A PILOT STUDY

Edgar Celereau*¹, Daniella Dwir¹, Martine Cleusix², Jean-Baptiste Ledoux³, Zoé Schilliger¹, Pascal Steullet¹, Marco Armando⁴, Alessandra Solida⁵, Luis Alameda², Philippe Conus², Kerstin Jessica Plessen⁴, Patric Hagmann³, Paul Klauser¹

¹Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital (CHUV), ²Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), ³Service of Diagnostic and Interventional Radiology, Department of Medical Radiology, Lausanne University Hospital (CHUV), ⁴Service of Pedopsychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), ⁵Department of Adults Psychiatry II, Centre Neuchâtelois de Psychiatrie (CNP)

Background: Astrocytes are actively engaged in inflammatory responses, regulation of redox states, and the reuptake of glutamate, which are all pathophysiological nodes previously underscored in research on psychosis. These cells can manifest an "activated" state characterized by heightened pro-inflammatory status. Consequently, reactive astrocytes may exert a significant and early influence on the pathological mechanisms contributing to the onset of psychosis.

Myo-inositol (MI) is a key brain metabolite, mainly regulated by astrocytes, which was found to be increased concomitantly with the presence of reactive astrocytes. Interestingly, meta-analyses demonstrated heightened MI concentrations in individuals diagnosed with psychosis or at risk for psychosis, suggesting a link between activated astrocytes and the disease. The in vivo and non-invasive detection of MI is made feasible through proton magnetic resonance spectroscopy. While the development of whole-brain MR spectroscopic imaging (MRSI) has been underway for 15 years, it was constrained by limitations in spatial resolution, suboptimal signal quality for myo-inositol, and prolonged acquisition times. Notably, a recent promising 3D high-resolution MRSI technique enables comprehensive brain metabolite mapping with a 5mm isotropic resolution across the entire brain (Klauser et al, 2022). We propose the first pilot

study to assess MI in the whole brain of subjects at clinical high risk for psychosis (CHR-P) and healthy controls. The aim of this pilot study is to develop the use of MI measurement in the brain as a biomarker of astrocytic activation in psychosis.

Methods: CHR-P patients and healthy controls were recruited from the Lausanne Psychosis Cohort (33 patients including 9 women, 13 controls including 5 women). Patients were clinically evaluated with the SPI-A/SPI-CY (Schizophrenia Proneness Instrument for Adult or Child/Adolescent) and the SIPS (Structured Interview for Prodromal Syndroms), and all participants were assessed with the Global Assessment of Functioning (GAF) scale. Participants underwent T1-weighted anatomical and MRSI brain scans on a 3T MRI scanner. Metabolic maps were generated with water signal as reference, aligned to the anatomical images and registered in standard space. A voxel-based analysis was performed on the whole brain (gray and white matter) and corrected with a non-parametric cluster-based approach. Clusters were considered significant with a corrected p-value LESS THAN .05. Participants also underwent measurement of a blood inflammatory marker (i.e., sRAGE) in the plasma using an ELISA kit.

Results: We found an association between increased MI concentration in gray matter and altered global functioning in the whole sample as well as in the group of patients. Increased MI concentration in the postcentral gyrus was also associated with the severity of negative symptoms in CHR-P patients. Last, in the significant regions where MI was elevated in the precedent analyses, we found that an increased MI concentration correlated with an increased inflammatory biomarker (sRAGE).

Discussion: These pilot findings suggest the presence of reactive astrocytes in CHR-P patients, especially in those with a low level of functioning. The relatively small sample size / relative lack of statistical power could hinder significant results in group comparisons, and for the correlations with other symptom categories. The association between MI concentration and blood sRAGE also supports the presence of an astrocyte reactivity, which may represent a biomarker and a target for psychosis.

S179. ENHANCED SLOW-FREQUENCY ENTRAINMENT IN PATIENTS WITH SCHIZOPHRENIA – A PARALLEL EEG AND OPM-MEG STUDY

Marion Brickwedde*¹, Fabian Symanowski¹, Tineke Grent-'t-Jong¹, Paul Anders², Peter Krüger², Tilmann Sander², Peter Uhlhaas¹

¹Charité Berlin, Germany, ²PTB, Berlin, Germany

Background: Schizophrenia (ScZ) has been associated with aberrant sensory information processing which can be investigated with psychophysical and electrophysiological methodologies, such as rhythmic sensory stimulation, eliciting steady-state responses (SSRs). Prior research has observed reduced high-frequency visual SSRs in ScZ patients, while findings concerning SSRs at lower frequencies (LESS THAN 10 Hz) remain inconclusive (Krishnan et al., 2005. Clin Neurophysiol.) To further investigate the nature of SSR impairments in ScZ, we employed optically pumped magnetometers (OPMs) in conjunction with EEG to capture visual SSRs at 7.5 and 10 Hz stimulation. OPMs are novel MEG-sensors, which can be applied directly onto the scalp without helium cooling, potentially offering superior signal-to-noise as well as localization accuracy when compared to conventional SQUID-MEG and EEG methods (Brookes et al., 2023; Trends Neurosci.).

Methods: For this study, 20 ScZ-patients as well as 20 age- and gender- matched healthy controls (HCs) were recruited. Visual SSRs were elicited by reversing checkerboard patterns either at 7.5 Hz or at a 10 Hz frequency (total = 100 trials per condition). To control for attention, participants were asked to respond to rare stimuli of one specified colour with a button press. Measurements took place in a magnetically shielded room employing a 56-electrode EEG-system and a 22-channel OPM system. OPM sensors were distributed over occipito-parietal sites. SSRs were analysed using time- as well as frequency decomposition and inter-trial phase coherence (ITPC) measures. Significance was tested using a cluster-based permutation approach.

Results: We observed significantly increased SSRs for both 7.5 and 10 Hz stimulation in ScZ patients compared to the HC group in ITPC analyses. Intriguingly, in the baseline-corrected power spectrum, condition differences between stimulation frequencies were only observable in the HC group. Moreover, within the ScZ group, the presence of ~3-7 Hz activity was observable when stimulating at 10 Hz, which was absent in the HC group. Finally, SSR responses in patients with ScZ were very focal, predominantly measured by a singular lateral occipital sensor, contrasting with the broader distribution of SSR responses across parietal sensors observed in the healthy controls (HCs).

Discussion: Patients with ScZ showed increased SSR responses to 7.5 Hz and 10 Hz stimulation. Importantly, these effects diminished when power-values were baseline-corrected, indicating a potential continuation of entrainment beyond the stimulation period. SSR responses are indicative of cortical excitability (Brickwedde et al., J. Neurosci. Methods) and activity in the theta- (~3 – 8 Hz) and alpha- (~8 – 12 Hz) range to inhibitory processes (Köster et al., 2018. Sci Rep.; Jensen et al., 2014. Trends Neurosci.). Accordingly, heightened responses to rhythmic stimulation within these frequencies could reflect heightened excitability of inhibitory networks. These networks are believed to modulate information processing conveyed by high-frequency activity (Bonnefond et al., 2017. ENeuro). Therefore, an increased activity within these slow-rhythm inhibitory networks would align with the observation of decreased SSR responses to higher frequency stimulation.

S180. SYNAPTIC TERMINAL DENSITY EARLY IN THE COURSE OF SCHIZOPHRENIA: A UCB-J POSITRON EMISSION TOMOGRAPHIC IMAGING STUDY

Ellis Chika Onwordi^{*1}, Thomas Whitehurst², Ekaterina Shatalina³, Richard Carr⁴, Ayla Mansur⁵, Atheeshaan Arumham⁴, Martin Osugo⁴, Ben Statton⁶, Elaine Berry⁶, Marina Quinlan⁶, Declan O'Regan⁶, Tiago Reis Marques⁷, Sameer Jauhar⁸, Susham Gupta⁹, Ravi Mehrotra¹⁰, Eugenii Rabiner¹¹, Roger Gunn⁵, Sridhar Natesan⁴, Oliver Howes¹²

¹Bart's and The London School of Medicine, Queen Mary University of London, ²Robert Steiner MRI Unit, Imperial College London, ³Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, London, UK, ⁴Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁵Department of Brain Sciences, Imperial College London, ⁶Institute of Clinical Sciences (ICS), Faculty of Medicine, Imperial College London, ⁷Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, ⁸Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College, ⁹Early Detection and Early Intervention, East London NHS foundation Trust, ¹⁰Early Intervention in Psychosis Team, West Middlesex University Hospital, West London NHS Trust,

¹¹*Center for Neuroimaging Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London; Imanova Ltd., Centre for Imaging Sciences, Hammersmith Hospital,*
¹²*Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London*

Background: The hypothesis that excessive synaptic elimination underlies schizophrenia pathogenesis has been highly influential. Supporting this, there is evidence for large and widespread deficits in the uptake of [11C]UCB-J, a marker of synaptic terminal density, in patients with chronic schizophrenia compared to healthy volunteers. Moreover, the normal relationship between synaptic terminal density and glutamate levels seen in healthy controls is not present in patients with chronic schizophrenia, suggestive of lower glutamatergic terminal density in chronic schizophrenia. However, it is unclear if these differences are present at the onset of illness in unmedicated patients. Here, we used multimodal imaging to address these questions. First, we investigated [11C]UCB-J uptake in antipsychotic-naïve/free patients with schizophrenia recruited from first-episode services (FE-SCZ) and healthy volunteers (HV). Second, we explored whether SV2A levels are related to markers of glutamatergic function in FE-SCZ and HV groups.

Methods: Forty-two volunteers (FE-SCZ n=21, HV n=21) underwent [11C]UCB-J positron emission tomography to index grey matter [11C]UCB-J volume of distribution (VT) and distribution volume ratio (DVR). Our primary analysis tested for group differences in VT in the frontal cortex (FC), anterior cingulate cortex (ACC) and hippocampus. Exploratory analyses tested for group differences in DVR, and in VT in other brain regions. To adjust for [11C]UCB-J plasma-free fraction (fp), we also tested for differences in VT/fp. In addition, volunteers underwent proton magnetic resonance spectroscopy, estimating creatine-scaled glutamate (Glu/Cr) and glutamate+glutamine (Glx/Cr) in the anterior cingulate cortex (ACC) and left hippocampus. We collected clinical data including PANSS score.

Results: Repeated measures ANOVA revealed a significant region ($F_{2,40}=609.4$, $p < 0.0001$) but not group effect ($F_{1,20}=0.09$, $p=0.77$) on [11C]UCB-J VT. There were no significant group differences in mean [SEM] VT in the FC (HV=19.63 [0.65], FE-SCZ=20.01 [0.65], $t=0.41$, $p=0.69$, Cohen's $d=0.1$), ACC (HV=22.37 [0.70], FE-SCZ=22.37 [0.62], $t=0.004$, $p=1.00$, $d=0.0$), or hippocampus (HV=15.04 [0.50], FE-SCZ=15.46 [0.42], $t=0.65$, $p=0.52$, $d=0.2$). Exploratory analyses revealed significantly lower ACC VT/fp (HV=91.71 [1.93], FE-SCZ=83.79 [2.70], $t=2.38$, uncorrected $p=0.02$, $d=0.7$) and temporal lobe DVR (HV=3.72 [0.11], FE-SCZ=3.35 [0.13], Kolmogorov-Smirnov $Z=1.54$, uncorrected $p=0.02$, $d=0.7$) in the FE-SCZ group. PANSS total score was inversely associated with hippocampal VT in the FE-SCZ group ($r=-0.48$, $p=0.03$). There were no significant group differences in Glu/Cr or Glx/Cr in the ACC or left hippocampus ($p > 0.05$). [11C]UCB-J DVR was significantly positively associated with Glu/Cr in the HV group (ACC: $r=0.46$, $p=0.048$; left hippocampus: $r=0.67$, $p=0.002$) but not FE-SCZ group ($p > 0.05$ in both regions). [11C]UCB-J DVR was significantly positively associated with Glx/Cr in the ACC in the HV group ($r=0.66$, $p=0.002$) but not FE-SCZ group ($p > 0.05$), and there were no significant DVR-Glx/Cr associations in either group in the left hippocampus ($p > 0.05$).

Discussion: These findings indicate that large differences in synaptic terminal density are not present early in the course of schizophrenia, but there may be subtler effects in the temporal lobe and ACC, and lower hippocampal synaptic terminal levels are linked to greater symptom severity. Moreover, they show that the normal relationship between glutamate and synaptic terminal density is lost in vivo early in the course of schizophrenia. When taken with prior in vivo evidence of lower VT in patients with chronic illness, this may suggest synaptic density

changes during the course of schizophrenia, potentially resulting in lower levels of glutamatergic terminals and/or a lower glutamatergic-to-GABAergic terminal ratio.

S181. THE AMYGDALAR SUBREGIONAL CONNECTIVITY STUDY USING RESTING STATE FMRI

Harah Kwon^{*1}, Minji Ha², Sunah Choi², Sunghyun Park¹, Moonyoung Jang¹, Minah Kim¹, Jun Soo Kwon²

¹Seoul National University Hospital, ²Seoul National University

Background: Schizophrenia and Obsessive-Compulsive Disorder (OCD) share many epidemiological and clinical characteristics, and indeed, several neurophysiological and neuroimaging studies have confirmed substantial overlap in their biological mechanisms and, in particular, the brain region that has been receiving notable attention is the amygdala. Recent neural correlate studies have revealed that the distinct functions of subregions within the amygdala in emotional processing contribute to the heterogeneity observed in both OCD and schizophrenia. In this pilot study, our primary focus was to examine the variations in functional connectivity (FC) of these subregions among different symptom phenotypes of OCD within a group of individuals not receiving medication.

Methods: Functional magnetic resonance imaging (fMRI) was performed in resting state on 110 healthy controls (HCs) and 107 OCD patients. Whole-brain FC between OCD patients and HCs, as well as between the different OCD symptom phenotypes, was compared using seeds from the bilateral amygdala's centromedial, laterobasal, and superficial subregions.

Results: Among the three OCD subgroups as well as the overall OCD and HC groups, there were no appreciable differences in core demographic profiles. When comparing symmetry-type OCD patients to HCs, they demonstrated hypoconnectivity between the superior frontal gyrus and left centromedial amygdala. Similarly, when comparing contamination-type OCD patients, they demonstrated hypoconnectivity between the left frontal cortex and left centromedial amygdala.

Discussion: These findings suggest that by impairing the modulation of motor reactions regarding emotional information, hypoconnectivity between the centromedial amygdala and the frontal cortex could be linked to the compulsion-focused phenotype of OCD. This underscores the importance of elucidating changes in FC within amygdala subregions for understanding the heterogeneity of OCD. Furthermore, it suggests that such insights may also be valuable in comprehending the diverse phenotypes of schizophrenia that share the significant neural underpinnings regarding emotional processing with OCD.

S182. THE FUNCTIONAL HIERARCHY OF THALAMOCORTICAL CONNECTIVITY IN CHRONIC SCHIZOPHRENIA

Harin Oh^{*1}, Han Byul Cho², Shinwon Park³, Sunah Choi⁴, Jung-ha Lee⁴, Minah Kim⁵, Seok-Jun Hong⁶, Jun Soo Kwon⁷

¹Seoul National University College of Medicine, ²Center for Neuroscience Imaging Research, Institute for Basic Science, ³Autism Center, Child Mind Institute, United States, ⁴Seoul National University College of Natural Sciences, ⁵Department of Neuropsychiatry, Seoul National

University Hospital, Department of Psychiatry, Seoul National University College of Medicine, ⁶Department of Biomedical Engineering, Sungkyunkwan University, ⁷Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Department of Neuropsychiatry, Seoul National University Hospital, Department of Psychiatry, Seoul National University College of Medicine, Institute of Human Behavioral Medicine, SNU-MRC

Background: Schizophrenia is recognized for diverse heterogeneity, putting pressure on identifying the exact pathophysiology and better treatment for individuals. One of the consistent findings is the disruption of thalamocortical functional connectivity throughout the disease progression, characterized by reduced connectivity (hypoconnectivity) between the thalamus and prefrontal cortex (PFC), and increased connectivity (hyperconnectivity) with somatosensory and motor cortex^{1,2,3}. Recent studies have demonstrated a negative correlation between hyper- and hypo-connectivities, indicating an interconnected relationship between these connectivities and potential dysfunction stemming from a shared mechanism⁴. However, their correlation with specific symptoms or their potential as a diagnostic indicator remains uncertain due to current limitations in analyzing the relationship between multiple regions. Thus, a major focus has been given to identifying the causal relationship between the hyper- and hypo-connectivity patterns. Understanding the functional role of each region is crucial to identify their causal relationship. The prefrontal-thalamic connectivity is heavily implicated in higher-order functions, while somatosensory-thalamic connectivity plays a critical role in sensory processing and motor coordination^{5,6}. To clarify the association between higher-order and sensory processing in chronic schizophrenia, exploring the functional hierarchy and organization of those changes could be the next step to identifying causal relationships between two dysconnectivities. Hence, this study aims to investigate the thalamic functional gradient to identify the association between thalamic dysconnectivity patterns in chronic schizophrenia.

Methods: Resting-state fMRI images were obtained from 63 individuals diagnosed with chronic schizophrenia (SCZ, average age=33.4yrs, M/F=36/27) and 70 healthy individuals (HC, average age=25.5yrs, M/F=39/31). The thalamic functional connectome method was adapted from Haak⁷ or analysis with the thalamus as the inner region of interest (ROI) and the prefrontal cortex and somatosensory cortex as outer ROIs. The thalamocortical connection matrix was derived from each individual, and then a similarity matrix and manifold learning were constructed. We extracted two thalamic gradient maps that are known to reflect the thalamic structure (gradient 1) and the hierarchy of behavioural characterization ranging from perception to cognition (gradient 2)⁸. The statistical difference between gradient values and the functional network disruptions related to thalamic dysconnectivity in chronic schizophrenia was examined, with age as a covariate, between SCZ and HC.

Results: The left thalamus showed a statistical (MANOVA) difference in SCZ compared to HC. Substantial differences were observed in the statistically significant group difference voxel regions, indicating a decrease in the 1st gradient and an increase in the 2nd gradient. Specifically, the ANOVA analysis revealed the second gradient of the left thalamus exhibited a compression within SCZ in comparison to HC at a trend level. Moreover, the functional network distribution within the 2nd gradient revealed a significant decrease in the visual and default mode networks, while there was an increase in the frontoparietal network. This indicates a segregation of the visual network and frontoparietal network in patients.

Discussion: In alignment with previous studies, the 2nd gradient demonstrated changes which reflect the functional hierarchy of thalamocortical connectivity patterns^{8,9}. Our findings offer insights into the issues related to sensory-to-cognition processing proposed in chronic schizophrenia at the level of neuroimaging-informed functional networks.

S183. THE IMPACT OF CUMULATIVE OBSTETRIC COMPLICATIONS AND CHILDHOOD TRAUMA ON BRAIN VOLUME IN YOUNG PEOPLE WITH PSYCHOTIC EXPERIENCES

Kate Merritt¹, Pedro Luque Laguna², Arjun Sethi³, Mark Drakesmith², Sarah Ashley¹, Michael Bloomfield¹, Leon Fonville⁴, Gavin Perry², Tom Lancaster², Stavros Dimitriadis², Stanley Zammit⁵, C. John Evans², Glyn Lewis¹, Matthew J. Kempton⁶, David E. J. Linden⁷, Abraham Reichenberg⁸, Derek K. Jones², Anthony S. David¹, Anthony David*⁹

¹*Institute of Mental Health, UCL*, ²*CUBRIC, Cardiff*, ³*IOPPN, King's College London*, ⁴*Invicro LLC, London*, ⁵*Cardiff University and University of Bristol*, ⁶*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ⁷*School for Mental Health and Neuroscience, Maastricht University*, ⁸*Icahn School of Medicine at Mount Sinai*, ⁹*University College London*

Background: Psychotic experiences (PEs) occur in 5-10% of the general population and are associated with exposure to childhood trauma and obstetric complications. However, the neurobiological mechanisms underlying these associations are unclear.

Methods: Using the Avon Longitudinal Study of Parents and Children (ALSPAC), we studied 138 young people aged 20 with PEs (n=49 suspected, n=53 definite, n=36 psychotic disorder) and 275 controls. Voxel-based morphometry assessed whether MRI measures of grey matter volume were associated with i) PEs, ii) cumulative childhood psychological trauma (weighted summary score of 6 trauma types), iii) cumulative pre/peri-natal risk factors for psychosis (weighted summary score of 16 risk factors), and iv) the interaction between PEs and cumulative trauma or pre/peri-natal risk.

Results: PEs were associated with smaller left posterior cingulate (pFWE LESS THAN 0.001, Z=4.19) and thalamus volumes (pFWE=.006, Z=3.91). Cumulative pre/perinatal risk was associated with smaller left subgenual cingulate volume (pFWE LESS THAN 0.001, Z=4.54). A significant interaction between PEs and cumulative pre/perinatal risk found larger striatum (pFWE=0.04, Z=3.89) and smaller right insula volume extending into the supramarginal gyrus and superior temporal gyrus (pFWE=0.002, Z=4.79), specifically in those with definite PEs and psychotic disorder. Cumulative childhood trauma was associated with larger left dorsal striatum (pFWE=0.002, Z=3.65), right prefrontal cortex (pFWE LESS THAN 0.001, Z=4.63) and smaller left insula volume in all participants (pFWE=0.03, Z=3.60), and there was no interaction with PEs group.

Discussion: In summary, pre/peri-natal risk factors and psychological trauma impact similar brain pathways, namely smaller insula and larger striatum volumes. The effect of pre/perinatal risk was greatest in those with more severe PEs, whereas effects of trauma were seen in all participants. In conclusion, environmental risk factors affect brain networks implicated in schizophrenia, namely the salience network, which may increase an individual's propensity to develop later psychotic disorders.

S184. PARSING HETEROGENEITY IN WHITE MATTER INTEGRITY ALONG THE PROGRESSION OF PSYCHOSIS – A MULTI-SITE DIFFUSION TENSOR IMAGING STUDY

Galya Iseli*¹, Sarah Ulrich², Philipp Stämpfli³, Erich Studerus⁴, Anita Riecher-Rössler⁵, Philipp Homan⁶, Stefan Kaiser⁷, Stefan Borgwardt⁸, Matthias Kirschner⁹, André Schmidt¹⁰

¹University Psychiatric Clinics, Translational Neurosciences, ²University Psychiatric Clinics (UPK), ³Psychiatric University Hospital Zurich, ⁴University of Basel, ⁵University of Basel Psychiatric Clinics, ⁶Psychiatric Hospital of the University of Zurich, ⁷Geneva University Hospitals, ⁸University of Lübeck, ⁹University Hospitals of Geneva, ¹⁰University of Basel Psychiatric Hospital Basel

Background: Psychosis develops along a continuum ranging from subclinical psychotic experiences in healthy volunteers from the general population and individuals at clinical high risk to patients with clinically relevant psychosis. Each stage along the continuum demonstrates heterogeneity in clinical profiles and outcome features. While previous research also indicated structural brain heterogeneity at both ends of the continuum, it remains unknown whether it evolves with disease progression and whether divergence from the norm is associated with more adverse clinical features.

Methods: Data of 212 participants collected at three different centers was included in this post-hoc analysis. Samples ranging from five different groups of disease progression were collected at the Department of Psychiatry (UPK) of the University of Basel, the University Hospital of Psychiatry, Bern and the Department of Psychiatry, Psychotherapy and Psychosomatics at the Psychiatric Hospital, University of Zurich: healthy controls (HC, n = 59), schizotypal (SPT, n = 27), at risk mental state (ARMS, n = 35), first episode psychosis (FEP, n = 50), and patients diagnosed with schizophrenia (SZ, n = 41). Structural brain heterogeneity of diffusion tensor imaging (DTI) parameters including fractional anisotropy (FA), mean diffusivity (MD) and fiber density (FD) was computed using the person-based similarity index (PBSI) scores, a novel index that expresses an individual's similarity towards others of the same group. Besides comparing the different DTI PBSIs across groups using the Kruskal-Wallis test, normalized PBSIs were further converted into z-scores (z-nPBSI) indicating deviators to the normative reference. Furthermore, age, sex and diagnostic group adjusted ANCOVAs were performed to determine whether individuals with deviating PBSIs differ in verbal IQ (MWT-B), psychiatric symptoms (BPRS, SANS) and general ability to function (GAF) compared to subjects with non-deviating PBSIs.

Results: Across diagnostic groups significant differences in the PBSI were found for all three diffusion measures FA (H = 51.81, p LESS THAN 0.001). MD (H = 44.49, p LESS THAN 0.001), and FD (H = 55.80, p LESS THAN 0.001). Group differences in FA heterogeneity were found between ARMS-SPT (U = -2.87, p = 0.04), FEP-SZ (U = -4.04, p = LESS THAN 0.001), ARMS-SZ (U = -6.13, p = LESS THAN 0.001), and HC-SZ (U = -6.25, p = LESS THAN 0.001). For MD significant differences were found between HC-SPT (U = -3.39, p = 0.007), FEP-SPT (U = -3.56, p = 0.003), HC-ARMS (U = -4.02, p = LESS THAN 0.001), ARMS-FEP (U = 4.17, p = LESS THAN 0.001), HC-SZ (U = -4.74, p = LESS THAN 0.001), and FEP-SZ (U = -4.87, p = LESS THAN 0.001). For FD, FEP-SZ (U = -2.91, p = 0.03), FEP-SPT (U = -4.31, p = LESS THAN 0.001), ARMS-SZ (U = -4.81, p = LESS THAN 0.001), HC-SZ (U = -4.51, p = LESS THAN 0.001), HC-SPT (U = -5.67, p = LESS THAN 0.001), and ARMS-SPT (U = -5.88, p = LESS THAN 0.001) differed significantly. For FA, SZ showed the greatest percentage of deviators (24.390%) followed by SPT (14.815%), HC (8.475%), FEP (8%) and ARMS (2.857%). For MD 22.5% deviators in SZ, 20% in ARMS, 11.111% in SPT 8% in FEP, and 6.780% in HC. And for FD 25.926% in SPT, 14.634% in SZ, followed by 13.793% in HC, 5.714% in ARMS, and 8.0% in FEP. Across all DTI parameters, the number

of deviators differed significantly across the groups ($\chi^2 = 11.24$, $df = 1$, $p = 0.02$). Post-hoc comparisons revealed significant differences between the groups HC-SPT (OR = 2.94, $p = 0.04$), FEP-SZ (OR = 2.8, $p = 0.04$) and SPT-FEP (OR = 3.64, $p = 0.02$). Furthermore, there were statistical trends for lower GAF scores in SZ patients ($F(1,1) = 3.61$, $p = 0.08$) and individuals with SPT ($F(1,1) = 3.66$, $p = 0.07$) who exhibited deviating nPBSIs compared to those with non-deviating nPBSIs.

Discussion: Our results indicate progressive increases in structural brain heterogeneity. Further large-scale studies are encouraged to examine whether those with marked deviance from normative data reveal more severe clinical features. Such approaches may enable improved prognosis of disease progression and stratified interventions.

S185. EXAMINING RESTING STATE CONNECTIVITY AND ROLE OF ANTIPSYCHOTICS IN SCHIZOPHRENIA: ANALYSIS OF DRUG-NAIVE PATIENTS AT BASELINE AND SIX WEEKS, AND TWO YEARS OF TREATMENT WITH RISPERIDONE

Chithra Uppinkudru^{*1}, Neelabja Roy², Shreshth Shekhar³, Jagadisha Thirthalli⁴, Ganesan Venkatasubramanian⁵, Urvakhsh Mehta⁶

¹Department of Psychiatry, ²National Institute of Mental Health and Neurosciences (NIMHANS), India, ³IISER, Thiruvananthapuram, ⁴National Institute of Mental Health and Neurosciences, ⁵National Institute of Mental Health and Neurosciences, ⁶National Institute of Mental Health and Neuro Sciences (NIMHANS)

Background: The disconnection hypothesis of schizophrenia emphasizes the functional disintegration in the structural connectivity sensorimotor integration, perception, and cognitive processes. Antipsychotics, through their predominant D2 receptor antagonism, are thought to exert their clinical effects, and functional MRI can play a vital role in elucidating these mechanisms. This study aimed to evaluate the changes in the resting state connectivity among drug naïve patients at baseline and two-time points after treatment with risperidone.

Methods: This study enrolled 54 drug-naïve participants (mean age = 33.77 years, SD = 9.2 years, 27 females) who underwent baseline resting-state scans. Follow-up scans were acquired for those initiated on risperidone at six weeks (N=19) and those in symptomatic remission while on treatment after an average of two years (N=21). The paired analysis was conducted in two segments: the first examined participants with good quality baseline and 6-week scans (n=14), while the second part involved participants with good quality baseline and 2-year follow-up scans (n=14). Resting state-fMRI scans for participants across three study phases were obtained on a 3-Tesla MRI scanner (MAGNETOM Skyra, Siemens) over a single run of 10m 6s, with 2s relaxation time to yield 303 volumes. A high-resolution structural MRI (T1 MPRAGE sequence; 5m) of 1-mm section with no inter-slice gap was also acquired. The FMRIB Software Library (FSL version 6.0.5.2) was used for pre-processing and data analysis. Meta ICA-based (Independent Component Analysis) parcellation of 25 networks was applied, and within-network connectivity was analyzed using Generalized Linear Modeling.

Results: The study revealed diminished connectivity in the left sensorimotor network area relative to baseline among individuals following six weeks of Risperidone treatment (P-FWER LESS THAN 0.01). This reduction was also evident at two years of continuous treatment and attainment of symptomatic remission (P-FWER LESS THAN 0.01). Furthermore, the medial

occipital network also exhibited reduced connectivity compared to the baseline ($p=0.02$) at 2-year follow-up.

Discussion: The study findings underscore a potential mechanism of action for risperidone in modulating hyperactivity within the left sensorimotor network, which is instrumental in processing external stimuli, bodily experiences, speech, and motor control. Furthermore, the study sheds light on the conceivable role of the striatal dopaminergic projections to the sensorimotor cortices in possibly mediating symptom response. In conclusion, our study underscores risperidone's potential to reduce hyperactivity in vital sensorimotor and occipital networks. Early reduction in sensorimotor network activity persisted at 2-year follow-up, highlighting its potential as a marker of prospective treatment response.

S186. REVISITING THE KETAMINE ‘MODEL’ FOR SCHIZOPHRENIA THROUGH THE ELECTROPHYSIOLOGY LOOKING GLASS

Larry Ereshefsky^{*1}, Marco Cecchi², Daniel Mathalon³, K.C. Fadem², Elan Cohen⁴, David Walling⁵, Daniel Javitt⁶, Brett English⁷, William Potter⁸

¹*CenExel/Follow the Molecule*, ²*Cognition*, ³*Department of Psychiatry, University of California San Francisco*, ⁴*CenExel Hassman Research Institute*, ⁵*CenExel - CNS*, ⁶*Department of Psychiatry, Columbia University*, ⁷*Cenexel Clinical Sciences*, ⁸*FNIH*

Background: Glutamate dysfunction is thought to play a significant role in the underlying disease course and symptoms in Schizophrenia (SCZ). Recent data suggest that non-D2 modulating mechanisms, i.e., Muscarinic M1 and M4 agonists, demonstrate an efficacy signal. A unifying thread from preclinical studies is that NMDA antagonists impairment i.e., ketamine or MK-801 are reversed by putative antipsychotics across a wide array of pharmacological targets. Following ketamine or phencyclidine exposure in healthy normal volunteers (HNVs) symptoms mimicking some aspects of schizophrenia (SCZ) are observed. In the current investigation, we pooled results from studies sponsored by the ERP Biomarker Qualification Consortium (<https://erpbiomarkers.org>). In the EBS-A trial (NCT04025502; Cecchi et al., 2023), we compared the electrophysiology of stable patients with SCZ against matched HNVs. In EBS-B (NCT04928703; Ereshefsky et al., 2023), we studied HNVs who received ketamine (HNV-K) or placebo. A Consortium member's trial (NCT05049343) data was also included. Data presented elsewhere showed significant differences in ERP/qEEG between HNVs and SCZ, and separately between ketamine vs saline infusions in HNVs. We report the cross-study ERP/EEG findings comparing Ketamine in HNV-K, to no treatment in HNVs to people with stable SCZ.

Methods: EBS-A: 81 HNVs and 80 SCZ were evaluated at 4 sites. Subjects were administered two ERP/EEG testing sessions on separate visits. EBS-B: A three way randomized cross over design in 24 HNVs at one site received 2 ketamine and a single saline infusion. The ketamine protocol used: 0.23 mg/kg bolus over 1 minute, followed by 0.58 mg/kg per hour for 30 minutes, and 0.29 mg/kg per hour for 29 minutes (GunduZ-Bruce et al., 2012). The Consortium member study using similar methodology collected HNV baseline $n=20$ and ketamine infusion $n=19$ data. ERP/EEG data were combined from all these studies using COGNISION® System collecting. Duration-deviant mismatch negativity (MMN); Eyes-closed resting state quantitative (q)EEG; Auditory active deviant oddball (AOB); and 40Hz auditory steady-state response (ASSR). Electrode positions at Fz, Cz, Pz, F3, P3, F4, and P4 matched up to international 10–20 system (Jasper, 1958). qEEG/ERP Group data were

calculated using a One-Way ANOVA comparing HNVs n=124, SCZ n=80, and HNV-K n=43 followed by multiple pair-wise post-hoc ANOVA comparisons with Bonferroni correction. Analyses of SCZ and HNV-K populations will also be reported by re-expressing raw data to z-scores comparing SCZ relative to HNVs against HNV-K relative to HNVs.

Results: Data for selected parameters are reported: Significant Group differences by ANOVA between HNVs, SCZ, and HNV-K as well as Pairwise analyses are reported below the Group stats ($p \leq 0.05$ except where specified, as a trend $p=0.1-0.05$) 1. QEEG Group, Absolute Power $\mu V^2/Hz$ (AP) differences for: Delta, Theta, Alpha1/2, Beta1/2, Gamma ($p=0.051$); Theta/Beta ratio (TBR); Relative Power differences for: Theta, Alpha1, and Beta 1/2/3; and Total Power and Dominant Frequency. QEEG differences across all 3 comparison pairs (pairs) were observed for: Delta AP: HNVs 109 v SCZ 144 v HNV-K 60.1. Theta AP: HNVs 54.2 v SCZ 74.6 v HNV-K 23.6. (RP pair wise data to be presented). Total Power HNVs 381 v SCZ 456 v HNV-K 198. Dominant Frequency HNVs 9.76 v SCZ 9.40 v HNV-K 10.37. Significant differences for 2 of 3 pairs: Alpha1 AP for HNVs 105 v HV-K and HNV-K 40.6 v SCZ 115 but not HNVs v SCZ. Alpha 2 AP for HNV-K 26.4 v SCZ 47.6 and HNVs 105.6 v HNV-K 26.4 but not HNVs v SCZ. Beta1 AP for HNVs 35.1 v HNV-K 17.7 and HNV-K 17.7 v SCZ (38.4), but not HNVs v SCZ. TBR for HNVs 1.20 v SCZ 1.71 and HNV-K 1.25 v SCZ 1.71 but not HNVs v HNV-K. 2. MMN (passive) Group differences: @Fz Amp (μV) and Latency msec (Lat); also @Cz: P50 Amp, P200 Amp and Lat ($p=0.07$), and P3a Amp. MMN differences for all 3 pairs: Lat Fz HNVs 186 v SCZ 203, SCZ 203 v HNV-K 167, and HNVs 186 v HNV-K 167. MMN differences for 2 of 3 pairs: Amp Fz: HNVs -4.08 v SCZ -2.58, SCZ -2.58 v HV-K -4.56, not HNVs v HNV-K; P200 Amp Cz: HNVs 2.86 v SCZ 2.66, HNV-K 1.69 v SCZ 2.66, not HNVs v SCZ; P3a Amp Cz: HNVs 5.21 v SCZ 4.038, HNVs 5.21 v HNV-K 3.78, not HNV-K v SCZ. 3. AOB Group: @Pz P3b Amp and Lat. Button Press Accuracy (BPA) and Mean Reaction Time (MRT). AOB differences for all 3 pairs P3b Pz Amp: HNVs 9.08 v HNV-K 6.00, HNVs 9.08 v SCZ 7.42 and HNV-K 6.00 v SCZ 7.42 ($p=0.051$). AOB differences for 2 of 3 pairs: P3b Lat SCZ 321 v HNV-K 293, HNVs 317 v HNV-K 293, but not HNVs v SCZ; BPA HNVs 95.5 v SCZ 89.8, HNVs 95.5 v HNV-K 89.9, but not SCZ v HNV-K; MRT HNVs 375 v SCZ 457, HNVs 375 v HNV-K 427, but not SCZ v HNV-K. 4. ASSR40 Group: @Fz Intra-Trial Coherence (ITC) 200-500 msec, ITC 500, ITC Evoked Power (EP). ASSR ITC500 Fz differences for 2 pairs: HNVs 0.307 v SCZ 0.256, SCZ 0.256 v HNV-K 0.299 ($p=0.092$), not HNVs v HNV-K. ITC200-500 Fz for 1 pair: HNVs 0.453 v SCZ 0.307, not HNVs v HNV-K and SCZ v HNV-K.

Discussion: The data demonstrate the feasibility of including ERP/qEEG as translational/biomarkers in Early Phase studies. Similarities as well as differences in ERP/qEEG between HNVs and HNV-K and HNVs v SCZ as well as between HNV-K and SCZ suggest utility of the ketamine model for SCZ but with limitations. Variables affecting our results are ketamine dose, sequence of testing, and patient characteristics (age, stable atypical meds).

S187. HERITABILITY OF WHITE MATTER MICROSTRUCTURE AND ASSOCIATIONS WITH SCHIZOPHRENIA LIABILITY AND CHILDHOOD TRAUMA: A DANISH NATION-WIDE TWIN STUDY

Cecilie Lemvig^{*1}, Rachel Brouwer², Jayachandra M. Raghava³, Tina Dam Kristensen⁴, Birte Y. Glenthøj⁵, Bjørn H. Ebdrup⁶

¹Center For Neuropsychiatric Schizophrenia Research, ²Vrije Universiteit Amsterdam, ³Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, Functional Imaging Unit, Copenhagen University Hospital, ⁴Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, ⁵Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup, ⁶Centre for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Centre

Background: Schizophrenia is a highly heritable disorder associated with altered white matter microstructure. White matter microstructure in itself is also heritable, and some evidence suggest a genetic overlap with schizophrenia. Moreover, childhood trauma is a well-documented risk factor for schizophrenia and has been linked to white matter abnormalities. Dissecting the complex relationship between schizophrenia liability, white matter abnormalities and childhood trauma may increase our understanding of the underlying processes of the disorder.

Methods: Participants were recruited nationwide by linkage of two registers in 2011, The Danish Twin Register and The Danish Psychiatric Central Research Register. We included monozygotic (MZ) and dizygotic (DZ) proband pairs concordant or discordant for a schizophrenia spectrum disorder and healthy controls twin pairs (HC) matched on age and sex. Register diagnoses were confirmed using diagnostic SCAN interviews. Diffusion weighted magnetic resonance imaging scans were conducted on a Philips 3.0 T Achieva whole-body scanner with a 32-channel SENSE head coil. Diffusion tensor model was applied to derive measures of fractional anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity. Childhood trauma was examined using the Childhood Trauma Questionnaire, a self-report questionnaire used to assess five domains of trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.

In ongoing analyses, we examine the heritability of white matter microstructure in a cohort enriched for schizophrenia using structural equation modelling to quantify the genetic and environmental contributions to the variability. In addition, we examine genetic or environmental associations between white matter abnormalities, childhood trauma and schizophrenia liability. As an exploratory aim we will examine sex differences in these relationships.

Results: 216 twins participated in the study (mean age: 41.7 (SD 10.3), 49% females), including 32 complete MZ proband pairs, 24 complete DZ proband pairs, 29 complete MZ HC pairs and 20 complete DZ HC pairs. Additionally, six twins from proband pairs participated without their siblings. Most patients were diagnosed with schizophrenia (N=39 (61%)), and the mean age of diagnosis was 27.4 (SD 7.4) years. Proband pairs reported higher levels of childhood trauma compared to HC twin pairs, $t(202) = 7.35$, $p < .001$, and patients reported higher levels compared to their unaffected co-twins $t(43) = 2.68$, $p = .010$.

Discussion: This study aims to provide further evidence that altered white matter microstructure in schizophrenia is heritable and associated with schizophrenia liability, suggesting a partially shared genetic etiology. White matter abnormalities may then constitute an endophenotypes for the disorder and provide a basis to explore genes common to white matter and schizophrenia. Furthermore, we aim to provide a basis to understand the underlying processes involved in the associations between childhood trauma, white matter, and

schizophrenia liability. Results from the structural equation modelling will be presented and discussed at the 2024 SIRS conference.

S188. IDENTIFICATION OF SCHIZOPHRENIA BY APPLYING INTERPRETABLE RADIOMICS MODELING WITH STRUCTURAL MAGNETIC RESONANCE IMAGING OF THE CEREBELLUM

Minji Bang^{*1}, Yaewon Park², Sang-Hyuk Lee¹

¹CHA Bundang Medical Center, ²Yonsei University College of Medicine

Background: The cerebellum is involved in higher-order mental processing as well as sensorimotor functions. Although structural abnormalities in the cerebellum have been demonstrated in patients with schizophrenia, neuroimaging techniques are not yet applicable to identify them given the lack of biomarkers. We aimed to develop a robust diagnostic model for schizophrenia using radiomic features extracted from T1-weighted magnetic resonance imaging (MRI) of the cerebellum.

Methods: A total of 336 participants (174 schizophrenia; 162 healthy controls [HCs]) were allocated to training (122 schizophrenia; 115 HCs) and test (52 schizophrenia; 47 HCs) sets. We obtained 2,568 radiomic features from T1-weighted images of the cerebellar subregions. After feature selection using mutual information, a histogram-based gradient boosting classifier was trained. Discrimination and calibration of the model were evaluated. SHapley Additive exPlanations (SHAP) was applied for determining model interpretability.

Results: We identified 17 radiomic features to differentiate participants with schizophrenia from HCs. In the test set, the radiomics model had an area under the curve, accuracy, sensitivity, and specificity of 0.89 (95% confidence interval: 0.82–0.95), 78.8%, 88.5%, and 75.4%, respectively. The model explanation by SHAP suggested that the second-order size zone non-uniformity feature from the right lobule IX and first-order energy feature from the right lobules V and VI were highly associated with the risk of schizophrenia.

Discussion: The cerebellum-focused radiomics model shows its robustness for the diagnosis of schizophrenia. Our results suggest that microcircuit disruption in the posterior cerebellum is a disease-defining feature of schizophrenia and radiomics modeling has potential for supporting biomarker-based decision-making in clinical practice.

S189. INVESTIGATION OF BRAIN WHITE MATTER IN SCHIZOPHRENIA AND SCHIZOTYPAL PERSONALITY DISORDER USING COMPLEMENTARY DIFFUSION IMAGING MODELS

Philip Szeszko^{*1}, Sean Hollander¹, Mary Kowalchuk¹, Sana Aladin¹, Elen-Sarrah Dolgopolskaia¹, Margaret Zhong¹, Sabrina Ng¹, M. Mercedes Perez-Rodriguez¹, King-Wai Chu¹, Margaret McClure¹, Lazar Fleysher¹, Rene Kahn¹, Mehmet Haznedar¹, Chi Chan¹, Kim Goldstein¹, Erin Hazlett¹

¹Icahn School of Medicine at Mount Sinai

Background: Schizotypal personality disorder (SPD) bears a close resemblance to schizophrenia (SZ), but with fewer and attenuated abnormalities, thus representing a

potentially important and understudied intermediate SZ-spectrum phenotype. There is considerable evidence implicating putative white matter (WM) abnormalities in the pathophysiology of SZ, but such studies are limited in SPD and have relied predominantly on diffusion tensor imaging, which is sensitive, but nonspecific. Deficits in social cognition are considered integral to SZ and SPD, but their neurobiological underpinnings are not well understood. In this study diffusion data were obtained and analyzed using 3 complementary approaches to assess WM and examined in relationship with social cognition in the SZ spectrum from healthy to SPD to SZ to investigate differential impairment and mechanisms of risk and resilience to psychosis.

Methods: This study included 42 (18M/24F) healthy controls (HC; mean age=32.4; SD=5.6), 33 (14M,19F) individuals with SPD (mean age=33.0; SD=7.6) and 42 (26M/16F) individuals with SZ or schizoaffective disorder (mean age=34.0; SD=6.7) assessed using the Structured Clinical Interview for DSM-5 who also received the Positive and Negative Syndrome Scale. In addition, all individuals received the Bell-Lysker Emotion Recognition Test (BLERT) and Mayer-Salovey-Caruso Emotional Intelligence Test to assess social cognition. We computed fractional anisotropy (FA) maps using weighted least squares in FSL's Diffusion Toolbox. We used the free water elimination model implemented in DIPY to deconstruct the diffusion signal into an extracellular free water (FW) map, fractional anisotropy (FA-t), axial (AD-t) and radial (RD-t) diffusivity tissue maps. Accelerated microstructure imaging via convex optimization (AMICO) was used to fit the neurite orientation dispersion and density imaging (NODDI) to derive WM compartments corresponding to the orientation dispersion index (OD) reflecting fiber orientation coherence and neurite density (ND) reflecting packing of axons or dendrites. We created a mean skeleton to represent the center of tracts common to the group, which were then projected onto the overall skeleton followed by voxelwise analyses conducted using tract-based spatial statistics. We compared groups on WM measures using one-way ANCOVA with family-wise error correction (p LESS THAN 0.05) while controlling for age and sex. Independent group t-tests were performed in WM regions for which overall group F-tests showed significant differences while maintaining Type-I error.

Results: Individuals with SZ had widespread lower FA compared to HC whereas individuals with SPD had lower FA compared to HC localized to the splenium of the corpus callosum, which was intermediate to and significantly different from SZ and HC (HC GREATER THAN SPD GREATER THAN SZ). Individuals with SZ had greater FW (but not FA-t) compared to SPD and HC within regions encompassing the splenium of the corpus callosum and extending anteriorly throughout cortico-striatal thalamic cortical circuitry. There was widespread higher OD and lower AD-t in SZ compared to both SPD and HC. Post-hoc analysis of the splenium revealed higher OD in SPD compared to HC that was consistent with the pattern observed in SZ. Greater WM abnormalities were associated with worse performance on the BLERT separately in individuals with SZ and SPD but did not correlate with symptom severity.

Discussion: This is the first study to utilize diffusion tensor imaging, free water imaging and NODDI to investigate putative WM microstructure in the SZ-spectrum. The use of these complementary approaches suggests that findings of lower FA in SZ (and to a lesser extent in SPD) may be related to greater dispersion of fiber orientation (involving cell bodies and glial cells), which could provide potential utility as an intermediate phenotype for SZ. Abnormalities in WM fiber orientation may play a role in social cognitive deficits within the SZ-spectrum.

S190. EVALUATION OF THE GLYMPHATIC SYSTEM IN SCHIZOPHRENIA USING H-MRS AND MRI

Ali Abdolizadeh*¹, Edgardo Torres-Carmona¹, Yasaman Kambari¹, Aron Amaev¹, Jianmeng Song¹, Fumihiko Ueno², Teruki Koizumi³, Shinichiro Nakajima⁴, Philip Gerretsen⁵, Ariel Graff-Guerrero⁵

¹Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada; Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, ²Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH); Department of Psychiatry, University of Toronto; Department of Neuropsychiatry, Keio University School of Medicine³Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto; Department of Psychiatry, National Hospital Organization Shimofusa Psychiatric Medical Center, Chiba, Japan, ⁴Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH); Department of Neuropsychiatry, Keio University School of Medicine, ⁵Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH); Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto; Department of Psychiatry, University of Toronto; Campbell Family Mental Health Research Institute, CAMH

Background: The glymphatic system (GS), a brain waste clearance pathway, has been reported to be disrupted in various neurodegenerative and vascular diseases. Schizophrenia presents features of accelerated biological brain aging with cognitive decline, premature death, and metabolic anomalies since prodromal stages. These features along with the genetic variations of AQP-4 channels and altered cerebral artery pulsation are also present in neurodegenerative diseases with dysfunctional GS. The cumulative evidence suggests that the GS might be impaired in patients with SCZ. Notably, pathologies have been shown to alter the contribution of macromolecules (MM) to 1H spectrum. Accumulation of brain waste including MM, attributed to impaired GS and/or disruption in the clearance of MM to transfer into the ventricular CSF, have been recently observed in patients with idiopathic normal pressure hydrocephalus. Thus, we hypothesized that patients with schizophrenia would show elevated brain MM levels compared to healthy control (HC) participants. Furthermore, diffusion tensor image analysis along the perivascular space (DTI-ALPS) has been introduced as a non-invasive technique to measure glymphatic activity. The DTI-ALPS method assesses interstitial fluid dynamics by evaluating diffusivity of water molecules in the direction of the perivascular spaces of deep medullary veins. A lower DTI-ALPS index reflecting impaired brain waste clearance has been observed in various neurodegenerative diseases. Thus, we hypothesized that patients with schizophrenia would show lower DTI-ALPS index compared to HC participants. As an external validity for our analyses, we hypothesized that age would be positively correlated with MM and negatively correlated with DTI-ALPS indices due to the age-related decline in the glymphatic function. Additionally, we hypothesized an inverse association between MM and DTI-ALPS indices as construct validity for our methods.

Methods: Forty-seven healthy controls (HCs) and 103 patients with schizophrenia were studied. Data included 135 proton magnetic resonance spectroscopy sets (1H-MRS), 96 DTI sets, with 79 participants contributing both. MM levels were quantified in the dorsal-anterior-cingulate-cortex (dACC), dorsolateral-prefrontal-cortex (DLPFC), and dorsal-caudate (point resolved spectroscopy, echo time=35ms). Diffusivity values in the projection and association fibers near the lateral ventricle body were measured to calculate DTI-ALPS indices. General linear models were performed, adjusting for age, sex, and smoking. Correlation analyses examined relationships with age and clinical variables.

Results: MM levels were not different between the entire patient group and HC group. However, left, right, and bilateral DTI-ALPS indices were lower in the entire patient group compared with HC group (P LESS THAN .001). In the HC group, age was positively correlated with dACC MM and negatively correlated with left, right, and bilateral DTI-ALPS indices (P LESS THAN .001). In the entire patient group, illness duration was positively correlated with dACC MM and negatively correlated with the right DTI-ALPS index (P LESS THAN .05). In the entire population, dACC MM and DTI-ALPS indices showed an inverse correlation (P LESS THAN .01).

Discussion: The results showed a positive correlation between age and MM levels and an inverse correlation between age and DTI-ALPS indices, indicating external validity for our analysis. Furthermore, our finding of an inverse correlation between dACC MM and DTI-ALPS indices provides construct validation for our methods. Our results suggest potential disruptions in the GS of patients with schizophrenia. Improving brain's waste clearance may offer a potential therapeutic approach for patients with schizophrenia.

S191. DECODING THE NEURAL REPRESENTATION OF VALUE IN SCHIZOPHRENIA WITH NEGATIVE SYMPTOMS

Reihaneh Forouhandehpour*¹, Guillermo Horga², Clifford Cassidy¹

¹University of Ottawa, ²Columbia University,

Background: Deficits in pleasure and motivation, a prevalent and debilitating aspect of many neuropsychiatric conditions, remain poorly understood at a mechanistic, neural level. Treatments for these deficits are inefficient at best, so understanding the neural mechanisms underlying these deficits is a necessary first step towards the discovery of urgently needed therapies. Among the most common and disabling of this type of deficits are those comprising a portion of the 'negative symptoms' of schizophrenia (SCZ). The existing theories of negative symptoms, including deficits in motivation and pleasure, cast these deficits as arising from abnormalities in the neural representation of value or cost/benefit computations in the presence of spared pleasure responses. Prior work has not clarified these mechanisms likely due to limitations of existing paradigms which could be improved by disentangling multiple aspects of value-based decision making and using multivariate pattern analyses (MVPA), a commonly used means of quantifying value representation. In this fMRI study we used a novel decision-making task (the Movie Shopping Task) in which brain activity is monitored while participants experience pleasurable stimuli (movie trailers) and make value-based decisions (willingness to pay/work to win the movies advertised).

Methods: Participants: We recruited 37 participants, 17 people with schizophrenia (female=4, aged 39±9) with at least moderate levels of negative symptoms and 20 healthy participants (female=4, aged 30±9).

Data collection: Participants underwent MRI scanning using the Siemens Biograph MR PET scanner (3-Tesla) located at The Royal Ottawa Mental Health Centre. For each participant, we collected 10 BOLD fMRI, structural T1 and spin-echo susceptibility images.

fMRI task: Participants performed the Movie Shopping Task. On each trial participants watched a movie trailer and received a \$5 endowment to bid on the movie advertised. High bids increased the odds of winning a copy of the movie (willingness-to-pay (WTP), following the Becker-DeGroot-Marschak (BDM) procedure). Participants then have had another chance to win the movie by making repeated key presses (willingness-to-work (WTW)). There were

90 trials divided into two 70-minute scan sessions. Following each session, two trials were randomly selected for prize payout (1 for auction, 1 for effort).

fMRI data analysis: Standard fMRI preprocessing was performed using Fmrip:20.0.2. For each participant a support vector regression was performed using Nilearn and Scikit-learn relating brain activity to participant responses. For this, the brain activity patterns during the trailer viewing were decoded to predict participant willingness-to-pay. This primary analysis was performed within a value-encoding regions of ventromedial prefrontal cortex (vmPFC) and Ventral Striatum (VSt).

Results: Using MVPA, patterns of brain activity were identified in two groups (healthy controls and schizophrenia patients) and related to willingness-to-pay. Preliminary results showed patterns of brain activity in the ventromedial prefrontal cortex during movie trailer viewing ($t_{19}=4.40$, $p=0.0002$, 1-sample t-tests) significantly predicted financial decisions in the control group. Compared to controls, these patterns of brain activity were significantly less predictive of willingness-to-pay in the schizophrenia group ($t_{35}=2.73$, $p=0.009$, 2-sample t-test)

Discussion: Our preliminary data suggest that value regions in the prefrontal cortex and striatum are not effectively representing value to support decision making in individuals with schizophrenia, consistent with a leading theory of negative symptoms in schizophrenia.

S192. USING EDGE TIME SERIES TO ANALYSE TIME-VARYING FUNCTIONAL CONNECTIVITY IN PSYCHOSIS

Abigail Gee^{*1}, Edward Bullmore², Morgan Sarah²

¹*Kings College London*, ²*University of Cambridge*

Background: Several authors have identified differences in dynamic resting-state functional connectivity in patients with psychotic disorders compared to healthy control subjects (Cattarinussi et al., 2023; Du et al., 2017). However, to date most studies have used methods such as the sliding-window technique, which is sensitive to choice of parameters such as the length of the window and how far the window should move at each step (Savva et al., 2019). In this study edge-centric analysis (Faskowitz et al., 2020) was used to examine differences in time-varying connectivity in patients with psychotic disorders compared to healthy control subjects, which has higher temporal resolution than other methods and unwraps the data without applying additional modelling.

Methods: We analysed resting-state fMRI data from 67 patients with schizophrenia and 81 healthy control subjects using the Center for Biomedical Research Excellence (COBRE) dataset. We then replicated these results in the larger, transdiagnostic Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) dataset which included 176 healthy controls, 91 patients with bipolar disorder with psychotic symptoms, 96 patients with schizoaffective disorder and 148 patients with schizophrenia (total N=337 patients).

The edge-time series (ETS) for these subjects was calculated by first standardising the regional time series and then calculating the element-wise product between every pair of regions (nodes) in the brain. This unwrapped the functional connectivity correlations and produced a measure of co-fluctuation between each pair of nodes, at each timeframe. The ETS can be aggregated into a single measure of whole brain co-fluctuation by calculating the root sum square (RSS). The “peaks”, or high amplitude frames, were identified by comparing the RSS time series to

an ensemble RSS generated using a null model. A linear regression model was used to compare the peak frequency and amplitude, while controlling for age and sex. Network Based Statistics (NBS) was used to compare the mean co-fluctuation patterns at these timepoints.

Results: In the COBRE dataset, patients with schizophrenia had less frequent peaks ($t = -2.80$, $p = 0.0058$) and lower amplitude peaks ($t = -3.13$, $p = 0.0021$) compared to control subjects. Using NBS, we identified a network that was significantly less activated in patients than in controls during the peak time points, which included connections between the fusiform, lateral occipital, orbitofrontal, post-central, insula, superior temporal and superior parietal regions bilaterally, and the right cingulate and inferior parietal regions. The strongest connections were between the Yeo (Yeo et al., 2011) visual and default mode networks. In the replication BSNIP dataset, collectively the patients with psychotic disorders had significantly less frequent peaks ($t = -4.56$, $p = \text{LESS THAN } 0.001$), but peak amplitude was not significantly different ($t = -1.07$, $p = 0.28$). The peak frequency was also lower in patients with bipolar disorder ($t = -3.34$, $p = \text{LESS THAN } 0.001$) and schizoaffective disorder ($t = -3.71$, $p = \text{LESS THAN } 0.001$) when compared to control subjects. The mean functional connectivity in the previously identified NBS network was significantly lower in BSNIP patients compared to control subjects during peak time points ($t = -4.93$, $p = \text{LESS THAN } 0.001$).

Discussion: These results suggest that whole brain co-fluctuations are less frequent in patients with schizophrenia. Our results replicated in a larger transdiagnostic dataset and were also observed in patients with bipolar disorder and schizoaffective disorder. This is consistent with previous studies which identified that patients with schizophrenia spend significantly less time than controls in states of large-scale connectivity (Miller et al., 2016). We identified specific networks which were less activated in patients compared to controls during the peak timepoints. Further studies looking at early psychosis and antipsychotic naïve patients will be important to build on these results.

S193. CEREBELLAR DYSCONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER IS ASSOCIATED WITH COGNITIVE FUNCTIONING AND PSYCHOTIC SYMPTOMS

Giulia Cattarinussi^{*1}, Annabella Di Giorgio², Fabio Sambataro¹

¹*Department of Neuroscience, University of Padova,* ²*Department of Mental Health and Addictions, ASST Papa Giovanni XXIII,*

Background: Abnormal cerebellar functional connectivity (FC) has been independently implicated in the pathophysiology of schizophrenia (SCZ) and bipolar disorder (BD). However, cerebellar dysconnectivity patterns in these two disorders and their association with cognitive functioning and clinical symptoms have not been fully clarified. In this study, we examined cerebellar FC alterations in SCZ and BD-I and their association with cognitive and psychotic symptoms.

Methods: Resting-state functional magnetic resonance imaging (rs-fMRI) data of 39 patients with SCZ, 43 BD-I, and 61 healthy controls from the Consortium for Neuropsychiatric Phenomics dataset were examined. The cerebellum was parcellated into ten functional systems, and seed-based FC was calculated for each cerebellar system. Principal component analyses were used to reduce the dimensionality of the diagnosis-related FC and cognitive variables. Multiple regression analyses were used to assess the relationship between FC and cognitive and clinical data.

Results: We observed decreased cerebellar FC with the frontal, temporal, occipital, and thalamic areas in patients with SCZ, and a more widespread decrease in cerebellar FC in patients with BD-I, involving the frontal, cingulate, parietal, temporal, occipital, and thalamic regions. SCZ patients presented increased within-cerebellum and cerebellar-frontal FC compared to BD-I patients. In BD-I, memory and verbal learning performances, that were higher compared to SCZ, showed a greater interaction effect of cerebellar FC patterns. Additionally, patterns of increased cortico-cerebellar FC were marginally associated with positive symptoms in patients.

Discussion: Our findings suggest shared and distinct patterns of cortico-cerebellar dysconnectivity in SCZ and BD-I, that are associated with cognitive impairments and psychotic symptoms.

S194. NEURODEVELOPMENTALLY-ROOTED BRAIN EPICENTERS OF EARLY-ONSET SCHIZOPHRENIA

Yun-Shuang Fan^{*1}, Yong Xu², Meike Dorothee Hettwer³, Pengfei Yang¹, Wei Sheng¹, Chong Wang¹, Matthias Kirschner⁴, Sofie Louise Valk³, Huaifu Chen¹

¹University of Electronic Science and Technology of China, ²First Hospital/First Clinical Medical College of Shanxi Medical University, ³Max Planck Institute for Human Cognitive and Brain Sciences, ⁴McGill University

Background: Schizophrenia (SZ) is increasingly conceptualized as a neurodevelopmental disorder with a polygenic architecture, whose pathological process originates early in brain development. However, why, when, and where these alterations take place in the brain is incompletely understood.

Numerous neuroimaging studies have indicated that SZ has pronounced brain structural alterations, typically showing cortical thinning in widespread brain regions. Moreover, SZ-related brain alterations are not randomly distributed but follow the intrinsic network organization of the human connectome. During neurodevelopment, the human brain exhibits systematic patterns of maturation along anatomically and functionally connected regions, referred to as the “connectome”. Despite the many biological and functional benefits for resource sharing facilitated by a refined connectome, pathological perturbations are also suggested to propagate via connections among regions.

To investigate the putative early pathological origins that propagate through the connectome, here called “disease epicenters”, we used early-onset SZ (EOS) patients aged 7-17 as a neurodevelopmental disease model. Based on the assumption that regions with large (or less) deformation are more likely to be interconnected, we identified early disease epicenters of EOS by evaluating the influence of normative functional and structural connectivity profiles on the spatial distribution of cortical thickness alterations in patients.

Methods: Multimodal MRI data of 95 antipsychotic-naïve first-episode EOS patients and demographically-matched 99 typically developing (TD) controls were collected from the First Hospital of Shanxi Medical University. Cortical thickness was extracted from T1-weighted structural data and compared between patients and controls. Following, disease epicenters were determined by correlating cortical thickness abnormalities in patients with normative patterns of structural and functional connectivity separately derived from diffusion tensor imaging and resting-state fMRI data. Next, we tested whether epicenters showed patterns of disease

progression as a function of age of onset by conducting group-specific epicenter mappings. To contextualize these observations within microscale transcriptomic architecture, we applied partial least squares (PLS) analysis to disease epicenters and ex vivo microarray gene expression maps. We further linked gene PLS weights with the differential gene expressions of six major psychiatric disorders including SZ, autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder, alcoholism, and inflammatory bowel disease. Finally, we explored the overlap between epicenter-related genes and evolution-related genes located in human accelerated regions (HARs) of the genome, given previous hypothesis on the relationship between brain expansion and SZ.

Results: Disease epicenters of cortical thickness increases in EOS were located in sensorimotor regions subserving visual, somatosensory and motor functions, while the epicenter end of cortical thickness decreases was situated in association regions linked to language, affective and cognitive functions. When comparing epicenter maps from childhood to adolescence, we observed that disease epicenters of EOS shifted and gradually faded out with increased age. Using transcriptomic decoding we observed that disease epicenters of cortical thickening were associated with axon-related genes predominantly expressed in oligodendrocytes; while disease epicenters of cortical thinning were associated with synapse-related genes mainly expressed in excited/inhibitory neurons. These epicenter-related genes were correlated with dysregulated gene expression observed in SZ, ASD and BD. Moreover, the epicenter axis was associated with brain expression maps of evolution-related HARs genes.

Discussion: In this study, we used the epicenter model to identify probable pathological origins in SZ and found a sensorimotor (thickening) to association (thinning) (S-A) pattern of cortical thickness alterations in EOS. The S-A epicenter map aligns with the human neurodevelopmental axis from childhood to adolescence, subserving a cognitive continuum from visual, motor, memory, affective to language. The developmental delay of the sensorimotor pole in SZ might be attributed to excessive expressions of oligodendrocytes-related genes during childhood, while the overgrowth of association regions in SZ could result from excessive expressions of neurons themselves.

The associations between epicenter-related genes and dysregulated genes specific to SZ, ASD and BD suggest that the S-A epicenter axis might serve as a converging pathophysiological framework across multiple complex psychiatric disorders. Moreover, the overlap between epicenter-related genes and HARs genes indirectly supports the “evolution hypothesis”, pointing that these mental illnesses emerge as costly by-products of human evolution.

Our findings suggest developmentally-rooted pathological origins of SZ during brain maturation and may contribute to a better understanding of the etiology of these neurodevelopmental disorders.

S195. CORTICO-STRIATAL WHITE MATTER DYSCONNECTIVITY IN SCHIZOPHRENIA SPECTRUM DISORDER: A MULTISITE HARMONIZED TRACTOGRAPHY STUDY

Hyungyou Park^{*1}, Minah Kim², Kang-Ik Kevin Cho³, Minji Ha⁴, Moonyoung Jang², Sunghyun Park², Jun Soo Kwon⁴

¹Seoul National University College of Natural Sciences, ²Department of Neuropsychiatry, Seoul National University Hospital, ³Brigham and Women's Hospital, Harvard Medical School, ⁴Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences

Background: Dysfunction of the striatum and its upstream cortex is central to the pathophysiology of psychosis in its clinical stages. Cortical projections, either segregated or integrated, regulate striatal functions; however, the anatomical disruptions of cortico-striatal connections in psychosis remain poorly understood. The aim of this study was to elucidate alterations in white matter (WM) connectivity between the cerebral cortices and the striatum and their association with symptomatology in different phases of psychosis.

Methods: Datasets were collected from 277 healthy controls (HCs), 162 participants at clinical high risk for psychosis (CHR), 132 patients with first-episode psychosis (FEP), and 173 patients with chronic schizophrenia (CSZ). All participants underwent T1 and diffusion-weighted imaging (DWI) scans at four sites using five different acquisition parameter sets. Retrospective harmonization was performed on all DWI data to minimize site-specific variation, and probabilistic tractography was then used to examine cortico-striatal WM connectivity. Connectivity values showing significant group differences were subjected to regression analysis to demonstrate their associations with symptom severity.

Results: Reduced striatal WM connectivity with the temporal cortex was significantly presented in FEP patients compared to other groups. In CSZ patients, connectivity of executive (dorsal frontal) and occipital cortices was significantly diminished relative to HCs and CHR individuals. Furthermore, decreased executive connectivity was negatively associated with the severity of both positive and negative symptoms in CSZ patients.

Discussion: This study highlights the disrupted striatal WM connectivity in the executive (dorsal) circuit as a significant pathological and symptomatic underpinning in CSZ, along with the involvement of temporal (ventral) connectivity in the early stage of psychosis. Demonstrating specific WM dysconnectivity across phases of psychosis, these findings provide the anatomical basis of cortico-striatal dysfunctions, particularly integration of executive and sensory inputs, throughout the disease progression.

S196. LARGE-SCALE CROSS-DISORDER ANALYSIS OF CEREBRAL CORTICAL PATTERNS IN THE FOUR MAJOR PSYCHIATRIC DISORDERS: A MULTI-INSTITUTIONAL STRUCTURAL MRI IMAGING STUDY

Junya Matsumoto*¹, Masaki Fukunaga², Kenichiro Miura¹, Kiyotaka Nemoto³, Naohiro Okada⁴, Naoki Hashimoto⁵, Kazutaka Ohi⁶, Tsutomu Takahashi⁷, Michihiko Koeda⁸, Hidenaga Yamamori⁹, Michiko Fujimoto¹⁰, Yuka Yasuda¹¹, Satsuki Ito¹, Naomi Hasegawa¹, Shinsuke Koike⁴, Motoaki Nakamura¹², Go Okada¹³, Theo G.M. van Erp¹⁴, Jessica Turner¹⁵, Paul M. Thompson¹⁶, Jun Miyata¹⁷, Shusuke Numata¹⁸, Toshiaki Onitsuka¹⁹, Reiji Yoshimura²⁰, Shin Nakagawa²¹, Yoshiyuki Watanabe²², Norio Ozaki²³, Ryota Hashimoto¹

¹National Institute of Mental Health, National Center of Neurology and Psychiatry, ²National Institute for Physiological Sciences, ³University of Tsukuba, ⁴The University of Tokyo, ⁵Hokkaido University Graduate School of Medicine, ⁶Gifu University Graduate School of Medicine, ⁷University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, ⁸Nippon Medical School, ⁹Japan Community Health Care Organization Osaka Hospital, ¹⁰Osaka University Graduate School of Medicine, ¹¹Life Grow Brilliant Mental Clinic, ¹²Showa University, ¹³Hiroshima University, ¹⁴University of California Irvine, ¹⁵The Ohio State University, ¹⁶University of Southern California, ¹⁷Kyoto University, ¹⁸Tokushima University Hospital, ¹⁹National Hospital Organization Sakakibara Hospital, ²⁰University of Occupational

Background: Psychiatric disorders such as schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), and autism spectrum disorder (ASD) are operationally classified based on symptoms. While different symptoms separate diagnoses, some symptoms are common to other diagnoses. We hypothesize that some cortical structural alterations detected by neuroimaging also have some commonality between four major psychiatric disorders.

Methods: From 14 institutes, 3,068 healthy subjects, 1,426 patients with schizophrenia, 237 with bipolar disorder, 612 with major depressive disorder, and 206 with autism spectrum disorder participated in the study. A total of 5,549 T1-weighted MRI data were used. Cortical structural analysis was performed with FreeSurfer. For each scanner, the effect sizes of the difference between the healthy comparison subjects and patients with each disorder were calculated using a linear regression model, and after that, they were meta-analyzed. The effect sizes for 68 regions of interest (ROIs) of the DK atlas regions were made into a 68-dimensional vector for each disorder, and the cosine similarity was calculated from the inner product of the vectors between the disorder groups to examine whether the patterns were similar.

Results: The results showed that cortical thickness was generally thinner in individuals with schizophrenia, bipolar disorder, and major depressive disorder, but not in autism spectrum disorder. On the other hand, the cortical surface area of the cortex was found to be smaller in individuals with schizophrenia and major depressive disorder, but not in bipolar disorder. The cortical thickness pattern between each disorder group and healthy comparison subjects was similar in the pair of SZ and BD (0.943), SZ and MDD (0.959), and BD and MDD (0.934). The cortical surface area pattern between each disorder group and healthy comparison subjects was similar in the pair of SZ and MDD (0.945), SZ and ASD (0.867), and MDD and ASD (0.811).

Discussion: The difference in similarity of cortical thickness and surface area patterns in each of the four major psychiatric disorders was revealed. Genetic correlation studies report that schizophrenia, bipolar disorder, and major depressive disorder correlate with each other, while autism spectrum disorder does not so correlate with major depressive disorder and bipolar disorder, which is consistent with the similarity patterns of cortical thickness. Cortical thickness and surface area have also been found to show a negative genetic correlation, and neurobiological mechanisms of cortical thickness and surface area are different. Cortical thickness is affected by myelination, branching, and pruning, while cortical surface area is expanded by the proliferation of neural progenitor cells. Therefore, differences in cortical thickness and surface area patterns may reflect differences in genetic and neurobiological brain pathology.

S197. THE ASSOCIATION BETWEEN CHRONIC TOBACCO SMOKING AND BRAIN ALTERATIONS IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW OF MAGNETIC RESONANCE IMAGING STUDIES

Merel Koster^{*1}, Lilli Mannsdörfer¹, Marieke van der Pluijm¹, Lieuwe de Haan¹, Tim Ziermans², Guido van Wingen¹, Jentien Vermeulen¹

¹Amsterdam UMC, ²University of Amsterdam

Background: The high comorbidity of tobacco smoking in patients with schizophrenia spectrum disorders (SSD) poses a serious health concern, linked to increased mortality and adverse clinical outcomes in SSD patients. The neurobiological mechanisms underlying this comorbidity are complex and not fully understood. Addressing the need for a comprehensive overview of the impact of tobacco use on the neurobiology of SSD, we conducted a systematic review on the association of chronic tobacco smoking in patients with SSD across all magnetic resonance imaging (MRI) modalities.

Methods: PsycINFO, Web of Science, PubMed, and Biosis were searched from inception to the 7th of June 2023. We included all MRI studies in patients diagnosed with a schizophrenia spectrum disorder (SSD) who investigated the effects of current habitual cigarette smoking. Twenty-two studies were included, comprising eight structural and fourteen functional MRI studies.

Results: Structural studies showed widespread independent and additive reductions in grey matter in relation to smoking and SSD. Results of functional studies were mixed, but mainly suggested that smoking might reverse or preserve functional deficits associated SSD. However, it is important to consider that results of five of these studies (83%) stem from the same sample, and studies in other samples do not support this. Interestingly, although results are mixed, smoking appears to have distinct effects on neural dynamics in patients versus controls, advocating for a different neural foundation of tobacco addiction in patients compared to controls. Task-based studies also point towards this, as results mostly imply a unique neural activation pattern in smokers with schizophrenia involving the brain reward system. Thus, functional results indicate a distinct neurobiological mechanism for tobacco addiction in patients with SSD.

Discussion: The nicotinic acetylcholine receptor (nAChR) may play a key role in explaining functional differences observed in smoking between SSD patients and controls. Genetic variations and expression changes of the nAChR associated with SSD could affect neurotransmitter release and thus the brain's response to nicotine, compared to controls. Hence, SSD-related neurobiological alterations at the nAChR level might explain the differential effects of nicotine on the psychotic versus non-psychotic brain. However, the limited number of studies and high sample overlap between these studies make it challenging to conclusively ascertain the nature and extent of smoking's impact on the brain function of patients with SSD. Our findings highlight the need for longitudinal and exposure-dependent studies to differentiate between inherent anatomical and physiological differences and the (long-term) effects of smoking on SSD, and to unravel the complex interaction between smoking and SSD at various disease stages. This could lead to more effective strategies for addressing smoking susceptibility in patients with SSD, potentially improving clinical outcomes.

S198. ALTERED HIPPOCAMPAL SHAPE MORPHOLOGY IN SCHIZOPHRENIA AND AT-RISK MENTAL STATE

Yoichiro Takayanagi^{*1}, Dominic Padova², Can Ceritoglu², Daiki Sasabayashi³, Tsutomu Takahashi³, Shimako Nishiyama⁴, Haruko Kobayashi³, Kazumi Sakamoto³, Misako Torigoe³, Mizuho Takayanagi³, Kyo Noguchi⁵, Noa Tsujii⁶, Michio Suzuki³

¹University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, ²Center for Imaging Science and Institute for Computational Medicine, Department of Biomedical Engineering, ³Department of Neuropsychiatry, University of Toyama Graduate School of

Medicine and Pharmaceutical Sciences, ⁴Centre for Health Care and Human Sciences, University of Toyama, ⁵Department of Radiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, ⁶Department of Child Mental Health and Development, Toyama University Hospital

Background: Hippocampus are involved in a variety of important roles such as memory, learning and emotional regulation. Past studies indicate that in individuals with psychotic disorders such as schizophrenia (SZ) and those with clinical/genetical high risk for psychosis, structural alterations (e.g., volume reduction) of hippocampus as a whole, or those of hippocampal subregions are related to their pathophysiology. In this study, we evaluated the morphological alterations of substructures of hippocampus in subjects with SZ and at-risk mental state (ARMS) by the large deformation diffeomorphic metric mapping (LDDMM), which can analyze shape datasets, and define statistically significant shape variations in the considered structure.

Methods: Eighty-one SZ patients, 56 individuals with ARMS, and 90 healthy controls were recruited at the Toyama University hospital. Subjects underwent a 3-D T1-weighted magnetic resonance imaging (MRI) scanning using a 3-T scanner. Bilateral hippocampi were extracted by FreeSurfer (version 7.2). Using LDDMM, all vertices of each subject's hippocampus were mapped on to the population template. Hippocampus were subdivided into 20 clusters. We measured the logarithm of the surface Jacobian determinant (surface area change), and the logarithm of the ratio of the full Jacobian determinant to the surface Jacobian determinant (normal surface change) for each cluster. A significant negative (positive) log-Jacobian ratio paired with an insignificant or significant negative (positive) log-surface Jacobian in a cluster is interpreted as surface compression (expansion).

The association between the response variable (surface area or normal surface change) and diagnostic group, covarying for age, sex, antipsychotic (AP) medication dosage and log-intracranial volume, was assessed using multiple linear regression. The p-values from 10,000 permutation testing simulations across clusters are corrected for family-wise error rate (FWER) at the 0.05 significance level.

Results: The SZ and ARMS groups exhibited no significant surface area changes. The SZ group displayed expansion normal to the surface in the subiculum (3.7-6.8%) and CA1 (3.7-5.9%) on the right side compared to healthy controls. The ARMS group exhibited a 3.9% normal surface expansion of the subiculum on the right side. Higher doses of AP medication were associated with a compression normal to the surface in the CA1 clusters on the right side. A higher dose of AP was linked to normal surface compression in the left side CA1 region on the dorsal lateral tail of the right hippocampus.

Discussion: A common surface expansion in SZ and ARMS groups found in the right subiculum may be related to the vulnerability to psychosis. Further surface expansion in the right CA1 and subiculum might underlie the manifestation of overt psychotic symptoms. Our data also suggests that human hippocampal tissue could dynamically change, and such changes may be associated with prodromal conditions of psychosis, psychotic symptoms, or antipsychotic medications.

S199. TRANSDIAGNOSTIC TYPES OF FORMAL THOUGHT DISORDER AND THEIR ASSOCIATION WITH GRAY MATTER BRAIN STRUCTURE: A MODEL-BASED CLUSTER ANALYTIC APPROACH

Frederike Stein*¹, Anna Merle Gudjons², Katharina Brosch², Lea Teutenber², Dominik Grotegerd³, Susanne Meinert³, Nina Alexander², Benjamin Straube², Udo Dannlowski³, Tilo Kircher²

¹University of Marburg, ²Department of Psychiatry and Psychotherapy, University of Marburg, Germany, ³Institute for Translational Psychiatry, University of Münster

Background: Formal thought disorder (FTD) is a complex syndrome referring to impaired language and thought processes prevalent in psychotic and affective disorders. Clustering (i.e., identification of new data-driven clinical subtypes) approaches have established latent structures in several syndromes. But there is no data yet on FTD clustering across different disorders and particularly not on their brain structural correlates. Therefore, this study aims to identify transdiagnostic subtypes of FTD using a data-driven approach.

Methods: In N=1,032 patients meeting DSM-IV-TR criteria for Schizophrenia (SZ), Schizoaffective Disorder (SZA), Major Depressive Disorder (MDD), and Bipolar Disorder (BD), a latent profile analysis (LPA) of FTD was performed using ratings of 15 speech and language symptoms from rater-based scales (SANS, SAPS, YMRS, HAM-D). Identified clusters were compared with regard to FTD symptoms and neurocognitive functioning. We explored associations of FTD clusters with gray matter volume (GMV) and cortical surface using T1-weighted magnet-resonance-imaging data and full factorial models in SPM.

Results: LPA revealed four FTD symptom clusters: minimal, poverty, inhibition, and severe. Post-hoc tests showed that clusters differed in neurocognitive functioning. Patients exhibiting severe FTD compared to minimal FTD showed GMV reductions in the right superior and middle frontal gyri. The inhibition cluster showed a GMV reduction in the right inferior and middle temporal gyri, and fusiform gyrus compared with minimal and severe FTD. Sulcal depth was reduced around the left insula, superior temporal sulcus and temporal pole in the poverty cluster, and in the bilateral insula in the severe FTD cluster, both compared to the inhibition cluster. None of the results was related to DSM-IV diagnosis.

Discussion: Our results unravel the clinical heterogeneity of FTD across affective and psychotic disorders. Associations of FTD clusters with neuroanatomical substrates imply language-related GMV and surface structures being involved in thought and language impairment across disorders.

S200. NEURAL CIRCUITRY AND THERAPEUTIC TARGETING OF DEPRESSIVE SYMPTOMS IN SCHIZOPHRENIA SPECTRUM DISORDERS

Julia Gallucci*¹, Ju-Chi Yu², Lindsay D. Oliver², Hajer Nakua¹, Peter Zhukovsky², Erin W. Dickie², Zafiris J Daskalakis³, George Foussias², Daniel M. Blumberger¹, Colin Hawco¹, Aristotle N. Voineskos¹

¹Centre for Addiction and Mental Health, University of Toronto, ²Centre for Addiction and Mental Health, ³University of California San Diego

Background: Conceptual similarities between depressive and negative symptoms complicate biomarker and intervention development. This study employed a data-driven approach to delineate the neural circuitry underlying depressive and negative symptoms in schizophrenia spectrum disorders (SSDs).

Methods: Data from three studies: two neuroimaging studies and a randomized repetitive transcranial magnetic stimulation (rTMS) trial were analyzed (n=157 SSDs) to assess brain-behavior relationships. Partial Least Squares Correlation (PLSC) investigated associations between resting-state functional connectivity and depressive and negative symptoms. Secondary analysis of rTMS trial data (active n=37, sham n=33) were used to assess relationships between

PLSC-derived symptom profiles and treatment outcomes.

Results: PLSC identified three latent variables (LVs) relating functional brain circuitry with symptom profiles. LV1 related a general depressive symptom factor with positive associations between and within Default Mode Network (DMN), Frontoparietal Network (FPN), and Cingulo-Opercular Network (CON). LV2 related negative symptoms (no depressive symptoms) via negative associations, especially between FPN and CON, but also between DMN with FPN

and CON. LV3 related a guilt and early wakening depression factor via negative rather than positive associations to the DMN, FPN, and CON. The secondary visual network had a positive association with general depressive symptoms and negative associations with guilt and negative symptoms. Active (but not sham) rTMS to the bilateral dorsolateral prefrontal cortex (DLPFC)

reduced general depressive but not guilt-related or negative symptoms.

Discussion: Our findings clearly differentiate the neural circuitry underlying depressive and negative symptoms, and even segregated across the two-factor structure of depression in SSDs. These findings support divergent neurobiological pathways of depressive symptoms and negative symptoms in people with SSDs. As treatment options are currently limited, rTMS to the bilateral DLPFC is worth exploring further for general depressive symptoms in people with SSDs.

S201. TEMPORO-FRONTAL MMN IN SCHIZOPHRENIA AND ITS ASSOCIATION WITH COGNITION, CLINICAL SYMPTOMS, AND FUNCTIONAL OUTCOME: AN ESTIMATED SOURCE-LEVEL EEG STUDY

Daisuke Koshiyama^{*1}, Makoto Miyakoshi², Kumiko Tanaka-Koshiyama³, Gregory Light⁴

¹*Department of Neuropsychiatry, The University of Tokyo,* ²*Swartz Center for Neural Computation, University of California San Diego,* ³*Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital,* ⁴*Department of Psychiatry, University of California San Diego*

Background: Mismatch negativity (MMN) is a sensitive translational biomarker of schizophrenia. MMN amplitude is reduced in schizophrenia patients and associated with clinical symptoms and impairments in cognitive and psychosocial functioning. While MMN is generated by temporo-frontal neural networks, the contribution of these sources to clinical implications has not been previously fully described. This study aimed to explore the impaired temporo-frontal MMN source relationships to cognition, clinical symptoms and functional outcome in schizophrenia patients.

Methods: We measured MMN using electroencephalography in 449 healthy subjects and 589 schizophrenia patients and evaluated cognition both in the groups and clinical symptoms and functional outcome in patients. We performed source level analyses using EEGLAB.

Results: We demonstrated that estimated temporo-frontal cortical MMN amplitude that was reduced in schizophrenia compared to healthy subjects contributed to wide range of cognition, clinical symptoms and functional outcome in patients. Cognitive function was mainly correlated with MMN in the prefrontal cortex in patients ($r = -0.13$, $p = 0.0087$); MMN in the temporal cortex was correlated with negative symptoms ($r = -0.15$, $p = 0.0050$) and functional outcomes ($r = 0.16$, $p = 0.0035$) in patients. Secondary analyses showed a correlation between hallucination and MMN in the left middle temporal cortex in patients ($r = -0.14$, $p = 0.0092$).

Discussion: It is an interesting and important phenomenon that MMN reflects different clinical symptoms in various regions in the brain. Clarification of the neural mechanisms underlying the MMN source locations detected in this study, in both future clinical and animal studies, will strengthen the utility of MMN as a translational brain marker; this should further pave the way for clarifying the pathophysiology of schizophrenia and the development of novel drugs.

S202. GRAY MATTER COVARIANCE NETWORKS ASSOCIATED WITH SEVERITY OF CLINICAL SYMPTOMS BEFORE AND AFTER SWITCHING TO CLOZAPINE IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

Wi Hoon Jung^{*1}, Euitae Kim²

¹Gachon University, ²Seoul National University Bundang Hospital

Background: Investigations have demonstrated that patients' use of antipsychotic medications is associated with loss of gray matter volume (GMV) (Lawrie, 2018). In patients with treatment-resistant schizophrenia taking clozapine, reductions in GMV have been observed, especially in cortico-striatal regions such as the caudate and putamen (Mouchlianitis et al., 2016). However, to date, the effects of clozapine on brain alteration, particularly GMV, and its association with clinical symptoms have been primarily investigated using univariate approaches [i.e., voxel or cluster level of inference on GMV maps generated from voxel-based morphometry (VBM)]. Adoption of a multivariate approach – source-based morphometry (SBM), a multivariate extension of VBM utilizing spatially independent component analysis (ICA) to obtain patterns of common GMV variation among participants (hereinafter referred to as “gray matter covariance network”) – may be more powerful in ascertaining the effects of clozapine on brain structures and their association with clinical symptoms (Xu et al., 2009; Kašpárek et al., 2010). Therefore, here we apply SBM to investigate differences between pre- and post-switching to clozapine in gray matter covariance networks and the association between clinical symptom severity (i.e., total PANSS scores) and the networks.

Methods: We recruited patients with schizophrenia ($n = 38$) planning to start clozapine and prospectively investigated changes in symptom severity (total Positive and Negative Syndrome Scale [PANSS] scores) and structural brain, particularly GMV. Of these, data from 29 patients (18 females; age [mean±S.D.], 35.66 ± 10.75 years old; duration of illness, 102.97 ± 100.72 months) were used in the final analysis due to several reasons (e.g., poor image quality or dropout). T1-weighted brain magnetic images were obtained before and 18 weeks after the initiation of clozapine treatment. The VBM method with the Computational Anatomy Toolbox (CAT) was performed to extract GMV images. Next, the SBM method with the GIFT toolbox was applied to the GMV images of all participants to extract 41 gray matter covariance networks. The number of independent components (ICs; i.e., gray matter covariance networks)

was determined by the minimum description length (MDL) algorithm. Based on the stability index (GREATER THAN 0.95) for ICA estimate-clusters, 15 ICs were selected and used for the subsequent statistical analyses. For the fifteen ICs, paired t-tests were performed to investigate which networks' loading coefficients changed significantly after switching to clozapine. We then performed correlation analyses between each network's loading coefficient and total PANSS score over time to determine which networks' loading coefficient was associated with clinical symptom severity (i.e., total PANSS score). Significant threshold was set at p LESS THAN 0.05 and corrected for multiple comparisons using Bonferroni correction (i.e., p LESS THAN 0.0033 = 0.05/15).

Results: We observed a significant improvement in patients' symptoms after treatment with clozapine (total PANSS score before and after treatment [mean±S.D.], 71.45±13.35 and 60.41±7.56; total PANSS score reduction after treatment, 14.18±10.49%, t-value = 3.87; p LESS THAN 0.001). We then observed a significant decrease in the loading coefficients of IC 10, composed of striatum, after switching to clozapine (t = 11.61, p LESS THAN 0.001). We also found that the total PANSS score was positively associated with the loading coefficients of IC 9, composed of thalamus and cerebellum, over time (r = 0.45, p LESS THAN 0.001).

Discussion: Consistent with previous studies, this study confirmed structural brain changes in the striatum after switching to clozapine, showing a reduced loading coefficient of IC 10. This study also showed that patients' clinical symptom severity was related to specific gray matter covariance networks (IC 9), composed with the thalamus and cerebellum. These results provide evidence that the use of clozapine can lead to improvement in clinical symptoms and changes in brain structure in the patients with treatment-resistant schizophrenia. These results also suggest that the severity of clinical symptoms may be related to specific brain structures.

S203. ANTIPSYCHOTIC UTILIZATION PATTERNS IN SCHIZOPHRENIA-SPECTRUM DISORDER PATIENTS BETWEEN 2006 AND 2016 IN HONG KONG: A POPULATION-BASED COHORT STUDY

Catherine Zhiqian Fan¹, Nicole Lau¹, Joe Kwun Nam Chan¹, Corine Sau Man Wong¹, Wing Chung Chang^{*1}

¹The University of Hong Kong,

Background: There are limited studies examining real-world antipsychotic use in patients with schizophrenia-spectrum disorders (SSD). Previous studies found an increasing trend in the antipsychotic prescription rates in SSD in some Western countries, while some studies identified an opposite trend in Asian regions. We aimed to examine antipsychotic utilization patterns and the temporal trends in SSD patients in Hong Kong between 2006 and 2016.

Methods: This population-based cohort study comprised 32,128 patients aged 18 years or above diagnosed with SSD between January 2006 and December 2016. The cohort was extracted from a territory-wide medical record database of public healthcare services in Hong Kong. The annual prevalence was calculated for any antipsychotic, first-generation antipsychotic (FGA) only, second-generation antipsychotic (SGA) only, FGA+SGA (i.e., use of both FGA and SGA in a year), and individual antipsychotic agents. Joinpoint regression analysis was performed to examine temporal changes in antipsychotic prescription. We calculated average annual percent change (AAPC) and annual percent change (APC) to examine the trends during the study period.

Results: Annual prevalence of overall antipsychotic use decreased over the study period with an AAPC of -1.76 ([-1.84–1.68]; p LESS THAN 0.001). There was a steeper decrease in antipsychotic prevalence (APC: -2.40; [-2.83–1.96]; p LESS THAN 0.001) from 2006 to 2008, followed by a lesser degree of decrease (APC: -1.60; [-1.65–1.957]; p LESS THAN 0.001) during 2008-2016. Over 11 years, the use of SGA increased with an AAPC of 8.00 ([7.84–8.17]; p LESS THAN 0.001), while FGA decreased steadily with an AAPC of -7.99 ([-8.63–7.35]; p LESS THAN 0.001). For FGA only and SGA only, the two-joinpoint model is selected as the optimal solution (FGA: wBIC = 1.08; SGA: wBIC = 0.79). A one-joinpoint model is selected for FGA+SGA (wBIC = 1.52). The FGA and SGA prevalence trends intersected at 2010. The FGA+SGA use over the 11 years was relatively stable with an AAPC of 0.85 ([-0.06–1.77]; p=0.07). Risperidone, olanzapine, and haloperidol represented the three most frequently-prescribed individual antipsychotic agents over 11 years. In particular, risperidone (AAPC: 10.11 [9.38–10.86]; p LESS THAN 0.001) and olanzapine (AAPC: 11.97 [9.67–14.32]; p LESS THAN 0.001) showed the sharpest increase in prevalence over the study period.

Discussion: Our results show decreasing antipsychotic prevalence among SSD patients in Hong Kong from 2006 to 2016, which adds supporting evidence to previous findings in other Asian countries. The heterogeneity in antipsychotic prevalence between Asian and Western countries may be explained by differences in cultural context, healthcare system and prescribing practices. Also, we affirm the rising SGA use and declining FGA use across years. Future research should clarify if utilisation patterns regarding the antipsychotic polypharmacy and the usage of long-acting injectable formulation and clozapine for treatment-resistance SSD.

S204. PATTERN OF USE OF CLOZAPINE IN ARGENTINA

Alejo Corrales^{*1}, Federrico Rebok², Manuel Villapriño³, Pedro Damian Gargoloff⁴

¹Argentine National University UNT, ²Hospital "Dr. Braulio A. Moyano", Servicio de Emergencia, ³Departamento de Neurociencias., Facultad de Ciencias Medicas. Universidad de Cuyo, ⁴Hospital "Dr. Alejandro Korn", Servicio de Subagudos Hombres.,

Background: Clozapine is a complex antipsychotic with binding affinities for a wide variety of receptors and pharmacologically active metabolites. Clozapine is currently the most effective antipsychotic in the therapy of Treatment Resistant Schizophrenia (TRS), however clozapine is not effective in 40-70 % of patients with adequate dosage and duration [2]. The term treatment resistance is widely used in the context of psychiatric disorders, but defining it, both conceptually and in practice, has proven to be complex. The concept of TRS remain inconsistent and vary considerably between countries. A number of pharmacological and non-pharmacological approaches for TRS have been evaluated in clinical trials. Despite the efficacy of clozapine in the treatment of TRS, there is some evidence that it is underutilized in patients with this condition. There are a variety of potential reasons for this underutilization, including concerns regarding side-effects and differences in local practice patterns. To date there is no data about pattern of use of clozapine in Argentina.

Objectives: 1-To describe clozapine treatment patterns among psychiatrists in Argentina. 2-To compare if the use is in accordance to international standard. 3-To assess the management patterns of those patients with schizophrenia resistant to clozapine.

Methods: This was an Argentinean study, utilizing an online survey that was conducted between May to August 2020. The questionnaire was administrated through google drive

platform. A cross-sectional questionnaire including 24 common issues related to clozapine therapy divided into three sections, was distributed to psychiatrists treating schizophrenic patients and answered anonymously. The first section includes items detailing professional practices characteristics; the second section includes items asking about the use of clozapine for the treatment schizophrenia, the third section includes items about management of clozapine resistant treatment patients. Statistical analysis was performed using Chi-Square test.

Results: Key findings of the clozapine patten use survey of Argentina show that 57.4% of psychiatric clozapine prescribers work in both public and private practice. The majority of the surveyed psychiatrists manage psychotic disorders (98.2%) as well as mood disorders (94.1%), anxiety disorders (89.9%) and personality disorders (74.2%), and 62.3 % manage 10 or less patients under clozapine treatment. TRS was the main indication of clozapine treatment, however lack of antipsychotic response without full criteria of TRS was also considered an indication. Although, increasing the clozapine plasma levels was considered the first strategy utilized in persistent positive negative and mixed symptoms, clozapine combined with other antipsychotic drugs has also been considered. Augmentation of clozapine with a mood stabilizer was a frequently selected strategy for treating patients with suicidal and aggressive behavior. There is not a statistically significant differences regarding the relationship between the two variables. (Chi Square=1.2, df=1, p GREATER THAN .05).

Discussion: We observe that, like other countries, clozapine is underutilized in patients with TRS. Perhaps the reason of this underutilization is the fact of that there is not a local TRS treatment guideline. The doses and clozapine indication were consistent with international standards. Regarding the management of clozapine fails in TRS, similar strategies were observed in our sample compared to international recommendations.

S205. ROLE OF THE GUT MICROBIOME IN ABSORPTION OF ARIPIPRAZOLE AND QUETIAPINE IN SCHIZOPHRENIA SPECTRUM AND BIPOLAR DISORDER PATIENTS

Anton Scheurink*¹, Jenny Borkent¹, Magda Iouannou¹, Bartholomeus C. M. Haarman², Iris Sommer³

¹University Medical Center Groningen, ²Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands, ³UMC Groningen

Background: The human gut microbiome has been recognized as a key factor in absorbing and digesting medicine. Especially the absorption of medicines with low solubility, such as antipsychotic medications (APM), may be influenced by composition of the gut microbiome. It is unclear which features of the microbiome are beneficial or detrimental to APM absorption and transformation. More insight on this topic may optimize current treatments and improve response rates to APM. To this end, we analyzed early data of the gut microbiome and uptake of APM of patients with a schizophrenia spectrum or bipolar disorder.

Methods: We collected stool samples, blood plasma samples and self-reports on oral APM use from patients with a schizophrenia spectrum or bipolar disorder. Stool samples were frozen and stored at -80 degrees Celcius. Microbial DNA was isolated from the stool samples using the QIAamp Fast DNA Stool kit and were shotgun-sequenced using the Illumina Novaseq 6000, by Novogene, UK. Absorption of APM was determined by dividing plasma APM levels by reported APM dose. Analysis was performed in R using Mia within the Bioconductor environment.

Results: 23 patients (4 SSD, 19 BD; 20 female, 3 male) used quetiapine and 11 (10 SSD, 1 BD; 5 female, 3 male) used aripiprazole. Whether participants used aripiprazole or quetiapine did not significantly explain variance between microbiome samples (explained variance = 0.03, $p = 0.28$). BMI near-significantly explained 3 percent of variance between samples ($p = 0.051$). Reported medication intake and plasma concentrations of APM correlated well for both quetiapine (adjusted $R^2 = 0.28$, $p = 0.006$) and aripiprazole (adjusted $R^2 = 0.60$, $p = 0.003$). When corrected for age, we found a negative significant relation between alpha diversity and uptake of aripiprazole (standardized $b = -0.6 \pm 0.2$, $p = 0.04$, model $p = 0.04$, adjusted $R^2 = 0.43$), but not for quetiapine (standardized $b = -0.1 \pm 0.2$, $p = 0.54$, model $p = 0.75$, adjusted $R^2 = -0.07$). However, this relationship between alpha diversity and aripiprazole uptake disappears when also including BMI as a covariate (standardized $b = -0.6 \pm 0.5$, $p = 0.26$, model $p = 0.07$, adjusted $R^2 = -0.46$), which may be due to our small sample size.

Discussion: This pilot projects hints that there may be a link between low gut microbiome diversity and the increased absorption of APM. This is somewhat in line with animal studies reporting that antibiotic depletion of the microbiome leads to increased bioavailability of olanzapine. Interestingly, decreased species diversity is also associated with metabolic problems such as obesity and cardiovascular problems. For now, our study does not include enough data to identify individual responsible bacterial species. Our future analysis of new stool samples may help elucidate these issues and reduce the response rates to current APM.

S206. RISK OF CONGENITAL MALFORMATIONS ASSOCIATED WITH FIRST-TRIMESTER EXPOSURE TO ANTIPSYCHOTICS: A POPULATION-BASED COHORT STUDY

Kwun Nam Chan^{*1}, Krystal Chi Kei Lee², Corine Sau Man Wong³, Wing Chung Chang⁴

¹*Li Ka Shing Faculty of Medicine, University of Hong Kong*, ²*Department of Psychiatry, School of Clinical medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong*, ³*School of Public Health, LKS Faculty of Medicine, The University of Hong Kong*, ⁴*Department of Psychiatry, School of Clinical medicine, LKS Faculty of Medicine, The University of Hong Kong*

Background: A growing number of studies has evaluated the teratogenic effects of antipsychotics. A recent meta-analysis revealed that first-trimester exposure to second-generation antipsychotics (SGA) was associated with increased risk of major congenital malformations. Yet, prior studies were generally based on small sample size and did not take into consideration important confounding effect of maternal physical and psychiatric morbidities. This study aimed to examine the risk of major and organ-specific congenital malformations among infants exposed to SGA, first-generation antipsychotics (FGA) and commonly-prescribed antipsychotic agents.

Methods: This population-based cohort study comprised 465,069 pregnant women (of which 419 and 420 redeemed ≥ 1 prescription of SGA and FGA during first-trimester, respectively) aged 15–50 years who gave a singleton livebirth or stillbirth between January 2003 and December 2018, using a territory-wide medical-record database of public healthcare services in Hong Kong. Propensity-score (PS)-adjusted logistic regression analyses were conducted to examine the risk of congenital malformations following first-trimester exposure to antipsychotic classes (SGA and FGA), and six most frequently-prescribed individual antipsychotics. Exploratory analyses were also performed to evaluate dose-response

relationship by assessing associations of dose levels (i.e., high, low and unexposed) of individual antipsychotics with the risk of major congenital malformations.

Results: Prevalence of any major malformations was 4.9% (95% CI: 4.9%-5.0%) in unexposed infants, 9.1% (6.7%-12.3%) in SGA-exposed infants, and 6.2% (4.3%-9.0%) in FGA-exposed infants. Exposure to SGA (adjusted odds ratio: 1.59 [95% CI: 1.03–2.38]), but not FGA (1.29 [0.79-2.02]), was associated with an increased risk of major malformations. Among individual antipsychotics, quetiapine (1.99 [1.15–3.29]) and risperidone (in sensitivity analysis on women with psychiatric-diagnosis; 3.81 [1.49–9.77]) were associated with elevated rates of major malformations. Analyses stratified by dose levels revealed that only high-dose quetiapine exposure was related to increased risk of major malformations (2.51 [1.14–4.95]). A significant association between SGA and an increased risk of respiratory-system anomalies was noted (5.00 [1.05–15.46]). Generally, the significant results were inconsistent across sensitivity analyses, precluding firm conclusions.

Discussion: Our study observed a small increased risk of major malformations associated with SGA and quetiapine in a predominantly Chinese population, which was not robustly affirmed in sensitivity analyses. On the whole, our findings did not provide strong evidence of the association of prenatal antipsychotic exposure and increased risk for congenital malformations. Research with large sample size clarifying comparative safety of individual antipsychotics on specific malformations is warranted to provide clinically-useful data on the risk of teratogenicity that can better inform the complex decision-making in the maintenance or discontinuation of antipsychotic treatment during early pregnancy.

S207. A META-ANALYSIS OF AUGMENTATION THERAPY WITH SEROTONIN1A RECEPTOR PARTIAL AGONISTS ON COGNITIVE FUNCTION IN SCHIZOPHRENIA

Tomiki Sumiyoshi*¹, Ayumu Wada², Andrew Stickley², Yuma Yokoi², Risa Yamada²

¹*Department of Preventive Intervention for Psychiatric Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry*, ²*National Center of Neurology and Psychiatry*

Background: The use of serotonin (5-HT)_{1A} receptor partial agonists (5-HT_{1A}- PAs) of the azapirone class (e.g., buspirone and tandospirone) as an add-on therapy was associated with beneficial effects on psychotic symptoms, especially positive symptoms, in patients with schizophrenia (Yamada et al. IJNP 2023). By conducting a systematic review and meta-analysis, we evaluated whether augmentation with 5-HT_{1A}-PAs would improve specific domains of neurocognitive function in schizophrenia patients.

Methods: A literature search was performed from 1987 to May 2023 to identify randomized controlled trials. The standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated when there were 2 or more studies (Yamada et al. Schizophr Res Cogn 2023).

Results: Random-effects model meta-analyses revealed that add-on therapy with buspirone or tandospirone had a significant beneficial effect on attention/processing speed (SMD = 0.37, 95% CI = 0.12 to 0.61). By contrast, these 5-HT_{1A}-PAs did not have a significant effect on verbal learning (SMD = 0.08, 95 % CI = 0.31 to 0.47) or working memory (SMD = 0.15, 95 % CI = 0.09 to 0.39). Regarding executive functions (Wisconsin Card Sorting Test), positive but non-significant results were seen with the category number (SMD = 0.26, 95 % CI = 0.81

to 1.32), while non-significant effects were noted for percent preservation errors (SMD = 0.10, 95 % CI = 0.53 to 0.33).

Discussion: These findings support the idea that some compounds that stimulate 5-HT1A receptors provide an effective pharmacologic enhancer for a key domain of cognition in patients with schizophrenia. Further studies with various types of 5-HT1A agonists, e.g., brexpiprazole and ulotaront, are warranted to examine the potential cognitive efficacy of optimally stimulating these receptors.

S208. EFFECTS OF CANNABIDIOL ON GLUTAMATE, PERFUSION AND EMOTION PROCESSING FMRI IN PSYCHOSIS RISK

Cathy Davies^{*1}, Matthijs Bosson², Daniel Martins¹, Robin Wilson¹, Elizabeth Appiah-Kusi¹, Grace Blest-Hopley¹, Paul Allen¹, Fernando Zelaya¹, David Lythgoe¹, Michael Brammer¹, Jesus Perez³, Philip McGuire⁴, Sagnik Bhattacharyya¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*Brain Center Rudolf Magnus, University Medical Center Utrecht*, ³*CAMEO Early Intervention Service, Cambridgeshire and Peterborough NHS Foundation Trust*, ⁴*University of Oxford*

Background: The pathophysiology driving psychosis onset is thought to involve dysfunction in a hippocampal-midbrain-striatal circuit. Evidence suggests that patients at Clinical High Risk (CHR) for psychosis show altered levels of hippocampal glutamate, elevated hippocampal/striatal perfusion, and emotion-processing deficits associated with aberrant neural responses (particularly to fear-related stimuli) in these regions. Cannabidiol (CBD) is a non-intoxicating constituent of the cannabis plant with antipsychotic and anxiolytic properties. Previous work suggests that CBD modulates hippocampal glutamate, cerebral perfusion and activation within the mediotemporal cortex and striatum during various emotional/cognitive paradigms. However, whether CBD has ameliorative effects on these parameters in CHR individuals remains unclear.

Methods: Using a randomised, double-blind, parallel-group design, 33 CHR patients were randomised to a single oral dose of CBD (600 mg) or placebo. Healthy controls (n=19) were studied under identical conditions but did not receive any drug. Participants underwent 3T MRI during a fearful face-processing paradigm (fMRI) to measure mediotemporal and striatal activation, arterial spin labelling (ASL) to examine hippocampal perfusion, and 1H-MRS to measure hippocampal glutamate. Differences related to the CHR state (CHR-placebo vs controls), effects of CBD (CHR-placebo vs CHR-CBD), and linear relationship analyses (i.e. for CHR-placebo GREATER THAN CHR-CBD GREATER THAN controls, or vice versa) were examined for all three imaging modalities.

Results: During fear processing, relative to controls the CHR-placebo group showed significantly greater activation in the parahippocampal gyrus but lower striatal activation (all pcorr LESS THAN .01). Within these regions, activation in the CHR-CBD group was significantly intermediate between that of CHR-placebo and healthy controls (all pcorr LESS THAN .01). The CHR-placebo group also had significantly greater hippocampal perfusion bilaterally vs controls (both pFWE LESS THAN .01), and a significant linear relationship was identified in a small right hippocampal cluster (pFWE=.035), such that CHR-placebo GREATER THAN CHR-CBD GREATER THAN controls. Finally, CHR-placebo patients had significantly lower hippocampal glutamate relative to controls (p=.015), and a significant linear relationship was observed across groups, such that controls GREATER THAN CHR-CBD

GREATER THAN CHR-placebo ($p=.031$). However, direct CBD vs placebo effects were only observed for the fMRI results.

Discussion: Our findings suggest that CBD may partially modulate function of the neural circuitry implicated in aberrant emotion processing and psychosis onset, and in a direction indicative of normalisation. These results add to evidence that CBD may be a promising novel therapeutic for CHR patients. Further (within-subject) research is required to replicate these findings and examine whether acute neurofunctional/physiological effects translate into clinical efficacy after a period of treatment.

S209. ANTIPSYCHOTICS AND BRAIN INSULIN ACTION: A DOUBLE-EDGED SWORD

Sally Wu^{*1}, Laurie Hamel², Sandra Pereira², Roger Raymond², Raghunath Singh², Emily Au¹, Dan Li³, Jose Nobrega², Adria Giacca⁴, Ariel Graff², Gary Remington², Margaret Hahn², Sri Mahavir Agarwal²

¹*Institute of Medical Science, University of Toronto*, ²*Centre for Addiction and Mental Health (CAMH)*, ³*University of Toronto*, ⁴*Department of Psychiatry, University of Toronto*

Background: Antipsychotics (APs) are the cornerstone of treatment in schizophrenia but are associated with an increased risk of type 2 diabetes. While the field has primarily focused on metabolic effects induced by high liability agents such as clozapine and olanzapine, all APs have similar risk propensity for diabetes. APs have a highly heterogeneous receptor affinity, and all of them are, without exception, dopamine 2 receptor (D2R) antagonists. An interesting body of work suggest that the cross talk between central insulin and dopamine facilitates the antipsychotic effects of APs. However, this effect may be diminished with chronic treatment of APs as these agents induce central and peripheral insulin resistance, resulting in impairments in both metabolic health and cognition. Previous studies examining the effects of APs on insulin and glucose regulation has primarily focused on peripheral pathways. However, insulin receptors and insulin-responsive glucose transporters are widely distributed throughout the brain. Aberrant brain insulin signaling is posited to lie at the crossroads of metabolic and cognitive disorders, and evidence suggests that the central nervous system (CNS) is involved in AP-induced metabolic dysregulation. Our pilot data using [1-14C]2-deoxy-D-glucose (2DG) autoradiography suggests that olanzapine attenuates insulin-mediated glucose uptake across multiple regions in the brain. However, it is not known whether this effect is limited to olanzapine, or if other APs induce similar changes in brain insulin action. Thus, we want to further explore whether this is a class or D2R antagonism driven effect by using other APs such as haloperidol (HAL) (a D2R only antagonist) and raclopride (RAC) (a selective D2R antagonist).

Methods: 2DG autoradiography procedures were used to measure cerebral glucose uptake alongside a central infusion of insulin or vehicle into the third ventricle. Male rats were pretreated with HAL (0.25 mg/kg) or RAC (0.3 mg/kg) or vehicle. Each dose was chosen to reflect clinically relevant D2R occupancy (GREATER THAN 70%). Groups included (central-peripheral) vehicle-vehicle ($n = 6$), insulin-vehicle ($n = 6$), vehicle-HAL ($n = 6$), insulin-HAL ($n = 6$), vehicle-RAC ($n = 5$), and insulin-RAC ($n = 5$). Regions of interests for analysis included the frontal cortex, nucleus accumbens, hypothalamus, hippocampus, amygdala, cerebellum, and dorsal vagal complex, based on their role in metabolism, energy homeostasis,

and cognition. Regional tissue radioactivity was quantified on coded films using the MCID Elite system as an index of glucose uptake.

Results: Intracerebroventricular (ICV) insulin significantly increased cerebral glucose uptake in all regions of interests compared to ICV vehicle. This effect was attenuated by HAL and RAC, such that the levels of cerebral glucose uptake in the insulin-HAL and insulin-RAC groups were comparable to the control groups. Interestingly, the effect of HAL and RAC were not as potent compared to olanzapine, where in the insulin-olanzapine the level of cerebral glucose uptake was completely abolished.

Discussion: Acute dosing of HAL and RAC can induce central insulin resistance in the brain beyond areas responsible for metabolism and energy homeostasis, including areas involved in cognition. Our findings provide corroborating evidence that strengthen the role of the CNS in modulating peripheral AP-induced metabolic effects. Notably, our results demonstrate that all classes of APs may induce cerebral insulin resistance, and the culprit may be the effect of D2R antagonism. This knowledge may aid in translation to humans by suggesting treatment interventions targeting these mechanisms.

S210. BRAIN STRUCTURAL CHANGES AFTER ONE-WEEK EXPOSURE TO ANTIPSYCHOTICS IN HEALTHY VOLUNTEERS

Pierluigi Selvaggi^{*1}, Martin Osugo¹, Uzma Zahid¹, Thomas Whitehurst², Ellis Chika Onwordi², Ben Statton², Tobias Wood¹, Valeria Finelli¹, George Chapman², Robin Murray¹, Tiago Reis Marques¹, Mitul A Mehta¹, Oliver Howes¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital*

Background: The effect of antipsychotics on brain structure is still hotly debated. Studies in patients reported mixed results with difficulties in separating disease and treatment effects. Single-dose studies in healthy volunteers (HV) have shown no change or reduction in striatal volumes. Pre-clinical studies in rodents reported reduced cortical and increased striatal volumes. In addition, some authors have questioned whether changes or differences in brain volumes assessed with MRI might represent epiphenomena of different biochemical or physical effects not necessarily linked with the pathophysiological process. Nonetheless, determining the effects of antipsychotics on brain physiology is critical to the understanding of biological mechanisms driving their clinical efficacy side effects.

Methods: A total of 50 HV (28 females, mean age 26.7 years) completed a double-blinded, randomized, crossover, placebo-controlled study composed of two arms. In Arm 1 participants (N= 25, 14 females) received either amisulpride 400mg or placebo daily for seven days. In Arm 2 (N= 25, 14 females) participants received either aripiprazole 10mg or placebo daily for seven days. MRI was performed at the end of each treatment period. The MP2RAGE sequence was used to derive T1-weighted (T1w) images and T1 maps. T1 mapping is more informative on brain microstructure as compared with standard T1w images as it can measure the magnetic resonance properties of the tissue (e.g., T1 relaxation time) quantitatively. T1w-images were processed using FreeSurfer to extract brain volume, cortical thickness, and cortical surface. We focused on striatal changes in light of earlier results. Eight striatal ROIs were selected from the subcortical parcellation available in FreeSurfer to extract volume and T1 signal. In each ROI, the main effects of the condition (i.e., drug or placebo) within each arm and the condition-by-arm interaction were tested by applying FDR correction. The same analysis was also performed

on cortical thickness and surface. Also, both T1w images and T1-maps entered a whole-brain voxel-wise analysis in FSL randomise. In all analyses order (i.e., drug first or placebo first) was used as a covariate of no interest.

Results: The ROI analysis in the striatum revealed an increased volume in the left putamen after amisulpride (pFDR= 0.042) and in the right putamen after aripiprazole (pFDR= 0.016). No other main effects or condition-by-arms interaction were found in the ROI analysis (all pFDR GREATER THAN 0.291). No main effects of condition or condition-by-arms interaction were found in ROI analysis on T1 maps (all pFDR GREATER THAN 0.253). We did not find differences between amisulpride/aripiprazole and placebo or condition-by-arm interactions in the whole-brain voxel-wise analyses. No main effects or interactions were found on cortical thickness and surface metrics.

Discussion: These results are in line with pre-clinical and longitudinal studies in patients reporting increased striatal volume after exposure to antipsychotics. The lack of an effect on quantitative T1 maps may suggest that the volumetric changes observed here and in previous studies do not reflect actual changes in brain tissue. It might be possible that other factors (e.g., peripheral effects or changes in water content) could explain changes in brain volume. Another possible interpretation is that short-term exposure produces small-to-negligible effects, and that long-term exposure is needed to produce tissue remodelling. Taken together these results encourage further investigations aimed at clarifying whether changes detected with MRI after short- and long-term antipsychotic exposure are associated with brain tissue microstructural changes or are rather only "apparent" morphometric changes.

S211. THE EVER-GROWING CASE FOR CLOZAPINE IN THE TREATMENT OF SCHIZOPHRENIA: AN OBLIGATION FOR PSYCHIATRISTS AND PSYCHIATRY

Robert Bittner*¹, Mishal Qubad²

¹*University Hospital Frankfurt, Goethe University,* ²*Goethe University*

Background: Like no other medication, clozapine epitomizes two fundamental challenges in the pharmacotherapy of schizophrenia: a dearth of innovation, and insufficient implementation of established treatments. Clozapine remains the most effective antipsychotic and the only drug approved for treatment-resistant schizophrenia (TRS) – not least, because the neurobiological underpinnings of its unique efficacy continue to elude researchers. Consequently, clozapine should be widely used for TRS but also for certain non-TRS patients. Yet, only a fraction of suitable patients actually receives clozapine – often years after treatment resistance becomes evident. Analyzing the causes and consequences of this problem is crucial for substantially improving the quality of care for TRS patients.

Methods: In this review, we contrast the literature advocating its safe and effective use with current evidence regarding the causes and consequences of clozapine underutilization. We based our review on a Medline and Google Scholar search for all relevant topics, selecting both relevant individual clinical studies as well as meta-analyses and reviews. We included all articles that were published until January 2023. We searched for publications containing the following MeSH terms: treatment-resistant schizophrenia [AND] criteria, treatment-resistant schizophrenia [AND] treatment, treatment-resistant schizophrenia [AND] neurobiology, clozapine [AND] xx, with xx reflecting the topic we aimed to focus at that timepoint (e.g. side effects, neutropenia, agranulocytosis, hypersalivation, pneumonia, myocarditis, withdrawal, discontinuation, metabolic syndrome, gastrointestinal side effects, sedation, mortality,

pharmacokinetics, pharmacodynamics, clinical effects, clozapine-resistant schizophrenia, shared decision-making, patient satisfaction).

Results: Clozapine has a singular impact on key mediators of poor illness outcome. It is the most effective drug for improving positive symptoms and global psychopathology both in the most severely ill and in the full spectrum of patients. Its effects on negative and depressive symptoms rank among the best of all antipsychotics. Clozapine shows superior anti-suicidal efficacy and the largest reduction of aggression. It also decreases the risk for new and persisting co-morbid substance use disorders (SUDs). Additional long-term benefits include improved treatment adherence and reduced rehospitalization rates. Furthermore, clozapine is the most effective antipsychotic for reducing all-cause mortality in TRS. Delaying clozapine treatment has a negative impact on long-term outcome. Patients' experience with clozapine treatment is largely positive despite a comparatively high rate of side effects. Patients prefer clozapine, while psychiatrists regard it as a burden due to concerns regarding safety and side effect management. Shared decision-making, which increases the likelihood of a clozapine recommendation, is not routinely used, possibly due to stigmatization of TRS patients.

Discussion: Compared to all other available pharmacological treatment options the broad beneficial impact of clozapine on patients' life remains second to none. The mortality-reducing effects of clozapine alone warrant its regular use. Therefore, psychiatrists must not exclude patients from the decision regarding a clozapine trial by not even offering it. Rather, they have a clear obligation to align their actions more closely with the existing evidence and patients' needs and to facilitate the timely initiation of clozapine.

S212. EFFECTS OF ANTICHOLINERGIC BURDEN ON FUNCTIONING IN FIRST-EPISODE PSYCHOSIS

Agnes Belkacem^{*1}, Katie Lavigne², Ridha Joober³, Ashok Malla³, Jai Shah⁴, Martin Lepage³

¹McGill University, ²McGill University; Douglas Mental Health University Institute; Montreal Neurological Institute-Hospital, ³Douglas Mental Health Research Institute, ⁴Douglas Mental Health University Institute

Background: Treatment for a first-episode of psychosis (FEP) typically begins with antipsychotics. However, these medications and others (e.g., antidepressants) may have an anticholinergic burden, i.e., an accumulation of medications that block the cholinergic system. Recent evidence suggests that anticholinergic burden is associated with cognitive deficits and some studies have reported an association between the two. However, very few have examined a link between the two in the early stages of the disease, whether cross-sectionally or longitudinally. We hypothesized that FEP patients with the highest anticholinergic burden would show the poorest levels of functioning compared to those in the low anticholinergic burden group at program entry (three months after admission). Longitudinally, we expected all groups to improve at month 12, but the high anticholinergic burden group would still have the lowest level of functioning.

Methods: Patients (n=444) completed the Social and Occupational Functioning Assessment Scale (SOFAS) at both timepoints. They were divided into two groups; low anticholinergic burden (n=349) and high anticholinergic burden (n=95), based on a Drug Burden Index (DBI) cutoff of 1.

Results: Our results suggest that patients exposed to a high anticholinergic burden have reduced functioning compared with those with a low anticholinergic burden ($F(1,439)=4.40$, P

LESS THAN 0.05). Our longitudinal results indicate that although functioning may improve over time, patients exposed to a high anticholinergic burden have reduced functioning compared to those in the other group ($\chi^2=5.52$, $df=1$, P LESS THAN 0.05).

Discussion: Our study highlights the need to properly assess exposure to anticholinergic burden when prescribing medication for psychosis.

S213. EXPOSURE TO CHRONIC STRESS PRODUCES MOTIVATIONAL ANHEDONIA AND SOCIABILITY DEFICITS IN RATS: RESTORATIVE PROPERTIES OF CHRONIC LURASIDONE TREATMENT

Marco Andrea Riva^{*1}, Veronica Begni¹, Alessia Marchesin¹, Eleonora Corridori², Sara Salviati², Simona Scheggi²

¹University of Milan, ²University of Siena

Background:

Exposure to stress is one of the most important factors for the development of mental disorders. Indeed, exposure to stress may interfere with an array of neurobiological mechanisms leading to the manifestation of selected psychopathologic domains that represent an important target for pharmacological interventions. With this respect, stress-based animal models are instrumental in investigating the occurrence of specific behavioral deficits, their molecular underpinnings as well as the potential impact for drug treatment. As an example, we have previously demonstrated that chronic treatment with lurasidone, a multi-receptor antipsychotic drug, is able to normalize consummatory anhedonia in the chronic mild stress model [1] [2]. In the present study, we used two different stress paradigms to investigate the ability of lurasidone to ameliorate motivational anhedonia as well as reduced sociability, which represent key psychopathologic domains that are shared between different disorders and that have a strong impact on patient functioning.

Methods: In the first experimental paradigm, Sprague-Dawley male rats were exposed to an unavoidable chronic stress (UCS) protocol for 3 weeks in order to disrupt the motivation to acquire a reward-directed behavior [3]. Motivational anhedonia was assessed using sucrose self-administration in operant chambers provided with one active lever delivering a sucrose pellet. Rats were tested in fixed-ratio (FR) sessions (FR-1 and FR-5) as well as in the progressive ratio (PR) task. After having established the behavioral deficit, the animals ($n=10$ /experimental group) were then divided into two subgroups that continued (or did not) stress exposure and received vehicle or lurasidone (3 mg/kg) once daily. Next, to verify their reactivity to avoidable aversive stimuli, stressed animals were exposed to the escape test. In the second paradigm, we used the social defeat stress model to investigate motivational deficits as well as to study sociability impairment as a consequence of stress exposure and the modulation by chronic lurasidone treatment.

Results: We confirmed that exposure of rats to UCS was able to produce a significant reduction in the competence to acquire self-administration, at FR1 and FR5 schedules. Moreover, UCS rats show impaired motivation in the progressive ratio protocol (-50% in breaking point, p LESS THAN 0.001 vs. control/vehicle). After two weeks of drug administration, lurasidone treatment at the lowest dose (3 mg/kg) was able to rescue the motivation in stressed rats, an effect that was not observed using the highest dose (10 mg/kg) of the antipsychotic drug. Conversely, when we investigated the emotional reactivity to negative stimuli, we found that

animals exposed to UCS and treated with vehicle showed a significant impairment of the escape competence and that such changes were restored by chronic treatment with lurasidone at both doses. The social defeat model was also associated with motivational deficits that were improved by lurasidone (3 mg/kg), a treatment that was fully effective in restoring sociability deficits in rats exposed to stress.

Discussion: Conclusions

In summary, these novel data provide support for the ability of lurasidone treatment to ameliorate different psychopathologic domains, including impaired motivation and reduced sociability, which represent core elements for the disability associated with mental disorders.

References:

- [1] Luoni A. et al., *Int J Neuropsychopharmacol.* 18(4):1–12, 2015.
- [2] Rossetti A.C. et al., *Int J Neuropsychopharmacol.* 21(9):883-893, 2018.
- [3] Scheggi, S. et al., *Neuroscience*, 291, 189–202, 2015.

S214. EFFECTS OF ALSTONINE ON MK-801-INDUCED BEHAVIORS IN ZEBRAFISH

Leonardo Bastos^{*1}, Matheus Gallas-Lopes¹, Thailana Stahlhofer-Buss¹, Stefani M. Portela¹, Rafael Chitolina¹, Carlos G. Reis¹, Sofia Z. Becker¹, Maurice M. Iwu², Angelo Piato¹, Elaine Elisabetsky¹, Ana P. Herrmann¹

¹*Universidade Federal do Rio Grande do Sul*, ²*Bioresources Institute of Nigeria*

Background: Alstonine (ALS) is an indole alkaloid identified as the major compound of a plant-based remedy traditionally used in Nigeria to treat mentally ill patients. Studies using mice showed that ALS behaves as an antipsychotic, counteracting behavioral phenotypes associated with positive (MK-801-induced hyperlocomotion and apomorphine-induced stereotypy), negative (MK-801-induced social withdrawal) and cognitive (MK-801-induced induced memory deficits) symptoms of schizophrenia. However, the external validity of these findings is limited by the use of a single model organism, justifying the need to further explore the therapeutic potential of ALS. This study aimed to evaluate the effects of acute administration of ALS on MK-801-induced behavioral phenotypes in zebrafish (*Danio rerio*).

Methods: 120 male and female adult short-fin wild-type zebrafish (4 months old, 300-500 mg) were used. Fish were allocated to the treatment groups (n=15) using block randomization to counterbalance baseline characteristics (sex, home tank, and day of testing). Animals were individually exposed to 200 mL of water or ALS at 2.5, 5 or 10 mg/L for 20 min, and then exposed to either water or 5 μ M MK-801 for another 20 minutes. Social preference, locomotion, and stereotypic behavior were assessed using the social preference (SPT) and the open tank (OTT) tests. The ANY-Maze software was used for outcome assessment by researchers blinded to the treatment groups. Data were analyzed by two-way ANOVA, with ALS pretreatment and MK-801 treatment as the main factors; Bonferroni post hoc test was applied as appropriate. All procedures were approved by the ethics committee at Universidade Federal do Rio Grande do Sul (no. 48858).

Results: In the SPT, MK-801 induced social withdrawal and hyperlocomotion, as indicated by a decrease in the time spent in the interaction zone (MK-801 main effect: $F_{1,112} = 28.73$, $p=0.0001$) and an increase in the total distance traveled (MK-801 main effect: $F_{1,112} = 12.05$, $p=0.0007$) in comparison to the control group. Unexpectedly, 5 and 10 mg/L ALS also

decreased the time spent in the interaction zone (ALS main effect: $F_{3,112} = 4.327$, $p=0.0063$) in comparison to the control group. Moreover, 5 mg/L ALS before MK-801 increased the number of crossings as compared to MK-801 alone (interaction effect: $F_{3,112} = 3.327$, $p=0.0222$). In the OTT, MK-801 decreased the total distance traveled (MK-801 main effect: $F_{1,112} = 40.23$, $p \text{ LESS THAN } 0.0001$), absolute turn angle (MK-801 main effect: $F_{1,112} = 113.2$, $p \text{ LESS THAN } 0.0001$), and clockwise rotations (MK-801 main effect: $F_{1,112} = 34.35$, $p \text{ LESS THAN } 0.0001$), while increased the time spent immobile (MK-801 main effect: $F_{1,112} = 61.34$, $p \text{ LESS THAN } 0.0001$). In this test, ALS was devoid of effects in all parameters. No sex effects were observed, so data were pooled together.

Discussion: Acute exposure to MK-801 induced behavioral alterations of translational relevance to schizophrenia in zebrafish. However, contrasting with results consistently obtained in rodents, ALS did not counteract MK-801-induced behavioral alterations. ALS exerted an effect in the opposite direction than expected in the SPT, decreasing social preference and increasing locomotor behavior. The meaning of such biological effects remains to be elucidated by comparing ALS to known antipsychotics in the same behavioral assays. We tested a limited range of ALS concentrations based on back-calculations from rodent doses, so we cannot rule out that other concentrations could yield different results. These findings highlight the need for a wider characterization of ALS effects as a potential antipsychotic candidate in zebrafish.

Jaguar Health Inc. provided financial support for this work.

S215. EFFECTS OF MK-801 ON SHOAL COHESION IN ADULT ZEBRAFISH

Amanda Patelli-Alves^{*1}, Matheus Gallas-Lopes¹, Thailana Stahlhofer-Buss¹, Stefani M. Portela¹, Angelo Piato¹, Ana P. Herrmann¹

¹*Universidade Federal do Rio Grande do Sul*

Background: Schizophrenia is a heterogeneous neurodevelopmental disorder characterized by positive, negative, and cognitive symptoms. Despite its unclear pathophysiology, several studies implicate a dopaminergic hyperactivity in subcortical circuits associated with the hypofunction of NMDA glutamate receptors in GABAergic interneurons. MK-801, an NMDA receptor antagonist, is frequently used to recapitulate behavioral phenotypes relevant to schizophrenia symptoms in preclinical assays. Zebrafish (*Danio rerio*) is a model organism widely used in neuroscience research as an alternative to rodents. However, there are conflicting and heterogeneous reports regarding the effects of NMDA receptor antagonists on outcomes related to negative symptoms in this species. Therefore, this study aimed to evaluate the impact of acute MK-801 exposure on social behavior as measured by shoal cohesion in adult zebrafish.

Methods: We used 192 wild-type male and female (1:1 ratio) adult zebrafish (ethical approval: CEUA UFRGS #35525/2019). Animals were randomly allocated to two experimental groups: control and MK-801 (5 μ M). Zebrafish were individually exposed to water or MK-801 in a 200-mL beaker for 20 minutes. Subsequently, they were introduced to a test tank in shoals of four fish ($n=24$ shoals) for 6 minutes. The test was recorded for 6 minutes and edited to quantify the shoal behavior using screenshots captured every 15 seconds. The following measures of shoal cohesion were computed by researchers blinded to the treatment groups using the ImageJ software: shoal area, shoal perimeter, mean interfish distance, distance from the nearest

neighbor and distance from the farthest neighbor. Experiments were run in two batches and the pooled data were analyzed by two-way repeated measures ANOVA with time and treatment group as factors.

Results: Acute exposure to MK-801 significantly increased the shoal area ($F(1,46) = 11.48$, $p=0.0014$), shoal perimeter ($F(1,46) = 28.68$, $p \text{ LESS THAN } 0.0001$), mean interfish distance ($F(1,46) = 22.46$, $p \text{ LESS THAN } 0.0001$), and nearest ($F(1,46) = 13.83$, $p=0.0005$) and farthest ($F(1,46) = 27.63$, $p \text{ LESS THAN } 0.0001$) neighbors distance. Effect sizes (Cohen's d) were large for all outcomes, ranging from 0.98 to 1.55. These findings indicate that MK-801 reduced shoal cohesion, manifested by increased shoal dispersion. There was no effect of time or interaction effects between the factors on any of the measured outcomes.

Discussion: The robust reduction in social behavior induced by MK-801 in the shoal cohesion test contrasts with the variable results we obtained with the social preference test, an assay in which the preference of individual animals to swim close to a tank containing a group of ten conspecifics is measured as a proxy for social interaction. The increased shoal dispersion may be considered a phenotype with relevance to the negative symptoms of schizophrenia, which include social withdrawal. These findings underscore the potential of the zebrafish model in elucidating the behavioral consequences of NMDA receptor modulation, reproducing the results of experiments conducted in rodents. However, shoal cohesion may also be influenced by anxiolytic and anxiogenic interventions. Therefore, future research is needed to precisely understand the mechanisms and the interplay between NMDA receptor modulation, anxiety-related pathways and social behavior.

S216. N-METHYL-D-ASPARTATE GLUTAMATERGIC RECEPTOR ANTAGONISTS WITH RELEVANCE TO SCHIZOPHRENIA: A REVIEW OF ZEBRAFISH STUDIES

Matheus Gallas Lopes^{*1}, Radharani Benvenuti¹, Matheus Marcon¹, Cristina R. Reschke², Ana P. Herrmann¹, Angelo Piato¹

¹*Universidade Federal do Rio Grande do Sul*, ²*Royal College of Surgeons in Ireland*

Background: Hypofunction of glutamate NMDA receptors (NMDAR) in GABAergic interneurons and hyperactivation of dopaminergic pathways in subcortical brain regions are linked to the pathophysiology of schizophrenia. The administration of NMDAR antagonists is often used in model organisms to replicate behavioral phenotypes relevant to the positive, negative, and cognitive symptoms of schizophrenia. Nevertheless, the predominant reliance on rodents in such models raises concerns about species-specific biases and limited translatability of the findings. Zebrafish, on the other hand, is increasingly used as a model organism to study evolutionarily conserved aspects of behavior. In this context, our aim was to comprehensively review and integrate key findings reported in the zebrafish literature regarding the behavioral effects of NMDAR antagonists with relevance to schizophrenia.

Methods: Literature searches were conducted in two bibliographic databases (PubMed and Web of Science) including terms that describe the intervention (NMDAR antagonists) and the desired population (zebrafish). Searches were conducted using filters for date limiting the scope for the period between January 1st 2000 and September 30th 2020. After the removal of duplicates, the selection of eligible studies was conducted in a two-step process based, initially, on title and abstract, followed by a full-text analysis based on criteria for the study design, population, intervention, and outcomes of interest.

Results: From the search in the selected databases 590 studies were retrieved altogether. After the removal of duplicates, the total number of records was 393. We then excluded 266 entries based on title and abstract and 83 based on the full-text screening that did not fulfill the eligibility criteria. This resulted in 44 research articles that met our inclusion criteria and were included in the review. Among these, dizocilpine (MK-801) featured in 29 studies, while ketamine was used in 10 studies. Other NMDAR antagonists, namely phencyclidine (PCP), APV, memantine, and tiletamine, were discussed in 6 studies. Frequently reported findings are the social interaction and memory deficits induced by MK-801 and circling behavior induced by ketamine. However, mixed results were described for several locomotor and exploratory parameters in the novel tank and open tank tests.

Discussion: The zebrafish literature examined here consistently highlights deficits in social interaction and memory impairment resulting from MK-801, alongside the prominent circular behavior induced by ketamine. However, the reports of locomotor and anxiety parameters reveal mixed findings, likely influenced by considerable variability in experimental design. Our review synthesizes key findings from the zebrafish literature pertaining to the schizophrenia-related behavioral effects of NMDAR antagonists. Our conclusion underscores the zebrafish as a valuable model organism for investigating drug-induced behavioral phenotypes relevant to schizophrenia. Nevertheless, additional studies are imperative to comprehensively understand the distinct zebrafish behavioral characteristics as compared to mammals.

S217. COMPARISONS OF THE TREATMENT DISCONTINUATION RATES BETWEEN LONG-ACTING INJECTABLE PALIPERIDONE 1-MONTH AND 3-MONTHS IN A NATIONWIDE POPULATION DATABASE

Sung Woo Joo^{*1}, Sun Min Kim¹, Daegeun Kim¹, Jinah Kim¹, Jungsun Lee¹

¹*Asan Medical Center*

Background: Long-acting injectable (LAI) antipsychotics have been shown to be more effective than oral antipsychotics in reducing treatment discontinuation and the risk of psychiatric hospitalization among patients with schizophrenia. In light of this, LAI antipsychotics with extended durations of action have been developed and LAI paliperidone palmitate with a 3-month interval (PP3M) (Invega Trinza) has been introduced. It is expected to improve treatment outcomes due to its extended injection interval of 3 months. However, evidence is lacking to determine whether LAI PP3M leads to better treatment outcomes than LAI paliperidone palmitate with a 1-month interval (PP1M) (Invega Sustenna) in real-world observational studies.

Methods: We analyzed data from the Health Insurance Review and Assessment Service database in South Korea, spanning July 2009 to August 2021. From patients who had at least one insurance claim with a primary diagnosis of F20 during the observation period, we selected those who had been prescribed either LAI PP1M or LAI PP3M. We compared the treatment duration and discontinuation rates following the initiation of each treatment.

Results: We included 13,344 patients with schizophrenia who had been prescribed either LAI PP1M or LAI PP3M. The mean treatment duration was significantly longer in the PP3M group than in the PP1M group ($t = -39.951$, $p < 0.001$). A Cox proportional-hazards model indicated that LAI PP3M was associated with lower treatment discontinuation compared to LAI PP1M (HR=0.594, CI=0.557–0.633).

Discussion: Our study suggests that LAI PP3M is superior to LAI PP1M in reducing treatment discontinuation. Further studies are needed to explore other clinical advantages of PP3M over PP1M, such as long-term benefits derived from sustained treatment adherence.

S218. NALTREXONE-ASSOCIATED VISUAL HALLUCINATIONS: A CASE REPORT

Kwanghun Lee^{*1}, Won-Myong Bahk², MoonDoo Kim³, Bo-Hyun Yoon⁴, Young-Joon Kwon⁵

¹*Dongguk University Hospital*, ²*Yeouido St. Mary's Hospital, The Catholic University of Korea*, ³*Dept. of Psychiatry, School of Medicine, Jeju National University, Jeju, Korea*, ⁴*Naju National Hospital*, ⁵*Soonchunhyang University Chunan Hospital*

Background: Naltrexone is a competitive antagonist of opioid receptors. It has usually been used for the treatment of alcohol dependence and opiate addiction. Recently, the naltrexone–bupropion combination pill for obesity treatment was approved by the US Food and Drug Administration and the European Medicines Agency. Currently, naltrexone has been studied as an anti-obesity agent for general populations and patients with severe mental illnesses, including schizophrenia. In schizophrenia, however, naltrexone-induced visual hallucinations (VHs) are not well known as an adverse effect.

Methods: We report a case which a patient with schizophrenia experienced VHs after taking naltrexone.

Results: A 24-year-old female patient suffering from persecutory delusions, auditory hallucinations (AHs), and aggressive behavior was admitted to the Department of Psychiatry, Yeouido St. Mary's Hospital, in November 2013. She had no history of substance use disorder. She met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-IV. Antipsychotics were started and her psychotic symptoms gradually decreased. After the last discharge, she was maintained on aripiprazole 25 mg, amisulpride 800 mg, procyclidine 20 mg, propranolol 80 mg, lorazepam 1.5 mg, and valproic acid 250 mg per day, for several years. She had no psychotic symptoms except intermittent AHs (3-4 times/week). In April 2016, the frequency of the AHs increased, and amisulpride was increased to 1,000 mg/day. Two weeks later, AHs were substantially reduced but the patient complained of increased appetite and weight gain. She was prescribed naltrexone 50 mg once a day for 2 weeks. Two weeks later, the patient reported that she had started to see a blurred black object passing by after 2 to 3 days of taking 50 mg of naltrexone, which occurred several times a day. She reported that VHs occurred almost every day while taking naltrexone. The ophthalmic consult was recommended to exclude organic causes for presenting symptoms but refused by her. Naltrexone was ceased. At the next visit, she reported that the VHs had completely disappeared 3 to 4 days after stopping naltrexone.

Discussion: we suggest that naltrexone might be associated the emergence of VHs. Although the pathophysiology of naltrexone-associated VHs remains unclear, clinicians should be aware of the potential emergence of VHs associated with naltrexone.

S219. SEMAGLUTIDE FOR THE TREATMENT OF ANTIPSYCHOTIC-ASSOCIATED WEIGHT GAIN IN PATIENTS NOT RESPONDING TO METFORMIN – A CASE SERIES

Riddhita De*¹, Femin Prasad¹, Vittal Korann¹, Araba Chintoh², Gary Remington¹, Bjorn Ebdrup³, Dan Siskind⁴, Filip K Knop⁵, Tina Villsbøll⁶, Anders Fink-Jensen⁷, Margaret Hahn¹, Sri Mahavir Agarwal¹

¹Centre for Addiction and Mental Health, University of Toronto, ²University of Toronto, ³University of Copenhagen, ⁴Metro South Addiction and Mental Health Service, ⁵Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen; Steno Diabetes Center Copenhagen, ⁶Copenhagen University; Gentofte Hospital, ⁷Psychiatric Centre Copenhagen, Mental Health Services, Capital Region of Denmark

Background: While antipsychotic (AP) medications are considered the cornerstone of treatment in schizophrenia and other psychiatric conditions, contributing effects of these medications on weight gain have been well-established. Comorbid obesity among individuals with severe mental illness (SMI) have been associated with poorer quality of life, barriers to social engagement, worse adherence, and impaired cognition. Despite this, the available treatment strategies for managing this growing problem are significantly lacking. At present, metformin has the most evidence for modest weight gain mitigation in individuals with SMI who experience antipsychotic-associated weight gain (AAWG). However, it is effective in only approximately 20% of patients, with no clear recommendations for the subgroup failing to respond to metformin. Among agents approved for chronic weight management in Canada, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reductions in cardiovascular mortality, with the recent addition of once-weekly semaglutide for this indication. The long-acting, once-weekly formulation has shown promising preliminary evidence for both effectiveness and tolerability. Therefore, in this case series involving the SMI population, the primary objective was to study changes in weight over 12 months following the initiation of semaglutide among metformin non-responders.

Methods: A retrospective chart review was conducted for individuals between 2019 and 2021, in the Mental Health and Metabolism clinic at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. The inclusion criteria consisted of patients who were on a stable dose of an antipsychotic medication, who failed to lose GREATER THAN =5% body weight on metformin (highest tolerated dose) at the end of 3 months or those who continued to meet criteria for metabolic syndrome at the end of 3 months. They were then initiated on semaglutide of up to a 2 mg dose per week. All demographics and metabolic data were collected at baseline, 3, 6 and 12 months.

Results: Twelve patients in total were included with a mean age of 36.09 ± 13.32 years, who were on a mean semaglutide dose of 0.71 ± 0.47 mg/week at the end of 12 months. At baseline, the mean weight was 111.4 ± 31.7 kg, and the BMI was 36.7 ± 8.2 kg/m² with a mean waist circumference of 118.1 ± 19.3 cm. After initiation of semaglutide, weight loss of 4.56 ± 3.15 kg (p LESS THAN 0.001) was noted at 3 months, 5.16 ± 6.27 kg ($p = 0.04$) at 6 months, and 8.67 ± 9 kg ($p = 0.04$) at 12 months. No serious adverse events were reported on the medication, with some experiencing tolerable gastrointestinal side-effects which subsided with time.

Discussion: This case series from a naturalistic, clinical setting suggests that among metformin non-responders, semaglutide appears to be effective in reducing AAWG. However, well-

powered randomized control trials investigating semaglutide for AAWG in the SMI population are required.

S220. NEUROMETABOLITES IN ANTIPSYCHOTIC-RESPONSIVE VERSUS NON-RESPONSIVE PSYCHOSIS: A META-ANALYSIS.

Bridget King^{*1}, Junyu Sun¹, Kate Merritt², Matthew J. Kempton¹, Alice Egerton¹

¹King's College London, Institute of Psychiatry, Psychology and Neuroscience, ²Institute of Mental Health, UCL

Background: Proton magnetic resonance spectroscopy (1H-MRS) is an MRI-based imaging technique which provides measures of neurometabolites which may be relevant to the pathophysiology of schizophrenia. These include glutamate (Glu), glutamine (Gln) and their combined signal (Glx), n-acetyl aspartate (NAA), choline (Cho), myoinositol (mI), GABA and glutathione (GSH). Several studies suggest that regional neurometabolite levels may differ in schizophrenia in relation to antipsychotic treatment response, with a primary finding that a poor response to treatment is associated with elevations in glutamate in the medial frontal cortex (MFC). However, there are differences in findings between individual studies which may relate to variation in patient selection, study design or data acquisition. We therefore conducted a meta-analysis of studies reporting 1H-MRS metabolites in individuals with schizophrenia classified as antipsychotic non-responders compared to responders or healthy controls.

Methods: A systematic literature search was conducted using The Web of Science database. 1H-MRS studies that reported metabolite levels (Glu, Glx, Gln, NAA, Cho, mI, GABA, GSH) in patient groups classified as responders or non-responders to antipsychotic treatment and healthy controls were included. Metabolite levels were compared between groups in random effects models using standardised mean differences (Hedge's g). Regions of interest included the MFC, dorsolateral prefrontal cortex (DLPFC), thalamus, and basal ganglia. Subgroup analyses investigated the impact of differences in patient subgroups (treatment resistant or non-treatment resistant), study design (cross-sectional or prospective) and MFC voxel placement (anterior or mid cingulate cortex).

Results: 20 eligible studies reporting data for 428 treatment non-responders, 484 treatment responders with schizophrenia and 380 healthy controls were included. In the MFC, treatment non-responders showed elevations in mI (Hedge's g = 0.25, P = 0.017) and choline (g = 0.42, P = 0.016) compared to treatment responders, with no significant difference in glutamate (P = 0.148, I² = 56) or Glx (P = 0.145, I² = 52). In the DLPFC, treatment non-responders showed elevations in choline (g = 1.03, P = 0.018) but lower levels of glutamate (g = 0.86, P = 0.002) compared to responders. Subgroup analyses indicated that in the MFC, treatment non-responders had higher levels of mI compared to controls for studies with treatment resistant samples (g = 0.85, P LESS THAN 0.001), csf corrected values (g = 0.74, P = 0.006) and cross-sectional designs (g = 0.85, P LESS THAN 0.001). MFC choline was higher in non-responders compared to responders or controls in studies with treatment resistant samples (g = 0.62, P = 0.006), voxels in the anterior cingulate (g = 0.55, P = 0.014) and cross-sectional designs (g = 0.58, P = 0.003).

Discussion: Elevated choline and mI levels in cortical regions in individuals who show a poor response to treatment could indicate increased glial activation and membrane metabolism in this group. The lack of significant difference and high heterogeneity in MFC glutamatergic metabolites may indicate sensitivity to experimental design. Our findings of elevated and

choline and mI give novel mechanistic insight into the neurobiology of antipsychotic non-response and may provide additional biomarkers for clinical response.

S221. ELEVATED MRNA EXPRESSION AND ACTIVITY OF TOLL-LIKE RECEPTORS AND CYTOKINES IN PATIENTS WITH SCHIZOPHRENIA

Saahithh Redddi Patlola*¹, Laurena Holleran², Akhil Konkoth³, Daniel Kerr³, Gary Donohoe², Aodan Laighneach⁴, Derek Morris⁴, Declan McKernan³

¹University of Galway, ²School of Psychology, University of Galway, ³Dept. of Pharmacology and Therapeutics, University of Galway, ⁴Dept. of Biochemistry, University of Galway

Background: Schizophrenia is a psychiatric disorder with a complex aetiology. There has been growing interest in the role of the immune system in the pathophysiology of schizophrenia. Toll-like receptors (TLRs) are a group of pattern recognition receptors primarily involved in cytokine release in the inflammatory response to pathogens but also to cell damage. TLRs are suspected to play a significant role in neuroinflammation as studies consistently show cytokine imbalance in patients diagnosed with schizophrenia which are also associated with cognitive deficits[1]. This cytokine imbalance is possibly due to changes in Toll-like receptor (TLR) expression/activity. Such altered immune responses might lead to neuroinflammation in patients with schizophrenia[2, 3]. We aim to investigate if there is an altered expression and activity of peripheral cytokines and TLRs in patients with schizophrenia.

References:

[1] Patlola, S.R., Donohoe, G. and McKernan, D.P. 2022. The relationship between inflammatory biomarkers and cognitive dysfunction in patients with schizophrenia: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 110668.

[2] Squillace, S. and Salvemini, D. (2022) “Toll-like receptor-mediated neuroinflammation: Relevance for cognitive dysfunctions,” *Trends in Pharmacological Sciences*, 43(9), pp. 726–739. Available at: <https://doi.org/10.1016/j.tips.2022.05.004>.

[3] Patlola, S.R., Donohoe, G. and McKernan, D.P. (2023), “Counting the Toll of Inflammation on Schizophrenia—A Potential Role for Toll-like Receptors”, *Biomolecules*, MDPI AG, Vol. 13 No. 8, p. 1188, doi: 10.3390/biom13081188.

Methods: A total of 311 (Male/Female - 188/123) human participants were included in this study. We used highly sensitive ELISA kits to detect the peripheral levels of cytokines (IL-6, IL-8, IL-10, IL-12, TNF- α and IFN- γ) and C-reactive protein (CRP) in the plasma extracted from the blood of both healthy volunteers (N = 207) and patients with schizophrenia (N = 104). Whole blood was stimulated with TLR2, 3 and 4 agonists (HKLM, Poly (I:C) and LPS respectively) to investigate cytokine (IL-6, IL-8, IL-10 and TNF- α) activity. mRNA was purified from whole blood and cDNA synthesised from this was used to perform qRT-PCR and using a housekeeping gene (β -actin), we analysed the relative expression of all the aforementioned cytokines and TLR 1- 10.

Results: Results from ELISAs show significantly elevated levels of IL-6 (p LESS THAN 0.001), IL-8 (p LESS THAN 0.001), IL-10 (p LESS THAN 0.01), TNF- α (p LESS THAN 0.01) and CRP (p LESS THAN 0.001) in patients with schizophrenia when compared to controls. Significant higher levels of IL-6 (p LESS THAN 0.01, p LESS THAN 0.001), IL-8 (p LESS THAN 0.001, p LESS THAN 0.001) and IL-10 (p LESS THAN 0.05, p LESS

THAN 0.01) in patients were observed post-TLR2 and TLR4 receptor stimulation respectively. Data obtained from PCR was processed (quality control) and normalised relative to the housekeeping gene (β -actin). Gene (mRNA) expression changes between controls and patients was compared using an unpaired t-test. The resulting analysis illustrated a significantly higher expression of IL-6 (1.3-fold, p LESS THAN 0.06) and IL-8 (1.44-fold, p LESS THAN 0.001) but not TNF- α . A significant upregulation in the mRNA expression of TLR2 (1.1-fold, p LESS THAN 0.05), TLR4 (1.3-fold, p LESS THAN 0.01), TLR6 (1.07-fold, p LESS THAN 0.01) and TLR8 (1.1-fold, p LESS THAN 0.05) was observed but not TLR1, 3, 5, 7, 9 and 10.

Discussion: These results suggest that patients with schizophrenia show altered peripheral inflammatory activity. Upregulation of Toll-like receptors (TLRs) and pro-inflammatory cytokine expression from blood samples indicate increased inflammatory activity. The results also point in the direction of a possible role of Toll-like receptors in the mediation of neuroinflammation in schizophrenia. Further investigation on their molecular pathways and their association with cognitive impairment in Schizophrenia could open up more treatment options.

S222. CHANGES IN IMMUNOGLOBULIN LEVELS DURING THE FIRST SIX MONTHS OF CLOZAPINE TREATMENT

James MacCabe^{*1}, Kira Griffiths¹, María Ruiz Mellado¹, Raymond Chung¹, John Lally¹, Grant McQueen¹, Kyra-Verena Sendt¹, Amy Gillespie², Muhammad Ibrahim³, Alex Richter⁴, Adrian Shields⁴, Mark Ponsford⁵, Stephen Jolles⁵, John Hodsoll¹, Thomas Pollak¹, Rachel Upthegrove⁶, Alice Egerton¹

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*University of Oxford*, ³*Department of Immunobiology, Faculty of Life Sciences and Medicine, King's College London*, ⁴*Institute of Immunology and Immunotherapy, University of Birmingham*, ⁵*Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff*, ⁶*University of Birmingham*

Background: Clozapine is the only approved pharmacotherapy indicated for treatment-resistant schizophrenia but its mechanism of action is not understood, and it is generally underutilised in clinical practice. One reason for limited use is risk of adverse effects. Several adverse effects involve the immune system, such as severe neutropenia and eosinophilia, increased risk of pneumonia and COVID-19. There is growing evidence that clozapine has multiple immunomodulatory effects, and it has been suggested that immune modulation may play a role in the efficacy of clozapine as well as in its adverse effects.

Circulating immunoglobulins (Igs), also known as antibodies, are an essential component of the adaptive immune response. Cross-sectional analyses have found a higher prevalence of Ig deficiency (hypogammaglobulinaemia) in patients prescribed clozapine compared to those prescribed non-clozapine antipsychotics. Since hypogammaglobulinaemia increases risk of infection, this association could have important safety implications. Any clozapine-associated changes in immunoglobulin levels may also have implications for the mechanism of action of clozapine. However, since clozapine is prescribed almost exclusively to patients with treatment-resistant schizophrenia, the results of existing cross-sectional studies are compatible with hypogammaglobulinaemia being part of the phenotype of treatment-resistant schizophrenia,

rather than being specific to clozapine. Prospective studies are required to establish temporal relationships between clozapine treatment and changes in immunoglobulin levels.

We tested two hypotheses: (1) that reductions in immunoglobulin levels occur over the first 6 months following initiation of clozapine treatment, and (2) that any changes in Ig level would be correlated with clinical response.

Methods: This prospective observational study measured immunoglobulin levels (IgA, IgM and IgG) in 56 patients with treatment-resistant schizophrenia at 6-, 12- and 24-weeks following clozapine initiation. Clinical symptoms were measured at baseline and 12 weeks using the positive and negative syndrome scale (PANSS). The main analysis used linear mixed models with maximum likelihood estimation to model the effect of clozapine treatment on immunoglobulin levels over time. Four separate models were applied, with level of IgA, IgG or IgM and total Ig as the outcomes. In each model, time was modelled as a fixed effect and treated as a categorical variable (baseline, week 12, and week 24). Models were adjusted for baseline smoking status and exposure to non-clozapine antipsychotic treatment. The correlation between Ig and percentage change in PANSS total scores after 12 weeks of clozapine treatment was calculated.

Results: IgA, IgG and IgM all decreased during clozapine treatment. For IgA and IgG the reduction was significant at 24 weeks (IgA: $\beta = -32.66$, 95% CI = -62.38, -2.93, $p = 0.03$; IgG: $\beta = -63.96$, 95% CI = -118, -9.31, $p = 0.02$). For IgM the reduction was significant at both 12 and 24 weeks (12 weeks: $\beta = -23.48$, 95% CI = -39.56, -7.42, $p = 0.004$; 24 weeks: $\beta = -33.12$, 95% CI = -50.30, -15.94, $p = \text{LESS THAN } 0.001$). There were no significant differences in baseline IgA, M or G levels between participants who dropped out of the study compared to those who continued. Reductions in both IgA and IgG levels were significantly correlated with reductions in PANSS total score from baseline to week 12 ($n = 32$, IgA $r = 0.59$, $p = 0.005$; IgG $r = 0.48$, $p = 0.03$).

Discussion: For the first time, we have demonstrated that clozapine treatment is associated with reductions in immunoglobulin levels over the first six months of treatment. These findings build on cross-section evidence of secondary antibody deficiency, by showing that reductions in immunoglobulins are associated with clozapine treatment, rather than merely with treatment resistant schizophrenia, and that they occur progressively during the first 6 months of treatment. The results suggest that assessment of immunoglobulin levels should be recommended for patients treated with clozapine, particularly those with a history of infections, as this could promote timely management. The association between Ig reduction and symptom improvement suggests that clozapine may be achieving its clinical efficacy via its immunomodulatory effects. Taken together, these data suggests that immune mechanisms contribute to both desirable and undesirable effects of clozapine.

S223. GLP-1 AGONISTS FOR WEIGHT MANAGEMENT IN ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Maarten Bak^{*1}, Bea Campforts¹, Patrick Domen¹, Therese Van Amelsvoort¹, Marjan Drukker¹

¹*Maastricht University*

Background: Managing body weight in patients with antipsychotic-induced weight gain (AIWG) is challenging. Besides lifestyle interventions, pharmacological interventions may contribute to weight loss. Relatively new are the Glucagon-Like-Peptides 1 (GLP1) agonists. GLP-1 agonist receive currently in great media attention, as in non-diabetic obese patients have

shown to lose a substantial amount of body weight. This systematic review and meta-analysis evaluated the effect on weight loss and adverse effects of GLP-1 agonists in patients with AIWG.

Methods: Following PRISMA guidelines, we performed a meta-analysis of blinded and open-label randomised controlled trials (RCTs), non-randomised controlled trials and cohort studies that evaluated treatment with GLP-1 in patients with AIWG, regardless of psychiatric diagnosis. PubMed, Embase, PsycINFO and Cochrane Library databases were searched. Primary outcome measures were changes in body weight and BMI. Secondary outcomes were changes in adverse effects and severity of psychopathology due to GLP-1 agonists.

Results: Only data for exenatide and liraglutide could be included, i.e. 5 RCTs and 1 cohort study. For exenatide the mean weight loss was -2.48 kg (95% Confidence Interval (CI) -5.12 to +0.64; $p=0.07$), for liraglutide the mean weight loss was -4.70 kg (95% CI -4.85 to -4.56; $p < 0.001$). The mean change in BMI was -0.82 (95% CI -1.56 to -0.09; $p=0.03$) in the exenatide groups and -1.52 (95% CI -1.83 to -1.22; $p < 0.001$) in the liraglutide groups. Exenatide and liraglutide did not adversely affect psychopathology. The most common adverse events were nausea, vomiting, and diarrhea.

Discussion: The GLP-1 agonists exenatide and liraglutide are promising drugs for inducing weight loss in patients with AIWG. The adverse effects are acceptable, and the addition of GLP-1 does not increase the severity of psychopathology. However, more research is needed to assess the effect of GLP-1 agonist in AIWG and long term effects on body weight. Also, research on the effect on body weight development after stopping GLP-1 medication in AIWG patient is needed.

S224. ISLANDS OF CALLEJA: THE HIDDEN NEUROANATOMICAL SUBSTRATE IN THE MECHANISM OF CARIPRAZINE

Susanne Prokop^{*1}, Péter Ábrányi-Balogh², Benjámín Barti¹, Márton Vámosi¹, Miklós Zöldi¹, László Barna¹, Gabriella M. Urbán¹, Barna Dudok³, Attila Egyed², Hui Deng⁴, Gian Marco Leggio⁵, András D. Tóth⁶, László Hunyady⁶, Mario van der Stelt⁴, György M. Keserű², István Katona¹

¹*Institute of Experimental Medicine, Hungary,* ²*Research Centre for Natural Sciences,* ³*Stanford University,* ⁴*Leiden Institute of Chemistry, the Netherlands,* ⁵*University of Catania,* ⁶*Semmelweis University*

Background: A comprehensive understanding of the mechanisms of existing clinical compounds is crucial to enhance the efficacy and minimize the side effects of future neuropsychiatric treatments. While in vitro pharmacological assays can provide the exact receptor binding profile of drugs, it is increasingly acknowledged that the same drug-target interaction can differently modulate complex neuronal networks in the brain, depending on its cell-type and subcellular compartment-specific localization. On the other hand, a significant gap exists in the availability of techniques capable of visualizing cell-type specific drug-target interactions within complex tissue specimens.

Methods: A comprehensive understanding of the mechanisms of existing clinical compounds is crucial to enhance the efficacy and minimize the side effects of future neuropsychiatric treatments. While in vitro pharmacological assays can provide the exact receptor binding profile of drugs, it is increasingly acknowledged that the same drug-target interaction can differently modulate complex neuronal networks in the brain, depending on its cell-type and

subcellular compartment-specific localization. On the other hand, a significant gap exists in the availability of techniques capable of visualizing cell-type specific drug-target interactions within complex tissue specimens.

Results: We presented our workflow by the investigation of cariprazine, a rapidly emerging new medication (Vraylar™/Reagila™). Cariprazine displays unique efficacy against the negative symptoms of schizophrenia and is approved for acute manic/mixed, or depressive episodes associated with bipolar I disorder. However, the neuroanatomical substance that mediates its unique therapeutic effectiveness remains elusive. We demonstrated that the majority of fluorescent cariprazine molecules bind to a largely understudied subregion of the ventral striatum, the Islands of Calleja (IoC) in the mouse brain. Moreover, our three-dimensional reconstruction of high-affinity drug binding sites unveiled that the IoC represents an unexpectedly large continuous network of granule cells. Cell-type specific nanoscale PharmacostORM imaging revealed that fluorescent cariprazine molecules bind D3 dopamine receptors (D3Rs) on the axons of granule cells, which represent the principal cell-type of this enigmatic brain region. We further showed that the IoC is densely innervated by dopaminergic fibers and found that D3Rs localized mostly extrasynaptically, suggesting that these receptors play a key role in dopaminergic volume transmission. Additionally, we demonstrated that the nanoscale binding sites of fluorescent compound in the IoC represent real in vivo targets of the original, unlabeled antipsychotic, cariprazine.

Discussion: Our results highlight the potential importance of IoC granule cells in neuropsychiatric diseases and their enormous potential as future pharmacological targets.

S225. MANAGEMENT OF OBESITY WITH SEMAGLUTIDE IN ANTIPSYCHOTIC-INDUCED WEIGHT GAIN (MOSA) - PRELIMINARY RESULTS FROM A NON-RANDOMISED, OPEN-LABEL PILOT STUDY

Bea Campforts^{*1}, Maarten Bak¹, Marjan Drukker¹, Therese van Amelsvoort¹

¹*Maastricht University, Department of Psychiatry and Neuropsychology*

Background: Social media and newspapers are full of stories about a new generation of weight loss drugs, such as semaglutide and tirzepatide. These antidiabetic medications have been studied in non-diabetic obese patients and have shown significant weight loss. A significant number of patients treated with antipsychotics also suffer from antipsychotic-induced weight gain (AIWG) and obesity (1). Current guidelines focus primarily on lifestyle interventions, such as improving physical activity and diet (2). However, lifestyle interventions are often difficult to implement in these patients because of motivation problems. In addition, the effect of lifestyle interventions on weight loss in patients with SMI is limited (3). Pharmacological interventions, such as the addition of metformin and topiramate, are options that have been shown to result in modest weight loss (4). Semaglutide, a glucagon-like peptide-1 (GLP-1) antidiabetic agent with a mild side-effect profile (mainly nausea and vomiting), showed a weight loss of about 15% in 6 months (5). Semaglutide has not yet been tested in patients with AIWG. The primary objective of our study was to test the feasibility of providing semaglutide to patients with AIWG. Second, we assessed efficacy in terms of weight loss. Thirdly, we assessed tolerability, side effects and psychiatric symptoms.

Methods: We conducted an open-label cohort study with 2 study arms of active medication, semaglutide versus metformin. Both cohorts were followed for 16 weeks. In addition to physical measurements (weight, waist circumference, blood pressure, venipuncture), psychiatric symptoms and side effects were assessed.

Results: Preliminary results show that after 16 weeks, patients on semaglutide lost an average of 5 kg (-1.9 BMI points), or about 4% of their body weight. Patients on metformin lost an average of 2.8 kg (-0.8 BMI points), or 2.5% of their body weight. Side effects were generally mild, mainly gastrointestinal. There was a small but significant improvement in psychiatric symptoms and quality of life after 16 weeks.

Discussion: Semaglutide seems promising for promoting weight loss in patients with AIWG. More research is needed, especially on longer-term follow-up and stopping strategies.

References

1. Afzal M, Siddiqi N, Ahmad B, Afsheen N, Aslam F, Ali A, Ayesha R, Bryant M, Holt R, Khalid H, Ishaq K, Koly KN, Rajan S, Saba J, Tirbhowan N, Zavala GA. Prevalence of Overweight and Obesity in People With Severe Mental Illness: Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2021 Nov 25;12:769309.
2. Vancampfort D, Firth J, Correll CU, Solmi M, Siskind D, De Hert M, et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry*. 2019;18(1):53-66.
3. Speyer H, Jakobsen AS, Westergaard C, Norgaard HCB, Jorgensen KB, Pisinger C, et al. Lifestyle Interventions for Weight Management in People with Serious Mental Illness: A Systematic Review with Meta-Analysis, Trial Sequential Analysis, and Meta-Regression Analysis Exploring the Mediators and Moderators of Treatment Effects. *Psychother Psychosom*. 2019;88(6):350-62.
4. Hiluy JC, Nazar BP, Goncalves WS, Coutinho W, Appolinario JC. Effectiveness of Pharmacologic Interventions in the Management of Weight Gain in Patients With Severe Mental Illness: A Systematic Review and Meta-Analysis. *Prim Care Companion CNS Disord*. 2019;21(6).
5. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989.

S226. IN-PERSON VS. TELEHEALTH COGNITIVE TRAINING AND PHYSICAL EXERCISE INTERVENTIONS: COMPARISON OF EFFECTS ON ATTENDANCE, COGNITION, AND ROLE AND SOCIAL FUNCTIONING

Keith Nuechterlein^{*1}, Joseph Ventura¹, Kenneth Subotnik¹, Trudy Niess¹, Juliane Nguyen¹, Luana Turner¹, Laurie Casaus¹, Margaret Distler¹, Michael Zito¹

¹*UCLA Semel Institute for Neuroscience and Human Behavior*

Background: Both systematic cognitive training and physical exercise interventions have shown promise for improving the severe cognitive deficits and functional impairments of individuals with schizophrenia. These interventions have usually been delivered through in-person group sessions with a trained leader. The COVID-19 restrictions on in-person group treatments forced a transition to Zoom videoconference treatments within our ongoing randomized controlled trial examining the impact of physical exercise and computerized cognitive training. This transition provided data on the impact of these interventions in in-person vs. telehealth formats.

Methods: Our computerized cognitive training used web-based neurocognitive and social cognitive programs from Posit Science, 4 hours/week for 6 months and then 2 hours/week for another 6 months. Initially all sessions were in-person in groups of 4-6 participants, but switched to videoconference sessions from their homes, again with 4-6 participants per group. Both included monitoring by cognitive coaches. Group physical exercise sessions led by a certified fitness trainer were initially in-person at our clinic, but were converted to Zoom videoconferences, typically with 4-6 participants. Two 45-min group exercise sessions/week and two 30-min sessions/week of individual exercise homework were assigned for 6 months, with half that dosage for another 6 months. The group exercise sessions included combined moderate-intensity aerobic conditioning (1-min intervals) and moderate-to-high-intensity strength and calisthenic conditioning (1-min intervals). A comparison group attended a didactic healthy living group of comparable duration to the physical exercise. Participants with a recent first episode of schizophrenia were randomized to either cognitive training plus physical exercise (n = 60) or cognitive training plus the healthy living group (n = 57). Sixty-four participants were treated in-person, and 53 participants were treated via telehealth sessions.

Results: Attendance at our cognitive training and aerobic exercise sessions did not differ between in-person sessions and telehealth videoconference sessions (cognitive training: 72.2% vs. 71.7%; exercise: 86.7% vs. 87.3%). Average heart rate during group exercise sessions was also similar for in-person and telehealth sessions (mean of 126.2 vs. 129.7 beats per minute). Repeated measures ANOVA across the full 12 months showed greater cognitive improvement in telehealth than in-person treatment (MCCB Overall Composite T score; $F = 3.52$, $p < 0.02$), but no interaction with the randomized treatment condition. At 12 months the T score gain was 4.2 for in-person and 7.4 for telehealth ($d = 0.53$). Work/school functioning across the full 12 months also showed greater improvement in telehealth than in-person treatment (Global Functioning Scale: Role; $F = 3.93$, $p < 0.01$), with a mean gain of 1.7 for in-person and 3.0 for telehealth by 12 months ($d = 0.48$). Social functioning (Global Functioning Scale: Social) showed no differential effects of mode of delivery.

Discussion: Telehealth delivery of computerized cognitive training and physical exercise interventions for individuals in the early course of schizophrenia is feasible and produces very similar attendance and exercise intensity levels. The improvements in overall cognition and work/school functioning were significantly larger in telehealth than in-person delivery by 12 months, encouraging further work with telehealth interventions as that delivery mode should be easier to disseminate across clinical settings. Advantages of videoconference group interventions include individual breakout rooms and decreased travel burden, which may increase impact.

S227. EFFICACY OF THE COMBINATION OF WATER AEROBICS AND METACOGNITIVE TRAINING ON PSYCHOLOGICAL AND PHYSICAL HEALTH VARIABLES AND THEIR RELATIONSHIP WITH SP1 AND SP4 BIOMARKERS IN PEOPLE WITH PSYCHOSIS: A RANDOMIZED TRIAL STUDY PROTOCOL

Susana Ochoa¹, Marina Verdaguer-Rodríguez^{*2}, Núria Batlle³, Francesc Garreta³, Berta Garcia³, Èlia Vila-Andreu⁴, Maria José Hernández³, Maria José Escandell⁴, Ana Muñoz⁴, Sònia Vilamala⁴, Sandra Marcos³, Laura Bassolas³, Maria Pascua³, Belén Ramos¹

¹*Institut de Recerca Sant Joan de Déu; Parc Sanitari Sant Joan de Déu; Investigació Biomèdica en Red de Salud Mental, CIBERSAM*, ²*Institut de Recerca Sant Joan de Déu; Parc Sanitari Sant Joan de Déu; Departament de Psicologia Clínica i de la Salut, Facultat de*

Background: Metacognitive Training (MCT) is widely used and effective in reducing positive symptoms in psychosis. Physical exercise, such as water aerobic exercise (WAE), could be a good option for improving general health, quality of life and symptoms with a low impact activity that allows social interactions. Preliminary results suggest a relationship between dopamine and psychotic symptoms, through SP transcription factors, SP1 and SP4 biomarkers. The aims of the project are to evaluate the efficacy of a combined intervention (WAE and MCT) in people with schizophrenia in psychotic symptoms, physical health, and transcription levels of SP biomarkers.

Methods: This will be a unicentric randomized controlled trial of 3 parallel intervention groups: MCT, WAE and combined intervention. The estimated sample will be 48 patients with a diagnosis in the psychotic spectrum. The assessment will be performed at baseline and at 3-months' follow-up. The instruments used for the assessment will be clinical, cognitive, metacognitive, social cognitive and psychosocial variables.

Results: The results of this study may have clinical implications, contributing to the improvement of treatment selection for psychosis. By incorporating physical exercise, we hypothesize the benefits of psychological interventions will be enhanced. Results are not presented since this is a protocol article.

Discussion: This will be the first time studying the impact of the combination of Metacognitive Training and Water Aerobic Exercise in people with psychosis. Moreover, it will be the first study that analyzes the changes in the transcriptional biomarkers SP1 and SP4 after both interventions.

S228. REQUIRED ELEMENTS FOR AN EDUCATIONAL PROGRAM FOR NON-HEALTH PROFESSIONAL EXERCISE INSTRUCTORS IN CHARGE OF COMMUNITY-BASED EXERCISE TARGETING YOUNG ADULTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS – A STAKEHOLDER FOCUS GROUP STUDY.

Martin Andersen^{*1}, Kickan Roed², Victor Sørensen³, Bolette S. Rafn⁴, Allan Riis⁵, Bjørn Hylsebeck Ebdrup⁶, Julie Midtgaard⁷

¹*Centre of Applied Research in Mental Health Care (CARMEN), Mental Health Centre Glostrup, University of Copenhagen,* ²*Centre for Applied Research in Mental Health Care, Mental Health Center, Glostrup, Copenhagen University Hospital - Mental Health Services CPH,* ³*Centre for Applied Research in Mental Health (CARMEN) AND The Department of Clinical Biochemistry, Copenhagen University Hospital,* ⁴*Centre for Applied Research in Mental Health Care (CARMEN), Mental Health Center Glostrup, University of Copenhagen, Danish Cancer Society National Cancer Survivorship and Late Effects Research Center (CASTLE), Department of Oncology, Copenhagen University Hospital Rigshospitalet,* ⁵*University College of Northern Denmark,* ⁶*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup, University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine,* ⁷*Centre for Applied Research in Mental Health Care (CARMEN), Mental Health*

Background: Exercise can be a preventive means for the increased prevalence of cardiometabolic morbidity and premature mortality in people with schizophrenia spectrum disorder (SSD). When delivered in community-based settings, exercise may also serve as an opportunity to provide life-skill training and reduce loneliness and stigma while promoting overall physically active behaviors in one single intervention. However, long-term engagement in community-based exercise among people with SSD requires intensive practical and emotional support. Hence, instructors delivering and supervising community-based exercise are essential; however, knowledge about their roles and required training is lacking. We investigated stakeholders' perspectives on components needed for an educational program for non-health professional exercise instructors delivering community-based exercise targeting young adults SSD.

Methods: We conducted six focus groups comprising a total of 30 individuals representing five different stakeholder groups, namely clinical staff within mental health, physiotherapists, exercise instructors, young adults in antipsychotic treatment, and relatives to young adults in antipsychotic treatment. Qualitative content analysis as described by Graneheim and Lundman, was applied to analyze the data using Nvivo 12 software.

Results: We identified the following three main categories to be considered in an educational program for exercise instructors delivering community-based exercise to young adults with SSD: (i) acknowledging mental illness, (ii) applying a resource-oriented approach, and (iii) promoting exercise as a shared activity. Furthermore, the analysis comprised an overarching theme, entitled, Instructors as guardians of an inclusive culture. The finding contributed to developing an educational program for non-health professional exercise instructors delivering community-based exercise targeting young adults SSD, which is currently implemented in the Vega Exercise Community trial (ClinicalTrials.gov ID: NCT05461885) The educational program encompasses: a) a written exercise instructor manual, b) a one-day educational course, and c) the possibility of a continuous exchange of experiences between instructors.

Discussion: An educational program for exercise instructors delivering community-based exercise targeting young adults with SSD includes educational content that enables instructors to promote exercise as a shared activity while acknowledging mental illness and having a resource-oriented approach. Indeed, instructors must act as guardians of an inclusive culture supporting personal recovery. Our results may be transferable to the education of non-health professional exercise instructors in other areas of mental health care where the aim is to facilitate sustainable, recreational, community-based activities.

S229. ECT-RELATED MICROSTRUCTURAL CHANGE IN THE GRAY MATTER OF THE LIMBIC SYSTEM IN PSYCHOSIS PATIENTS: EVIDENCE FROM MRI TEXTURE ANALYSIS

Eugenie Choe^{*1}, Minah Kim¹, Jun Soo Kwon¹

¹*Seoul National University Hospital*

Background: Although electroconvulsive therapy (ECT) is an important treatment modality for psychosis, the mechanism and effect of ECT in psychosis has been underinvestigated. Most studies that described structural brain changes related to ECT in psychosis patients focused on

macrostructural changes, such as volume change. However, as it has been reported from non-human studies that ECT may induce histopathological alterations in the gray matter, such macrostructural measures may not suffice to capture subtle changes in tissue characteristics. We therefore aimed to quantify microstructural changes induced by ECT in psychosis patients, by leveraging texture analysis, a methodology known to reflect microstructures of the brain in many pathological conditions, such as brain tumor or Alzheimer's disease. More specifically, we focused on changes in limbic structures, which have widely been implicated in studies on macrostructural changes after ECT in psychosis, and in studies on ECT in depression, an affective psychiatric condition more extensively explored in ECT research. We hypothesized that, psychosis patients would exhibit both macrostructural and microstructural changes in the gray matter of limbic structures following ECT, and these changes would correlate with clinical response.

Methods: Our dataset comprises schizophrenia and schizoaffective disorder patients who were treated either with both ECT and medication, or with medication only. It also includes healthy control individuals. Structural MRI data were collected before and after ECT for the ECT group and twice for the medication-only group, with the same time intervals as the ECT group. After preprocessing and segmentation, regions of interest (ROI) constituting the limbic system were identified. For each ROI, timepoint, and participant, gray matter volume was estimated, and MRI texture was computed using the Gray Level Size Zone Matrix (GLSZM). Values of each feature in the patient group were normalized based on the values of the control group, and feature selection from multiple GLSZM features was performed. Group-time interactions of each of volumetric or normalized texture feature changes were estimated using repeated-measures mixed models. Repeated-measures correlations between clinical variables and texture features that showed significant group-time interactions were calculated. Statistical significance was set at FDR-adjusted $p \leq 0.05$.

Results: In this study, 36 of the psychosis patients treated with both ECT and medication, 27 of the patients treated only with medication, and 70 healthy controls were included as study sample. Among the twelve limbic system ROIs, seven exhibited significant group-time interactions in terms of volumetric changes in the ECT group. Regarding GLSZM feature-ROI pairs, group-time interactions of Large Area Emphasis of the left hippocampus and the right amygdala reached statistical significance. In the ECT group, repeated-measures correlation revealed a negative correlation between changes in multiple clinical variables and changes in the Large Area Emphasis feature for both the left hippocampus and right amygdala. On the other hand, the medication-only group did not show any significant correlation between clinical changes and texture changes.

Discussion: Our findings are in line with existing literature highlighting the hippocampus and amygdala as key regions for ECT-related macrostructural alterations. Furthermore, our results suggest that these regions also undergo more subtle, microstructural changes, which correlate with clinical responses. This study therefore implies that structural alterations in limbic structures may be related to pivotal effects of ECT as a treatment of psychosis. It also supports the idea that changes in tissue characteristics resulting from ECT-induced neuroplasticity constitute a core mechanism of ECT.

S230. VIRTUAL REALITY THERAPY FOR VOICE HEARING (VR-VOICES): A RANDOMIZED CONTROLLED TRIAL

Chris Geraets*¹, Wim Veling¹

¹University Medical Center Groningen

Background: Auditory verbal hallucinations (AVH) are common in mental illnesses. Studies suggest that empowering psychological therapy using computer simulations representing the AVH (avatars) can be effective in reducing AVH distress and frequency. Virtual reality (VR) has the potential to improve this treatment. Therefore, we aim to investigate the effects of a VR treatment for AVH (VR-VOICES) in a broad spectrum of voice hearers, transdiagnostically, who have experienced distressing AVH for at least 3 months, and are 16 years or older. Effects on symptoms, quality of life, and healthcare costs will be investigated, as well as moderators.

Methods: The study is an assessor-blind randomized controlled intervention trial (RCT) with two arms: VR-VOICES and treatment as usual (TAU) as a control condition. The VR-VOICES intervention concerns 7-10 sessions (personalized to the needs of the patient) of 45 minutes of individual VR assisted therapy and two booster sessions. Participants allocated to VR-VOICES choose an avatar as a digital representation and create the voice of the avatar with the therapist. Patients have dialogues with the avatar, voiced by the therapist.

Assessments will be obtained at baseline, within VR-VOICES sessions, posttreatment (3 months after baseline), and 6-month follow-up. The primary outcome: severity of AVH at post-treatment. Secondary outcomes concern in-depth characteristics of AVH, and impact on daily life as measured with questionnaires and diary assessments in the flow of daily life, as well as clinical symptoms, cost-effectiveness and quality of life.

Results: The RCT is currently enrolling, in total 10% has been included.

Discussion: Voicehearing can have pronounced effects on people's lives, therefore it is important to investigate novel treatments in broad groups. The current study will inform on efficacy in such a broad group and enable to explore for whom this type of intervention works.

S231. ONE-YEAR ASSESSMENT OF PATIENT-CENTERED DIGITAL PSYCHOSOCIAL INTERVENTION (DIALOG+) IN OUTPATIENTS WITH PSYCHOSIS SPECTRUM DISORDERS: INSIGHTS FROM SERBIA

Sanja Andric Petrovic^{*1}, Nadja Maric², Ivan Ristic³, Stefan Jerotic⁴, Bojana Savic⁴, Mirjana Zebic⁵, Vuk Vukovic⁶, Tatjana Voskresenski⁶, Manuela Russo⁷, Nikolina Jovanovic⁸

¹*Institute of Mental Health, Faculty of Medicine, University of Belgrade*, ²*Institute of Mental Health, Faculty of Medicine, University of Belgrade*, ³*Institute of Mental Health*, ⁴*University Clinic for Psychiatry, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade*, ⁵*University Clinic for Psychiatry, Clinical Centre of Serbia*, ⁶*Special Hospital for Psychiatric Diseases "Dr Slavoljub Bakalović"*, ⁷*Unit for Social and Community Psychiatry, Wolfson Institute of Population Health, Queen Mary University of London*, ⁸*Centre for Implementation Science, Health Services and Population Research Department, Institute of Psychiatry, Psychology; Neuroscience, King's College London*, ⁸*Wolfson Institute of Population Health, Queen Mary University of London*

Background: In Serbia and the Balkans, conventional treatment for patients with psychosis spectrum disorders (PSD) largely relies on pharmacotherapy, with limited access to psychosocial interventions due to human and financial resource constraints. Addressing this gap, we introduce DIALOG+, a digital psychosocial intervention grounded in patient-centered communication theories, quality of life (QoL) research and solution-focused therapy principles, designed to enhance the therapeutic efficacy of routine care.

This study aimed to compare the effectiveness of DIALOG+ against standard care in treating PSD concerning QoL, clinical symptoms and treatment satisfaction, evaluating its potential as an innovative solution for holistic care challenges.

Methods: Our study was part of a multicounty, pragmatic, hybrid type II effectiveness–implementation, cluster-randomized, clinical trial (ISRCTN 11913964) aiming at implementing the psychosocial intervention DIALOG+ for patients with PSD in low- and middle-income countries in Southeastern Europe (grant agreement No 779334). It involved 71 adult outpatients (ICD-10 F20-29, F31) from two Serbian sites: a university hospital in an urban setting and a general psychiatric hospital in an urban/rural area. The participants had a history of at least one psychiatric hospitalization and were capable of providing informed consent (mean age 44.1 ± 11.0 years, 56.3% male). Clinicians were randomized 1:1 to the intervention arm ($n=35$, received DIALOG+ six times over 12 months during routine clinical appointments) and control arm ($n=36$, received usual care following the same delivery schedule). Session content varied based on patients' preferences allowing them to discuss various aspects of their life in each session. Primary outcomes were subjective QoL (Manchester Short Assessment of QoL - MANSA), clinical symptoms (Brief Symptom Inventory - BSI), and treatment satisfaction (Client Satisfaction Questionnaire - CSQ-8). Two-level multilevel regression models were employed to allow for data clustering by sites and clinicians. Initial analysis compared baseline arm characteristics, followed by a 12-month outcome measure comparison. Mean differences in outcomes between the arms, reflecting effect magnitude, were calculated, adjusting for potential confounders.

Results: No significant differences existed between intervention and control arms in terms of age, sex, diagnoses, or previous psychological treatment. No significant between-group differences occurred in self-reported mental health problems (BSI, $p=0.74$). Intervention arm improvements included higher MANSA total scores indicating a better QoL (5.2 ± 0.8 vs. 4.4 ± 0.6 , 95% CI 0.6 [0.2, 0.9], $p=0.004$) and greater treatment satisfaction as evidenced by higher scores on the CSQ-8 scale compared to the control group (29.2 ± 2.9 vs. 26.3 ± 4.2 , 95% CI 2.0 [0.6, 3.5], $p=0.007$).

Discussion: This study contributes to a limited body of nonpharmacological RCTs for PSD, demonstrating improvements with DIALOG+ in two important patient-reported outcome measures: subjective QoL and treatment satisfaction over 12 months. These findings bear clinical relevance given the scarcity of interventions addressing QoL enhancement for individuals with PSD. Despite the observed increased session duration with DIALOG+ in a recent study, providing structured interventions and ongoing patient evaluation could offer additional long-term care and QoL benefits for PSD patients.

In conclusion, the study suggests that DIALOG+ shows promise as a structured, integrative approach for individuals with PSD, particularly in routine mental health care settings and resource-constrained environments.

S232. RISK OF PSYCHOTIC AND BIPOLAR PRODROMAL SYMPTOMS IN CHILDREN AND ADOLESCENTS OFFSPRING OF PATIENTS DIAGNOSED WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Elena De la Serna¹, Patricia Camprodon-Boadas², Gisela Sugranyes³, Aitana Bigorra⁴, Dolores Moreno⁵, Inmaculada Baeza⁶, Yamila Tosetti⁷, Sara Parrilla⁸, Covadonga M. Diaz-Caneja⁹, Roger Borrás¹⁰, Josefina Castro-Fornieles¹¹

¹Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM, ²Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer

(IDIBAPS), ³Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic of Barcelona, 2014SGR489, CERCA-IDIBAPS, CIBERSAM, Catalonia, Spain., ⁴Department of Child and Adolescent Psychiatry and Psychology, Institut Clínic de Neurociències, Hospital Clínic Universitari, ⁵Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid, Spain. Department of Psychiatry, Hospital Universitario del Sureste, Madrid, Spain, ⁶Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic of Barcelona, 2014SGR489, CIBERSAM, CERCA-IDIBAPS, Barcelona, Catalonia, Spain., ⁷Department of Child and Adolescent Psychiatry and Psychology, Institut Clínic de Neurociències, Hospital Clínic Universitari, Barcelona, Spain.; Fundació Clínic per a la Recerca Biomèdica, Barcelona, Spain, ⁸Hospital General Universitario Gregorio Marañón, ⁹Department of Child and Adolescent Psychiatry. Hospital General Universitario Gregorio Marañón. IiSGM. School of Medicine, Universidad Complutense. CIBERSAM. Madrid, Spain, ¹⁰Instituto de Investigaciones Biomédicas de Barcelona, CSIC-IDIBAPS-CIBERSAM, ¹¹Hospital Clínic de Barcelona. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM Barcelona

Background: Previous literature have showed that offspring of patients diagnosed with schizophrenia (SZoff) or bipolar disorder (BDoff) had higher prevalence of psychotic experiences and mood prodromal symptoms than controls (CCoff) (Ellersgaard et al., 2021; Setieman et al., 2023). BASYS is a longitudinal, naturalistic study which aims to assess clinical, cognitive, genetic and neuroimaging characteristics of SZoff, BDoff and CCoff. The aim of this study is to analyze the risk of sub-clinical psychotic and bipolar symptoms in SZoff and BDoff compared with a community control sample (CCoff). We will also study the effect of some of the parents' characteristics on the risk of developing sub-clinical psychotic and bipolar symptoms.

Methods: At baseline, BASYS included 41 SZoff, 90 BDoff and 104 CCoff between the ages of six and 17 years. At four-year follow-up 169 offspring (71% of the sample) underwent clinical assessment (60 BDoff, 23 SZoff and 86 CCoff). Prodromal psychotic symptoms were assessed with the Semi-structured Interview for Prodromal Syndromes (SIPS) and scored on the Scale of Prodromal Symptoms, SOPS (Miller et al., 2002). Prodromal bipolar symptoms were assessed with the K-SADS-PL (Kaufman et al., 1997; Ulloa et al., 2006). The presence of sub-clinical psychotic and bipolar symptoms was also dichotomized (yes/no) based on the SIPS/SOPS and K-SADS-PL semi-structured interviews, respectively. Thus, having sub-clinical psychotic symptoms was defined as any SOPS positive or negative item rated greater than or equal to 3. Having sub-clinical bipolar symptoms was defined as a score of 2 (sub-threshold level) in any item of any mood disorder on the K-SADS-PL. Cumulative incidence of sub-clinical psychotic/bipolar symptoms at four-year follow-up were checked with the Kaplan-Meier method with the log rank test to determine differences between the groups (SZoff, BDoff and CCoff). Moreover, the association of some offspring and parents' variables and risk of sub-clinical psychotic/bipolar symptoms was also studied using the univariate Cox regression analysis. Offspring variables analyzed included: group (SZoff, BDoff or CCoff) gender, SES, age and being an adolescent. Parental variables studied were global functioning, SES and age at birth, all of them treated as continuous variables.

Results: There were significant differences between SZoff, BDoff and CCoff in the incidence of sub-clinical psychotic symptoms (SPS) (Log Rank test: $\chi^2=13.101$; $p=0.001$). At four-year follow-up, the incidence of SPS was 30.6% in the SZoff, 20.5% in the BDoff and 9.1% in the CCoff. Only the SZoff group showed higher risk of developing SPS compared to the CCoff group. No other offspring variables were significantly associated with risk of SPS. Higher scores of mothers' global functioning was associated with lower risk of SPS. The incidence of

sub-clinical bipolar symptoms was significantly different between the three groups (Log Rank test: $\chi^2=7.728$; $p=0.021$). Thus, 29.2% of BDOff, 17.8% of the SZoff and 12.5% of the CCOff had sub-clinical bipolar symptoms at four-year follow-up. BDOff showed twice the risk of developing sub-clinical bipolar symptoms compared with the CCOff group. No significant differences were detected between SZoff and CCOff. Any parental or family variable showed an association with the risk of sub-clinical bipolar symptoms in the offspring

Discussion: The primary findings of this study indicate that SZoff showed higher risk for sub-clinical psychotic symptoms, while the BDOff displayed a heightened risk for sub-clinical bipolar symptoms when compared to CCOff. Moreover, higher parental psycho-social functioning emerged as protective factor against sub-clinical psychotic symptoms. These results are in line with previous literature that observed a higher prevalence of psychotic experiences in SZoff and BDOff than in CCOff (Ellersgaard et al., 2021). Regarding sub-clinical bipolar symptoms, our results partially agreed with the study by Setieman et al. (2023), since this study observed more mood sub-clinical symptoms in SZoff and BDOff compared with the control group. Interestingly, SZoff showed even more mood sub-clinical symptoms than BDOff. This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project "20/00654" and co-funded by the European Union.

S233. AN ACUTE EXERCISE INTERVENTION TO AMELIORATE BEHAVIORAL AND NEUROPHYSIOLOGICAL INDICES OF INHIBITORY CONTROL DEFICITS IN SCHIZOPHRENIA: A MOBILE BRAIN/BODY IMAGING (MOBI) STUDY

Victoria Popov^{*1}, Edward Freedman¹, John Foxe¹

¹*University of Rochester*

Background: Inhibitory control deficits are a core feature of schizophrenia spectrum disorders (SSDs), with clear manifestations seen in both psychophysiological and electrophysiological measures of these processes. Addressing these symptoms is of critical clinical relevance since they are a main predictor of negative vocational and psychosocial outcomes. An intriguing set of findings has suggested physical activity and exercise can have a positive effect on SSD symptomatology, but the exercise-linked neural changes that may result in improved inhibitory control are unknown.

Methods: Male and female individuals with SSDs ($n=16$) and neurotypical, age-matched healthy controls (HCs) ($n=14$) completed the Go/NoGo response inhibition (RI) task while sitting and walking. The emergence of Mobile Brain/Body Imaging (MoBI) technologies allowed for the successful assessment of cognitive control processes through high density electroencephalography (hd-EEG), behavioral performance on the RI task, and motoric function through motion capture technologies while participants were engaged in treadmill walking or were sitting. Here, we leverage MoBI to ask whether a single acute exercise intervention, particularly treadmill walking in this study, would lead to improved performance on a canonical RI task, and if previously well-characterized deficits in the generation of inhibition-related event-related-potential (ERP) components can be ameliorated in individuals with SSDs.

Results: A two-way repeated measures ANOVA was performed to compare the effect of groups (HCs, SSDs) or motion state (sitting, walking) on d' scores (RI task performance). Simple main effects analysis showed that groups had a statistically significant effect on d' scores ($F(1, 29) = 11.30$, $p = .001$) and motion state did not ($F(1, 29) = 0.20$, $p = .65$). Preliminary data suggest, overall, HCs had better inhibitory control than SSDs, and walking

did not improve inhibitory control performance of SSDs to be like those of HCs. The cluster-based permutation approach allowed for exploring the existence of walking-related effects on ERPs in the entire electrode set and at all the epoch timepoints. The effects this approach revealed were significant ERP amplitude increases during walking over frontal and frontocentral scalp regions and reductions over parietal and occipital scalp regions during the RI related ERP component intervals for HCs and SSDs. Additionally, in HCs there was substantial reconfiguration over RI related scalp regions when walking relative to sitting that happened earlier than SSDs.

Discussion: Preliminary findings suggest a single intervention of treadmill walking showed no improvement in inhibitory control performance but normalization of neurophysiological processes in SSDs to those of HCs. We expect when we are sufficiently powered SSDs will show inhibitory control performance like those of controls when walking. To our knowledge, this is the first study of its kind to date to examine inhibitory control in real time during an acute exercise intervention. A longer-term fitness intervention trial could assess whether these positive outcomes can be established more durably.

S234. TYPES OF MEDIA USE AND THEIR ASSOCIATIONS WITH PARANOIA: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

Vincent Paquin*¹, Robert A. Ackerman², Colin A. Depp³, Raeanne C. Moore³, Philip D. Harvey⁴, Amy E. Pinkham²

¹*McGill University*, ²*The University of Texas at Dallas*, ³*University of California San Diego*,
⁴*University of Miami*

Background: Paranoia is a spectrum of fear-related experiences that spans diagnostic categories and is shaped by the environment. Traditional media (e.g., books) and digital media (e.g., social media) enable cognitive and social possibilities that may have various effects on paranoia; however, the extent to which media use is associated with paranoia remains unknown. We aimed to examine associations between media use and paranoia at the within- and between-person levels.

Methods: Participants were 409 adults (245 [59.5%] female) diagnosed with schizophrenia spectrum (n=189) or bipolar disorder (n=220). Measures included sociodemographic and clinical characteristics at baseline, followed by ecological momentary assessments (EMA) collected three times daily over 30 days. EMA evaluated paranoia and five types of media use: TV viewing, social media use, listening to music, reading or writing, and other internet or computer use. Logistic regression was used to examine sociodemographic and clinical characteristics associated with any vs. no media use. Then, generalized linear mixed models were used to examine paranoia as a function of each type of media use and vice-versa.

Results: Female (vs. male) gender was associated with higher odds of social media use (OR=2.19; 95% CI: 1.45, 3.33). Black or African American individuals (vs. White group) had lower odds of other internet or computer use (OR=0.34; 95% CI: 0.21, 0.53). Diagnosis of bipolar disorder vs. schizophrenia (OR=2.53; 95% CI: 1.63, 3.94) and having a college degree or higher (OR=8.29; 95% CI: 4.57, 15.69) were associated with higher odds of other internet or computer use. In the schizophrenia group, a within-person increase in social media use was associated with a 10% reduction in paranoia at the next time point: fold-change=0.900; 95% CI: 0.840, 0.965. In the bipolar disorder group, a within-person increase in listening to music was associated with a 5% reduction in paranoia at the next time point: fold-change=0.949; 95%

CI: 0.906, 0.995. Other associations, including those at the between-person level or involving TV viewing, reading or writing, and other internet or computer use, were not significant. Across models, there was no significant interaction with gender.

Discussion: Media use was either associated with no significant change in paranoia, or some improvement, depending on the type of media and diagnostic group. By modeling associations between media use and paranoia at the within-person level, we were able to remove potential influences from time-invariant confounders such as sociodemographic features. The associations of social media use and listening to music with reductions in paranoia may reflect clinical benefits of social interaction and distraction. Of course, the strength and direction of effect of media use on paranoia is likely to vary according to the specific contents of use, such as using social media to connect with family vs. to watch videos of distressing news. Better understanding the ecological effects of media as a function of individual and content features may help guide the development of media-based interventions for paranoia. Future research, however, should also consider the impacts of gender, racialized group, education, and diagnosis on the accessibility of media-based interventions, especially since the same systemic inequities that limit access to media technologies may also contribute to the progression of illness.

S235. ANESTHESIA WITH DEXMEDETOMIDINE AND NITROUS OXIDE IN ELECTROCONVULSIVE THERAPY

In Won Chung^{*1}, Hee Yeon Jung², Jun Hee Lee³, Heung Sik Kim¹, Kyuyoung Lee⁴, Yong Sik Kim⁴

¹*Yong-In Mental Hospital*, ²*Department of Psychiatry, SMG-SNU Boramae Medical Center*, *Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea*, ³*Department of Psychiatry, Uijeongbu Eulji University Hospital*, ⁴*Department of Psychiatry, Nowon Eulji University Hospital*

Background: Most anesthetic agents used in modern electroconvulsive therapy (ECT) produce anticonvulsant effects by increasing the seizure threshold over repeated sessions in the course of acute ECT. This requires an increase in charge, which eventually raises the risk of adverse cognitive effects.

Methods: We present a case of acute ECT in which anesthesia induction with nitrous oxide and dexmedetomidine was able to produce adequate seizure duration while maintaining up to 16 sessions without a significant increase in charge in a patient with schizoaffective disorder. The patient had received 14 sessions of acute ECT at another university hospital but was transferred to our hospital because they could no longer continue ECT. Propofol was used for anesthetic induction, and the charge was increased to 576 mC after the 11th session. The patient resumed ECT sessions at our hospital 11 days after the last session. The ECT procedure was the same with upward titration, bilateral electrode placement, and use of succinylcholine as a muscle relaxant.

Results: The mean charge of 14 sessions at the previous hospital was 542.0 ± 270.9 mC, and the mean durations of motor and EEG seizures were 23.8 ± 8.0 and 34.9 ± 8.3 seconds, respectively. For comparison, the mean charge (242.0 ± 51.9 mC, $t = 5.6463$, $p < 0.0000$) and motor seizure duration (35.3 ± 11.1 sec, $t = -2.5339$, $p = 0.0070$) at our hospital were respectively significantly different, but not the EEG seizure duration (38.1 ± 14.1 mC, $t = -0.5374$, $p = 0.5954$).

Discussion: The combined use of dexmedetomidine and nitrous oxide as anesthetics in acute ECT allowed us to maintain an effective seizure duration without an increase in charge.

S236. PRAGMATIC LANGUAGE DISORDER IN SCHIZOPHRENIA: ASSESSMENT THROUGH A NOVEL BRIEF TOOL

Margherita Bechi^{*1}, Gulia Agostoni², Luca Bischetti³, Giorgio Arcara⁴, Mariachiara Buonocore⁵, Francesca Martini², Marco Spangaro⁶, Valentina Bambini³, Roberto Cavallaro⁷, Marta Bosia⁸

¹IRCCS H.S. San Raffaele, DSNP, ²IRCCS San Raffaele University Scientific Institute, ³Center for Neurocognition, Epistemology and theoretical Syntax (NEtS), University School for Advanced Studies IUSS, ⁴IRCCS San Camillo Hospital, ⁵Department of Clinical Neurosciences, IRCCS San Raffaele Scientific Institute, ⁶IRCCS San Raffaele University Scientific Institute, ⁷Vita Salute San Raffaele University, ⁸IRCCS San Raffaele Scientific Institute

Background: Pragmatics is a communicative ability that allows appropriately using and interpreting language in a wide range of contexts and situations. Pragmatic disruption is a main feature in schizophrenia, which affects around 80% of patients and contributes to the functional disability associated with the illness. Despite its relevance, pragmatic impairment is seldom considered in assessment, as the available tests share the limitation of a significantly long administration time, thus making them unfeasible into routine evaluation.

This study aims at testing a novel and brief tool for pragmatics (APACS Brief) in schizophrenia compared with healthy controls, to evaluate its feasibility as well as the equivalence with a previous and standardized tool (APACS test).

Methods: We enrolled 56 patients affected by schizophrenia and 56 healthy controls matched for age and education. The patients' assessment include a cognitive evaluation (Brief assessment of cognition in schizophrenia- BACS) a Theory of mind (ToM) evaluation (Picture sequencing task –PST) a clinical evaluation (PANSS) APACS long and APACS Brief for pragmatics' evaluation, while healthy controls were evaluated for APACS Brief. Several ANOVAs were run to compare APACS Brief between patients with schizophrenia and healthy controls. To explore the discriminatory power of APACS Brief Total score in differentiating people with schizophrenia from healthy subjects, we run a ROC curve analysis. Then, we run a Pearson correlation analysis between APACS Total score and APACS Brief Total score in the schizophrenia group, to further confirm the correlation between APACS long and short versions. Lastly, the interplay between pragmatic abilities and cognitive and ToM abilities was evaluated with Pearson correlations.

Results: Results showed significant differences between patients and controls in all APACS Brief scores (Total score F55.59, p LESS THAN .0001), and the ROC curve showed that an APACS Brief Total score (AUC = 0.83, p LESS THAN 0001) of 0.89 had the best discriminant validity (sensitivity = 95%, specificity = 69%) in differentiating patients vs controls. Significant correlations between APACS long and brief versions (Pearson r = 0.65, p LESS THAN .0001), as well as between the latter and both cognitive (Pearson r = 0.32, p = .01) and sociocognitive (Pearson r = 0.38, p = .004) data, were found, further confirming the validity of the tool.

Discussion:

Overall, data suggest that APACS Brief is a tool able to evaluate pragmatic disruption in schizophrenia and that, if supported by other studies, it could be considered equal to a long and validated task such as the APACS test. The brief administration time makes APACS Brief a useful and adaptable task for numerous contexts, including the National Health System services, where the time constraints do not allow for longer evaluations. The identification of people with schizophrenia showing a pragmatic deficit could maximize the application of the available rehabilitative interventions, such as PragmaCom, with significant consequence on people's daily functioning and quality of life. As functional disruption is still a major issue in schizophrenia, contributing to the economic burden associated with the disorder, the identification of treatment targets and the availability of tools to assess them is crucial. Clinical implications of APACS Brief also include its use for refined diagnosis and treatment outcome prediction, as well as for monitoring the course of the disorder in chronic patients.

S237. TESTOSTERONE USE AS A TREATMENT OF CACHEXIA IN PATIENTS WITH SCHIZOPHRENIA

Naista Zhand¹, Fatima Al Quraish^{*2}

¹*Schizophrenia Program, The Royal Ottawa Mental Health Centre,* ²*Royal Ottawa Hospital*

Background: Aberrant feeding behaviors in schizophrenia, which could result in cachexia and starvation status, have been described in the literature. Testosterone is used as an adjunct treatment in patients with cancer and HIV-induced cachexia to increase lean body mass and could be considered as a potential option for management of cachexia due to other causes such as schizophrenia. In this case report, we describe use of adjunct testosterone in a patient with schizophrenia and significant weight loss.

Methods: We present a case report of a patient with chronic schizophrenia who was admitted to our Schizophrenia inpatient unit with relapse of psychosis, catatonia and significant weight loss/malnutrition. His weight on admission was 38.2 kg with a body mass index (BMI) of 14. He was treated with antipsychotic medication and ECT, to which he responded favorably. However, after 6 months in hospital and despite improvement of his mental status, his oral intake and weight were still suboptimal. He was started on intramuscular testosterone to enhance muscle mass, address low weight and improve energy.

Results: An improvement in energy, appetite and weight was observed. Following 13 weeks of regular treatment with testosterone, his weight increased from 45 kg to 52 kg, correlating to a 15.5% increase in total body weight. There were no adverse effects.

Discussion: Supplementary testosterone can be considered as an adjunct option for treatment of persistent cachexia in patients with schizophrenia who continue to struggle with low body weight and low energy, despite optimized psychiatric treatment.

S238. NETWORK ANALYSIS OF SOCIAL COGNITIVE AND INTERPERSONAL BIASES RELATED TO SUICIDAL THOUGHTS AND BEHAVIOR IN PEOPLE WITH SERIOUS MENTAL ILLNESS

Emma Parrish^{*1}, Kevin Kuehn², Amy Pinkham³, Raeanne C. Moore², Philip D. Harvey⁴, Eric Granholm⁵, Scott Roesch⁶, Thomas Joiner⁷, Varsha D. Badal², Colin A. Depp⁵

¹San Diego State University / University of California San Diego Joint Doctoral Program in Clinical Psychology, ²University of California San Diego, Department of Psychiatry, ³The University of Texas at Dallas, ⁴University of Miami Miller School of Medicine, Research Service Miami VA Medical Center, ⁵University of California San Diego, Department of Psychiatry; Veterans Affairs San Diego Healthcare System, ⁶San Diego State University Department of Psychology, ⁷Department of Psychology, Florida State University

Background: People with serious mental illness (SMI; i.e., schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder with psychosis) are at an increased risk of suicidal ideation (SI) and behavior. There is limited understanding of the factors contributing to suicide in SMI nor are there many suicide prevention interventions developed or adapted for this group. Interpersonal biases (i.e., perceived burdensomeness [PB] and thwarted belongingness [TB]) are key to contemporary theories of suicide, and social cognitive biases such as over-attribution of threat that accompany SMI may foster sustained SI. Social motivations (i.e., approach and avoidance) may strengthen the association between PB, TB, and sustained SI. Due to the complex, dynamic, and interconnected associations between these variables, a network analysis provides a novel approach for hypothesis-generation and deeper understanding of these relationships.

Methods: Participants with SMI (N=273) completed three in-lab visits (baseline, 6-month, and 12-month) and ten days of ecological momentary assessment (EMA; 3x/day) immediately following the baseline visit. At all timepoints, participants were stratified as having SI (SI+) or no SI (SI-), and over 12-months participants were classified as having sustained SI if they reported SI at all three timepoints or had attempted suicide since the baseline visit. Mean EMA variables were compared between sustained SI+/- groups using independent samples t-tests. Network analyses identify partial correlations between variables represented as weighted connections and adjust for relationships between all variables in the network model. Network analysis was used to compare SI+/- participants' baseline EMA data in contemporaneous and temporal (time-lagged, lag-1) networks including PB, TB, social approach, social avoidance, and psychotic symptom EMA variables. Missing data was managed using multiple imputation.

Results: Baseline EMA variables were significantly different between sustained SI +/- groups. Contemporaneous models in groups with or without sustained SI indicate strong links between momentary interpersonal variables related to suicide and psychotic symptoms, with little difference in correlation direction or significance. Comparisons of time-lagged networks between sustained SI+/- groups revealed much denser connections between momentary variables in the sustained SI+ group than the sustained SI- group. The sustained SI+ group model included time-lagged links between mistrust to increased burdensomeness ($B=.10$, $SE=.03$, $p=.003$) and mistrust to decreased belongingness ($B=-.09$, $SE=.03$, $p=.007$) that were not present in sustained SI- model. Additionally, the sustained SI+ group model included time-lagged links between social approach motivation to decreased voices ($B=-.06$, $SE=.03$, $p=.008$) and social approach motivation to decreased social avoidance ($B=-.123$, $SE=.04$, $p=.001$) that were not present in the SI- model.

Discussion: Baseline network analysis of EMA was related to sustained SI over 12 months, suggesting the potential predictive ability of relationships between these variables in long-term SI trajectory. Network analyses revealed strong links between mistrust and other variables, particularly PB and TB, in the sustained SI+ group that were not evident in the sustained SI- group. These networks disentangle a complex set of interactions between variables, highlighting the links between mistrust, PB, TB, and social motivations, to identify potential suicide prevention treatment targets for people with SMI.

S239. SYSTEMATIC REVIEW AND META-ANALYSIS ON THE EFFECTS OF CHRONIC PERI-ADOLESCENT CANNABINOID EXPOSURE ON SCHIZOPHRENIA-LIKE BEHAVIOUR IN RODENTS

Zhikun Li^{*1}, Diptendu Mukherjee¹, Bea Duric¹, Isabelle Austin-Zimmerman¹, Giulia Trotta¹, Edoardo Spinazzola¹, Diego Quattrone¹, Robin Murray¹, Marta Di Forti¹

¹*King's College London*

Background: Epidemiological studies consistently establish a strong correlation between early-onset cannabis use and an increased risk of schizophrenia. In contrast, findings from rodent models exploring this association exhibit significant variability. This meta-analysis investigates the impact of adolescent cannabinoid exposure on diverse schizophrenia-like behaviours in rodents and explores the influence of experimental variables on outcomes.

Methods: We conducted a comprehensive review of English-language rodent studies up to June 2022. Synthesising data from 291 experiments across 91 articles, we assessed nine distinct schizophrenia-like behaviours following repeated adolescent (P23-45) cannabinoid exposure in rats and mice.

Results: Our analysis revealed that adolescent exposure to CB1R agonists induced pronounced schizophrenia-like alterations in cognition, memory, social motivation, sensorimotor gating, and anhedonia. However, locomotor hyperactivity, a proxy for positive symptoms of schizophrenia, exhibited negligible effects. These outcomes remained consistent across sexes and species. Moreover, substantial variations in experimental protocols and moderate-to-high heterogeneity in behavioural outcomes were observed across studies. Limited data also hinted at potential beneficial effects of CBD on specific phenotypes.

Discussion: This work provides the first meta-analytic evidence linking adolescent cannabinoid exposure to schizophrenia-like changes in rodents, contributing to the expanding body of research implicating cannabis use in schizophrenia. Our findings underscore the translational validity and robustness of animal models while emphasising the urgent need for standardising experimental protocols, which is essential for enhancing reproducibility and facilitating meaningful cross-study comparisons.

S240. REDUCED FORWARD HEAD POSTURE AND THE RELATIONSHIP WITH CARDIO-RESPIRATORY FUNCTION IN INDIVIDUALS WITH PSYCHOSIS SPECTRUM DISORDER, COMPARED TO AUTISM SPECTRUM DISORDER AND HEALTHY VOLUNTEERS

Ilona van de Meent¹, Lisanne Koomen¹, Arija Maat², Edwin van Dellen³, Wiepke Cahn⁴, Wiepke Cahn^{*5}

¹*UMC Utrecht*, ²*University Medical Center Utrecht, NL*, ³*Department of Psychiatry, University Medical Center Utrecht and Brain Center Rudolf Magnus, the Netherlands*, ⁴*Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands.*, ⁵*University Medical Center Utrecht*

Background: A forward head posture is often associated with both inactivity and immobility, reflecting characteristics commonly associated with sedentary lifestyles in individuals

diagnosed with psychotic disorders. A forward head posture, induces stress and muscle weakness in the cervical spine, potentially leading to respiratory problems. We examined the prevalence of forward head posture in individuals with psychosis. Individuals with Autism Spectrum Disorder receiving the same supporting household care and healthy volunteers were studied as independent control groups. Subsequently, we explored whether age and diminished cardio-respiratory fitness results serves as a prognostic indicator for reduced forward head posture.

Methods: A total of 85 participants with psychosis-spectrum disorder N=32, autism spectrum disorder N=26, and healthy volunteers N=27 were recruited. Photogrammetric quantification was employed to measure the craniocervical angle regarding a forward head posture. Information for Descriptive analyses was collected and contains information about, BMI, sex, age, psychotropic medication. The Sint Hans Rating Scale was assed to determine motor disturbances, Symptom severity was assessed by the brief symptom inventory and overall wellbeing by the world health organization quality of life questionnaire. The Åstrand bike test (VO₂ max) was employed to assess oxygen uptake in cardio-respiratory fitness.

Results: Individuals with psychosis had mean difference of GREATER THAN 11 degrees in craniovertebral angle, indicating a forward head position of 36.07C ($\pm$ 10.85) compared to individuals with autism spectrum disorder 47.45C ($\pm$ 9.09, P= 0.02) and healthy volunteers 48.13C ($\pm$ 6.39, P= LESS THAN 0.00). A linear relation with diminished cardio-respiratory fitness and reduced craniovertebral angle was particularly found in participants with psychosis spectrum disorder (R²= 0.45, P= LESS THAN 0.00). Age exhibited no significant predictive factor for the reduced craniovertebral angle in participants with psychosis spectrum disorder.

Discussion: Individuals with psychosis demonstrate a reduction of more than 11 degrees in vertebral angle compared to the control groups in this study, categorized as severe forward head posture. This correlates with diminished cardio-respiratory fitness. Recognizing the presence of a forward head posture in individuals with psychosis is crucial, as it may influence daily activities and potentially serve as a hindrance to initiating and sustaining physical exercises. Further research is recommended to investigate the underlying causes of this phenomenon, investigate potential treatment and its relation with cardiovascular and respiratory systems.

S241. ADDRESSING METABOLIC COMORBIDITY IN INDIVIDUALS WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITY ON ANTIPSYCHOTICS: A CLINICAL CASE SERIES

Nicolette Stogios*¹, Margaret Hahn², Yona Lunskey³, Pushpal Desarkar³, Sri Mahavir Agarwal⁴

¹*Institute of Medical Science, University of Toronto, Centre for Addiction and Mental Health,*
²*Center for Addiction and Mental Health; University of Toronto,* ³*Centre for Addiction and Mental Health, University of Toronto,* ⁴*Centre for Addiction and Mental Health; University of Toronto*

Background: Individuals with intellectual and developmental disabilities (IDDs) have exceedingly high rates of serious metabolic comorbidities. This risk is further compounded by the use of antipsychotic (AP) drugs in this population. Despite the high prevalence, there is a lack of effective treatment options for metabolic comorbidity in IDD, particularly in the context of AP use. To date, metformin is the best researched agent for treating AP-induced weight

gain in severe mental illness; however, there is a paucity of literature examining the use of metformin for this purpose in individuals with IDD. This case series reports on the clinical use of metformin in patients with IDD on APs.

Methods: We conducted a retrospective review of patients in the Adult Neurodevelopmental Services Mental Health and Metabolic Clinic at the Centre for Addiction and Mental Health in Toronto, Canada. This is a novel clinical service for adults with IDD experiencing AP-related weight gain and other metabolic aberrations. We included patients of all ages that had an IDD diagnosis and were being treated with APs. Clinical records were reviewed for demographic, anthropometric, and metabolic data. These data were extracted for each patient at 2 timepoints: pre-metformin (values at the time of clinic referral/consolation) and post-metformin (their most recent follow-up data, as available). All variables were determined to have a normal distribution using the Shapiro-Wilk test; therefore, parametric tests were conducted. Categorical data were handled with Chi-squared tests and quantitative data with paired t tests.

Results: Eleven patients (8 male; mean age = 29.5 years) were enrolled into this program and were initiated on metformin to address metabolic concerns. All patients were on second-generation AP medications, including clozapine, olanzapine, and risperidone, for an average duration of about 7 years. Before commencing metformin, the mean weight of the group was 101.2 kg, which demonstrates a weight gain trajectory of approximately 34 kg compared with their mean weight of 67.2 kg before starting APs; the mean BMI was 34.5 kg/m² and the waist circumference was 112.5 cm before metformin. Four patients had a constellation of metabolic aberrations that met criteria for metabolic syndrome, whereas the remaining patients met at least 1 criterion. Mean weight loss while on metformin treatment was 11.1 kg, with over 50% of the sample achieving clinically meaningful weight loss of GREATER THAN 7% (p=0.01). Additional adaptive changes were observed for fasting glucose (p=0.049), glycated hemoglobin (p=0.01), triglycerides (p=0.01), and high-density lipoprotein cholesterol levels (p=0.08). One patient no longer met the criteria for metabolic syndrome. Furthermore, no significant tolerability concerns were reported by patients.

Discussion: In line with its use in severe mental illness, metformin may be a safe, effective, and accessible treatment option for patients with IDD experiencing metabolic adverse effects of AP medication. Clinically meaningful weight loss is associated with many favourable outcomes, including reduced rates of cardiometabolic comorbidities and improved quality of life. Lifestyle interventions demonstrate effectiveness in reducing obesity; however, people with IDD often experience barriers in the initiation and maintenance of such interventions, which limits the utility of lifestyle interventions in this population. Taking this into consideration, pharmacological interventions may be a necessary adjunctive strategy for weight loss for individuals with IDD who gain weight with AP use. Further research and randomized controlled trials are needed to examine the efficacy of metformin in this population.

S242. EXCESSIVE MORTALITY-TO-INCIDENCE RATIO OF CANCER RELATE TO HEALTH CARE DISPARITIES IN PATIENTS WITH SCHIZOPHRENIA: A NATIONWIDE COHORT IN TAIWAN

Chian-Jue Kuo^{*1}, Chu-Syuan Cheng¹, Shang-Ying Tsai², Chiao-Chicy Chen³

¹Taipei City Psychiatric Center, Taipei City Hospital, ²Taipei Medical University Hospital,

³Department of Psychiatry, Mackay Memorial Hospital

Background: Research on the occurrence and fatality of cancer in individuals with schizophrenia has yielded inconsistent results. In this study, we simultaneously investigated cancer incidence and mortality in patients with schizophrenia and evaluated the cancer mortality-to-incidence ratio (MIR), which is rare in the literature.

Methods: We collected the data of 107,489 patients who received a diagnosis of schizophrenia between 2000 and 2019 from the Taiwan National Health Insurance Database. Data regarding cancer incidence and mortality were obtained from the Taiwan Cancer Registry and National Mortality Database, respectively. In total, 3881 incident cancer cases and 2288 cancer mortality cases were identified. Standardized incidence ratios (SIRs), mortality rate ratio (MRRs), and MIRs were compared between patients with schizophrenia and the general population.

Results: Patients with schizophrenia showed a slightly lower cancer incidence rate (SIR: 0.95; 95% confidence interval [CI]: 0.92–0.98; $p < 0.001$) and a higher cancer mortality rate (MRR: 1.29; 95% CI: 1.23–1.3; $p < 0.001$) compared to the general population. The MIR for overall cancer was significantly higher in patients with schizophrenia. The relative MIR (MIR of patients with schizophrenia divided by that of the general population) was 1.36; 95% CI: 1.30–1.42. Several site-specific cancers were with excessive relative MIR: oral cavity, nasopharyngeal, stomach, colorectal, laryngeal, lung, breast, cervical, uterine, ovarian, and bladder cancers.

Discussion: Patients with schizophrenia exhibited lower cancer incidence but higher cancer mortality rates than the general population. The significantly higher MIR in patients with schizophrenia suggests disparities in cancer-related healthcare compared to the general population, potentially stemming from underdiagnosis and undertreatment of cancer in this patient group. Notably, potential healthcare disparities appeared to be greater for several cancers covered by Taiwan's nationwide population-based screening program, including oral cavity, colorectal, breast, and cervical cancers.

S243. EFFECT OF STAGE AT DIAGNOSIS, TREATMENT, AND PHYSICAL COMORBIDITIES ON MORTALITY FOLLOWING CANCER DIAGNOSIS AMONG PEOPLE WITH NON-AFFECTIVE PSYCHOTIC DISORDERS: A CAUSAL MEDIATION ANALYSIS

Jared Wootten^{*1}, Lucie Richard², Melody Lam³, Phillip Blanchette⁴, Igor Karp⁵, Marco Solmi⁶, Kelly Anderson¹

¹University of Western Ontario, ²MAP Centre for Urban Health Solutions, ³ICES Western, ⁴London Health Sciences Center, ⁵Western University, ⁶Department of Psychiatry, University of Ottawa

Background: People with psychotic disorders—which include schizophrenia and bipolar disorder—have a 10- to 15-year shorter life expectancy compared to the general population; concurrent medical illnesses such as cardiovascular disease and cancer account for much of this disparity (Hjorthøj et al., 2017). It has been previously suggested that the effect of having a psychotic disorder on mortality following cancer diagnosis is mediated through delayed stage at diagnosis, treatment disparities, and other physical comorbidities. (Mahar et al., 2020). Prior research has attempted to estimate the indirect effects through each of these factors using traditional regression methods. However, the structure of these variables in relation to one

another poses several challenges in traditional analyses. Namely, stage at diagnosis acts as a post-exposure confounder of the indirect effects through treatment. Conditioning on stage using traditional regression analyses results in collider bias.

Methods: We constructed a retrospective cohort of cases of non-affective psychotic disorder (NAPD) and a general population comparison group using Ontario health administrative data. We identified cases of cancer diagnosed between 1995 and 2019 and obtained information on stage at diagnosis, cancer-related treatment, comorbidities, and mortality. We will construct marginal structural Cox models with G-computation to estimate the Randomized Interventional Analogues of Indirect Effects (RIANIE) from diagnosis with NAPD to mortality following cancer diagnosis through stage at diagnosis, treatment received, and physical comorbidities, adjusting for baseline covariates.

Results: We anticipate that a large proportion of the total causal effects of prior diagnosis with NAPD on mortality following cancer diagnosis are mediated through these 3 variables.

Discussion: Conclusion: This study will be the first to examine the indirect effects of having a NAPD through stage at diagnosis and treatment using marginal structural models, which are equipped to manage post-exposure confounding, unlike traditional regression mediation analyses. Providing an estimate of these indirect effects through stage at diagnosis and treatment will determine the proportion of the mortality gap among people with NAPD can be accounted for by delays in diagnosis and treatment disparities. By identifying how these variables account for mortality, we can work to develop effective programs to target these disparities, in turn reducing the mortality gap.

S244. PHYSICAL HEALTH COMORBIDITIES AMONG PERSONS WITH UNTREATED PSYCHOTIC DISORDER IN DIVERSE SETTINGS OF THE GLOBAL SOUTH

Akin Ojagbemi^{*1}, Idowu Olufemi¹, Bola Olley¹, Georgina Miguel Esponda², Tessa Roberts², Sujit John³, Vijaya Raghavan³, Joni Lee Pow⁴, Casswina Donald⁴, Olatunde Ayinde¹, Joseph Lam², Paola Dazzan², Fiona Gaughran², Alex Cohen⁵, Helen Weiss⁵, Robin Murray², Rangaswamy Thara³, Gerard Hutchinson⁴, Craig Morgan², Oye Gureje¹

¹University of Ibadan College of Medicine, ²King's College London, ³Schizophrenia Research Foundation, Chennai, India, ⁴University of the West Indies, Saint Augustine, Trinidad, ⁵London School of Hygiene and Tropical Medicine

Background: There is limited information on the prevalence and profile of comorbid physical health conditions in persons with untreated psychotic disorder in the Global South.

Methods: Data were collected as part of the International Research Programme on Psychoses in Diverse Settings (INTREPID II), a population-based incidence and case-control study conducted in selected catchment areas in India, Nigeria and Trinidad. Cases were aged 18-64 years with an untreated psychotic disorder diagnosed according to ICD 10 criteria. Controls were matched for age, sex, and recruited from the same neighbourhood as cases. Physical health measurements were acquired using the WHO STEPwise approach to non-communicable disease risk factors surveillance instrument (WHO STEPS). We estimated adjusted odds ratios (aOR) using unconditional logistic regression.

Results: We enrolled 225, 209, and 212 case-control pairs in India, Nigeria, and Trinidad, respectively. Among cases and controls across all sites, high cholesterol and raised C-reactive protein were common (i.e., over 50% for both in all groups and sites), but with no consistent

associations with psychotic disorder. Undernutrition was more common among cases compared with controls in India (26.9% vs 8.4%, aOR= 2.86, 95% C.I=1.56 – 5.28) and Nigeria (24.9% vs 10.1%, aOR= 3.01, 95% C.I= 1.70 - 5.33). Hypertension was less common among cases compared with controls in India (Self report: 6.7% vs 22.2%, aOR=0.24, 95% C.I=0.13 - 0.45) and Nigeria Measured: 8.9% vs 22.0%, aOR=0.30, 0.16 - 0.57). Differences between cases and controls were more modest (albeit in the same direction) for both undernutrition and hypertension in Trinidad.

Discussion: We found a unique pattern of elevated physical health comorbidity with untreated psychotic disorder in three diverse settings of the Global South. Elevated cardiometabolic risk was not evident, but cases were more likely to be undernourished, possibly reflecting increased association of psychotic disorder with severe economic and social disadvantage in these settings.

S245. EXPLORING THE IMPACT OF PSYCHOTHERAPY ON PTSD SYMPTOMS IN PATIENTS WITH A PSYCHOTIC DISORDER: A NON-TRAUMA-FOCUSED INTERVENTION APPROACH

Vanessa McGrory*¹, Danielle Penney², Pascale Brillon¹, Martin Lepage³

¹*Université du Québec à Montréal*, ²*Douglas Mental Health University Institute and L'Université du Québec à Montréal*, ³*McGill University, Douglas Mental Health University Institute*

Background: Addressing post-traumatic stress symptoms (PTSS) in patients with psychotic disorders presents a critical dichotomy. On one hand, interventions are offered and focused primarily on targeting PTSS. On the other, PTSS are either overlooked in the treatment of psychosis, fearing adverse outcomes such as symptom exacerbation or relapse, or fall under the radar. In fact, research reports that 96.9% of comorbid PTSD in this population remains undiagnosed; therefore, PTSS prevail untreated. With a lack of evidence-based treatments for addressing post-traumatic effects in the early stages of psychosis, and with the routine exclusion of individuals with psychotic disorders from research trials for PTSS, there is a need to develop a deeper understanding of appropriate interventions, and barriers to recovery in a population with comorbid trauma and psychotic symptoms. Considering these circumstances, exploring the effects of psychosocial interventions for individuals with psychosis on comorbid PTSS would be beneficial to estimate whether interventions that are not explicitly trauma-focused are associated with improvement in these comorbid symptoms.

Methods: We sought to uncover the relationship between completion patterns in psychosocial interventions for psychosis, and the presence and severity of comorbid PTSS pre- and post-intervention. Data were collected from adults (n=39) receiving different group-based interventions for psychosis from the Psychotic Disorders Program at the Douglas Mental Health University Institute in Montreal, Canada. PTSS severity was collected using the PTSD Checklist for DSM-5 (PCL-5) both prior to and following the intervention. Participants attended either of the following psychotherapies: Social Cognition and Interaction Training (SCIT; n=4), Cognitive Restructuring Therapy (CRT; n=11), or Cognitive Behavioural Therapy (CBT; n=24).

Results: Results revealed that 64.1% (n=25) of participants qualified as completers for their respective intervention, whereas 35.9% (n=14) did not. Intervention completion status was determined based on attending more than 50% of sessions of a given intervention. On average,

participants qualifying as completers attended 83% of psychotherapy sessions. Furthermore, results indicated that receiving a psychological intervention for psychosis, albeit non-trauma focused, was associated with a significant decrease in PTSS ($t(19) = 3.63$, $p < .001$) for therapy completers and the effect size was large (Cohen's $d = 0.81$; CI: 0.30, 1.31). Moreover, decrease in symptom severity was most pronounced for the hyperarousal ($t(19) = 4.02$, $p < .001$) and negative alteration ($t(19) = 2.71$, $p = .007$) dimensions and these results showed large (Cohen's $d = 0.90$; CI: 0.37, 1.41) and medium (Cohen's $d = 0.61$; CI: 0.12, 1.08) effect sizes, respectively.

Discussion: The significant finding that a non-trauma-focused psychosocial intervention is associated with a marked reduction in PTSS challenges existing notions about the management of comorbid PTSD in patients with psychosis. This underscores the potential of general psychosocial support in addressing broader psychopathological issues beyond primary psychotic symptoms. The pronounced decrease in hyperarousal and negative alteration symptoms could indicate that certain components of psychosocial therapy may inadvertently target mechanisms that maintain PTSS. These findings argue against the prevailing hesitancy to engage individuals with psychotic disorders in PTSD treatment.

S246. SCHEMA CHARGE AND PERMEABILITY IN SCHIZOPHRENIA SPECTRUM DISORDERS

Jessica D'Arcey^{*1}, Michael Best²

¹University of Toronto Scarborough, Centre for Addiction and Mental Health, ²University of Toronto Scarborough

Background: Cognitive models of psychopathology, including psychosis, highlight cognitive schemas and biases as key cognitive mechanisms in the development and maintenance of symptoms. Schemas provide the organizational structure to our beliefs and, when maladaptive, are characterized by a pattern of over-activation (i.e., schema charge) and rigidity (i.e., low schema permeability). Cognitive biases, such as externalizing biases and attention to threat bias, are skewed information processing mechanisms. Maladaptive schemas give rise to cognitive biases, which serve as the basis of delusional and hallucinatory belief systems through interpretation. The current study investigated whether schema charge and permeability differ in individuals with schizophrenia-spectrum disorders (SSDs) compared to healthy controls to provide potential insights into the role of these mechanisms in psychosis. Secondary aims investigated the relationship between schema permeability and charge and whether it's mediated by cognitive biases.

Methods: This study uses an experimental design consisting of two computerized manipulations designed to increase and decrease the activation of maladaptive cognitive schemas and biases. Participants first participated in an exclusion version of Cyberball (a computerized game of toss/catch) wherein participants were tossed the ball twice at the beginning of the task and subsequently completely excluded. Following is an inclusion version wherein one of the computerized players apologized, provided an explanation for the prior exclusion, and subsequently fully included the participant. Measures of cognitive mechanisms were conducted prior to the exclusion version, between the exclusion and inclusion version, and the post-inclusion version. Primary measures included the Brief Core Schema Scale (negative self and other subscales), the Davos Assessment of Cognitive Biases Scale (DACOBS) and the Bias Against Disconfirmatory Evidence (BADE) task. Group differences

across the three different time points were investigated using ten mixed methods 2X2 ANOVAs, and eight mediations were used to investigate relationships between schema charge, permeability and cognitive biases.

Results: Seventeen individuals with SSDs and 16 controls completed the experimental visit to date. Interim analyses show the following results. Individuals with SSDs endorsed stronger negative schemas (other schemas $2 = .20$, $p = .009$, self-schemas $2 = .19$, $p = .013$) and self-reported cognitive biases (DACOBS $2 = .197$, $p = .01$) than controls across experimental conditions, and no significant interactions with Cyberball conditions were found. The BADE did not show significant differences between groups. The bias against disconfirmatory evidence significantly mediated the relationship between schema charge and schema permeability ($b = .13$, CI [.02, .29]). No other mediation models were significant.

Discussion: Results of this study suggest that cognitive schemas and biases can be successfully manipulated in brief periods of time using stressful stimuli such as Cyberball, which has important implications for future study design. Further, overall, results support the cognitive theory that negative cognitive schemas are more activated in individuals with SSDs and have important relationships with cognitive biases. Results should be interpreted considering the small sample size, which impacts generalizability. Larger longitudinal trials are required to further elucidate these relationships. Further, future studies may consider including other types of psychopathologies, such as depression, as a comparison group in addition to psychiatrically healthy controls.

S247. FAMILY METACOGNITIVE TRAINING (MCT-F): ADAPTING MCT TO MOTHERS WITH PSYCHOSIS AND THEIR ADOLESCENT CHILDREN

Victoria Espinosa^{*1}, Paula Arin-González², Alba Jiménez Lafuente², Nerea Pardo², Raquel López Carrilero², Irene Birulés², Ana Barajas³, Trinidad Pélaez², Luciana Díaz-Cutraró¹, Marina Verdaguer-Rodríguez¹, Alfonso Gutiérrez Zotes⁴, Carolina Palma-Sevillano⁵, Paloma Varela Casals⁶, Miriam Salas-Sender⁷, Ana Aznar⁸, Rosa Ayesa-Arriola⁹, Esther Pousa¹⁰, Manuel Canal-Rivero¹¹, Nathalia Garrido-Torres¹¹, Clara Montserrat¹², Laura Muñoz-Lorenzo¹³, Josep Maria Crosas¹⁴, Susana Ochoa¹

¹Institut de Recerca Sant Joan de Déu, ²Parc Sanitari Sant Joan de Déu, ³Departament de Psicologia, Facultat de Psicologia Clínica I de la Salut. Serra Húnter Programme, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, ⁴Hospital Universitari Institut Pere Mata, Institut d'Investigació Sanitària Pere Virgili-CERCA, Universitat Rovira i Virgili, ⁵Psychology Department, FPCEE Blanquerna, Universitat Ramon Llull, ⁶Hospital de Mataró, Consorci Sanitari del Maresme, ⁷Miriam Salas-Sender Parc Sanitari Sant Joan de Déu, ⁸Departament de Psicologia, Facultat de Psicologia Clínica I de la Salut. Serra Húnter Programme, Universitat Autònoma de Barcelona, ⁹Department of Psychiatry, Marqués de Valdecilla University Hospital, IDIVAL. School of Medicine, University of Cantabria, ¹⁰Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica-Sant Pau (IIB-Sant Pau), ¹¹Virgen del Rocío University Hospital, Network Centre for Biomedical Research in Mental Health (CIBERSAM), Institute of Biomedicine of Seville (IBiS), University of Seville, First-episode Psychosis Research Network of Andalusia (Red PEPSur), ¹²Hospital del Mar Medical Research Institute (IMIM) of Barcelona, Autonomous University of Barcelona, ¹³Departamento de Psiquiatría, IIS-Fundación Jiménez Díaz,

Background: Over half of women with psychosis are mothers, a similar percentage to that found in females without a mental disorder diagnosis. Research suggests that mothers with psychosis face unique challenges affecting both their mental health prognosis and the relationship with their children. Symptoms are associated with deficits in social cognitive skills, potentially affecting patients' relationship with their children. Furthermore, in comparison to their male counterparts, mothers with psychosis were more likely to be a single parent, perform most parenting tasks or report having parenting-related stress. In consequence, custody loss is experienced more often than in mothers without mental health problems and their children have a higher risk of developing a mental health disorder. Notwithstanding, interventions specifically tailored to mothers with psychosis and their adolescent children remain largely uncovered. The Metacognitive Training has demonstrated its efficacy in improving cognitive insight, symptom management and social cognition in people with psychosis. Additionally, MCT has shown better results in females than males with psychosis. However, there is no evidence of the efficacy of MCT in a family setting (MCT-F).

Methods: This study describes the formative phases, processes, and methods used to adapt the evidence-based MCT for mothers with psychosis and their adolescent children in an online group setting. The paper presents how the phases (assessment, decision, adaptation, production, topical experts-integration) of the ADAPT-ITT model were systematically applied through a participatory approach (n=22), including first-person perspective and involving qualitative (e.g., topical expert literature review and consensus groups, interviews, thematic analyses) and quantitative methods.

Different types of triangulations were implemented to ensure the validity and transferability of the adaptation process.

Results: Patients, relatives, adolescents, and experts broadly perceived the intervention to be helpful, acceptable, and necessary. While MCT's core components were retained, participants guided adaptations both in the structure, format, content and delivery of the intervention, optimizing acceptability and feasibility of implementation.

Discussion: A main limitation of the study was the relatively low number of mothers with psychosis or adolescents involved in adaptation step. Nevertheless, participants' suggestions were congruent with topical expert's opinions. Findings suggest the importance of community engagement and sharing decision-making to demonstrate the acceptability and feasibility of the adapted intervention. Employing a structured approach such as the ADAPT-ITT model ensures readiness and suitability of the new training for efficacy trials. Implementation of MCT-F could enhance mothers with psychosis and adolescents' functioning and better understanding of the disease. Additionally, it may have a protective and preventive effect on adolescents, who are known to be at higher risk of developing severe mental disorders.

S248. "I AM PROUD OF HOW I HANDLED IT." EXPLORING THE IMPACT OF THE COVID-19 PANDEMIC AND RELATED RESTRICTIONS ON WELL-BEING OF ADULTS WITH SEVERE MENTAL ILLNESS USING PARTICIPATORY ACTION RESEARCH

Lotte van Rijn*¹, Margot Metz², Pip van der Velden², Pleun Mathijssen², Wilma Swildens³, Arnt Schellekens⁴, Wiepke Cahn⁵, Megan Milota⁶, Janneke Zinkstok⁴

¹*Radboud University Nijmegen*, ²*GGz Breburg, Institute for Mental Health Care, Breda, The Netherlands*, ³*Altrecht, Institute for Mental Health Care*, ⁴*Department of Psychiatry, Radboud University Medical Center, Donders Institute For Brain, Cognition, and Behavior*, ⁵*Department of Psychiatry, University Medical Center Utrecht*, ⁶*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht*

Background: The COVID-19 pandemic and related restrictions globally impacted mental health, particularly for those with pre-existing severe mental illness (SMI) including schizophrenia. This qualitative study examined how adults with SMI perceived the effects of the COVID-19 pandemic and related restrictions in the Netherlands, focusing on their personal recovery, well-being and daily life, including an exploration of factors influencing these effects.

Methods: Semi-structured interviews were conducted, audio-recorded and transcribed verbatim. Reflexive thematic analysis was applied. The study used a participatory action research approach, with experts-by-experience involved in every stage of the project as part of the research team.

Results: Twenty participants (median age 45 (SD: 12,8) ; 11 female) were interviewed between May and July 2023. Findings revealed a wide range of experiences: while some individuals reported a negative impact on their existing psychiatric symptoms, others described adaptability, resilience, and even positive effects of COVID-restrictions on their mental health and well-being. Factors influencing the heterogeneous perceptions of COVID-19 pandemic and related restrictions include the availability of trusted social relationships and enduring interactions with health professionals.

Discussion: Personalized support, both socially and professionally, is crucial for addressing fears, building resilience, reducing isolation, and encouraging positive coping strategies for individuals with SMI during external crises. In this project, a participatory research approach that integrated the lived experience perspective helped uncover the unique perceptions of people with SMI with regards to the pandemic and related restrictions.

S249. BURDEN AND MANAGEMENT OF TARDIVE DYSKINESIA (TD): A CROSS-SECTIONAL, INTERNATIONAL SURVEY STUDY TO ASSESS THE PERCEPTIONS AND EXPERIENCES OF PHYSICIANS AND PATIENTS WITH TD

Rinat Ribalov¹, Ayelet Yaari*², Aviva Peyser Levin³, Amy Yang⁴, Dahbia Horchi⁵, Erwan Berjonneau⁵, Perrine Le Calvé⁵, Marc Tian⁶, Shoshana Reshef⁷, Suzanne Reed⁵

¹*Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research*, ²*Teva Pharmaceutical Industries, Ltd.*, ³*Teva Pharmaceutical Industries Ltd., International Markets Medical Affairs*, ⁴*Teva Branded Pharmaceutical Products R and D, Inc., Global Health Economics and Outcomes Research*, ⁵*Oracle, Paris, France*, ⁶*Teva Branded Pharmaceutical Products R and D, Inc., Real World Evidence Statistics*, ⁷*Teva Branded Pharmaceutical Products R and D, Inc., Epidemiology and Global Health Economics and Outcomes Research*

Background: Data on the perceptions of physicians and patients in Australia, Brazil, China, Israel, and South Korea toward TD management and impact on daily living are limited, particularly on patient quality of life (QoL). This study assessed physician and patient perceptions of the management of TD and its impact on daily life.

Methods: Patients (aged ≥ 18 years) who self-reported a physician diagnosis of TD, experienced TD-related movements, and had a diagnosis of schizophrenia or schizoaffective disorder, bipolar disorder, or major depressive disorder were recruited via online panels, social media, or physician referral to participate in a 20-minute online survey (27 June through 17 October 2022). Certified neurologists and psychiatrists (in practice ≥ 3 years, $\geq 60\%$ of time in direct patient care, treating ≥ 3 patients with TD in prior 2 years) were invited via panels to participate in a separate 20-minute online survey (27 June through 27 July 2022). Physician and patient data were unlinked.

Results: 435 patients and 340 physicians from Australia, Brazil, China, South Korea, and Israel (physicians only) were included in the study. 29% of patients reported that TD always/often interfered with treatment adherence for their underlying psychiatric condition, 25% reported that TD always/often worsened their underlying psychiatric condition, and 47% reported that they developed additional psychiatric conditions. In comparison, most physicians reported a moderate to very strong impact of TD on worsening adherence with treatment for the underlying condition (75%), an effect of TD on underlying psychiatric condition symptoms (71%), and development of other psychiatric symptoms (78%). While the majority believed that TD had a moderate to strong impact on QoL (85% patients, 88% physicians), 63% of patients reported strong impact on their QoL compared with 46% of physicians.

Discussion: In this survey, both patients and physicians agreed that TD has a substantial impact on patient QoL. These results indicate that TD could undermine psychiatric stability by worsening underlying psychiatric conditions and treatment adherence. The difference between the level of importance that patients and physicians give to the impact of TD highlights the need for better dialogue between them.

S250. THE RELATIONSHIPS BETWEEN PSYCHOLOGICAL RESILIENCE, SCHIZOPHRENIA, AND SUICIDAL EXPERIENCES: A LONGITUDINAL STUDY

Kamelia Harris^{*1}, Gillian Haddock¹, Sarah Peters¹, Patricia Gooding¹

¹*University of Manchester*

Background: Schizophrenia is a severe mental health problem which is associated with a considerably higher risk of suicide death compared to that in the general population. In addition, experiencing suicidal thoughts and attempts is even more frequent in people with schizophrenia. Suicide deaths in that population present a significant healthcare concern. Research suggests that schizophrenia and the associated distress heighten the risk of suicidal experiences, while psychological resilience mitigates the impact of key suicide precursors, such as defeat, entrapment, and hopelessness. However, there is a gap in longitudinal testing regarding the moderating roles of psychosis symptoms, the associated distress, and psychological resilience in the relationships between defeat, entrapment, hopelessness, and suicidal thoughts and behaviours.

Methods: Participants (N=100) with schizophrenia-spectrum diagnoses (including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or

unspecified psychotic disorders) and a history of suicidal thoughts, plans, and/or acts, were recruited from community mental health and inpatient services in Northern England, UK. This three-month longitudinal study used moderated mediation analyses to examine two key aspects: (1) the influence of defeat/entrapment and hopelessness on suicidal thoughts and behaviours, and (2) the moderating effects of psychosis, the associated distress, and psychological resilience in the associations between defeat/entrapment, hopelessness, and suicidal thoughts and behaviours.

Results: Of the 100 participants at baseline, 80% were female, 73% were White British, approximately 60% had a diagnosis of schizophrenia, and their mean age was 41 years. Ninety participants completed the three-month follow-up assessment. Baseline data revealed that most participants had experienced one or more lifetime suicide attempts. Suicidal thoughts and behaviours scores were significantly lower at follow-up compared to baseline. Delusions and hallucinations severity strengthened the relationship between defeat/entrapment and subsequent suicidal thoughts and behaviours. Additionally, the baseline level of distress associated with delusions and hallucinations strengthened the link between defeat/entrapment and suicidal thoughts and behaviours at follow-up. These associations were significant when the severity of baseline delusions and hallucinations, coupled with distress, was of moderate to high levels, and baseline resilience was low.

Discussion: The relationship between baseline defeat/entrapment and suicidal thoughts and behaviours at follow-up was not mediated by hopelessness. This finding contrasts with prior studies that have identified hopelessness as a significant precursor to suicidal thoughts and behaviours. One possible explanation for this result is the overlap of defeat, entrapment, and hopelessness as constructs within the current sample. In addition, there is an argument that perceptions of hopelessness may precede or follow experiences of defeat and entrapment. To achieve conceptual clarity on the roles of defeat, entrapment, and hopelessness in suicidal experiences among individuals with schizophrenia, further research is warranted. The combined impact of defeat/entrapment, psychosis, the associated distress, and psychological resilience should be considered in interventions aimed at reducing suicidal experiences. These findings emphasise the need to tailor suicide prevention interventions to address the complex dynamics of psychosis and resilience in individuals with schizophrenia diagnoses.

S251. DIFFERENTIAL RISK: HOW RACIAL DISCRIMINATION LEADS TO VARYING RISK IN THE RELATIONSHIP BETWEEN TRAUMA AND MULTIDIMENSIONAL SCHIZOTYPY

Mahogany Monette^{*1}, Madisen Russell², Danielle Abel², Jarrett Lewis³, Jessica Mickens², Evan Myers⁴, Megan Hricovec⁵, David Cicero⁵, J Wolny⁶, William P. Hetrick⁶, Michael Masucci⁷, Alex Cohen⁷, Christopher Burgin⁸, Kyle S. Minor⁹, Thomas R. Kwapil¹⁰

¹Indiana University Purdue University Indianapolis, ²Indiana University- Purdue University, Indianapolis, ³University of Illinois at Urbana-Champaign, ⁴Indiana University - Purdue University Indianapolis, ⁵University of North Texas, ⁶Indiana University, ⁷Louisiana State University, ⁸Tennessee Technological University, ⁹Indiana University Purdue University, ¹⁰Department of Psychology, University of Illinois at Urbana-Champaign

Background: Traumatic experiences are associated with experiencing positive schizotypy. This may be especially important for People of Color, who endorse higher rates of trauma and

racial discrimination. The present study aimed to examine racial disparities in how multidimensional schizotypy traits (positive, negative, and disorganized) are observed.

Methods: 770 Black, Asian, and Latine college students from six universities completed measures of trauma (Life Events Checklist and Post Traumatic Stress Disorder Checklist 5), racial discrimination (Experiences of Discrimination Scale), and multidimensional schizotypy (Multidimensional Schizotypy Scale). One-way ANOVAs were conducted to examine racial and gender differences in trauma, racial discrimination, and multidimensional schizotypy. Stepwise hierarchical regression analyses were used to examine if racial discrimination moderated the relationship between trauma and multidimensional schizotypy.

Results: As hypothesized, Black students endorsed significantly higher racial discrimination than Latine and Asian students. Furthermore, Black and Latine students endorsed significantly higher multidimensional schizotypy and trauma than Asian students. Racial discrimination and trauma explained 8 to 23% of the variance in each dimension of schizotypy. Only one moderation model approached significance: trauma X racial discrimination predicting disorganized schizotypy ($\beta=.13$, $p=0.09$).

Discussion: Our findings suggest that racial discrimination and trauma account for up to nearly a quarter of the variance in multidimensional schizotypy. Additionally, there were race and gender differences in the severity of trauma, discrimination, and schizotypy. Psychological interventions must account for how racial discrimination and trauma may impact symptom presentation.

S252. FINANCIAL DISSATISFACTION IN PEOPLE WITH PSYCHOTIC DISORDERS- A SHORT REPORT ON ITS PREVALENCE AND CORRELATES IN A LARGE NATURALISTIC PSYCHOSIS COHORT

Josephien Jansen^{*1}, Richard Bruggeman², Henk Kiers¹, Marieke (Gerdina) Pijnenborg³, Stynke Castelein⁴, Wim Veling⁵, Ellen Visser⁶, Lydia Krabbendam⁷, Janneke Koerts¹

¹University of Groningen, ²University of Groningen / University Medical Center Groningen, ³University of Groningen / GGZ Drenthe Mental Health Institute, ⁴Lentis Research / University of Groningen, ⁵University Medical Center Groningen, ⁶Rob Giel Research Center of University Medical Center Groningen, ⁷Vrije Universiteit Amsterdam

Background: Psychotic disorders have a strong negative impact on multiple aspects of daily life, including people's financial situation. This exploratory study examines the level of financial dissatisfaction and its correlates in a large cohort of people with psychotic disorders.

Methods: Data from the first assessments of people with psychotic disorders ($n = 5271$) who were included in the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS; 2006-2020), which is conducted in the northern Netherlands, were used. The Manchester Short Assessment of Quality of Life (MANSA) was used to measure financial dissatisfaction. In addition, sociodemographic and psychiatric characteristics, substance use and global and social functioning were assessed.

Results: One-fifth to one-third of people with psychotic disorders report financial dissatisfaction, fluctuating over the year in which they were assessed. These proportions are three to four times higher than in the general Dutch population. Cannabis and other substance use were associated with higher levels of financial dissatisfaction (small to medium effect). Financial dissatisfaction appears to be relatively independent of sociodemographic and

psychiatric characteristics, and global and social functioning in people with psychotic disorders.

Discussion: These findings are an important first step for increasing knowledge on financial dissatisfaction among people with psychotic disorders. The findings can also contribute to raising awareness about the topic for healthcare professionals working in this field, as financial dissatisfaction seems a crucial stressor to consider in clinical practice.

S253. WORKING WITH SCHIZOPHRENIA: A MIXED-METHOD STUDY OF EMPLOYMENT STATUS AND EMPLOYABILITY AMONG THE PEOPLE LIVING WITH SCHIZOPHRENIA IN CHINA

Yilu Li*¹

¹*Xiangya School of Public Health, Central South University*

Background: People living with schizophrenia (PLS) have long challenged the presumption that having schizophrenia means that a person cannot work. They hope, and strive to prove, that they can work, regain independence and recover. It is not surprising that so many PLS express a strong desire to work and regard getting a job as their goal of recovery. Too often, however, PLS are unwelcome and invisible in the labor market. Employment rates for PLS have been particularly low. To date, the employment status of PLS in China is still unclear, and explanations of PLS unemployment generally focus only on supply-side factors. New evidence and understanding of potential external and internal factors on the employment outcomes of PLS are needed. The purpose of this mixed-methods study was to assess the employment status of PLS in China and identify factors related to their employability.

Methods: To answer the research questions, the mixed methods approach was used in this study. This study used a sequential explanatory mixed methods design. At the first stage, the quantitative data is collected and analyzed to understand employment status and identify potential influenced factors on the PLS' employment. Then, the qualitative data is collected and analyzed to explain why the employment status of PLS presents the current picture and to explain what factors may affect PLS's employability. Quantitative results on employment status were obtained from a survey of 823 PLS from four cities in China. The working status during the last month and before the diagnosis of schizophrenia of PLS were measured by self-administered questionnaires. In addition, in-depth interviews were conducted with 24 purposively selected respondents. The techniques of thematic analysis were adopted in qualitative data analysis.

Results: Quantitative findings indicate that 15.2% of PLS are competitively full-time employed and 3.5% are competitively part-time employed. Only 13.5% of PLS maintained their competitive employment after being diagnosed with schizophrenia. Competitively employed PLS reported higher levels of social functioning, lower levels of disability, and less severe symptoms than unemployed PLS. Qualitative findings explain the employment status of PLS and illustrate what factors influence the employability of PLS in China. This study proposes a framework for the employability of PLS based on individual factors, personal circumstances, and external factors. Individual factors, including health and well-being, work skills, work experience, educational attainment, "guanxi" network, gender and age are important factors influencing the work motivation and work performance of PLS in China. Personal circumstances, such as socioeconomic contextual factors in PLS's family and family caregiving responsibilities, are a contextual factor in PLS's consideration of whether to seek and maintain competitive employment. External factors, including the labor market and

macroeconomic context, stigma and discrimination, mental health services and policy factors, determine how likely PLS are to be employed and what types of jobs they are likely to obtain. PLS also internalize their perceptions and opinions about the external employment environment (e.g., whether the market is buoyant, whether employers discriminate against PLS), which affects their motivation and incentives to work. Individual factors, personal circumstances, and external factors interact with each other, and a multifaceted combination of these factors shape the employability of PLS.

Discussion: This study suggests that PLS in China face considerable difficulties in maintaining employment after being diagnosed with schizophrenia. Although the government has increased its commitment to supporting the employment of PLS in recent years, the employment rate of PLS in China remains low. The PLS employability framework in this study suggests how PLS households, the macroeconomic context, mental health systems, and social welfare systems influence PLS employment. The employed PLS in China mainly work in the low-skilled service sector, reflecting the large increase of low-skilled service employment in China. However, a large number of workers have been laid off from the manufacturing sector due to its decline and have flocked to the service sector to find employment. Moreover, wages in the low-skilled service sector have been declining in China since 2014. This means that PLS have to facing increased competition and declining wages, which greatly reduces their willingness to work. There is an urgent need to implement targeted employment support programs for PLS. Based on the findings of this study, several recommendations have been made to support the employment of PLS. First, the findings of this study suggest that the "supply-side orthodoxy" in employment support policy and practice needs a significant shift. The development of employment support programs should explore more effective ways to expand employment opportunities for PLS. Second, mental health services should provide employment support for PLS, such as helping PLS cope with work stress and medication management. Finally, in addition to workplace stigma, associated and structural stigma are equally important to the employment of PLS.

S254. HUMANISTIC BURDEN OF COGNITIVE IMPAIRMENT AMONG PATIENTS WITH SCHIZOPHRENIA USING UNITED STATES MEDICAL EXPENDITURE PANEL SURVEY DATA

Tavneet Singh¹, Mona Nili², Briana Choi¹, Cindy Lam¹, Pin Xiang^{*2}, November McGarvey¹, Christoph Correll³

¹BluePath Solutions, ²Boehringer Ingelheim, ³The Zucker Hillside Hospital

Background: Cognitive impairment is a critical yet often overlooked aspect of schizophrenia. Individuals with schizophrenia frequently struggle with memory, attention, and executive functioning. These challenges can significantly impair their ability to plan, adapt, solve problems, or engage in social interactions. This study aims to assess the impact of cognitive impairment on humanistic outcomes in patients with schizophrenia.

Methods: This cross-sectional study analyzed data from the 1997-2021 Medical Expenditure Panel Survey (MEPS), which represents non-institutionalized individuals in the United States. This study included adults (≥ 18 years old) with schizophrenia. For capturing cognitive impairment, two variables, cognitive limitations (CL) and cognitive difficulties (CD) were used. CL included reports of interferences with daily activities due to confusion/memory loss, problems making decisions, or requiring supervision for their own safety (data available from 1997-2021). CD included reports of difficulty in concentration, memory, or decision-making

(data available from 2013-2021). Patient characteristics and health-related quality of life measures such as the short form 12 physical component score (SF-12 PCS) and short form 12 mental component score (SF-12 MCS) were analyzed in this study. The complex survey design of MEPS was accounted for in all analyses.

Results: The study included 1,827 participants, representing 661,243 adults with schizophrenia in the United States. The average age was 45.6 years, with 56.7% being male. Among the participants, 57.6% reported having CL, and 53.5% had CD. Those with CL had significantly lower scores in SF-12 PCS (0.64 vs. 0.71, p LESS THAN 0.01), SF-12 MCS (0.75 vs. 0.96, p LESS THAN 0.01), and SF-6D (0.61 vs. 0.74, p LESS THAN 0.01) compared to individuals without CL. Additionally, a higher percentage of individuals with CL reported poor perceived physical health status (15.8% vs. 5.7%, p LESS THAN 0.01) and poor perceived mental health status (29.5% vs. 10.0%, p LESS THAN 0.01) compared to those without CL. Individuals with CL also experienced more limitations in activities of daily living (ADL) (16.4% vs. 3.1%, p LESS THAN 0.01) and instrumental activities of daily living (IADL) (53.8% vs. 19.2%, p LESS THAN 0.01). Limitations in social/recreational activities (62.0% vs. 18.7%, p LESS THAN 0.01) and in work/house/school activities (89.0% vs. 49.9%, p LESS THAN 0.01) were also more reported among those with CL. Similarly, individuals with CD had lower SF-12 and SF-6D health utility scores, poorer perceived health, and greater limitations in various activities compared to those without CD.

Discussion: This study is representative of the United States population and highlights the profound impact of cognitive impairment on individuals with schizophrenia. The association between cognitive limitations and reduced quality of life, as well as limitations in daily activities, underscores the need for healthcare strategies tailored to the humanistic outcomes of cognitive impairment in schizophrenia. These findings reinforce the importance of cognitive impairment management in overall treatment plans for individuals living with schizophrenia.

S255. CONCEPTUALISATION AND DEVELOPMENT OF THE SELF-DEHUMANISATION IN PSYCHOSIS SCALE (DIPS)

Tom Jenkins*¹, Pamela Jacobsen¹, Bethany O'Brien-Venus², Paul Chadwick¹

¹University of Bath, ²Aneurin Bevan University Health Board

Background: People with psychosis have reported that a distressing aspect of their experience is self-dehumanisation – feeling less, or other than human. These feelings may arise from how people with psychosis are perceived and treated in society, and from the nature of psychosis itself. Existing measures of self-dehumanisation have not been developed with input from people with lived experience, or properly validated. The aim of the present study is to first build a conceptual framework of self-dehumanisation in psychosis, and second to develop a measure of self-dehumanisation in psychosis.

Methods: We first conducted semi-structured interviews with people who hear distressing voices to understand the phenomenology of self-dehumanisation and build a conceptual framework of the experience. We then used this model, along with interview transcripts and a literature review to develop a long list of items with potential to be included in the measure. PPI consultations with people with psychosis were conducted to discuss these items and develop the list further. A Delphi consensus study asked a team of expert stakeholders (people with psychosis, mental health professionals, academics, and carers) to rate the importance of each item for measuring self-dehumanisation. This whittled down the number of items, and

determined those which are most reflective of the construct. Cognitive interviews using the ‘think aloud’ method were also conducted to improve the comprehensibility of the measure.

Results: The experience of self-dehumanisation in psychosis is one characterised by a loss in personal agency, reduced sense of belonging with others, distressing sensory experiences, lower self-worth, a diminished sense of self, and a loss in trust in oneself. Self-dehumanisation theory suggests the experience may comprise denying the self ‘human nature’ or ‘uniquely human’ attributes. We have generated items pertaining to each of these domains to form the Dehumanisation in Psychosis Scale (DiPS).

Discussion: Self-dehumanisation could be a target for psychological therapies for psychosis, such as mindfulness or Cognitive Behavioural Therapy (CBT). Group-based mindfulness for psychosis in particular has been posited as a ‘humanising’ therapeutic process (Chadwick, 2019). A well-developed measure is useful both within clinical formulation to understand how a person feels, and research to understand mechanisms of change in therapy.

S256. SELF-STIGMA IN INTIMATE RELATIONSHIPS OF PERSONS WITH SERIOUS MENTAL ILLNESS: SCALE DEVELOPMENT AND VALIDATION

Meryl Caiada*¹, Simon Felix¹, Sarah Guionnet¹, Justin Lamontagne², Emma Tison¹, Kevin Marc Valery¹, Luc Vigneault³, Antoinette Prouteau¹, Tania Lecomte²

¹University of Bordeaux, ²University of Montreal, ³University of Laval

Background: Persons with Serious Mental Illness (SMI) frequently report difficulties in developing and maintaining Intimate Relationships (IR, McCann, 2010; White et al., 2021). Several barriers, such as stigma, including self-stigma, have been identified (Cloutier et al., 2021). Previous studies have highlighted i) a negative association between IR and self-stigma (Sariso et al., 2013; Stewart et al., 2013) and ii) that specific stereotypes related to IR might be internalized by persons with SMI (Elkington et al., 2013; Wainberg et al., 2016 ; Wright et al., 2007). However, there is a scarcity of literature on self-stigma in the context of IR, and, to date, there is no validated tool specifically designed to assess self-stigma within this field. This study aims to develop and validate a scale assessing self-stigma in IR, among persons with SMI (major depression, schizophrenia, bipolar disorder).

Methods: The scale’s items were collaboratively developed through focus groups involving peer supporters. Subsequently, a validation protocol was then disseminated online among adults with SMI. The study will evaluate psychometric properties, including structural validity, convergent validity, internal consistency, and test-retest reliability.

Results: In total, 40 items were generated, and six themes were qualitatively described: incompetence in IR (e.g., "I am not able to keeping my commitments in my relationship"), negative self-image (e.g., "I have nothing to offer to a partner"), fear of losing control (e.g., "When I fall in love, I lose my mind"), hopelessness (e.g., "It is impossible for me to find love"), concerns about mental health (e.g., "A romantic partner could harm my recovery"), and disclosure of the disorder (e.g., "My partner will not accept my diagnosis if I reveal my condition to him/her"). Analyses of the psychometric properties of the tool are ongoing and will be presented at the Schizophrenia International Research Society in 2024.

Discussion: This study will provide a novel scale assessing self-stigma in IR among persons with SMI. The development of tools evaluating IR and the associated barriers could encourage professionals to support persons expressing need in this area. Furthermore, on a research level,

the development of this scale will contribute robust data on i) the phenomenon of self-stigma in IR, ii) the underlying processes involved.

S257. ADHD AND PSYCHOTIC DISORDER: MULTIDISCIPLINARY PERSPECTIVES AND POSSIBLE THERAPEUTIC AVENUES

Catherine Lehoux*¹, Olivier Corbeil², Élisabeth Anderson³, Charles Desmeules⁴, Luc Vigneault⁵, Catherine Beaulieu⁶, Amélie M Achim⁷, Marie-France Demers⁸, Marc-André Roy⁹, Caroline Cellard¹⁰

¹Centre Intégré de Santé et de Services Sociaux de Chaudière-Appalaches et Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-Nationale, ²Faculty of Pharmacy, Université Laval, ³School of Psychology, Laval University, ⁴Université Laval Faculty of Medicine, ⁵Laval University, ⁶Clinique Notre-Dame des Victoires, Institut Universitaire en Santé Mentale de Québec, CIUSSS-CN, ⁷Université Laval, CERVO Brain research center, Vitam – Centre de recherche en santé durable, ⁸Pharmacy Faculty, Laval University, ⁹Département de psychiatrie et neurosciences, Faculté de Médecine, Université Laval. Institut universitaire en santé mentale de Québec., ¹⁰École de Psychologie, Université Laval

Background: ADHD remains neglected and undertreated in psychotic disorders, while an estimated 10% to 47% of adults with a psychotic disorder also meet criteria for ADHD. Although DSM-5 diagnostic criteria for ADHD do not exclude the possibility of a co-occurrence with a psychotic disorder, they may contribute to a reluctance in clinical practice to diagnose ADHD in this population. Moreover, psychostimulants are still generally avoided in psychotic disorder, due to a fear of psychotic relapse. However, this concern is largely based on studies in which psychostimulants were used to explore abnormalities in dopaminergic transmission rather than for therapeutic purposes. More recent observational studies have not found significant associations between psychotic relapse and the use of psychostimulants in people with psychotic disorders, suggesting that this risk is lower than generally perceived. Recent observational data from a Québec Province registry also reveal that nearly 5% of people with a psychotic disorder receive a psychostimulant even though this practice is not supported by formal guidelines, and that this practice is not associated with an increased risk of hospitalization for psychosis in the following year in more than 2,200 people also receiving an antipsychotic.

Methods: We conducted a narrative literature review and consulted various clinical, scientific, and experiential knowledge experts, to provide multidisciplinary clinical recommendations aimed at better supporting people dealing with ADHD co-occurring with a psychotic disorder.

Results: The latest recommendations that emerged from this procedure are as follows. First, the diagnosis of ADHD should follow a rigorous approach, including a developmental history taken with parents and a comprehensive diagnostic interview. Second, the treatment of ADHD co-occurring with psychotic disorder should be undertaken using a comprehensive, interdisciplinary approach, which includes the following: 1) Psychotic symptoms should be adequately treated with antipsychotic and psychological therapy; 2) Antipsychotic treatment should aim for the use of the lowest possible effective dose and minimal recourse to polypharmacy to prevent detrimental effects on cognition; 3) Recognition and correction of adverse effects of drug treatment should be part of treatment targets; 4) Various concomitant clinical conditions also associated with possible cognitive difficulties should also be managed, such as, at the psychiatric level, substance use disorders or anxiety and mood disorders and, at

the physical level, sleep apnea or nutritional deficiencies; 5) Clinical support should be provided for the maintenance and development of healthy lifestyle habits given their known impact on cognition; 6) various psychosocial therapeutic options should be considered, including cognitive remediation; and 7) finally, if manifestations of ADHD persist and interfere significantly with functioning, a specific pharmacological treatment of ADHD manifestations should be discussed. Long-acting formulations should be preferred to short-acting ones. Clinical discussion should take place in a shared-decision making process with patients and their relatives, where the advantages and disadvantages of the different therapeutic options are set out in relation to the person's values, preferences and life goals.

Discussion: Further studies are needed to develop treatment guidelines specific to ADHD co-occurring with psychotic disorder. Pending such clear clinical recommendations, and from a recovery-oriented perspective, certain actions should nevertheless be taken to support people struggling with these co-occurring conditions.

S258. IS THERE EVIDENCE OF COGNITIVE DECLINE 5+ YEARS AFTER THE ONSET OF PSYCHOSIS? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Joseph Ghanem*¹, Christy Au-Yeung¹, Samantha Aversa², Marie Starzer³, Katie M. Lavigne¹, Martin Lepage¹

¹*McGill University*, ²*Douglas Mental Health Research Institute*, ³*Copenhagen University Hospital, Mental Health Center Copenhagen, Copenhagen Research Center for Mental Health - CORE*

Background: In addition to positive and negative symptoms that have historically served as the hallmarks of psychotic disorders, cognitive impairments are also a distinct symptom dimension that is apparent prior to psychosis onset and persistent thereafter. However, whether these cognitive impairments decline, stabilize, or improve in the long-term remains contentious. Previous systematic reviews and meta-analyses were focused on the first 5 years following psychosis onset and identified improvements in cognition – improvements that appeared to reflect practice effects. Some studies with follow-ups of a decade have suggested that cognitive decline may be apparent in some cognitive domains, but others observed that although cognition was impaired early in the course of illness, it stabilized over time. In the present review, we aimed to synthesize evidence from longitudinal studies with follow-ups of 10+ years to evaluate whether cognition declines, stabilizes, or improves over time.

Methods: The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered on PROSPERO (CRD42023447589). MEDLINE, SCOPUS, and PsycINFO were searched for articles that evaluated neurocognition in individuals with psychotic disorders over a period of 10 years or more. Included studies were written in English; reported longitudinal neurocognitive data; had a minimum follow-up period of 10 years; used standardized neuropsychological tests; included a minimum of 85% of individuals with psychotic disorders. Excluded studies were those reporting multiple reports of the same data; unpublished studies, reviews, and conference abstracts; studies using non-standardized cognitive tests. Two authors (JG, SA) conducted title and abstract screening as well as full-text screening on Covidence. Discrepancies were resolved through discussion with each other and with another author (CA). Extraction of relevant data including study characteristics, demographics, cognition data, and main findings was

performed by two authors (JG and SA). The same two authors also assessed the quality of the studies using the Mixed Methods Appraisal Tool.

Results: Twelve studies with independent samples met inclusion criteria for the review and were included in the present study (N Patients= 1028 (range: 21 – 244) and N Controls = 601 (range: 8 – 260)). The patient sample was 61% male, with an average age at first assessment of 26.3 (SD= 6.5). The control sample was 56% male, with an average age at first assessment of 29.41 (SD=7.21). The mean follow-up period was 11.9 years (range: 10-20). Of the 12 studies, 6 were first episode psychosis samples, 5 assessed schizophrenia spectrum disorders, and 1 assessed schizophrenia only.

Most studies (8 out of the 12) identified that cognition was stable over follow-up when evaluating the patient group as a whole, consistent with previous reviews and studies with shorter follow-up periods. In studies with control groups that observed stability, patients and controls did not significantly differ in degree of cognitive change over time. In studies that identified progressive cognitive decline (4 out of the 12), the decline was of small to moderate magnitude. In one study, cognitive decline was associated with worsening of negative symptoms and work functioning, specifically being unemployed. Furthermore, the specific cognitive domains that declined varied significantly from study to study, and the inconsistent use of control groups in those studies did not allow for the proper identification of age-dependent cognitive change. In general, baseline cognitive performance emerged as a strong predictor of long-term cognitive performance. In addition to a systematic review, a meta-analysis will be conducted and presented at the congress to quantify the degree of cognitive change per cognitive domain (e.g., verbal memory, attention, executive functioning).

Discussion: The present review is novel in systematically synthesizing evidence from longitudinal studies with follow-ups ranging from a decade to two decades. When evaluating samples globally, our findings are consistent with the neurodevelopmental model of psychotic disorders, which suggests that cognitive impairment is present prior to and at the onset of the disorder but stabilizes over time. However, trajectory analysis studies to identify subgroups that may be susceptible to cognitive decline over time are needed, to better understand the heterogeneity of psychotic disorders and the predictors of long-term cognitive outcomes. When studies identified cognitive decline over time, the decline was small to moderate in effect but identifying predictors of decline was not always possible. That short-term cognitive performance was predictive of later cognitive outcomes emphasizes the importance of early intervention in the critical period, in addition to longer-term treatments that target cognitive impairment such as cognitive remediation.

S259. SYMPTOMATIC REMISSION, CLINICAL SEVERITY, COGNITIVE FUNCTIONS IN THE LONG-TERM COURSE OF SCHIZOPHRENIA AND POTENTIAL COGNITIVE PREDICTORS FOR SYMPTOMATIC REMISSION STATUS

Eldem Güvercin^{*1}, Banu Değirmencioğlu², Tufan Buran³, Tolga Binbay³, Emre Bora⁴, Köksal Alptekin⁴, Berna Binnur Akdede⁴

¹Dokuz Eylul University, Faculty of Medicine, ²İzmir University of Economics, Department of Neuroscience, ³Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, ⁴Dokuz Eylul University Department of Neuroscience, Dokuz Eylül University, School of Medicine, Department of Psychiatry

Background: Schizophrenia is a severe mental disorder that negatively effects quality of life and increases morbidity and mortality. Cognitive impairments mostly occurred at early phase of disease, had already been before the presentation of the diagnostic symptoms and persisted for a long time, regarded as a core symptom of schizophrenia. Clinical severity, cognitive functions and symptomatic remission status change in time and long-term course of disease may not be predictable.

Methods: 64 schizophrenia patients, who applied Dokuz Eylül University Hospital outpatient Psychiatry Unit were included into the study. Both baseline and follow-up evaluations include clinical severity, cognitive functions and their association with symptomatic remission status. Median follow-up period were 132 months. Clinical severities were assessed by Positive and Negative Symptom Scale (PANSS), symptomatic remission status was determined by the Remission in Schizophrenia Working Group (RSWG) criterion. Cognitive tests include Trail-Making Test A and B (TMT-A, TMT-B), Digit Symbol Substitution Test (DSST), Wisconsin Card Sorting Test (WCST), Digit Span Test (DST), Auditory Consonant Trigrams Test (ACT), Stroop Color and Word Test (SCWT), Rey Auditory Verbal Learning Test (RAVLT), Controlled Oral Word Association Test (COWAT), Category Fluency Test, Wechsler Memory Scale- Revised (WMS-R) Visual Reproduction Test.

Results: 25 of 64 patients (%39.06) were in symptomatic remission, both baseline and follow-up cognitive evaluation. During follow-up period, Positive and Negative Symptom Scale (PANSS) total score, and PANSS general psychopathology subscale has significantly decreased compared to baseline evaluation. Cognitive evaluation revealed that verbal and visual memory functions (significantly poor RAVLT and WMS-R Visual Reproduction Test) consistently deteriorated both remitted and non-remitted patients. SCWT word+color+interference completing time were found significantly longer after the follow-up period, pointed out impaired processing speed and executive functions. On the other hand, patients displayed better DST forward and total score performance after the follow up period, indicating improvement of simple attentional skills performance in time. ACT, COWAT/ total word score, DST backward score and TMT-A/ error score was better in remitted patients than non-remitted patients, in connection with better verbal fluency, working memory and complex attention performance.

Discussion: Positive symptoms and general psychopathology improve in the natural course of schizophrenia, but negative symptoms tend to be persisted and do not display satisfactory improvement. Memory, executive functions, processing speed and visuospatial functions may get worse, but simple attention may improve in time. On the other hand, verbal fluency, working memory and complex attentional performance depend on symptomatic remission status and it may be considering potential cognitive predictors of symptomatic remission status in schizophrenia.

S260. QUALITY OF RESIDENTIAL FACILITIES IN ITALY: SATISFACTION AND QUALITY OF LIFE OF RESIDENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

Alessandra Martinelli^{*1}, Helen Killaspy², Cristina Zarbo¹, Sara Agosta³, Letizia Casiraghi⁴, Manuel Zamparini¹, Fabrizio Starace³, Matteo Rocchetti⁴, Giovanni de Girolamo¹

¹IRCCS St. John of God Clinical Research Centre, ²UCL, ³Mental Health and Dependence, AUSL of Modena, ⁴Department of Mental Health and Dependence, ASST of Pavia

Background: Recovery and human rights promotion for people with Schizophrenia Spectrum Disorders (SSDs) is fundamental to provide good care in Residential Facilities (RFs). However, there is a concern about rehabilitation ethos in RFs. This study aimed to investigate the care quality of Italian RFs, the quality of life (QoL) and care experience of residents with SSD.

Methods: Forty-eight RFs were assessed using a quality assessment tool (QuIRC-SA) and 161 residents with SSD were enrolled. Seventeen RFs provided high intensity rehabilitation (SRP1), 15 medium intensity (SRP2), and 16 medium-low level support (SRP3). Staff-rated tools measured psychiatric symptoms and psychosocial functioning; user-rated tools assessed QoL and satisfaction with services. RFs comparisons were made using ANOVA and Chi-squared.

Results: Over two-thirds patients (41.5 y.o., SD 9.7) were male. Seventy-six were recruited from SRP1 services, 48 from SRP2, and 27 from SRP3. The lowest QuIRC-SA scoring was Recovery Based Practice (45.8%), and the highest was promotion of Human Rights (58.4%). SRP2 had the lowest QuIRC-SA ratings and SRP3 the highest. Residents had similar psychopathology ($p=0.140$) and functioning ($p=0.537$). SRP3 residents were more employed (18.9%) than SRP1 (7.9%) or SRP2 (2.2%) ones and had less severe negative symptoms ($p=0.016$) and better QoL ($p=0.020$) than SRP2 residents. There were no differences in the RF therapeutic milieu and their satisfaction with care.

Discussion: Residents of the lowest supported RFs in Italy had less severe negative symptoms, better QoL and more employment than others. The lowest ratings for Recovery Based Practice across all RFs suggest more work is needed to improve recovery.

S261. EFFICACY AND TOLERABILITY OF BLONANSERIN IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Jing Tian^{*1}, Johannes Schneider-Thoma¹, Shimeng Dong¹, Xiao Lin¹, Nobuyuki Nomura¹, Hui Wu¹, Spyridon Sifas¹, Mengchang Qin¹, Stefan Leucht¹

¹*School of Medicine, Technical University of Munich,*

Background: Blonanserin is currently approved for the treatment of schizophrenia in Japan, South Korea, and China. However, the efficacy and safety of blonanserin in managing schizophrenia remain subjects of debate and scrutiny. This study aimed to perform a comprehensive meta-analysis to assess the efficacy and safety related to blonanserin treatment in individuals with schizophrenia.

Methods: We searched in duplicate the study-based trial register of the Cochrane Schizophrenia Group, encompassing studies up until Jun 25, 2023. The inclusion criteria comprised open, single, and double-blinded randomized controlled trials (RCTs) with a minimum duration of 3 weeks comparing blonanserin to other antipsychotics in participants with schizophrenia. We extracted 28 efficacy and tolerability outcomes, with the primary outcome being overall symptoms of schizophrenia. Secondary outcomes included response to treatment, positive, negative, and depressive symptoms of schizophrenia, discontinuation, functioning, quality of life, and side effects. These outcomes were analysed in random-effects pairwise inverse variance meta-analyses. The study was registered in Open Science Framework (<https://osf.io/e7jfa/>).

Results: The analysis included 17 studies with 2903 participants. The antipsychotics included in the analysis were olanzapine, haloperidol, risperidone, paliperidone, aripiprazole, and amisulpride, which were compared with blonanserin. In the primary outcome “overall symptoms of schizophrenia”, there were no significant differences between blonanserin and other antipsychotics. In secondary outcomes, blonanserin demonstrated a lower risk of weight gain (RR= 0.57; 95%CI= 0.35-0.93) and hyperprolactinemia (SMD= -1.11, 95% CI= -2.22 to -0.01) compared to risperidone. However, it had a higher risk of akathisia (RR= 1.65, 95% CI= 1.20-2.25) and dropout (RR= 1.36, 95% CI= 1.07-1.71) compared to risperidone. Blonanserin was superior to paliperidone in hyperprolactinemia (RR= -0.06, 95% CI= 0.00-0.99). Blonanserin was found to be superior to haloperidol in terms of depressive symptoms (SMD= -0.35, 95% CI= -0.60 to -0.10) and negative symptoms (SMD= -0.28, 95% CI= -0.48 to -0.07). Additionally, it had a lower risk of akathisia (RR= 0.66, 95% CI= 0.48-0.91) and parkinsonism (RR= 0.59, 95% CI= 0.40-0.87) compared to haloperidol.

Discussion: The results of this meta-analysis indicate that blonanserin is comparable to other commonly used antipsychotics in terms of overall symptom improvement in individuals with schizophrenia. This suggests that blonanserin can be considered a viable treatment option for managing symptoms of schizophrenia. Blonanserin offers advantages in terms of weight gain, hyperprolactinemia, depressive symptoms, negative symptoms, and certain movement-related side effects. However, the higher risk of akathisia and drop-out rates should be taken into consideration. Further research, including head-to-head comparisons and long-term studies, is needed to consolidate these findings and guide clinical decision-making regarding the use of blonanserin in the management of schizophrenia.

S262. THE RELATIONSHIP BETWEEN LONELINESS AND MOMENTARY NEGATIVE PSYCHOTIC EXPERIENCES: AN EXPERIENCE SAMPLING STUDY IN NON-CLINICAL YOUNG ADULTS

Anson Kai Chun Chau*¹, Suzanne Ho-wai So²

¹*The University of New South Wales*, ²*Department of Psychology, The Chinese University of Hong Kong*

Background: Loneliness refers to the negative experience arising from the mismatch between perceived and actual social relationships. When loneliness is left unsolved, it could be expressed as a trait-like phenomenon, potentially leading to psychopathology including psychosis. Findings from previous studies offer converging evidence for the association between loneliness and positive symptoms (such as paranoia and hallucinations) in clinical populations, as well as their subclinical manifestations in the general population. However, the relationship between loneliness and negative symptoms is less often examined. In particular, loneliness is proposed to be maintained by social withdrawal and reduced pleasure in current and anticipated social interactions, corresponding to asociality and social anhedonia respectively. The experience sampling method (ESM) is suitable for capturing moment-by-moment negative psychotic experiences in daily life. Using ESM, the present study examined the relationship between loneliness and negative psychotic experiences (i.e., asociality and social anhedonia), in a sample of non-clinical young adults who were at a life stage most vulnerable to developing psychosis.

Methods: Participants aged 18-30 were recruited from either the subject pool of introductory psychology courses or campus mass email. Consented participants without any past and current

psychiatric diagnosis (confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders) completed the University of California Los Angeles Loneliness Scale-Version 3 and the Patient Health Questionnaire-9 as baseline measures of trait loneliness and depression respectively. Ten times per day over six days, participants were asked to fill in the same ESM questionnaire on a mobile phone app, which measured positive affect (PA, i.e., happy, relaxed, contented), negative affect (i.e., irritated, low, anxious), current social company, anticipated social company, and anticipated pleasantness of being with others (vs. being alone). Asociality was operationalized as being alone. Consummatory social anhedonia was operationalized as the within-moment association between PA and being with others (vs. being alone), whereas anticipatory social anhedonia was operationalized as the anticipated pleasantness of being with others (vs. being alone). Only participants who completed at least one-third of the ESM questionnaires were included in the data analysis. The associations between loneliness and momentary negative psychotic experiences were tested with multilevel modelling.

Results: The final sample consisted of 134 participants (58.2% female, mean age = 20.3 (SD= 2.91)). The mean compliance rate was 72.1% (range: 36.7-100%). Trait loneliness was associated with anticipatory social anhedonia ($B = 0.02$, $p = .011$), even after controlling for baseline level of depression ($B = 0.02$, $p = .010$). Trait loneliness was not associated with asociality or consummatory social anhedonia (p s GREATER THAN .050).

Discussion: Using ESM to assess negative psychotic experiences, we found that loneliness was uniquely associated with anticipatory social anhedonia (above and beyond the effect of depression), but not with asociality or consummatory social anhedonia. The specificity of the relationship between loneliness and individual negative psychotic experiences warrants further investigation.

S263. THE CHANGE OF ADMISSION PATTERN IN PSYCHIATRIC INPATIENTS FOLLOWING REVISION OF MENTAL HEALTH ACT IN KOREA

Jong-Ik Park^{*1}, Sun-hwan Lee²

¹Kangwon National University, ²Chuncheon National Hospital

Background: The main purpose of this study was to investigate the change of hospitalization type, length of hospitalization, readmission rates, and patient attributes of psychiatrically hospitalized patients since total revision of Mental Health Act in 2017.

Methods: We retrospectively reviewed medical records of 1,396 cases of inpatients who were hospitalized and discharged in both one national mental hospital and one private mental hospital from 1 year before revision to 1 year after one. We used either the t-test and chi square test, or the one-way analysis of variance to compare characteristics between each group and examined how revision of Mental Health Act has influenced.

Results: The rate of voluntary admission markedly increased from 32.8% to 86.7% without any significant change in patient attributes. The length of stay in a mental hospital significantly decreased from 84.9 (± 70.8) days to 54.6 (± 53.6) days. Individual factors affecting the length of stay were female sex, schizophrenia, unemployment, and involuntary admission type. However, the readmission rate significantly increased from 15.5% to 21.1%.

Discussion: The findings of this study suggests that the total revision of Mental Health Act resulted in voluntary admission and shorter length of stay, heightening of getting back to the community but the activation of community mental health service system should be prepared in Korea.

S264. THE RELATIONSHIP BETWEEN SELF-STIGMA AND QUALITY OF LIFE IN LONG-TERM HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA: A CROSS-SECTIONAL STUDY

Jiabao Chai^{*1}, Ying Li²

¹*Beijing Huilongguan Hospital, Peking University Huilongguan Clinical Medical School,*

²*Department of Psychiatry, Beijing Children's Hospital, Capital Medical University, National Center for Children Healthy*

Background: Schizophrenia is a profoundly debilitating chronic condition that markedly diminishes the quality of life for those afflicted. Numerous elements contribute to the life quality of individuals with schizophrenia, with self-stigma standing out as a pressing societal issue. This research delves into the repercussions of self-stigma on the quality of life in schizophrenia patients, further examining the intermediary factors at play.

Methods: This study employed a cross-sectional design, selecting 170 hospitalized schizophrenia patients at random for evaluation. The assessment instruments comprised the Positive and Negative Syndrome Scale (PANSS), Self-Esteem Inventory (SEI), Connor-Davidson Resilience Scale (CD-RISC), Internalized Stigma of Mental Illness Scale (ISMI), Schizophrenia Quality of Life Scale (SQLS), Coping Questionnaire for Schizophrenia Patients (CQSP), and the Social Support Rating Scale (SSRS). We utilized correlation analysis, regression analysis, and mediation analysis to investigate correlations and discern mediation effects.

Results: Self-stigma significantly influences the quality of life ($T = 8.13$, $p < 0.001$). Both self-esteem ($T = -2.11$, $p = 0.04$) and specific coping strategies, namely problem-solving ($T = -2.58$, $p = 0.01$) and avoidance ($T = 4.65$, $p < 0.001$), exert pronounced effects on self-stigma. With self-stigma acting as a mediator, the problem-solving aspect of coping strategies indirectly affects the quality of life, and this effect is statistically significant ($AB = -0.16$, $P = 0.02$). Conversely, the avoidance aspect of coping strategies directly ($C' = 0.54$, $p < 0.001$) and indirectly ($AB = 0.25$, $p < 0.001$) impacts the quality of life.

Discussion: Self-stigma profoundly influences the quality of life for individuals with schizophrenia. To enhance the quality of life for these patients, clinical interventions should prioritize addressing self-stigma and its underlying determinants, with particular emphasis on self-esteem and adaptive coping strategies.

S265. INFLAMMATORY MARKERS OF SYMPTOMATIC REMISSION AT 6 MONTHS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA

Honey Kim¹, Seon-Hwa Baek¹, Ju-Wan Kim¹, Seunghyong Ryu¹, Ju-Yeon Lee¹, Jae-Min Kim¹, Young-Chul Chung², Ji-Min Yoo¹, Joon-An Yoo³, Sung-Wan Kim^{*1}

¹*Chonnam National University Medical School,* ²*Chonbuk National University Medical School,* ³*St. John Hospital*

Background: Neuroinflammation contributes to the pathophysiology of various mental illnesses, including schizophrenia. We investigated peripheral inflammatory cytokines as a biomarker for predicting symptomatic remission in patients with first-episode schizophrenia.

Methods: The study included 224 patients aged 15-60 years who fulfilled the criteria for schizophrenia spectrum disorder with a treatment duration ≤ 6 months. Serum levels of tumor necrosis factor (TNF)- α , interferon- γ , interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, IL-10, and IL-12 were measured. Psychotic symptoms, depressive symptoms, and general functioning were assessed using the Positive and Negative Syndrome Scale (PANSS), Beck Depression Inventory (BDI), Calgary Depression Scale for Schizophrenia (CDSS), and Personal and Social Performance scale (PSP), respectively. Duration of untreated psychosis (DUP) was also recorded. We investigated the factors associated with remission for each sex in logistic regression analysis.

Results: Our study included 224 patients (46.0% males and 54.0% females) with first-episode schizophrenia. Table 1 shows the clinical characteristics and cytokine levels in relation to remission for each sex among patients with psychosis. In total, 174 patients achieved remission at the 6-month follow-up (males, 70.9%; females, 83.5%). Remission was associated with baseline scores on PANSS, PSP, BDI, and CDSS in male patients. Among female patients, baseline scores on PANSS, PSP, DUP, and TNF- α were associated with remission. Multivariate logistic regression analysis results indicate that a higher potential for symptomatic remission in men was associated with older age ($p = 0.042$) and lower baseline BDI scores ($p = 0.013$). For women, shorter DUP ($p = 0.025$) and lower baseline peripheral TNF- α levels ($p = 0.006$) were associated with a higher likelihood of symptomatic remission (Table 2).

Discussion: Our findings suggest that peripheral TNF- α levels may serve as a predictor of poor response to antipsychotic treatments in females with first-episode schizophrenia spectrum disorder. This could contribute to enhancing our understanding of the role of inflammation in the course of schizophrenia. Additionally, we observed that depressive symptoms in males and a longer DUP in females may be poor prognostic factors for early remission in patients with first-episode schizophrenia.

S266. EXPLORING THE INTERPLAY BETWEEN PSYCHOSIS VULNERABILITY, FUNCTIONAL SOMATIC SYMPTOMS AND HEALTH ANXIETY IN CHILDHOOD AND ADOLESCENCE – A LONGITUDINAL COHORT STUDY

Martin Køster Rimvall^{*1}, Charlotte Ulrikka Rask², Jens Søndergaard Jensen³, Else Marie Olsen⁴, Lars Clemmensen⁵, Anne Mette Skovgaard⁶, Frank Verhulst⁷, Jim van Os⁸, Pia Jeppesen⁹

¹Department of Child and Adolescent Psychiatry, Copenhagen University Hospital - Psychiatry Region Zealand; Child and Adolescent Mental Health Centre, Copenhagen University Hospital - Mental Health Services CPH, ²Aarhus University Hospital Psychiatry, Department of Child and Adolescent Psychiatry, Research Unit; Aarhus University, Department of Clinical Medicine, ³Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, ⁴Psychiatric Center Ballerup, Copenhagen University Hospital - Mental Health Services CPH; Center for Clinical Research and Prevention, the Capital Region of Denmark, ⁵VIRTU Research Group, Copenhagen Research Center on Mental Health (CORE), Copenhagen University Hospital, ⁶National Institute of Public Health, Faculty of Health Sciences, University of Southern Denmark, ⁷Child and

Adolescent Mental Health Centre, Copenhagen University Hospital - Mental Health Services CPH; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; Department of Child Psychiatry/Psychology, Erasmus University Medical Center, ⁸Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht; Department of Psychiatry and Psychology, Maastricht University Medical Centre; Department of Psychosis Studies, King's College London, King's Health Partners, Institute of Psychiatry, ⁹Department of Child and Adolescent Psychiatry, Copenhagen University Hospital - Psychiatry Region Zealand; Child and Adolescent Mental Health Centre, Copenhagen University Hospital - Mental Health Services CPH; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen

Background: Similarities exist between contemporary explanatory models underlying psychosis development, functional somatic symptoms, and health anxiety; namely aberrant attribution of salience and errors in top-down information processing. Functional somatic symptoms are bodily symptoms which cannot be attributed to a well-defined physical illness, whereas health anxiety is characterized by excessive and medically unwarranted fears regarding one's health. In the current study, we aimed to examine the potential interplay between functional somatic symptoms and psychosis vulnerability on the outcome of health anxiety in youths from the general population.

Methods: We utilized data from the 11- and 16-year follow-ups of the Copenhagen Child Cohort 2000. Psychosis vulnerability was assessed by interview- and self-report measures of psychotic experiences (ages 11 and 16), aberrant attribution of salience using the White Noise Task (age 11), and anomalous self-experiences assessed by self-report using the Self-Experience Life-time Frequency scale (age 16). Functional somatic symptoms and health anxiety were assessed by self-report using age-appropriate standardized questionnaires at both ages 11 and 16 years. We assessed the associations between psychosis vulnerability and functional somatic symptoms both cross-sectionally at both ages, and longitudinally from age 11 to 16, and examined if there was an interaction between psychosis vulnerability and functional somatic symptoms on the outcome of health anxiety. To quantify the potential interaction effect, we used the interaction contrast ratio, estimating the relative excess risk due to interaction.

Results: A total of 1122 participants contributed with data from both time points. In cross-sectional analyses, functional somatic symptoms and psychotic experiences were strongly associated with health anxiety at both ages 11 and 16, also after adjustment for general psychopathology. Aberrant attribution of salience (age 11) and anomalous self-experiences (age 16) were also associated with health anxiety. Additionally, there was some evidence of interaction between psychosis vulnerability and functional somatic symptoms on the outcome of health anxiety at age 16. In the longitudinal analyses, functional somatic symptoms, and psychotic experiences at age 11 were not individually associated with health anxiety at age 16 but having both functional somatic symptoms and psychotic experiences was: odds ratio 3.9, 95% CI 1.7-8.9. This association was attenuated after adjustment for general psychopathology: odds ratio 2.6, 95% CI 1.0 to 6.4.

Discussion: The strong associations between the domains support the notion of possible overlapping mechanisms underlying psychosis vulnerability, functional somatic symptoms, and health anxiety. While the current study could not unravel potential causal mechanisms, the findings highlight the importance of clinical attention and comprehensive assessment to address a broad spectrum of vulnerabilities among children presenting with mental health problems.

S267. VULNERABILITY AND RESILIENCE TO MENTAL PATHOLOGIES: EVALUATION OF THE EFFECTS OF EARLY LIFE STRESS EXPOSURE ON MENTAL HEALTH

Veronica Begni*¹, Kerstin Camile Creutzberg¹, Rodrigo Grassi Oliveira², Marco Andrea Riva¹

¹*University of Milan*, ²*Aarhus University*

Background: Early life stress (ELS) exposure is considered a major risk factor for mental disorders. However, the alterations produced by adverse experiences are highly variable and not all individuals exposed to stress develop a pathologic phenotype, since some of them appear to be resilient to the consequences of such experiences. We have recently reported (Creutzberg, Begni et al., 2023 10.1038/s41398-023-02653-6) that offspring exposed to ELS showed an overall emotional impairment during adolescence, as seen by depressive- and anxiety-like behaviors and a decreased sociability. Although these alterations were similar between male and female offspring, we could discriminate between vulnerable (PNS-V) and resilient (PNS-R) phenotypes during adolescence. Individual animals showed indeed different responses to stress exposure; among stressed animals we found that 30% showed low levels of anxiety-like behaviors and high levels of social interactions, while the remaining 70% displayed significant dysfunctions in anxiety-related and social behaviors.

In this respect, several open questions still exist regarding how ELS programs emotional and biological functions. Clarifying these mechanisms is vital as it could pave the way for identifying stress-vulnerable and resilient molecular phenotypes in offspring.

Methods: To tackle these points, I applied a well-characterized model of prenatal stress (PNS) exposure in rats, consisting of a restraint stress protocol during the last week of pregnancy as previously published (Creutzberg, Begni et al., 2023 10.1038/s41398-023-02653-6). To address the gap in knowledge of specific pathways that could be potentially involved in stress vulnerability and resilience, I employed a omics approach to provide a more comprehensive and in-depth explanation. Whole-genome RNA sequencing analysis was conducted using the Illumina NextSeq550 platform. Differentially expressed genes (DEGs) ($p_{adj} \text{ LESS THAN } 0.1$, $FC \text{ GREATER THAN } |1.2|$) were identified in the prefrontal cortex (PFC) of PNS and control (CT) animals.

Results: We found that 6 genes were significantly altered in the PFC of PNS female offspring during adolescence, while PNS exposure significantly altered the expression of 34 genes in the PFC of male offspring. Interestingly, 2 genes were commonly altered in the brain of male and female PNS offspring regardless of vulnerable or resilient phenotype, namely Catalase (Cat) and Mitochondrial Ribosomal Protein L48 (Mrpl48). Specifically, we found that PNS exposure significantly upregulated the expression of both Cat and Mrpl48 in both sexes.

When looking for DEGs in PNS-V and PNS-R separately, we found that the expression of 5 genes was significantly altered in the brain of both male PNS-V and PNS-R animals, as compared to CTs, and that these genes were mostly involved in mitochondria.

On the contrary, when focusing on differences between PNS-V and PNS-R rats, we found 9 and 3 DEGs in the PFC of female and male offspring respectively, although not strictly involved in mitochondria functionality.

Discussion: Overall, these data showed that mitochondria seem to be affected by ELS exposure, regardless of the presence or not of a pathological outcome, mainly in male adolescent offspring. Alterations of mitochondria-related mechanisms might therefore represent a permanent scar of ELS exposure, that may ultimately be a predisposing factor for

developing a full-blown pathologic condition later in life. Understanding the mechanisms by which stressors determine a pathological outcome will not only enhance our knowledge of normal development but will also open avenues for early interventions, either during pregnancy or the early postpartum period.

S268. POSITIVE FRAMING OF FEEDBACK ABOUT BEING AT-RISK FOR PSYCHOSIS IS SEEN BY CLINICIANS AS A PROMISING MEANS TO IMPROVE ITS BENEFICIAL TO HARMFUL EFFECTS: AN EXPERIMENTAL SIMULATED FEEDBACK SESSION STUDY

Yamit Sol-Nottes¹, Dan Koren*¹, David Roe¹, Shlomo Mendelovich²

¹University of Haifa, ²Shalvata Mental Health Center

Background: Recent studies, including a pioneering pre-post feedback one, show that feedback on clinical high-risk for psychosis (CHR-p) can offer relief, yet often triggers negative stereotypes in patients. Inspired by Tversky and Kahneman's (1981) seminal work on the framing effect and examples the way analog high-risk conditions in general medicine are framed (e.g., 'life-threatening condition'), this study aimed to explore if positive re-framing of CHR-p as 'residual health abilities (e.g., common sense) at high risk' could address these concerns. Specifically, the study aimed to assess mental health professionals' (MHPs) perceptions regarding feedback provided with negative versus positive framing. A secondary goal was to evaluate the extent to which the level of familiarity and experience with the concept of CHR-p influences these perceptions.

Methods: To achieve the above goal, the study implemented an experimental design, utilizing a simulated feedback session, recorded on video, involving a clinician, an adolescent, and their mother to compare negative versus positive feedback framing. Specifically, the study compared the impact of feedback provided with a negative versus positive framing on MPHs' perceptions of its potential benefits (such as mobilization towards help-seeking and the instillation of hope) versus its potential adverse effects (such as the provocation of stress and self-stigma) on the adolescent and mother. One hundred and forty-eight MPHs were randomized to view one of the two videotaped simulated feedback sessions. Upon completing watching the video, they were asked to respond to a questionnaire that evaluated their views on how the feedback session affected the adolescent and his mother.

Results: Consistent with our main hypothesis, the results showed significant differences in perceptions based on framing type, favoring positive framing in sensitivity, stress, stigma, mobilization to seek help, and hope. Contrary to our second hypothesis, the results did not show a significant framing type by subjective familiarity with the CHR-p concept interaction effect.

Discussion: The present results suggest that MPHs respond more favorably to positively framed feedback about psychosis risk. Furthermore, in contrast to our initial prediction, the results imply that this increased faith in positive framing is not diminished by the MPH's subjective familiarity and experience with the concept of CHR-p. However, these results need replication through studies with larger and more diverse samples. If future research replicates and validates the present findings, they will establish a solid conceptual and methodological basis for valuable new research directions. Most notably, they will lay the groundwork for randomized controlled trials to test the effectiveness of positively reframing risk for psychosis in real-world settings. The presentation will highlight and discuss possible misconceptions of

positive framing, such as re-labeling, positive psychology, and de-medicalization of normal human experience.

S269. EARLY AND LATER REMISSION FROM CLINICAL HIGH RISK OF PSYCHOSIS. A LATENT CLASS AND PREDICTOR ANALYSIS

Jone Bjornestad*¹, Tore Tjora², Inge Joa³, Jan Olav Johannessen³, Sjur Skjærshammer Sætre⁴, Wenche ten Velden Hegelstad⁵

¹*Faculty of Social Sciences, University of Stavanger /TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital,* ²*Faculty of Social Sciences, University of Stavanger,* ³*TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital, Stavanger, Norway. Network for Medical Sciences, Faculty of Social Sciences, University of Stavanger, Norway.,* ⁴*TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital, Stavanger, Norway.,* ⁵*TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital*

Background: In research on high-risk for psychosis (CHR-P) much focus has been on the transition to psychosis. However, the desired outcome remains symptomatic and functional remission as early as possible. This study aims to investigate predictors of sub-groups of remission and functional outcomes.

Methods: A two-year prospective follow-up study of 104 CHR-P participants recruited in Norway using systematic early detection strategies. The Structural Interview for Prodromal Syndromes (SIPS) was used to assess CHR-P. Participants were classified as remitted or non-remitted based on their SIPS scores. A latent class analysis was performed on the dichotomous data to identify latent classes with regard to timing of remission. T-tests and chi-squared tests were used to assess the association between class affiliations, predictors and outcomes.

Results: The latent class analysis showed moderate fit and divided the participants into three remission classes: "poor chance of remission" (16.7%), "later remission" (34.3%), and "early remission" (49.0%). The "early remission" class had the highest probability of fast and stable remission, and had better premorbid, baseline and 2-year global functioning than the "later remission" class. Baseline predictors such as age, SIPS symptoms, drug use, years in school and gender were not significantly associated with remission class.

Discussion: The study's main finding is the division of CHR-P remission into "early remission" and "later remission" and predictors of class affiliation. The monthly follow-up during the first six months allowed for the detection of this division. The findings highlight the importance of considering functioning in models of remission from CHR-P.

S270. SCREENING AND INTERVENTION FOR CARDIOMETABOLIC RISK IN PATIENTS TREATED IN A FIRST-EPISODE PSYCHOSIS PROGRAM: A RETROSPECTIVE CHART REVIEW

Felix Audet*¹, Olivier Corbeil², Laurent Béchard³, Chantale Thériault⁴, Colombe Claveau⁵, Lauryann Bachand⁴, Anne-Marie Essiambre⁴, Marc-André Roy⁶, Marie-France Demers³

¹University Laval, ²Faculty of Pharmacy, Laval University, ³Pharmacy Faculty, Laval University, ⁴CERVO Brain Research Centre, ⁵Psychology School, Laval University, ⁶Université Laval Faculty of Medicine

Background: Individuals with psychotic disorders have a reduced life expectancy, mainly associated with increased cardiovascular mortality. However, cardiometabolic complications are not routinely screened and treated in practice. Therefore, the objective was to describe the adherence to a cardiometabolic risk screening and intervention algorithm implemented in an early intervention service (EIS) for first-episode psychosis in Quebec City.

Methods: A retrospective chart review was conducted on 218 users followed in EIS between November 1, 2019, and March 31, 2023. Screenings and interventions performed during follow-up or until prolonged discontinuation of antipsychotic medication were recorded up to a maximum of 36 months.

Results: A total of 41% of users were screened on admission to the program. The proportion of screenings performed varied between 54% and 65% for the rest of the follow-up (average follow-up time of 16 months). Screenings were complete in 79 to 95% of cases. Among incomplete screenings, apolipoprotein-B and glycated hemoglobin accounted for 46% and 30% of missing elements, respectively. The percentage of patients with a metabolic syndrome increased over time, from 13% at admission to 19% at 12 months, 30% at 24 months and 47% at 36 months. A total of 34 patients developed dyslipidemia. Of these, 79% received at least one intervention, but only 18% were prescribed a lipid-lowering agent. Few patients developed impaired glucose tolerance.

Discussion: Screening, and particularly intervention, for cardiometabolic complications remains a challenge in practice, despite the introduction of a systematic algorithm. Efforts must be made in these regards to reduce long-term cardiovascular mortality.

S271. BLOOD CELL COUNT RATIOS AT BASELINE ARE ASSOCIATED WITH INITIAL CLINICAL RESPONSE TO CLOZAPINE IN TREATMENT-RESISTANT, CLOZAPINE-NAÏVE, SCHIZOPHRENIA-SPECTRUM DISORDER

Vicent Llorca-Bofi¹, Miquel Bioque*², Santiago Madero³, Andrea Mallorquí⁴, Cristina Oliveira⁵, Marina Garriga⁶, Eduard Parellada⁷, Clemente Garcia-Rizo⁸

¹Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. University of Barcelona. ²University of Barcelona, Hospital Clinic, ³Barcelona Clinic Schizophrenia Unit, Institute of Neurosciences, University of Barcelona, IDIBAPS, CIBERSAM, ⁴Psychiatry Department, Neuroscience Institute, Hospital Clinic, ⁵University of Coimbra, ⁶Bipolar and Depressive Disorder Unit. Institute Neuroscience. Hospital Clinic Barcelona, ⁷Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. University of Barcelona. CIBERSAM, IDIBAPS. ⁸Barcelona Clinic Schizophrenia Unit (BCSU). University of Barcelona. IDIBAPS; CIBERSAM

Background: Clozapine is the recommended treatment for managing treatment-resistant schizophrenia (TRS) and immunological mechanisms may be involved in its unique antipsychotic efficacy. Here, we investigate whether baseline immune abnormalities measured with blood cell count ratios can predict the clinical response after initiating treatment with clozapine in patients with clozapine naïve TRS.

Methods: A naturalistic longitudinal design, involving 32 patients diagnosed with treatment-resistant, clozapine-naïve schizophrenia-spectrum disorder was developed. Patients were evaluated at baseline before clozapine starting and 8 weeks of follow-up. Psychopathological status and immune abnormalities (blood cell count ratios: neutrophil-lymphocyte ratio [NLR], monocyte-lymphocyte ratio [MLR], platelet-lymphocyte ratio [PLR] and basophil-lymphocyte ratio [BLR]) were evaluated in each visit.

Results: Baseline NLR ($b = -0.364$; $p = 0.041$) and MLR ($b = -0.400$; $p = 0.023$) predicted the change in positive symptoms over the 8-week period. Patients who exhibited a clinical response showed higher baseline NLR (2.38 ± 0.96 vs. 1.75 ± 0.83 ; $p = 0.040$) and MLR (0.21 ± 0.06 vs. 0.17 ± 0.02 ; $p = 0.044$) compared to non-responders. In the ROC analysis, the threshold points to distinguish between responders and non-responders were approximately 1.62 for NLR and 0.144 for MLR, yielding AUC values of 0.714 and 0.712, respectively. No statistically significant differences were observed in the blood cell count ratios from baseline to the 8-week follow-up.

Discussion: Our study emphasizes the potential clinical significance of baseline NLR and MLR levels as predictors of initial clozapine treatment response in patients with TRS. Future studies with larger sample sizes and longer follow-ups should replicate our results.

S272. COMPUTATIONAL MODELING OF BELIEF UPDATING ACROSS SOCIAL VERSUS NON-SOCIAL CONTEXTS IN INDIVIDUALS WITH HIGH VERSUS LOW PARANOIA

Antonia Bott^{*1}, Julian L. Faße¹, Tania M. Lincoln¹

¹*Universität Hamburg, Institute of Psychology, Clinical Psychology and Psychotherapy*

Background: Predictive processing accounts propose that delusions arise from aberrant belief updating, particularly characterized by an overestimation of the volatility (rate of change) associated with the environment. Given that delusional contents, such as paranoia, predominantly revolve around social themes, we investigated whether the overestimation of volatility that has been associated with paranoia is particularly pronounced in social contexts.

Methods: In a laboratory experiment, we stratified 116 participants into high ($n = 57$) versus low ($n = 59$) paranoia groups. All participants completed two computerized three-option reversal learning tasks within both a social (trust game) and a non-social context (gambling game). Taking a computational modeling approach, we formalized belief updating using Hierarchical Gaussian Filters over trial-by-trial responses. We compared model-free choice switching as well as computational parameters of volatility beliefs across groups and contexts.

Results: Consistent with previous research, participants with high paranoia demonstrated higher average win-switch rates as well as higher initial volatility beliefs as compared to those with low paranoia. Moreover, we observed a main effect of context on lose-switch rates, indicating that participants were more inclined to switch choices after losses in the social as compared to the non-social context. However, there was no evidence for a significant modulation of volatility beliefs by context.

Discussion: Our results replicate previous findings supporting the notion that paranoia is linked to an overestimation of environmental volatility, emphasizing the role of aberrant belief updating in delusion etiology. While our context manipulation influenced choice switching behavior, our results suggest that heightened volatility beliefs in paranoia appear to be stable across different types of contexts within a well-controlled laboratory environment.

S273. PREFRONTAL GLUTAMATE LEVELS IN ANTIPSYCHOTIC-NAÏVE PATIENTS WITH PSYCHOSIS ARE RELATED TO BRAIN STRUCTURE AND CLINICAL OUTCOME AFTER TWO YEARS ILLNESS

Kirsten Bojesen*¹, Cecilie Lemvig², Jayachandra M. Ragahava³, Bjørn Hylsebeck Ebdrup⁴, Birte Yding Glenthøj⁵

¹*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup,* ²*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Schizophrenia Research (CINS), Mental Health Center Glostrup, University of Copenhagen,* ³*Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, and Center for Neuropsychiatric Schizophrenia Research, CNSR, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark, and Functional Imaging Unit, Department of Clinical Physiology, Nuclear Medicine and PET, University of Copenhagen,* ⁴*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup AND University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine, Copenhagen, Denmark,* ⁵*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS); University of Copenhagen*

Background: Prefrontal glutamate levels are suggested to underlie structural changes in patients with schizophrenia based on findings in animal models, but whether this translates to humans is unknown. Moreover, prefrontal glutamate levels have been related to cognition and short-term treatment response in patients with first-episode psychosis (FEP), but the association with long-term clinical outcomes remains to be elucidated.

Methods: This was a longitudinal study of 57 initially antipsychotic-naïve patients with FEP (22.6±5.0 years, 58% females) and 55 healthy controls (HCs) (22.2±4.3 years, 62% females) matched on age, sex and parental socioeconomic status that were followed-up after two years (35 patients and 44 HCs).

Glutamate levels were assessed in a 2*2*2cm³ spectroscopic voxel in dorsal Anterior Cingulate Cortex (dACC) on a 3T MR scanner with the PRESS sequence, and brain structure in dACC, hippocampus, and striatum with a T1-weighted sequence. LCMoel and Freesurfer were used for analyses of data. Clinical outcomes after two years included symptom reduction in positive symptoms, functional outcome, and performance in tests of the cognitive domains sustained attention and spatial working memory (SWM).

General linear models evaluated associations between baseline glutamate levels and structural volume as well as clinical outcomes after two years, and linear mixed models evaluated structural changes over time. Analyses were adjusted for age, sex, tobacco and cannabis smoking, and total grey matter volume.

Results: Glutamate levels at baseline: Glutamate levels in dACC were borderline significantly lower in the antipsychotic-naïve patients compared with HCs (p=0.05).

Structure in hippocampus, striatum, and dACC: The structural volumes did not differ between patients and HCs at baseline or after two years, but reductions were seen in the subcortical

areas after two years in both patients and HCs (main effect of time: left hippocampus: $p=0.002$; right hippocampus $p=0.009$; left striatum: $p=0.002$; right striatum: $p=0.003$) but not in dACC. Glutamate levels at baseline and brain structure after two years: For hippocampus, there was a significantly more positive association between prefrontal glutamate levels at baseline and hippocampal volume after two years in patients compared with HCs (group*glutamate: right hippocampus $p=0.019$; left hippocampus $p=0.04$). For striatum, a similar trend was found for right striatum (group*glutamate: right striatum $p=0.07$; left striatum $p=0.10$). In dACC, there was a trend for a more positive association in HCs between prefrontal glutamate levels at baseline and gray matter in the spectroscopic voxel after two years (group*glutamate: $p=0.06$). Glutamate levels at baseline and clinical outcome after two years: There was a significant positive association between glutamate levels at baseline in dACC and cognitive performance in the test of attention after two years in both patients and HCs ($p=0.012$) but not with SWM. Prefrontal glutamate levels at baseline were not significantly associated with reduction in positive symptoms or level of function after two years.

Discussion: The results suggest that glutamate levels in dACC are lower in antipsychotic-naïve patients with first-episode psychosis and that higher glutamate levels in the FEP patients at illness onset are related to better cognitive performance and less reductions of subcortical volumes after two years. In contrast, higher glutamate levels in HCs at baseline seem associated with greater reduction of gray matter in dACC after two years. This may suggest the existence of an optimal range of prefrontal glutamate levels for long-term structural alterations and cognitive function.

S274. META-ANALYSIS OF CEREBELLO-THALAMO-CORTICAL NETWORK DYSCONNECTIVITY IN SCHIZOPHRENIA

Orsolya Lanyi^{*1}, Dániel Zahemszky², Gábor Csukly²

¹*Semmelweis University*, ²*Semmelweis University, Department of Psychiatry and Psychotherapy*

Background: A growing body of evidence highlights the pivotal role of the thalamus and cerebellum in the pathomechanism of schizophrenia. While thalamo-cortico-cerebellar connectivity dysfunctions have been extensively investigated, existing evidence remains inconclusive regarding its reliability across illness stages and medication status. Additionally, resting-state fMRI studies suffer from limitations, such as small sample sizes and replication bias. This meta-analysis aims to comprehensively synthesize statistical evidence of thalamo-cortico-cerebellar network dysfunctions in the psychosis spectrum. Our focus spans prodromal and high-risk populations, as well as clinical cohorts, including first-episode psychosis and chronic schizophrenia, with the objective of elucidating the developmental and etiological aspects of thalamic and cerebellar dysconnectivity in the psychosis spectrum.

Methods: Adhering to the PRISMA guideline and the Cochrane Handbook, our study protocol was registered on PROSPERO (CRD42023482939). The systematic search, conducted in three databases in September 2023, included articles using seed-based resting-state fMRI in patients with schizophrenia-spectrum disorders, first-episode psychosis, clinical high-risk for psychosis, and healthy control groups. Seeds for connectivity analysis were selected within the thalamo-cortico-cerebellar network. For statistical hypothesis testing we employed Multilevel Kernel Density Analysis (MKDA), a coordinate-based meta-analytic method. Risk of Bias was

evaluated using the Newcastle-Ottawa scale and we followed the recommendations of Müller and colleagues (2018) for fMRI meta-analysis.

Results: Data extraction and analysis encompassed 100 studies. Of these, 48 focused on seed-based thalamocortical connectivity, 33 reported cerebellar connectivity, and 15 included both thalamic and cerebellar connectivity. Preliminary findings indicate a confirmatory pattern of thalamocortical hypoconnectivity between the thalamus and subregions of the prefrontal cortex, alongside hyperconnectivity between the thalamus and motor and sensory cortical areas. Moderate heterogeneity was found among the included articles concerning preprocessing methods, statistical analysis, and the conceptualization of seed ROIs. Analysis of the cerebellum is in progress as well as the analysis of thalamic and cerebellar connectivity to differentiate between high-risk and clinical disorder states. The final results of MDKA analyses will be presented at the SIRS 2024 conference.

Discussion: Thalamo-cortico-cerebellar network connectivity dysfunctions have been described as a core feature in the pathophysiology of schizophrenia. This meta-analysis aims to offer a comprehensive statistical summary of existing findings on thalamo-cortico-cerebellar dysconnectivity and evaluate the reliability and robustness of these findings. Preliminary results suggest that thalamocortical and corticocerebellar functional dysconnectivity represents a fundamental neurobiological abnormality in schizophrenia spectrum disorders. With a focus on different illness stages, we anticipate that our final results will confirm thalamo-cortico-cerebellar dysconnectivity emerging prior to the onset of psychosis, potentially serving as a predictive marker for the transition from prodromal to clinical states.

S275. CELLULAR ADHESION MOLECULES AND COGNITION IN DRUG-NAÏVE AND PREVIOUSLY MEDICATED PATIENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS: A LONGITUDINAL STUDY

Kristian Varden Gjerde*¹, Christoffer A. Bartz-Johannessen², Else-Marie Løberg³, Vidar M. Steen⁴, Nils Eiel Steen⁵, Ole A. Andreassen⁶, Thor Ueland⁷, Maria Rettenbacher⁸, Inge Joa⁹, Solveig Klæbo Reitan¹⁰, Erik Johnsen¹¹, Rune A. Kroken¹²

¹NKS Olaviken Gerontopsychiatric Hospital; University of Bergen; NORMENT Centre of Excellence, Division of Psychiatry, Haukeland University Hospital, ²NORMENT Center of Excellence, Division of Psychiatry, Haukeland University Hospital, ³NORMENT Center of Excellence, Division of Psychiatry, Haukeland University Hospital; Department of Clinical Psychology, University of Bergen, ⁴NORMENT Center of Excellence, Department of Clinical Science, University of Bergen; Dr. Einar Martens Research Group for Biological Psychiatry, Department of Medical Genetics, Haukeland University Hospital, ⁵NORMENT Centre of Excellence, Division of Mental Health and Addiction, Oslo University Hospital; Institute of Clinical Medicine, Faculty of Medicine, University of Oslo; Department of Psychiatric Research, Diakonhjemmet Hospital, ⁶NORMENT Centre of Excellence, Division of Mental Health and Addiction, Oslo University Hospital; Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, ⁷Research Institute of Internal Medicine, Oslo University Hospital, Rikshospitalet; Institute of Clinical Medicine, University of Oslo; Department of Clinical Medicine, Thrombosis Research Center, UiT - The Arctic University of Norway, ⁸Medical University Innsbruck; Department of Psychiatry, Psychotherapy and Psychosomatics, ⁹TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital; Department of Public Health, Network for Medical Sciences, Faculty of Health Sciences, University of Stavanger, ¹⁰St. Olav University Hospital, Nidelv Community Mental

Health Centre; Norwegian University of Science and Technology, Department of Mental Health, ¹¹Division of Psychiatry, Haukeland University Hospital; Department of Clinical Medicine, University of Bergen, ¹²Division of Psychiatry, Haukeland University Hospital; Department of Clinical Medicine, University of Bergen

Background: The pathoetiology of schizophrenia seems to involve inflammation. Endothelial inflammation, disruption of the blood-brain barrier (BBB) and the pathway of the cellular adhesion molecules (CAMs) have been associated with cognitive dysfunction, which can precede psychotic symptoms in the development of schizophrenia. The aim of the current study was to investigate the relationship between levels of soluble CAMs and measures of neurocognitive function in patients with schizophrenia-spectrum disorders, monitored at baseline, 6, 26 and 52 weeks after initiation of antipsychotic treatment in a randomized drug trial.

Methods: The study population includes 138 patients with schizophrenia-spectrum disorder, of which 54 were first episode and drug-naïve, and 84 were previously medicated. A brief neuropsychological battery, including Trail Making Test A (TMT-A) and Trail Making Test B (TMT-B), the Hopkins Verbal Learning Test (HVLT-R), WAIS Letter Number Sequencing, the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Tests (FAS) and Symbol Coding, were used to assess cognitive function. T-scores were converted from the test scores. The average t-scores were calculated, based on the subtests, for overall cognition (all subtests), working memory (TMT-B, WAIS Letter Number Sequencing), processing speed (TMT-A, Symbol Coding) and verbal abilities (HVLT-R, FAS). Analysis of soluble CAMs included neural cadherin (N-CAD), vascular adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, mucosal addressing cell adhesion molecule (MADCAM) and junctional adhesion molecule (JAM-A). The possible confounders age, gender, body mass index (BMI), smoking and years of education were adjusted for in the linear mixed effect models. The average effect of CAMs on cognitive outcome measures during the follow-up period were explored.

Results: Levels of N-CAD and test scores of overall cognition ($p=0.026$) and verbal abilities ($p=0.027$) were significantly positively correlated in the total patient group. Levels of VCAM-1 were significantly negatively correlated with test scores of overall cognition ($p=0.019$) and processing speed ($p=0.048$) in the drug-naïve patient group. Levels of N-CAD and test scores of overall cognition ($p=0.004$), verbal abilities ($p=0.019$), working memory ($p=0.036$) and processing speed ($p=0.040$) were significantly positively correlated in the previously medicated group.

Discussion: We found an association between levels of N-CAD and VCAM-1 and measures of neurocognitive function. This suggests that immune processes are involved in cognition and that N-CAD and VCAM-1 may have a role as future biomarkers of cognitive dysfunction.

S276. USING NEUROTRANSMITTER VULNERABILITY TO DISCRIMINATE SCHIZOPHRENIA PATIENTS FROM HEALTHY CONTROLS

Lisa Hahn^{*1}, Florian Raabe², Daniel Keeser², Moritz J. Rossner², John Fanning², Clara Vetter², Alkomiet Hasan³, Irina Papzova³, Peter Falkai², Nikolaos Koutsouleris²

¹Ludwig-Maximilian University, ²Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, ³Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg

Background: Aside to common psychotic symptoms such as hallucinations, delusions and disorganized thinking, schizophrenia (SCZ) is characterized by structural alterations such as volume reductions in the temporal, frontal, and parietal lobes. Here, we evaluated if the co-localization of these alterations with the distribution of specific neurotransmitter systems, i.e. an indication of neurotransmitter vulnerability) can be utilized to discriminate SCZ patients from healthy controls (HC).

Methods: Maps of grey matter volume (GMV) were derived from T1-weighted structural magnetic resonance imaging for 445 SCZ patients (mean age = 34.0 ± 11.3 , 103 females) and 416 HC (mean age = 33.5 ± 11.3 , 108 females) from the Multimodal Imaging in Chronic Schizophrenia Study (MIMICSS; part of the PsyCourse study), the Center for Biomedical Research Excellence (COBRE; part of the COIN study) cohort, Mind Clinical Imaging Consortium (MCIC; part of the COIN study) cohort, the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study, and the Munich cohort (internal dataset). Two linear classifiers utilizing a leave-site-out cross-validation (CV) design (CV1: 10x5, CV2: 1x10) for the discrimination of SCZ patients and HC were created. The preprocessing steps computed within the CV framework included offset correction using the global mean, correction for age and sex using partial correlations, the model-specific feature computation, and standardization. The model-specific features either entailed whole-brain correlation coefficients between GMV and 29 nuclear-imaging derived neurotransmitter maps (e.g., receptor and transporter density) from a healthy volunteer population computed using the JuSpace toolbox or 29 eigenvariates computed using principal component analysis (PCA) as a control model.

Results: The first classifier (using whole-brain correlation coefficients) discriminated SCZ from HC with a balanced accuracy of 64.1 % and area under the curve of 0.68 (sensitivity = 64.7 %, specificity = 63.6 %). The control classifier (using PCA eigenvariates) performed similarly, discriminating SCZ from HC with a balanced accuracy of 66.4 % and area under the curve of 0.72 (sensitivity = 75.2 %, specificity = 57.5 %).

Discussion: SCZ patients were distinguishable from HC based on the association of structural alterations with specific neurotransmitter systems. These findings suggest that this indication of neurotransmitter vulnerability might serve as a diagnostic biomarker.

S277. DISENTANGLING FACIAL EXPRESSIONS DURING PANSS INTERVIEWS AND THEIR ASSOCIATIONS WITH PSYCHOPATHOLOGY IN ANTIPSYCHOTIC-NAÏVE PATIENTS WITH FIRST-EPISODE PSYCHOSIS

Karen S. Ambrosen^{*1}, Cecilie K. Lemvig¹, Mette Ø. Nielsen², Birte Y. Glenthøj², Warda Syeda³, Bjørn H. Ebdrup²

¹Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), ²Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) AND University of Copenhagen, ³The University of Melbourne

Background: Facial expressions are an important aspect of non-verbal communication. Reduced emotional expressiveness is among the negative symptoms of schizophrenia. Identification and quantification of negative symptoms can be challenging and involve a large degree of subjectivity. Thus, an objective method for assessing these symptoms would

represent an important advancement. The Facial Action Coding System (FACS), developed by Ekman and Friesen in 1978, is a comprehensive, anatomically based system for describing all visually discernible facial movements. It breaks down facial expressions into individual components of muscle movement, called Action Units (AUs). Utilizing computer vision to measure facial expressions may provide a means of adding more objectivity and reliability in non-verbal symptom assessment. In this study, we explore the associations between facial expressions and psychopathology in antipsychotic-naïve patients with first-episode psychosis. Specifically, we hypothesize that coactivations of facial AUs, constituting distinct facial expressions, capture distinct dimensions of psychopathology.

Methods: Fifty antipsychotic-naïve individuals with first-episode psychosis (mean age 25.4 (6.1); 65.2% males) from the PECANS study (ClinicalTrials.gov Identifier: NCT01154829) were included. Psychopathology was rated using the Positive and Negative Syndrome Scale (PANSS) and the interviews were video-recorded. The videos were recorded under real-world clinical conditions, i.e., varying backgrounds, recording angles, and illumination. The recordings were 22-97 minutes long with an average duration of 48.7 minutes. The sampling rate was 25 Hz. All videos were preprocessed using OpenFace 2.0 (Baltrušaitis et al., 2018). The activation intensity of seventeen AUs from FACS and confidence estimates were computed frame-wise for the entire duration of each recording. Frames with a confidence level below 80% were removed and participants with less than 90% frames remaining were excluded from the analyses, resulting in a final sample of 46 patients. For each participant, a 17x17 connectivity matrix was calculated using temporal correlations between each pair of AUs. All connectivity matrices were Fisher's transformed. A group-level connectivity matrix was obtained by averaging the absolute values of the connectivity matrices across participants. Spectral clustering was performed on the averaged connectivity matrix to identify multiple facial expressions, such that AUs within each facial network showed maximal co-activation. These distinct facial expressions were identified within each participant's connectivity matrix. To establish the clinical relevance of facial expressions, associations between the facial expressions and psychopathology were investigated using linear regression.

Results: Individual-level connectivity matrices showed medium to high temporal correlations between AUs. Three facial expressions were identified. F1 nodes: AU1, AU2, AU4, AU5, AU7, AU9; F2 nodes: AU15, AU17, AU20, AU23, AU25, AU26, AU45; F3 nodes: AU6, AU10, AU12, AU14. F1 and F2 comprised AUs associated with negative valence, while F3 comprised AUs with positive valence. Within network temporal correlations showed the strongest associations between F1 and general symptoms ($\rho=0.54$, $p < 0.001$), F2 and negative symptoms ($\rho=0.69$, $p < 0.001$), and F3 and general symptoms ($\rho=0.51$, $p < 0.001$). Further analyses, e.g., associations with treatment response, are ongoing, and results will be presented at the SIRS 2024 congress.

Discussion: In summary, associations between the identified facial expressions and psychopathology indicate the clinical relevance of facial expressions.

S278. THE CONTRIBUTION OF COGNITIVE AND SOCIAL COGNITIVE IMPAIRMENTS TO INTERNALIZED STIGMA IN FIRST-EPISODE PSYCHOSIS

Élisabeth Thibaudeau^{*1}, Libby Lassman², Delphine Raucher-Chéné¹, Martin Lepage¹

¹McGill University, Douglas Mental Health University Institute, ²McGill University

Background: First-episode psychosis (FEP) is associated with impaired cognitive and social cognitive functioning that have shown detrimental effects on daily life. These impairments

represent one of the main complaints following a FEP which is also associated with internalized stigma (i.e. process by which individuals apply negative stereotypes to themselves). The latter is often accompanied with increased distress and poorer social functioning. While the relationship between clinical symptoms and internalized stigma has been shown in previous studies, its association with cognitive and social cognitive impairments is not yet well understood. The objective was to explore the associations between cognition, social cognition, and internalized stigma in FEP, and to assess the role of negative symptoms in these relationships, given their contribution to cognitive impairments and internalized stigma.

Methods: Data from a RCT on cognitive interventions for social anxiety in FEP were used, including 88 participants with a FEP (65.2% men, mean age of 24.8 years). Internalized stigma was assessed with the Internalized Stigma of Mental Illness Inventory (ISMI). The ISMI includes a total score as well as the following scales: alienation, stereotype endorsement, perceived discrimination, social withdrawal, and stigma resistance. Cognition and social cognition were assessed using the Cogstate battery, including verbal and visual memory, working memory, attention, executive functions, speed of processing and social cognition (emotion recognition). Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms. First, stepwise linear regressions were used with the ISMI scales as dependent variables and each cognitive and social cognitive domain as independent variables, controlling for negative symptoms. Then, the significant predictors for each ISMI scale were entered into a regression to assess their relative contribution.

Results: For the ISMI social withdrawal scale, a significant effect of social cognition was observed, explaining 21% of the variance [$F(1,87)=1.612$, $p=.044$], with no significant effect of negative symptoms. Attention was also a significant predictor of social withdrawal, explaining 35% of the variance [$F(1,87)=12.200$, $p < .001$], with no significant effect of negative symptoms. When social cognition, attention and negative symptoms were entered into a regression model, only the effect of attention remained significant. A similar pattern was observed for the perceived discrimination scale of the ISMI, with a significant effect of social cognition explaining 22% of the variance [$F(1,87)=4.598$, $p=.035$] and a significant effect of attention explaining 28% of the variance [$F(1,87)=7.547$, $p=.007$]. However, when attention, social cognition and negative symptoms were all entered into a regression model, only attention remained significant. For the ISMI stigma resistance scale, the regression model including only speed of processing explained 24% of the variance [$F(1,87)=5.344$, $p=.023$], while the model including speed of processing and negative symptoms explained 33% of the variance [$F(1,86)=5.379$, $p=.006$]. Finally, for the ISMI total score, attention was a significant predictor, explaining 27% of the variance [$F(1,87)=6.828$, $p=.011$], with no significant effect of negative symptoms. No significant effect was observed for the ISMI alienation and stereotype endorsement scales.

Discussion: Cognition and social cognition contribute uniquely to specific aspects of internalized stigma in FEP. This highlights the importance of treating cognitive impairments early in the illness, but also to address them in psychosocial interventions targeting internalized stigma.

S279. THE INTERPLAY BETWEEN SOCIAL REJECTION AND INTERPERSONAL FEAR CONDITIONING AS A PLAUSIBLE CAUSAL MECHANISM EXPLAINING PARANOIA-LIKE THOUGHTS

Łukasz Gawęda^{*1}, Paulina Bagrowska², Renata Pionke-Ubych², Justyna Piwińska²

Background: Paranoia is defined as a set of erroneous beliefs that other people are a source of intentional harm. It is hypothesized that paranoia results from complex interactions between various factors and psychological processes. However, the empirical knowledge of how different risk factors interact with each other in predicting and causally explaining paranoia is limited. Importantly, the role of interpersonal processes that are at the core of paranoia has been understudied. Hence, the aim of this study is to provide empirical verification of causal relations between social rejection, interpersonal fear-conditioning, and paranoia through a combination of experimental assessment in Virtual Reality settings and gold-standard clinical assessments of paranoia proneness in non-clinical individuals.

Methods: Participants aged 18-40 without neurological diseases, intellectual disabilities, a history of psychotic or bipolar disorders and substance abuse or dependence were recruited on the basis of an initial screening of levels of paranoid thoughts ($N = 3000$) and allocated to two groups - high paranoia (HP) (top 10% scores in R-GPTS ≥ 35) and low paranoia (LP) (bottom 10% scores in R-GPTS ≤ 1). Preliminary analyses were carried out on a group of 103 individuals (LP = 79, HP = 24). Semi-structured clinical interviews (M.I.N.I and CAARMS) preceded the experimental procedure. Initially, a VR version of the Cyberball game, which involves playing ball with virtual players, was used to elicit participants' feelings of being excluded. Participants were randomly assigned to one of two conditions: social inclusion or social exclusion. This was followed by a social fear conditioning procedure using interpersonal stimuli as a social stressor (offensive words shouted from a minimum distance by agents wearing blue or green T-shirts [conditioned stimulus] in front of the subject's face). This phase consisted of habituation, fear acquisition (16 stimuli, 75% reinforcement) and fear extinction (8 stimuli, no reinforcement). Measurements of state paranoia were collected after each phase (4 time points).

Results: The results of the 2 (Group: HP x LP) x 2 (Condition: Social inclusion x Social exclusion) x 3 (Time: T0, T1, T2, T3) mixed model ANOVA revealed a significant interaction effect ($F(3, 96) = 9.476$, $p < 0.001$, $\eta^2 = 0.23$). Pairwise comparisons revealed that in the LP group there were no significant differences in the level of paranoid thoughts between any time points and the Cyberball conditions. However, in the HP group in the social inclusion condition, there were significant differences in paranoia scores between T0 and T1 (before and after Cyberball) ($p = 0.006$), between T1 and T2 (after Cyberball and after fear acquisition) ($p = 0.001$), and between T1 and T3 (after Cyberball and after fear extinction) ($p = 0.004$). In the social exclusion condition, paranoia scores differed significantly between T0 and T1 (before and after Cyberball) ($p = 0.004$), T0 and T2 (before Cyberball and after fear acquisition) ($p = 0.019$), and between T2 and T3 (after fear acquisition and after fear extinction) ($p = 0.002$).

Discussion: The preliminary findings showed that LP group did not exhibit an increase in paranoid thoughts following social rejection and did not display susceptibility to interpersonal fear conditioning. HP group, however, demonstrated a significant reduction in paranoid thoughts following social inclusion, and a notable increase in paranoid thoughts after social rejection. Moreover, HP group was susceptible to interpersonal fear conditioning, displaying heightened paranoid thoughts regardless of Cyberball condition. While these initial findings are based on limited data forming unequal groups, one could tentatively suggest a plausible causal connection between social rejection and social fear conditioning. Alternatively, these may represent distinct processes, with either the social rejection experience or the fear conditioning process contributing to the escalation of paranoid thoughts.

S280. EMOTIONAL AND NON-EMOTIONAL MENTAL IMAGERY AND AUDITORY VERBAL HALLUCINATIONS (HEARING VOICES): A SYSTEMATIC REVIEW OF IMAGERY ASSESSMENT TOOLS

Hella Janssen¹, Karin C. van den Berg², Georgie Paulik³, Katherine Newman-Taylor⁴, Christopher D.J. Taylor⁵, Craig Steel⁶, Ger P.J. Keijsers⁷, Machteld C. Marcelis⁸, Machteld Marcelis^{*9}

¹Department of of Psychiatry and Neuropsychology, MHeNs Maastricht University, the Netherlands, ²Medical Psychiatric Research Group, Geestelijke Gezondheidszorg Eindhoven (GGzE), the Netherlands, ³School of Psychological Science, University of Western Australia, ⁴University of Southampton and Southern Health NHSF Trust, ⁵University of Manchester and Pennine Care NHS FT, ⁶Oxford Centre for psychological Health and Oxford Institute of Clinical Psychology Training and Research, ⁷Behavioural Science Institute, Radboud University, Nijmegen, the Netherlands, ⁸Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, EURON, Maastricht University Medical Center, Maastricht, the Netherlands; Institute for Mental Health Care Eindhoven (GGzE), Eindhoven, the Netherlands, ⁹Maastricht University Medical Center

Background: It is unknown to what extent mental imagery and auditory verbal hallucinations (AVHs) are related. Trials evaluating this issue used both emotional and non-emotional mental imagery tools, thereby complicating outcomes comparisons. The present study aimed to systematically review the literature on mental imagery in individuals with AVHs to 1) inventory imagery assessment tools used in this population, 2) to collect information on the relation between emotional and non-emotional mental imagery in all sensory domains and AVHs, and 3) to integrate the outcomes of this systematic review in a model of different mental imagery domains and related assessment tools.

Methods: We conducted a systematic literature search in the PubMed Database.

Results: After full-text screening 17 papers were included. Findings showed that a variety of assessments methods have been used to assess various aspects of mental imagery in people with AVHs, suggesting that there is a lack of agreed theoretical conceptualisation of mental imagery and AVHs. In addition, the studies confirmed as was expected that non-emotional mental imagery seemed unrelated to AVHs, whereas emotional mental imagery was related to AVHs.

Discussion: AVHs are associated with emotional mental imagery. Emotional and non-emotional mental imagery measures are poorly distinguished, resulting in inaccurate research conclusions. We proposed a model of mental imagery domains and corresponding assessment methods distinguishing between emotional and non-emotional mental imagery.

S281. MULTIMODAL BRAIN IMAGING MARKERS PREDICT AUDITORY HALLUCINATION IMPROVEMENT AFTER NEUROFEEDBACK INTERVENTION

Jiahe Zhang^{*1}, Emma Tusuzian¹, Clemens Bauer², Ann Shinn³, Francesca Morfini¹, Yoonji Lee¹, Angelina Awad⁴, Lena Stone³, Margaret Niznikiewicz⁵, Susan Whitfield-Gabrieli¹

Background: Approximately 75% of patients diagnosed with schizophrenia (SZ) suffer from auditory verbal hallucinations (AVH) and about one-third of those experiencing AVH do not respond to medication. We recently developed a real-time fMRI neurofeedback (NF) approach that trains participants to voluntarily down-regulate activity in their auditory cortices in the superior temporal gyrus (STG) aided by a display of moment-to-moment changes in their STG activation. In order to further optimize this approach, it is important to identify characteristics that can help predict outcome success. Altered STG and default mode network (DMN) morphometry and functional connectivity have been observed in SZ and AVH. This study aimed to test whether multimodal neuroimaging analyses of the STG and the DMN can predict AVH improvement in patients after a single session of NF.

Methods: Twenty-five participants with medication-resistant AVH were randomly assigned to receive either active STG NF (N = 12) or sham motor cortex NF (N = 13). All participants underwent structural MRI and resting state fMRI scanning before the NF session. During NF, patients listened to prerecorded sentences spoken in their own voice or in a gender-matched stranger's voice, delivered over headphones. Blood oxygen level dependent (BOLD) activation in the active or sham brain target was displayed in the form of a thermometer. Patients were asked to reduce BOLD activation when they listened to the stranger's voice, and to increase it when they listened to their own voice. Both STG and motor cortex targets were identified using a baseline localizer scan. AVH were assessed using the Psychotic Symptom Rating Scale (PSYRATS). For cortical thickness and functional connectivity analysis, we identified bilateral a priori STG regions from the Destrieux atlas and computed subject-specific DMN using a localizer resting state scan.

Results: ANOVA test on AVH change contrasting active and sham groups across pre- and post-NF timepoints showed a significant main effect of time ($F = 8.72$, $p = .007$), but did not reveal a significant main effect of group or group-by-time interaction. Nevertheless, participants who received STG NF reported significantly decreased AVH after NF [$t(11) = 2.30$, $p = .042$, two-tailed, paired-sample t-test]. Within the STG NF group, we found that more improvement in AVH was associated with the following characteristics at baseline: (1) more severe AVH ($r = .61$, $p = .037$), (2) thicker bilateral STG ($r = .63$, $p = .027$), (3) stronger functional connectivity within the DMN (between the whole DMN and bilateral posterior cingulate cortex, PCC; $r = .87$, $p < .001$), and (4) stronger anticorrelation (i.e., more negative connectivity) between the DMN and bilateral dorsolateral prefrontal cortex (DLPFC; $r = -.95$, $p < .001$).

Discussion: In participants who were trained to reduce STG activation with help from real-time STG NF, their post-NF AVH reductions were predicted by baseline STG thickness as well as within-DMN connectivity (i.e., DMN-PCC) and DMN-executive network connectivity (i.e., DMN-DLPFC). These results suggest that participants with more severe symptoms (i.e., higher PSYRATS scores), poorer brain indices of SZ disorder (i.e., thicker STG and stronger within-DMN connectivity) but preserved cognitive capacity (i.e., stronger DMN-CEN anticorrelation) at baseline may benefit more from STG NF. Consistent with principles of precision medicine, this study provides potential brain-based biomarkers that prospectively predict symptom improvement in AVH for SZ.

S282. NEURORADIOLOGICAL ABNORMALITIES IN FIRST EPISODE OF PSYCHOSIS: AN EPIDEMIOLOGICAL COHORT OF 331 PATIENTS

Jorge Romay*¹, Paula Suarez-Pinilla¹, Javier Vazquez-Bourgon¹, Marta Drake-Perez¹, Enrique Marco de Lucas¹, Fernando Roman-Rubio¹, Pilar García-Pelayo¹, Rocío Pérez-iglesias¹

¹*Hospital Universitario Marqués de Valdecilla*

Background: An increasing number of studies and a recent meta-analysis are trying to support the use of Magnetic Resonance Imaging (MRI) in the early phases of psychosis. Identify MRI abnormalities in these early stages could demonstrate markers and potential pathways involved in the onset of psychosis, despite the lack of a clear consensus on the use of MRI as part of the clinical evaluation.

This study aimed to investigate neuroimaging patterns and brain abnormalities in Magnetic Resonance Imaging performed on patients included in a cohort of 331 patients with a first-episode of psychosis treated in the early intervention program ITPCan.

Methods: A total of 331 patients in early stages of psychosis were included in this study. All of them were offered an imaging test (MRI or CT scan) at the beginning of the follow-up. Out of this total, 253 (76.4%) patients agreed to undergo the imaging test, while 78 (23.5%) were unable to undergo the imaging test due to either incompatibility or refusal. Among these 253 patients who underwent imaging, 161 received an MRI, while 92 received a CT scan. Data was recorded between January 2020 and September 2023, covering a population area of approximately 589765 inhabitants in Santander (Spain). Inclusion criteria were established for patients aged 17 to 65 years with an untreated first episode of psychosis and subsequent diagnosis of schizophrenia, schizophrenia related disorder or manic episode with psychotic symptoms. The imaging data and the associated clinical report were described and interpreted by two neuroradiologists (M. Drake-Pérez, E. Marco de Lucas), using an MRI protocol that included T1, T2, FLAIR, and diffusion-weighted images.

Results: Of the 161 patients undergoing MRI, 45.3% (N 73) showed no significant findings in the imaging test, while 54.7% (N 88) exhibited alterations in MRI. Among this subset with abnormalities in the imaging test, 42.04% presented high degrees of heterogeneity lesions in the white matter, which can be categorized into three groups: 1) Non-specific subcortical lesions accounting for 61.84% (N 26); 2) Subcortical lesions and periventricular lesions, deeper than those indicative of chronic microangiopathic ischemic leukoaraiosis (Fazekas 1), constituting 14.2% (N 6); 3) Infratentorial millimetric lesions at 4.7% (N 2). Other abnormalities in MRI included encephalomalacia 2.6 % (N 3), malformations 14.9% (N 17), or atrophies 6.1% (N 7). Analyzing these data with age as a variable, using a cutoff point of 35 years, we observed a statistically significant Chi-square relationship ($p = 0.001$) between individuals older than 35 years and abnormalities in MRI. Among patients without MRI, 27.8% (N 92) underwent a CT scan, with 98.9% of the results being normal.

Discussion: These findings contribute valuable insights for both clinical diagnosis and future research endeavors aimed at elucidating the neural correlates of early-stage psychotic disorders. Further exploration is warranted to establish the clinical relevance of these neuroimaging patterns and the implementation of MRI as strategy in early phases of psychosis.

S283. COROLLARY DISCHARGE DYSFUNCTION AS A POTENTIAL UNDERLYING MECHANISM FOR ABNORMAL SELF-EXPERIENCES AND ITS ASSOCIATION WITH CLINICAL SYMPTOMS IN SCHIZOPHRENIA

Rosa M. Beño-Ruiz-de-la-Sierra*¹, Antonio Arjona-Valladares¹, Sabela Fondevila Estévez², Inés Fernández-Linsenbarth¹, Alejandro Roig-Herrero¹, Alvaro Díez¹, Vicente Molina³

¹University of Valladolid, ²Center UCM-ISCIII for Human Evolution and Behaviour,

³University of Valladolid. Clinical Hospital of Valladolid

Background: The accurate differentiation between self-generated stimuli and those originating from external sources is crucial for the development of an intact sense of self, with Corollary Discharge (CD) representing a key mechanism in this process.

The N1 Event-Related Potential (ERP) in Electroencephalogram (EEG) studies serves as an indicator of CD-mediated auditory cortical suppression of self-generated speech in Healthy Controls (HC), but this phenomenon seems to be altered in people with schizophrenia (Sz). Challenges in discerning the source of stimuli may contribute to the manifestation of certain clinical symptoms and the prevalence of Anomalous Self-Experiences (ASEs) within the psychosis spectrum.

Methods: A 64-channel EEG system was used to record the data from forty-three participants with Sz (18 First Episode (FE) and 25 chronic) and 43 HC. Both men and women participated and there were no significant differences between groups in sex or age. The N1 ERP was elicited by two task conditions: 1) self-pronounced vowels (talk condition) and 2) playback of the previously self-uttered vowels (listen condition). ASEs, positive and negative symptoms were assessed using the Inventory of Psychotic-Like anomalous Self Experiences (IPASE), the Positive and Negative Syndrome Scale (PANSS), and the Brief Negative Symptom Scale (BNSS) respectively.

First, to assess the occurrence of CD, a within-group analysis was conducted to measure the differences between conditions (Talk vs. Listen) using a repeated measures Student's t-test. Secondly, the amplitude difference between conditions (Talk minus Listen) was used as an indicator of CD-mediated auditory cortical suppression of self-generated speech, and a between group analysis was performed using an independent measure Student's t-test. Finally, the relationship between sensory suppression and the intensity of ASEs and symptoms was studied using linear regression analysis.

Results: The N1 suppression in the Talk condition compared to the Listen condition was lower in both Sz and HC participants. However, N1 amplitude suppression was statistically significantly higher in HC than in Sz. In addition, N1 suppression was significantly and negatively correlated with IPASE, PANSS, and BNSS scores. The same results were found for FE and chronic participants. No significant relation was found between N1 amplitude suppression and antipsychotic doses in participants with schizophrenia.

Discussion: Sensory identification of our own voice when speaking occurs at a pre-stimulus level. By activating the CD mechanism, we can predict the consequences of our own actions and differentiate the source of stimuli. This study replicates previous findings of CD impairment in schizophrenia and supports the idea that CD dysfunction may be a potential substrate of ASEs and psychotic symptoms in people with schizophrenia.

S284. CLINICAL AND FUNCTIONAL OUTCOMES FOLLOWING TREATMENT OF ACUTE PHASE OF FIRST-EPISODE PSYCHOSIS TREATED IN A REAL-WORLD SETTING

Rocio Perez-Iglesias*¹, Javier Vázquez-Bourgon², M Luz Ramírez-Bonilla¹, Deirdre Sierra-Biddle¹, Patricia Cordero-Andrés¹, M Carmen Flor-Gómez¹, Elsa Gómez-Ruiz¹, Raquel Obeso-Menéndez¹, Jorge Romay-González¹, Paula Suárez-Pinilla¹

¹University Hospital Marques de Valdecilla, ²Department of Psychiatry, University Hospital Marqués de Valdecilla, Institute of Biomedical Research Valdecilla (IDIVAL), Santander, Spain. CIBERSAM

Background: The aim of this study is to examine the clinical and functional outcomes of an epidemiological cohort of first-episode patients treated in the Early Intervention (EI) Service of Cantabria (ITPCan).

Methods: This is an audit study of all the patients admitted to the EI Service of University Hospital Marqués de Valdecilla, Spain, from January 2020 to July 2023. The catchment area has a population of 310,000 habitants. Patients were included if they were residents in the area, aged from 17 to 65 and were experiencing a first episode of psychosis (affective or non-affective).

As part of the clinical protocol, patients were offered a comprehensive assessment by an experienced psychiatrist in EI within 24 hours of referral. They were treated with a very low dose of antipsychotic medication in monotherapy and CBT for psychosis and physical health interventions started within the first two weeks of contact with services. To maintain the continuity of care, the same EI team treated the patients in the ward and in the outpatient clinic. The response to treatment was assessed at baseline, 3, 6 and 12 weeks with standardized scales such as PANSS, Calgary and Young. The side effects of antipsychotics were assessed using UKU scale and the GAF scale was used to assess functional outcome. To measure Patient Related Outcomes, we used the ISMI (Internalized Stigma of Mental Illness) and PBIQ-R (Personal Beliefs about Illness) scales.

Results:

A total of 163 were included. Forty five percent were male (n=74); sixty three percent were single (n=102). The mean age was 37 and fifty three percent of the cohort (n=87) were more than 35 years old at first contact with services, particularly women (64,1%). Twenty percent were living alone and 34% were unemployed. Eighty four percent were non-affective psychosis (33% schizophrenia; 10% TID, 44% schizophreniform disorder ; 11% Non-specified psychosis) and 16% first manic episode with psychotic symptoms. The mean duration of untreated psychosis was 13 months and the median was 2,5 months. A hundred and one patients (61%) required hospital admission and 83 (51%) were involuntary. Twenty percent of patients used cannabis on a daily basis. The GAF at initial assessment was 36,6 (SD=12); all of them below 70.

The most frequently prescribed antipsychotic treatments at baseline were aripiprazole (44%); olanzapine (31%) and risperidone (17%). The maximum mean dose was 9,1 mg/d for aripiprazole, 10,5 mg/d for olanzapine and 2,6 mg/d for risperidone. The mean maintenance dose at 12 weeks was 7,1 mg/d for aripiprazole; 8,6 mg/d for olanzapine and 2,3 mg/d for risperidone. Only 14 patients did not attend the assessment at 12 weeks.

The rate of responders using the PANSS remission criteria proposed by Andreasen was 53% at 3 weeks, 70,3% at 6 weeks and 85% at 12 weeks. The mean GAF at 12 weeks was 71, 64% of them scored 70 or more. The majority of patients rated low in the PRO on perceived stigma, alienation, discrimination and social withdrawal.

Discussion: Very low dose of antipsychotic treatment is effective to treat acute phase of first episode of psychosis, achieving a high response rate and a good functional outcome.

S285. STRESS FROM ETHNIC AND GENDER MINORITY STATUS, ADVERSITY, PARENTAL SUPPORT, AND SELF-REPORTED MENTAL HEALTH ON PSYCHOTIC EXPERIENCES: A CROSS-SECTIONAL SCHOOL-BASED SURVEY OF IRISH ADOLESCENTS

John Hoey*¹, Ronan Fleury¹, Jessica Ohland¹, Lorna Staines¹, Niamh Dooley², Emmet Power¹, Ian Kelleher³, David Cotter¹, Mary Cannon¹

¹Royal College of Surgeons in Ireland, ²King's College London, ³University of Edinburgh

Background: Psychotic experiences (PEs) in adolescence are associated with poorer long-term mental health outcomes in adulthood. It is known that early adversity is associated with an increased risk of psychotic experiences, however, less is known about the role of minority stress (defined as the stress experienced due to being in a minority group based on ethnicity or gender) and the protective role of parental support.

Methods: Cross-sectional data were drawn from the 2021 Planet Youth Project. Students from Cavan, Monaghan, and North Dublin were recruited to complete a self-report questionnaire. Participants were assessed for risk of PEs using the 7-item Adolescent Psychotic Symptom Screener (APSS). Mental health was assessed using the Strengths and Difficulties Questionnaire (SDQ). We employed multivariate logistic regression to analyse how a range of factors, specifically race, gender, feelings of safety at home and school, parental support, and self-reported mental health independently and collectively influence the risk of PEs in a general population adolescent sample.

Results: Of the students who completed the self-report questionnaire, 2168 (50.7%) identified as male, 1902 (44.5%) as female, 118 (2.7%) as transgender or non-binary, and 68 (1.6%) chose not to disclose their gender. Regarding ethnicity, 1991 (51.1%) identified as White Irish, 456 (11.7%) as other White, and 258 (6.6%) as Black, Asian or another minority. We observed differences in the risk of PEs in gender and ethnic minority groups. The prevalence of PEs was notably higher in minoritised ethnic groups, as indicated by an OR of 1.44 (95% CI [1.14, 1.82], $p = 0.002$), as opposed to their white counterparts. Non-binary or transgender individuals with SDQ scores above 16 showed a substantially increased risk of PEs, with an odds ratio (OR) of 4.15 (95% CI [2.61, 6.60], $p < 0.001$) as compared to their cisgender counterparts with SDQ scores below 16. Cisgender individuals (those who identified as male/female) with SDQ scores above 16 also demonstrated a higher risk of PEs, with an OR of 3.52 (95% CI [2.93, 4.24], $p < 0.001$), albeit lower than the gender diverse group. Adolescents perceiving safety at home and school reported lower prevalence of psychotic experiences (PEs), with ORs of 0.72 (95% CI [0.60, 0.87], $p = 0.001$) and 0.71 (95% CI [0.59, 0.86], $p < 0.001$), respectively. Participants with high adversity and lacking parental support had a significantly increased risk of PEs, with an OR of 1.79 (95% CI [1.34, 2.40], $p < 0.001$). Adolescents facing high adversity, with parental support, still

showed an elevated risk, albeit less than those without support, with an OR of 1.58 (95% CI [1.18, 2.13], $p = 0.002$).

Discussion: This study has identified potential risk and protective factors for PEs from multiple demographic and psychosocial domains emphasizing the complex interaction between mental health, a safe living environment and the presence of supportive adults. While these findings are significant, the cross-sectional nature of this study limits our ability to infer causality necessitating cautious interpretation. Nevertheless, these findings can guide clinicians in understanding the psychosocial factors influencing PE onset and inform the development of targeted interventions for adolescents, especially those in minoritised high-risk groups.

S286. DURATION OF UNTREATED PSYCHOSIS AS A MODERATOR BETWEEN SOCIAL COGNITION AND SOCIAL FUNCTIONING IN FIRST EPISODE PSYCHOSIS

Silvia Corbera^{*1}, Hadar Hazan², Fangyong Li³, Bin Zhou³, Sneha Karmani², Toni Gibbs-Dean², Sumeyra Tayfur², Cenk Tek², Vinod Srihari²

¹Central Connecticut State University, ²Yale University School of Medicine, ³Yale Centre for Analytical Sciences

Background: Despite evidence of impaired social cognition (SC) in first episode psychosis (FEP), the precise relationship between SC and social functioning (SF) remains unclear. While cross-sectional studies have established a link between SC and SF in FEP, longitudinal studies have yielded mixed results, with some demonstrating a mediating effect of SC between cognition and SF and others finding no relationship with SF. Duration of untreated psychosis (DUP), the time elapsed from psychosis onset to treatment, is a crucial predictor of SF in FEP, with reductions in DUP associated with improved SF and diminished negative symptoms. Negative symptoms have been identified as a potential mediator in the relationship between SC and SF in FEP, and are particularly susceptible to delays in DUP. However, to date no study has examined the moderating effects of DUP on the SC-SF relationship and the role of DUP between SC and negative symptoms in FEP. This longitudinal study examined them at baseline, and at 6-and 12 months after receiving specialized first-episode services.

Methods: Participants: 246 FEP participants (16-35yo) with primary non-affective psychotic disorders (DUP LESS THAN 3 year) were assessed at baseline, 6 (n=228) and 12 -months (n=211) as part of a quasi-experimental trial of early detection campaign delivered at a program for Specialized Treatment Early in Psychosis (n=171) compared to a usual detection coordinated specialty care site (n=75). Measures: Baseline: Symptoms: Structured Clinical Interview for DSM-IV; Positive and Negative Syndrome Scale (PANSS); Structured Interview for Psychosis-Risk Syndromes; Premorbid Adjustment Scale (PAS). Cognition: Premorbid IQ estimate-WRAT-4 reading; Social Cognition-MATRICES- MSCEIT Managing Emotions Branch. Social Functioning: Global Assessment of Functioning (GAF); Heinrichs Quality of Life (QOL). 6-and 12-months measures: PANSS and SF. DUP was calculated using the median split of the DUP of the sample (227.5 days; Long DUP: LDUP; Short DUP: SDUP n=123). Analyses: 1) T tests were used to compare baseline SF, SC, symptoms and cognition between DUP groups; 2) Two multivariable linear regression models were done using baseline SC as the predictor and SF as Dependent Variable(s) (GAF and QOL) at 6-and 12-months, controlling for their values at baseline, PAS, recruitment site, and DUP as a moderator; 3) Bi-variate correlations between SC and negative symptoms in both groups were performed.

Results: At baseline, QOL and PANSS negative scores differed between groups with the SDUP group having higher QOL and lower negative symptoms (QOL: SDUP M=63.47(20.41); LDUP M=58.55(19.46); $p=0.06$; PANSS Neg: SDUP M=18.57(7.26); LDUP M=20.49(7.05); $p=0.037$) yet no differences were observed in premorbid IQ estimate, SC, and GAF. Moderation analyses revealed a significant positive relationship between SC and GAF at 12-months, (95% CI: 0.016 to 0.519; $p=0.03$) in the LDUP only. Similarly, a significant differential relationship between SC and QOL at 12-months between groups was found with only the LDUP having a positive relationship (95% CI: 0.003 to 0.944, $p=0.04$). SC correlated with negative symptoms in both groups at baseline (SDUP $r = -.275$; $p=0.003$; LDUP $r = -.238$ $p=0.011$). Only in the LDUP social cognition correlated with negative symptoms at 12-months ($r = -.211$; $p=0.038$).

Discussion: Despite that groups did not differ in SC at baseline, it predicted SF at 12months only in the LDUP. Similarly, higher SC was related with lower negative symptoms at baseline in both groups, but only related at 12-months in the LDUP. These results suggest that SC is a protective factor that may buffer from detrimental effects of DUP providing evidence for early intervention in this area in FEP.

S287. TRAUMA-INFORMED PREDICTIVE MODEL OF RECOVERY IN EARLY PSYCHOSIS

Sandra Vieira^{*1}, Philippe Golay², Raoul Jenni³, Giorgio Pistis⁴, Chin B. Eap⁵, Paul Klauser⁶, Luis Alameda⁷

¹*Institute of Psychiatry, Psychology and Neuroscience, King's College London*, ²*Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Switzerland*, ³*Center for Psychiatric Neuroscience, Lausanne University Hospital and University of Lausanne, Switzerland*, ⁴*Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Prilly, Lausanne, Switzerland*, ⁵*Department of Psychiatry, Unit of Pharmacogenetics and Clinical Psychopharmacology, Lausanne University Hospital, Prilly, Switzerland*, ⁶*Center for Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland*, ⁷*Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Switzerland - Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Switzerland*

Background: Treatment resistance affects about a fourth of patients diagnosed with a psychotic disorder. It is now well established that different forms of traumatic experiences including abuse (sexual, physical and emotional) and neglect (physical and emotional) during childhood and/or adolescence are associated with poorer recovery rates, poorer functioning, more pronounced cognitive deficits, more substance use (mainly cannabis), and higher suicide risk. Evidence shows that the effect of trauma is mediated by several psychological and biological mechanisms such as symptom severity, cognition, oxidative stress and genetic risk for psychosis. However, findings from trauma-related studies in psychosis come primarily from traditional group level analyses. This hinders clinical translation as it does not allow to disentangle which patients are more or less likely to improve after treatment. In this study, we used a machine learning approach to develop a trauma-informed predictive model of recovery for patients with first-episode psychosis (FEP) based on a comprehensive assessment of trauma and associated mechanisms.

Methods: 77 FEP patients from the Treatment and Early Intervention in Psychosis Program (TIPP, Lausanne, Switzerland) underwent an extensive assessment of exposure to traumatic life events including: 1) type of trauma (e.g. sexual abuse, physical abuse), 2) time of occurrence in relation to psychosis stage (premorbid, prodrome or after onset), 3) age at the time of first exposure, and 4) number of times exposed. Additional trauma-associated variables were also collected namely symptom severity, neurocognition (MATRICS), peripheral blood markers (oxidative stress) and genetic vulnerability (polygenic risk score for schizophrenia). All variables were used to predict level of socio-occupational functioning 18 months after entering the TIPP programme. Each input feature was scaled independently by removing the mean and scaling to unit variance. Missing values were imputed using k-nearest neighbours and dimensionality was reduced via principal component analysis (PCA). The resulting factors were entered in a regularised logistic regression (elastinet) to predict poor/good functioning (score ≥ 60 on the Global Assessment of Functioning scale). A total of 100 models were trained and tested with cross-validation. The most informative predictors were determined by retrieving the PCA components with the highest regression coefficients and respective items with highest loadings.

Results: At 18 months, 46 and 31 patients had poor and good functioning, respectively. There were no statistically significant differences between the two groups for age, sex and ethnicity. Across all 100 iterations, the model was able to predict good level of functioning at 18 months with 71.3% (6.1) accuracy, 64.5% (6.4) sensitivity and 78.1% (7.6) specificity. The most informative predictors were 1) depressive symptoms and baseline functioning, 2) cognition, 3) psychosis symptoms and mania, followed by 4) trauma (abuse and neglect), ethnicity and migrant status.

Discussion: This study sheds light on the role of trauma in the prediction response to treatment in early psychosis at the individual level. We found that patients of ethnic minorities, migrants and who experienced neglect or abuse are less likely to recover and therefore may need additional and specialised support. We encourage future studies in precision psychiatry to include information about history of trauma.

S288. CAUSAL INFERENCE IN FIRST EPISODE PSYCHOSIS: FINDINGS FROM THE FEP-CAUSAL COLLABORATION

Alejandro Szmulewicz*¹, Miguel Hernan², Dost Ongur³, Gonzalo Martinez-Ales⁴, Maria Ferrara⁵, Celso Arango⁶, Covadonga Díaz-Caneja⁷, Lakshmi Yatham⁸, Diane Fredrikson⁹

¹Harvard School of Public Health, ²Harvard TH Chan School of Public Health, ³Mclean Hospital, ⁴Icahn School of Medicine At Mount Sinai, ⁵Institute of Psychiatry, University of Ferrara, Italy, ⁶Hospital General Universitario Gregorio Marañón, ⁷Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain, ⁸The University of British Columbia, ⁹University of British Columbia

Background: Making informed decisions among several courses of action requires knowledge about their causal effects. Randomized trials are the preferred method to quantify those causal effects. When randomized trials are not available, causal effects are often estimated from sources of observational data. Causal inference from observational data can be viewed as an attempt to emulate a hypothetical randomized trial—the target trial—that would quantify the causal effect of interest. Contrary to popular belief, many well-known failures of observational

studies were the result of not adequately emulating a target trial rather than of limitations of the observational data. This talk describes those methodological failures in non-technical language and present examples that illustrate how observational data can be used to inform clinical and policy decisions when randomized trials do not exist. The example presented here is a target trial emulation on trying to determine the optimal timing of initiation of LAI antipsychotics (i.e., at presentation, after first relapse, or at second or subsequent relapse while on treatment with oral antipsychotics) in First Episode Psychosis, which remains an unanswered clinical question.

Methods: We will use data from the FEP-CAUSAL Collaboration, an international consortium of observational cohorts from USA (McLean OnTrack, STEP-Clinics at Yale and Pittsburgh, NYU Healthcare System, RAISE-ETP), Canada (UBC at Vancouver, PEPP-Montréal), and Spain (AGES-CM) to emulate a target trial of different strategies of initiation of LAI (paliperidone, aripiprazole, risperidone). Eligibility criteria were: age between 18-45, a diagnosis of a psychotic disorder, no prior use of clozapine or LAI agents in the past 6 months, no history of suicidality, and complete data on demographics. The treatment strategies that we compared were: to initiate a LAI agent or to maintain oral antipsychotic treatment at different clinical stages (before first relapse, after first relapse, after second or subsequent relapses). The primary outcome was all-cause psychiatry hospitalization after 3 years of follow-up. We adjusted for the following variables: age, race, sex, housing status, diagnosis, comorbid substance abuse, prior use of antipsychotics (including treatment failures), employment and educational status, and baseline symptomatic (Clinical Global Impression-Severity [CGI-S] score) and functional (Global Assessment of Functioning [GAF] score) statuses. We also included measures of frequency and intensity of substance use.

Results: Of the initial sample of 1420 FEP patients, a total of 803 individuals were eligible for the study. The median age (interquartile range, IQR) was 22 years (21, 27), 72% of individuals were female, 41% were White. Compared with oral users at baseline, LAI initiators had, on average, more markers of severity: higher baseline diagnoses of schizophrenia and substance use disorders, lower proportion of full-time students and workers, and a higher proportion of patients in CGI-S scores of 4-5.

The estimated observational analogue of the intention-to-treat 3-year relapse risk in LAI initiators and non-initiators was 55.1% (47.9, 68.7) and 52.9% (41.4, 58.6), respectively. The corresponding risk difference was 2.2% (-2.8, 7.6). The subgroup analysis revealed that LAI initiation before the first relapse showed no advantage as compared to oral continuation (3-year risk difference: -1.8, 95%CI: -8.1, 2.1). However, we found a strong protective effect for those initiating LAI after the first relapse (3-year risk difference -9.3, 95%CI: -22.9, 0.0).

Discussion: LAI use had no effect in preventing relapses over the study period but showed a small protective effect in preventing hospitalizations (risk difference: -4.1%, 95%CI: -9.5, 1.6). This result was consistent with the findings from the EULAST randomized trial that showed no benefit with the use of LAI in early phase psychosis. We found a strong protective effect of LAI initiation vs. oral maintenance in patients after their first relapse (with a risk difference of around 10%), suggesting that this might be the optimal timing for offering LAI in patients with early psychosis.

Our target trial emulation will pioneer the implementation of causal inference methodology to observational prospective cohorts in FEP. The superiority of this methodological approach has been demonstrated in several areas of medicine but not yet in psychiatry. We expect that our work will result in methodological advancements and case studies that will be generally applicable across many areas of research in mental health.

S289. DIAGNOSTIC TRAJECTORIES IN FIRST EPISODE PSYCHOSIS (FEP): FINDINGS FROM A RETROSPECTIVE STUDY IN THE FEP PROGRAM OF FERRARA, ITALY

Ludovica Vecchioni^{*1}, Maria Ferrara², Giulia Zaffarami², Martino Belvederi Murri², Spyridon Zotos³, Barbara Giroto³, Raffaella Bertelli³, Franca Emanuelli³, Luigi Grassi²

¹*Institute of Psychiatry, University of Ferrara*, ²*Institute of Psychiatry, University of Ferrara*,

³*Integrated Department of Mental Health and Pathological Addictions*,

Background: Diagnostic instability within First Episode Psychosis (FEP) has been the object of several studies over the last decade. Our study describes the evolution of FEP diagnosis over time, and analyzes demographic and clinical predictive factors of diagnostic changes amongst patients who were admitted to an Italian FEP program.

Methods: This retrospective study includes all the individuals admitted to the FEP program in Ferrara, Italy, from its inception (2012) to October 2023, that were diagnosed with an affective or non-affective psychosis or were considered Clinical High Risk for Psychosis (CHR), were not previously treated for psychosis more than two years, and were aged 15 to 35 years old. The FEP program excludes those who had severe intellectual disability, or were diagnosed with organic psychosis. The program guarantees an intensive clinical intervention for up to two-years, led by a multidisciplinary team, formalized within a PDTA. The PDTA has been further strengthened with its inclusion in a research project labeled the “Early Psychosis: Implementation and Care - Ferrara” (EPIC-FE), that has the goal to implement a real-time monitoring of access, process, and outcome indicators, to improve individual treatment.

This study analyzes the evolution of the initial diagnosis from admission to the time of discharge from the program and possible predictive factors, within the information collected at baseline including demographics, education, employment status, substance use, duration of untreated psychosis, referral to the program, and number and length of psychiatric hospitalizations. The severity of illness was evaluated by administering the Health of the Nation Outcomes Scale (HoNOS) at admission and every six months.

Results: Since its inception until October 2023, the FEP program has admitted 200 patients, of whom 11% were diagnosed with CHR and 89% with First Episode Psychosis (of which most had a non-affective psychosis diagnosis). The majority of the sample were male (71%), mean age was 24.2 (DS 5.2), 42% reported cannabis use, 51% had been previously admitted to the inpatient unit. Average HoNOS score at admission was 17.4 (6.8) indicative of a moderate overall clinical severity.

The preliminary analysis of a portion of the sample showed an overall diagnostic instability of 28%. Indeed, within the 120 patients discharged from the program, 10% were referred to a different PDTA (e.g.. Severe Personality Disorders). Moreover, 37.5% completed the two-years program and were discharged to the community mental health service for follow-up visits while 9% were referred to the General Practitioner and 6% to a different city’s mental health service; 18% dropped out from the program.

Further analysis on diagnostic change at the time of discharge is currently being conducted along with investigations on possible demographic and clinical predictors of diagnostic instability.

Discussion: This study, by analyzing the differences in diagnosis at discharge and their predictive factors, will provide useful insights for service planning, such as implementing

scheduled case discussion, promoting the collaboration between the First Episode Psychosis PDTA and other PDTA (e.g Severe Personality Disorders), general psychiatric services and general practitioners, aimed at implementing a tailored approach to therapeutic interventions for patients with FEP.

S290. INTERHEMISPHERIC COMMUNICATION, AUDITORY PERCEPTION AND AVH: THE ROLE OF GLUTAMATERGIC NEUROTRANSMISSION

Christoph Mulert^{*1}, Saskia Steinmann², Moritz Haaf², Gregor Leicht², Stjepan Curic³

¹*Justus-Liebig University*, ²*University Medical Center Hamburg-Eppendorf*, ³*University Medical Center Hamburg*

Background: The interhemispheric miscommunication hypothesis (IMH) of auditory verbal hallucinations (AVH) is based on findings with diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Moreover, recent findings link IMH findings with excitation inhibition (E/I) balance, glutamatergic and GABAergic function and especially the NMDA receptor.

Here, we were interested whether modulation at the NMDA receptor with either antagonist ketamine or the co-agonist glycine has impact on interhemispheric communication, auditory perception and AVH.

Methods: In a double-blind, randomized, placebo-controlled crossover design, 25 healthy volunteers were measured using 64-channel-electroencephalography (EEG) during a dichotic listening task (DL). Psychopathologic changes were assessed by PANSS and the 5D-ASC questionnaire. The current study examined the effects of ketamine, a NMDAR antagonist as well as glycine, a glutamate N-Methyl-D-Aspartate receptor (NMDAR)-coagonist on mechanisms underlying interhemispheric gamma-band connectivity, conscious auditory perception and AVH. Interhemispheric connectivity analysis were performed using eLORETA source estimation and lagged phase synchronization (LPS) in the gamma-band range (30–100 Hz).

Results: Ketamine induced a schizophrenia-like change in laterality of dichotic hearing that could be reversed by glycine-modulation. In addition, interhemispheric gamma-band connectivity was found to be altered both under ketamine and glycine (higher interhemispheric gamma-band connectivity). Pretreatment with glycine normalized the ketamine-induced alterations of interhemispheric connectivity. Moreover, we found a relationship between alterations of auditory perception, interhemispheric communication and the emergence of AVH in healthy subjects.

Discussion: These findings argue for an important role of glutamatergic neurotransmission for the interhemispheric communication between bilateral auditory cortices. NMDAR-modulation could help to restore E/I-imbalance causing disturbed auditory perception in schizophrenia.

S291. RATER DRIFT: REDUCING ERRANT RATINGS AND ANOMALOUS PANSS DATA IN SCHIZOPHRENIA CLINICAL TRIALS

Jenicka Engler^{*1}, Cristian Sirbu¹, Katrina Patrick¹, Cynthia McNamara¹

¹*Cronos, an IQVIA Business*

Background: Rater “drift” is the phenomenon where raters become less reliable and consistent over time which can introduce more variability and error into study data. Despite industry attention to this issue, no solution has been adopted consistently. We examined if rater surveillance and intervention could reduce the number of data inconsistencies observed in schizophrenia trials.

Methods: Four studies with comprehensive PANSS rater surveillance and intervention programs were included for analysis. Two of the studies used a single vendor for rater training and the oversight and intervention program, while the other two studies used a second vendor for rater training. We looked at pre-programmed quality flags (representing significant data anomalies from Risk-Based Data Monitoring (RBDM)) for the first five and the last five PANSS assessments for each rater as a proxy for data quality.

Results: The PANSS raters who received the rater training, oversight, and intervention from the same vendor (N=185) demonstrated a significant reduction in flags over time [$F(1,544) = 5.52, p=.02$], with one of those studies showing a nearly 30% reduction in data flags over the course of the study (M=.489 to .200 flags; Std DevFIRST 5 ASSESSMENTS=.546, Std DevLAST 5 ASSESSMENTS=.316). The other study had a smaller reduction (M=.265 to .214 flags; Std DevFIRST 5 ASSESSMENTS=.371, Std DevLAST 5 ASSESSMENTS=.525). The PANSS raters (N=361) in the two studies who received rater training from a second vendor had comparable flag rates across the studies and maintained the number of data flags over the course of the study (M=.082 to .086 flags; Std DevFIRST 5 ASSESSMENTS=.218, Std DevLAST 5 ASSESSMENTS=.196).

Discussion: Rater oversight and intervention programs may be helpful in preventing rater drift and anomalous PANSS data in schizophrenia clinical trials. Interestingly, the consistency of the vendor used across rater training and oversight and intervention programs may be an important variable that is often not considered in the literature or by sponsors, although it is logical the consistency of instruction used in rater training and in interventions with the raters over the course of the trial would matter. Limitations include future work required to examine any moderating and confounding factors (e.g., study features, rater experience, ongoing access to training materials throughout the study).

S292. RESTING-STATE EEG GAMMA-BAND SOURCE FUNCTIONAL CONNECTIVITY IN CLINICALLY REMITTED SCHIZOPHRENIA PATIENTS WITH SHORT DURATION OF DISEASE TREATED WITH FIRST- AND SECOND-GENERATION ANTIPSYCHOTICS.

Giorgio Di Lorenzo^{*1}, Tommaso B. Jannini², Antonio Carbone³, Chiara D'Amelio⁴, Carmine Gelormini⁴, Diego Cichetti⁴, Cherubino Di Lorenzo⁵, Tommaso Cassano⁶, Stefano Seri⁷

¹Laboratory of Psychophysiology and Cognitive Neuroscience, University of Rome Tor Vergata, ²Laboratory of Psychophysiology and Cognitive Neuroscience, Department of Systems Medicine, University of Rome Tor Vergata, ³Department of Physiology and Pharmacology "V. Erspamer", Sapienza University of Rome, ⁴Laboratory of Psychophysiology and Cognitive Neuroscience, Department of Systems Medicine, University of Rome Tor Vergata, ⁵Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Sapienza University of Rome, ⁶Department of Clinical and Experimental Medicine, University of Foggia, ⁷College of Health and Life, Wellcome Laboratory for MEG Studies, Aston Brain Centre, Aston University

Background: Alterations of synchronization in gamma-band oscillations are implicated in dysconnectivity of cortical networks observed in people affected by schizophrenia. This work aims to investigate to what extent these functional alterations may be influenced by antipsychotic treatment in the first phases of illness course.

Methods: Resting-state EEG gamma-band source functional connectivity was computed using lagged phase synchronization in clinically remitted patients with schizophrenia and a short duration of disease treated with first-generation vs. second-generation antipsychotics (FGA vs. SGA). We implemented network-based statistics (NBS) and graph theory (GT). NBS is a method to detect

functionally interconnected (functionally integrated) nodes (sources) in a graph that cluster into a single component, and which are significantly different between two groups. GT metrics provide quantification of behavior of nodes and paths (connections or edges between nodes).

Results: NBS revealed hyperconnectivity in the gamma band in the frontal regions in FGA compared to SGA. FGA had gamma band hyperconnectivity in the frontal and frontotemporal areas compared with HV. Finally, SGA also showed hyperconnectivity compared to HV but only in the frontal cortices.

Looking at the graph theory indices, FGA had higher mean values in ROI strength than SGA, but this was not significant. FGA showed higher strength values than HV although this did not exceed the significant threshold. Conversely, SGA had significantly higher strength values than HV.

Discussion: The results of the present study demonstrate that antipsychotic treatment with FGA and SGA affects gamma-band oscillation source connectivity differently in schizophrenia and should be considered when approaching interpretations of the connectivity alterations observed in people with schizophrenia in early stages of the disease.

Furthermore, this study was able to confirm that a gamma-band hyperconnectivity, mainly located in the fronto-temporo-parietal regions, is a key feature of people with schizophrenia in the early

years of the disease, and that FGA and SGA seem to influence hyperconnectivity differently in the gamma band.

S293. INCREASED MICROGLIA-MEDIATED PRUNING OF PREFRONTAL SYNAPSES IN A MOUSE MODEL OF HUMAN ENDOGENOUS RETROVIRUS EXPRESSION

Michelle Meier*¹, Felisa Herrero¹, Urs Meyer¹

¹*University of Zurich*

Background: Endogenous retroviruses (ERVs) are remnants of germline infections that took place several million years ago and represent approximately 8% of the human genome. Accumulating evidence implicates increased expression of ERVs in the spectrum of psychotic disorders, including schizophrenia and bipolar disorder. Thus far, however, the link between increased ERV expression and psychotic disorders largely remains circumstantial. To gain more mechanistic insights into the neurobiological disease pathways affected by ERVs, we

recently developed a novel mouse model that mimics the expression of the human-specific ERV type-W envelope protein (HERV-W env). Using this mouse model, we examined whether HERV-W affects microglia-mediated synaptic pruning in the prefrontal cortex (PFC) across early adolescence to adulthood. We also subjected transgenic HERV-W env and wild-type (WT) mice to cognitive testing in adolescence and adulthood with the aim to identify age-dependent cognitive phenotypes in mice expressing HERV-W.

Methods: Mice with transgenic HERV-W env expression were generated by inserting the multiple sclerosis-derived retrovirus (MSRV)-pvl4env sequence, featuring the HERV-W envelope open reading frame (ORF) and 3' long terminal repeat (3'LTR) under the CAG promoter, into the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. Brain samples (n = 6 per genotype and age) were collected at 4, 6 and 10 weeks of age for immunohistochemical colocalization studies using the microglial marker, Iba1, and the presynaptic marker, Bassoon. We quantified the number of Bassoon+ synaptic puncta colocalizing with prefrontal microglia, which were reconstructed and surface-rendered with Imaris software. Cognitive testing was conducted at 5 and 10 weeks of age (n = 10-12 per genotype and age) and included a test for prepulse inhibition (PPI) of the acoustic startle reflex and a novel object recognition test.

Results: Compared to age-matched WT mice, HERV-W env-expressing mice displayed a significant (p LESS THAN 0.05) increase in Bassoon+ synaptic puncta colocalizing with microglia at 6 weeks of age, but not during 4 or 10 weeks of age. At 10 weeks of age, however, HERV-W env-expressing mice demonstrated a significant (p LESS THAN 0.01) overall decrease in the Bassoon immunoreactivity in the PFC. Moreover, HERV-W env-expressing mice displayed age-dependent deficits in PPI and novel object recognition memory, which were manifest at 10 but not 5 weeks of age.

Discussion: Our data provide the first line of preclinical evidence linking the expression of HERV-W to abnormal synaptic pruning in the PFC across adolescent maturation. Furthermore, our results show that HERV-W expression leads to age-dependent deficits in sensorimotor gating and short-term declarative memory for objects. These findings add to the ongoing attempts to identify the neurobiological disease pathways affected by HERV-W in relation to schizophrenia and other psychosis-related disorders.

S294. THETA POWER DIFFERENCES DURING ASSOCIATIVE INFERENCE IN SCHIZOPHRENIA

Ingrid Martin*¹, Daniel Bush¹, Rick Adams¹, Neil Burgess¹

¹UCL

Background: Previous rodent and human studies have implicated the role of dysfunction in the hippocampal-prefrontal (HPC-PFC) network in the underlying pathophysiology of Schizophrenia (SCZ). Recent neuroimaging has shown patients display a loss of prefrontal theta power and PFC-HPC theta coupling (Adams et al, 2020). However, the link between this loss of oscillatory power/coupling and specific (psychotic) symptoms is less clear. We sought to investigate whether a loss of theta power and coupling may underlie associative inference impairments in the disorder and whether this relates to level of delusion symptoms.

Methods: We recruited 25 SCZ patients and 25 controls matched on IQ, years of education, sex, and age. Participants completed an associative inference task whilst undergoing Magnetoencephalography (MEG). During the task participants viewed pairs of images for 8s with each pair drawn from 3-stimuli 'events' comprising a Person, Place, and Object

(Encoding). After a short break, participants then completed a retrieval block. During retrieval each image was presented first individually to test for recognition memory. Then participants were asked to choose from 4 options what image it was most associated with. Importantly images could be directly (seen paired together) or indirectly (not directly viewed together) associated. Participants were then asked to rate their confidence in their choice from 1 (not at all) -3 (very confident).

Results: Hypothesised results based on previous work we will investigate differences in theta power on frontal scalp sensors during the encoding period between patients and controls. Next, we will assess across all participants the relationship between strength of theta power at encoding with associative inference performance. We hypothesise that patients will display a loss of prefrontal theta power which will correlate with poorer performance on the task. We will then look for this same differences/relation to task performance in theta power during retrieval.

Discussion: These results offer insight into the underlying pathophysiology of SCZ, translating findings from prominent rodent work.

S295. THE PARADOXICAL EFFECT OF LONG-USE OF CANNABIS ON COGNITION IN CHRONIC PSYCHOTIC DISORDERS

Fiorela Gorea¹, Martina Pelle^{*2}, Fatime Elezi³, Federico Fiori Nastro⁴, Giorgio Di Lorenzo⁴

¹*“Our Lady of Good Counsel” University of Tirana, Tirana, Albania,* ²*Tor Vergata University of Rome,* ³*University Hospital Center “Mother Teresa” of Tirana,* ⁴*Department of Systems Medicine, University of Rome Tor Vergata, Rome,*

Background: Neurocognitive deficits among patients with psychotic disorders are considered one of the core features of the disorder, relevant to its course and prognosis. The cognitive areas with the highest impairment are verbal skills, memory, attention, speed of processing, and executive functions. Cannabis is one of the most popular recreational drugs used among adolescents and young adults, particularly by youth with psychosis. Although the use of cannabis has been linked to a risk of developing psychotic spectrum symptoms, the effects on the brain and cognition remain controversial.

This study aims to investigate the association between neurocognitive deficits in subjects who suffer from psychosis, with or without cannabis use.

Methods: One-hundred-five patients (mean age, 40.3±11.84; 34 women) with psychotic disorders (n=75, 71.43%) were recruited from the University Hospital Center “Mother Teresa” of Tirana between January 2022 and January 2023. All of them were, at the time, hospitalized and had a history of more than one hospitalization. Fifty-six patients (53.33%) had a comorbid current cannabis use disorder (CUD). Socio-demographic information (such as age, sex, and marital status) and clinical data (such as use of alcohol or cannabis, years with diagnosis, number of hospitalizations, heredity for mental health problems, current therapy, as well as the use of long-acting antipsychotics) were collected. Psychopathological assessment was performed through Brief Negative Symptom Scale (BNSS), Calgary Depression Scale for Schizophrenia (CDSS), Psychotic Symptom Rating Scales (PSYRATS), and Thought Language and Communication Scale (TLC). The cognition was measured with the Montreal Cognitive Assessment (MoCA). Statistical analysis was done using JASP 0.18.3.

Results: Psychotic patients with CUD were significantly more men (p=0.003), younger (p LESS THAN 0.0001), and had earlier onset of psychosis (p=0.003) than those without CUD.

Except for the BNSS “motivation-pleasure” deficit significantly higher in psychotics without CUD than with CUD ($p=0.01$), no psychopathological difference emerged between groups. MoCA scores were significantly higher in psychotic patients with CUD than those without CUD ($p < 0.0001$). After controlling for gender, age, and psychosis onset, the difference was maintained significantly.

Discussion: Several studies have investigated the association between cannabis and cognitive deficits in psychotic disorders, revealing conflicting and paradoxical results.

Firstly, our study underscores that individuals with a history of chronic illness tend to use cannabis. Secondly, among patients with psychosis, subjects with cannabis use showed better performance in MoCA compared with patients without cannabis use.

In conclusion, our study not only contributes to the growing body of knowledge on cannabis and cognition in psychotic disorders but also underscores the importance of considering individual differences and underlying factors that may influence the complex relationship between cannabis use and cognitive outcomes in this vulnerable population to better-target interventions and treatments.

S296. NEURAL SIGNATURES OF HALLUCINATION EMERGENCE IN A CLINICAL HIGH-RISK POPULATION

Raina Vin^{*1}, William Palmer¹, Rashina Seabury¹, Scott W. Woods¹, Tyrone D. Cannon¹, Albert Powers¹

¹*Yale University*

Background: Hallucinations and delusions are prominent positive symptoms of psychosis. Although fully developed forms have been studied with some success, limited research has explored the neural basis of their emergence, development and interactions over time.

Recent research suggests that delusions may arise from overly noisy bottom-up input, causing aberrant prediction-error signaling and inappropriate learning. By contrast, hallucinations have been associated with a dominance of expectations (or priors) in perception, an abnormality that tracks with symptom severity. We hypothesize that these contradictory mechanisms may be causally related in time: top-down dominance of priors may arise to compensate for pre-existing bottom-up noise. New evidence supports this: delusions reliably emerge prior to hallucinations in psychosis. If our hypothesis holds, hallucination onset should coincide with a shift from bottom-up to top-down dominant connectivity between early sensory and higher-order processing regions in individuals with delusional ideation. We present evidence supporting this hypothesis.

Methods: We analyzed resting-state fMRI data from the Clinical High-Risk for Psychosis cohort in the North American Prodrome Longitudinal Study (NAPLS) 3. Our experimental group ($n = 26$) experienced only delusions at baseline, and developed hallucinations at follow-up. The control group ($n = 26$) was matched for time elapsed and change in symptom severity but did not develop hallucinations over that time.

Using the Human Brainnetome atlas, we identified 14 subcortical and cortical regions of interest (ROIs) that have been implicated in psychosis. The ROIs were grouped into three clusters: 1) visual/auditory cortex and thalamus (bottom-up sensory processing); 2) basal ganglia, hippocampus, insula, cingulate cortex, and superior temporal gyrus (integration of

bottom-up and top-down signals); and 3) medial and dorsolateral prefrontal cortex, and the inferior frontal gyrus (higher-order processing). We then analyzed the effective connectivity between these ROIs using regression dynamic causal modeling (rDCM) informed by the Brainnetome structural connectome. The rDCM-derived posterior parameter estimates were contrasted both within-group (across time points) and between groups.

Results: In the experimental group, there was greater bottom-up connectivity from the auditory cortex to the posterior insula and from the posterior thalamus to the basal ganglia at baseline. At follow-up, this relationship switched, with stronger top-down connectivity from the posterior insula to the auditory cortex, as well as from the basal ganglia to the supramarginal gyrus.

The control group did not exhibit large differences in effective connectivity between the time points; both were characterized by strong bottom-up connectivity from the auditory cortex to the insula (and weaker top-down connectivity from higher order regions to the auditory cortex).

Between-group contrasts of connectivity changes over time showed a strengthening of top-down connectivity from the basal ganglia to the auditory cortex and supramarginal gyrus in the experimental group compared to the control group.

Discussion: The present results are consistent with the hypothesis that early delusions are associated with bottom-up signaling, while hallucinations are characterized by top-down prior hyper-precision. We plan to conduct similar analyses to uncover network interactions during the emergence of hallucinations within specific modalities (auditory, visual, etc.), which could subsequently pave the way for novel treatment development and early therapeutic intervention.

S297. UNRAVELING THE PSYCHOSIS PRECIPICE: INFLUENCE OF THE COVID-19 PANDEMIC ON PSYCHOSIS CONVERSION RATES IN AT-RISK INDIVIDUALS

Federico Fiori Nastro^{*1}, Alice Clemente², Eleonora Esposto², Martina Pelle², Lucia Longo², Michele Ribolsi³, Alberto Siracusano², Cinzia Niolu², Giorgio Di Lorenzo²

¹*Tor Vergata University of Rome*, ²*Tor Vergata University of Rome*, ³*Psychiatry Unit, Campus Bio-Medico University*

Background: The COVID-19 pandemic has induced substantial worldwide upheaval, affecting virtually every aspect of human existence. Quarantine measures and social isolation have resulted in adolescents experiencing extended physical separation from their peers and community networks. Furthermore, economic instability and the fear surrounding the virus have led to elevated levels of stress, which promotes widespread psychological effects.

The existing literature presents mixed results on the influence of the pandemic on mental health. Although depression and anxiety seem to have worsened, the findings on schizophrenia and vulnerability to psychosis are contradictory.

This study seeks to examine how the COVID-19 pandemic has affected a group of people at clinical high risk (CHR) of psychosis presenting with Attenuated Psychotic Symptoms (APS). The research aims to analyse the incidence of transition to full-blown psychosis within this population and to investigate the related psychopathological characteristics.

Methods: We longitudinally evaluated a sample of 24 young help-seekers (12 female, 50%; age 21.79, $\pm$ 3.2 SD) with APS for one year to examine the impact of the COVID-19 pandemic

on conversion rates to psychosis. The patients were enrolled in the outpatient services of Policlinico of Tor Vergata.

Prodromal Questionnaire 16 (PQ-16) and Aberrant Salience Inventory (ASI) were administered to all participants. All patients were evaluated using the Structured Interview for Prodromal Syndromes (SIPS).

The inclusion criteria were as follows:

1. mental health help-seeking request;
2. age 16 - 30 years;
3. absence of any psychosis spectrum disorder diagnosed by the Structured Clinical Interview for DSM-5 (SCID);
4. no past or current substance dependence as defined in the DSM-5 criteria;
5. APS condition, as defined by the Scale of Prodromal Symptoms (SOPS) criteria.

Patients who did not meet the psychometric criteria for a diagnosis of a current psychotic episode but had already received treatment or were undergoing treatment with an antipsychotic were subsequently excluded from the data analysis and considered to have already converted to psychosis.

Results: After the one-year follow-up, a conversion rate to full psychosis was observed at 29.17%. Student's t-test and chi-square tests were used to investigate possible variations based on age, gender, cannabis use, and urbanicity in relation to the transition to full psychosis. However, none of the findings resulted in statistically significant differences.

Discussion: The impact of the COVID-19 pandemic and subsequent quarantine measures on psychosis is still debated. In our study, we observed a higher one-year transition rate to full psychosis among CHR patients compared to before the pandemic times. Although a small sample size represents a primary limitation of our study, this finding suggests several potential explanations. Throughout the two-year pandemic period, Italy underwent stringent phases of lockdown and social distancing, which could have contributed to increased distress and potentially served as adverse prognostic factors for the transition to psychosis. Additionally, longitudinal studies are required to expand the sample size and evaluate the true impact of the COVID-19 pandemic on the transition to psychosis.

S298. DESIGN POSTER: CHALLENGE-YOUNG-PILOT: A FEASIBILITY STUDY OF VIRTUAL-REALITY ASSISTED THERAPY FOR AUDITORY HALLUCINATIONS IN YOUTH WITH PSYCHOTIC DISORDERS

Ditte Lammers Vernal*¹, Lisbeth Joergensen², Marlene Briciet Lauritsen³, Ulla Schierup Nielsen³

¹Psychiatry, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, ²Privat Practice Psychologist, ³Research Unit for Child and Adolescent Psychiatry, Aalborg University Hospital

Background: Virtual Reality-assisted Therapy (VRT) has demonstrated efficacy in treating various mental disorders. In recent years, VRT for psychotic disorders, particularly targeting paranoia and auditory hallucinations, have shown promise.

The Danish randomized controlled trial, Challenge, inspired by the UK-Avatar Trial, commenced in 2020 and concluded recruitment in the summer of 2023. The Challenge trial focused on the treatment of auditory verbal hallucinations with VRT, using software developed by Heka VR. Although trial results are still pending, positive clinical experiences have inspired further exploration of this intervention in children and adolescents with psychotic disorders. To date, VRT studies targeting children and adolescents remain an under-researched area, especially with regards to psychotic disorders. The Challenge-YOUNG-Pilot (feasibility) study is a first steppingstone, providing valuable insights and contributing to the foundation for future research in this field.

Methods: Challenge-YOUNG-Pilot, a feasibility study, draws on the technology, insights, and experiences from the adult Challenge-trial. Twelve children and adolescents diagnosed with schizophrenia spectrum disorders from the Child and Adolescent Outpatient Clinic at Aalborg University Hospital will be recruited. All participants will receive VRT consisting of 7 sessions, using the same equipment and overall techniques as in the adult trial. To cater to the younger age group, changes were made to the assessment battery, including shortening it, and adapting scales and interviews. The revised therapy manual incorporates techniques known to foster agency and engagement in children and adolescents. Baseline and follow-up interviews, along with post-therapy qualitative interviews, will assess acceptability, adaptation needs, barriers, and engagement.

Results: Currently, the study is poised to begin recruitment but awaits approval from the Ethics Medical Committees.

The Challenge-YOUNG-Pilot results will inform the design of a large national randomized controlled trial involving approximately 250 patients, considering acceptability, adaptability, sample size justification, and barriers and enhancers of recruitment and implementation in a child and adolescent outpatient setting.

Discussion: The risk-benefit ratio for antipsychotic medication is generally less favorable for children and adolescents compared to adults, with more side-effects and reduced effectiveness. Moreover, studies indicate a worse prognosis in patients with early onset, underscoring the urgent need for evidence-based non-pharmacological interventions for this target group. While VRT is still in its infancy for treating mental disorders, studies thus far are promising, reflecting a positive outlook on integrating VR technology into psychiatry. For children and adolescents, the potential benefits may be even greater, given their expected familiarity and receptiveness to new technology. Evidence-based interventions targeting auditory hallucinations in the early course of a psychotic disorder could potentially reduce the risk of chronicity and mitigate the negative effects of the hallucinations on self-esteem and agency.

S299. ANTHROPOMETRIC AND PHYSIOLOGICAL MEASURES IN INDIVIDUALS WITH AT-RISK MENTAL STATE COMPARED WITH INDIVIDUALS WITH SCHIZOPHRENIA: FINDINGS FROM A LOWER MIDDLE-INCOME COUNTRY

Muhammad Husain^{*1}, Inti Qurashi², Nusrat Husain², George Foussias¹, Imran Chaudhry³

¹University of Toronto, ²Institute of Population and Mental Health, University of Liverpool, ³Department of Psychiatry, Ziauddin University

Background: Individuals with psychosis have reduced life expectancy and this is largely driven by cardiometabolic disease. Cardiometabolic risk increases with age and duration of psychotic illness. Anthropometric and physiologic abnormalities have been identified among individuals with at-risk mental state (ARMS) for psychosis. The prevalence of cardiometabolic disease is disproportionately higher in lower middle-income countries (LMIC); however, literature on cardiometabolic disease in individuals with psychosis spectrum disorders in LMIC is scarce.

Methods: This is a cross-sectional secondary analysis of data from two large randomised controlled trials that recruited individuals with ARMS (n=326) and schizophrenia (SCZ; n=303) from inpatient and outpatient settings in Pakistan. All participants completed anthropometric and physiological assessments.

Results: There was a statistically significant difference in BMI between groups, 21.42 (SD=4.11) in ARMS and 23.31 (SD=5.41) in the SCZ group (p=0.001). Although mean values were within the normal range, 17.8% (n=58) of ARMS individuals and 33.1% (n= 100) SCZ individuals were overweight or obese. Waist circumference was 32.75in (SD=3.13) in the ARMS group and 32.16in (SD=5.18) in SCZ. Although waist circumference was higher in ARMS, this was not statistically or clinically significant. The pulse rate and blood pressure in both groups were within normal range.

Discussion: We found evidence of abnormal anthropometric and physiological parameters that would indicate that individuals with psychotic-spectrum disorders in Pakistan are at an elevated cardiometabolic risk.

S300. PREDICTING DROPOUT IN CLINICAL HIGH-RISK FOR PSYCHOSIS STUDIES: ASSOCIATION WITH RISK OF DEVELOPING PSYCHOSIS AND PERCENT OF MISSING DATA AT BASELINE

Nora Penzel^{*1}, Daniel H. Mathalon², Robert J. Glynn³, Mark Vangel¹, Anastasia Haidar³, Pablo Polosecki⁴, Johanna Seitz-Holland³, Grace R. Jacobs³, Eduardo Castro⁴, Kang Ik Kevin Cho³, Sylvain Bouix⁵, Cheryl M. Corcoran⁶, Tina Kapur³, René Kahn⁶, Martha E. Shenton³, Guillermo A. Cecchi⁴, Ofer Pasternak³

¹Massachusetts General Hospital, Harvard Medical School, ²Department of Psychiatry, University of California, San Francisco, San Francisco, United States and Psychiatry Service, ³Brigham and Women's Hospital, Harvard Medical School, ⁴IBM, Thomas J. Watson Research Center, ⁵École de technologie supérieure, ⁶Icahn School of Medicine At Mount Sinai

Background: High dropout rates in clinical high-risk for psychosis (CHR) studies pose a challenge for research and treatment. Bias may be introduced when dropout rates are linked to the clinical outcome of interest (e.g., conversion to psychosis), leading to non-representative sample populations. Therefore, evaluating whether dropout occurs at random or is linked with an outcome of interest is important for statistical modeling approaches. Identifying predictors of dropout would also be useful for sample selection for future studies/clinical trials. Here, we test whether variables predictive of conversion to psychosis are also predictive of time to

dropout. We also test whether the percent of missing data across different domains at baseline predicts time to dropout.

Methods: We analyzed 698 CHR participants from the North American Psychosis Longitudinal Study - wave 3 (NAPLS 3). Individuals were divided into three groups: 1) 229 Dropouts: defined as dropping out of the study within one year of participation, 2) 414 Remainers: defined as remaining in the study for 1 year or more, and 3) 55 Converters: defined as those who develop psychosis within 1 year. Three independent multivariable cox regressions determined whether 1) the eight variables included in the psychosis risk predictor developed in NAPLS 2 predict time to conversion 2) the same variables predict time to dropout and 3) the percent of missing data from five different domains (4 modalities of magnetic resonance imaging [MRI], electroencephalography [EEG], cortisol measurement, cognition and interview-based variables) measured at baseline predict time to dropout.

Results: The model including the 8 psychosis risk factors did significantly predict time to conversion (Wald test=33.36, $p < .001$) but did not predict time to dropout (Wald test=12.64, $p = .100$). The model including information about percent of missing variables at baseline significantly predicted time to dropout (Wald test=59.32, $p < .001$). Higher percent of missing imaging modalities of MRI (hazard ratio=2.02, 95% confidence interval=1.50-2.72, $p < .001$) and non-participation in the EEG-domain were significantly associated with time to dropout (hazard ratio=2.38 $p < .001$, 95% confidence interval=1.62-3.48, $p < .001$).

Discussion: This study assessed whether variables associated with the development of psychosis or percent of missing variables at baseline can predict time to dropout in CHR individuals. While prediction based on variables associated with psychosis risk was not significant in predicting the time to dropout, percent of missing variables at baseline significantly predicted time to dropout. Our findings suggest that dropout might not be linked with the risk of conversion to psychosis, which is the primary clinical outcome of many CHR studies. Further, our study finds that participants who do not participate in all domains at baseline are also more likely to dropout. Future studies are encouraged to identify participants with missing assessments to apply strategies to keep these subjects in the study. However, it remains to be tested whether this pattern generalizes to other CHR studies.

S301. AUTISM DEVELOPMENTAL VULNERABILITY TO UNUSUAL EXPERIENCES AS A RESPONSE TO STRESSFUL EVENTS: THE ADVERSE STUDY

Riccardo Bortoletto^{*1}, Marco Garzitto¹, Marco Lamberti², Lorenzo Bassani², Donatella Arcangeli², Carla Comacchio¹, Matteo Balestrieri¹, Marco Colizzi¹

¹*Unit of Psychiatry, Department of Medicine (DMED), University of Udine,* ²*Department of Child and Adolescent Psychiatry, Hospital of Merano (SABES-ASDAA), Teaching Hospital of the Paracelsus Medizinischen Privatuniversität (PMU)*

Background: Accumulating research converges towards the evidence that psychosocial stressors can trigger psychotic episodes among individuals with pre-existing psychosis as well as in otherwise healthy subjects. Interestingly, autistic individuals were found to experience more childhood adversities (CAs) over the course of their lives (e.g., family poverty, sexual abuse, parental illness, parental alcoholism, and parental divorce) compared with neurotypical peers. This study aims at examining the impact of CAs on the occurrence of psychotic episodes

in adolescents with autism spectrum disorder (ASD) in-patiently admitted to a tertiary hospital Child and Adolescent Psychiatry ward.

Methods: Sixty-nine hospitalized ASD adolescents presenting with psychotic/manic symptoms (PSY) and other mental health issues (NPSY) were studied over a nine-year period (from May 2013 to May 2022). ASD diagnoses were based on International Statistical Classification of Diseases and Related Problems (ICD)-10 criteria, and psychotic/manic symptoms were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Sociodemographic and clinical data were retrospectively retrieved from electronic and paper clinical records of all consecutive autistic adolescents in-patiently admitted to the ward. CAs exposure was assessed independently during each admission and coded according to the multi-axial ICD-10 system. Initially, univariate comparisons between groups were performed. Subsequently, a binomial model was employed to explore associations with prior exposure to psychosocial stressors, with results presented in terms of change in Akaike Information Criterion (Δ AIC).

Results: PSY patients had a higher prevalence of exposure to adverse life events (30.43% vs. 6.52%, OR = 6.079 [1.209, 40.926], $p = 0.013$) and school/work difficulties (30.43% vs. 8.70%, OR = 4.478 [0.984, 23.846], $p = 0.034$) compared to NPSY patients. Admissions for psychotic/manic symptoms (PSY-h) were more likely to occur in the context of family disturbances (OR = 2.275 [1.045, 5.045], $p = 0.030$) and adverse life events (OR = 3.489 [1.194, 11.161], $p = 0.014$). The fitted binomial model was significant compared to the random effects model (Δ AIC = -1.962; $\chi^2_{10} = 21.96$, $p = 0.015$) and highlighted the significant impact of family disturbances ($z = +4.118$) and school/work difficulties ($z = +2.455$) on the risk of psychotic/manic symptoms in ASD adolescents.

Discussion: These findings underscore the importance of addressing psychosocial stressors in clinical and policy interventions for individuals with ASD. This seems of the utmost importance when autistic adolescents have experienced disability and/or psychiatric disturbances within their families and conflicts with peers, as these stressful events could potentially precipitate the developmental path from ASD to psychosis.

S302. THE ABERRANT CORTICAL FOLDING PATTERN: VERTEX-WISE ANALYSIS OF LOCAL GYRIFICATION INDEX USING T1-WEIGHTED MAGNETIC RESONANCE IMAGING

Inkyung Park^{*1}, Minah Kim², Minji Ha³, Dan Stein⁴, Odile van den Heuvel⁵, Paul Thompson⁶, Jun Soo Kwon²

¹Seoul National University College of Natural Sciences, ²Department of Psychiatry, Seoul National University College of Medicine, Department of Brain and Cognitive Sciences, Seoul National University, ³Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, ⁴SAMRC Unit on Risk and Resilience in Mental Disorders, Dept. of Psychiatry and Neuroscience Institute, University of Cape Town, ⁵Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands, ⁶Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California

Background: Schizophrenia and obsessive-compulsive disorder (OCD), both recognized as neurodevelopmental disorders, share numerous phenotypical and clinical characteristics. Indeed, numerous neuroimaging studies have underscored a considerable overlap in the

underlying neurobiological mechanisms of these conditions. However, it remains unclear whether there are common neurodevelopmental risks between the two disorders, underscoring the importance of investigating cortical gyrification in relation to the neurodevelopmental abnormalities shared in both schizophrenia and OCD. Cortical folding is primarily determined during the embryonic and early postnatal developmental period and maintains its pattern relatively stable over the lifespan, serving as a reliable neurobiological marker for early neurodevelopmental deficits. In this study, as part of an integrated series of research, the presence of gyrification abnormalities was examined in the OCD group.

Methods: The local Gyrification Index (LGI) was computed at each vertex to analyze whole-brain gyrification using T1-weighted magnetic resonance imaging in a total of 2611 OCD patients and 2723 HCs, collected from 32 sites (52 datasets) worldwide as part of the ENIGMA Working Group. Whole-brain LGI data were harmonized using ComBat to account for site and scanner effects within a mega-analysis framework. The vertex-wise LGI group comparisons were conducted between the patients with OCD and healthy controls (HCs) using a general linear model implemented in Freesurfer while controlling for age and sex.

Results: Both adult and pediatric patients with OCD exhibited significantly increased gyrification compared to the HCs in bilateral fronto-parietal, temporal, and cingulate regions including caudal middle frontal, precentral, postcentral, lateral orbitofrontal, superior frontal, supramarginal, inferior parietal, middle temporal, as well as posterior cingulate gyri. Furthermore, hypergyrification in the fronto-parietal clusters was significantly correlated with an earlier age of onset in pediatric OCD, even after correction for multiple comparisons.

Discussion: Our findings provided evidence that the early neurodevelopmental abnormalities exist in both adult and pediatric OCD patients. Particularly, hypergyrification observed in those pediatric cases near their illness onset, may serve as a biomarker for neurodevelopmental deficits that are present prior to the onset of the disorder. These findings may also enhance the understanding of the neurodevelopmental origins contributing to the shared etiology of schizophrenia and OCD, aligning with the existing evidence suggesting that both schizophrenia and OCD are neurodevelopmental disorders. This could further help categorize patients with psychiatric disorders into more neurodevelopmentally homogeneous subtypes.

S303. SEMANTIC SIMILARITY USING BERT MODELS AND PANSS CORRELATIONS

Mara Fennema^{*1}, Janna de Boer¹, Marieke van Vugt², Iris Sommer¹

¹University Medical Center Groningen, ²University of Groningen

Background: Natural Language Processing (NLP) techniques are increasingly used in schizophrenia research in an attempt to capture semantic similarity in language. Although these methods have been shown to be successful at separating patients with an (emerging) schizophrenia spectrum disorder from healthy controls, it is still unclear to what extent these measures reflect psychotic symptoms. Therefore, this study aims to analyse the relationship between psychotic symptoms and NLP semantic similarity measures in a large sample of Dutch speaking patients with a schizophrenia spectrum disorder.

Methods: Our data sample consists of speech recordings by 161 patients with a schizophrenia spectrum disorder. All participants took part in a 5-10 min semi-structured interview on neutral topics while their speech was recorded. Our sample consisted of 161 patients, all of whom diagnosed with schizophrenia spectrum disorder. Speech samples were cut at 120 seconds for analyses. Whisper was used for automated transcription. Vector representations per sentence

in each recording were calculated using a Dutch language sentence-based BERT model. The cosine similarity score was calculated between each sentence's vector representation and every other sentence in the transcription. The mean similarity score, the variance within the similarity scores and the minimum and maximum score present per transcription were then calculated. Associations between PANSS and semantic similarity measures were assessed using Spearman's correlation, and corrected for multiple comparisons with a False Discovery Rate.

Results: Of these 161 patients, 115 were cis-male and 46 were cis-female, and 1 patient was trans-male, with an average age of 31.2 (STD=11.7). The mean PANSS Total Score was 41.1 (STD 11.6). The total Negative subscore of the PANSS was significantly associated with the maximum similarity ($R=0.26$, adjusted $p=0.01$). Follow-up testing showed that N1, Blunted Effect, was also significantly associated with the maximum similarity ($R=0.20$, adjusted $p=0.04$), as were N3, Poor Rapport, ($R=0.19$, adjusted $p=0.02$) and N6, Lack of Spontaneity, ($R=0.30$, adjusted $p=0.0006$). None of the other tests resulted in a statistically significant correlation after correction for multiple comparisons.

Discussion: This study shows that negative psychotic symptoms are associated with the maximum cosine similarity. This implies that patients with more severe negative psychotic symptoms could be more likely to use multiple sentences to convey very similar information. Additionally, a significant positive association between the maximum similarity score and Blunted Effect, Poor Rapport and Lack of Spontaneity were found. This suggests that sentences spoken by patients that scored high on these PANSS subscores were more semantically similar than those of patients who scored lower on these PANSS subscores. Further research is needed to explore more in depth the correlation between semantic similarity in speech and psychosis symptoms.

S304. DETECTING PUTATIVE PSYCHOSIS-RISK SYMPTOMS WITH THE YOUTH EXPERIENCES AND HEALTH (YEAH) QUESTIONNAIRE

Sebastian Therman*¹, Majja Lindgren¹, Tommi Tolmunen²

¹*Finnish Institute for Health and Welfare*, ²*North Savo Welfare District*

Background: Two-stage screening with questionnaires and structured interviews has been proposed as a solution to make psychosis risk screening more effective, but current dedicated questionnaires have low accuracy, especially among adolescents.

Methods: Based on a literature review, a new 39-item Youth Experiences and Health (YEAH) questionnaire was constructed by combining individual questionnaire items proven to either predict psychosis prospectively or to be strongly associated with concurrent psychosis risk status assessed with gold-standard interviews. A seven-point frequency response scale with specific anchors (daily, weekly, etc.) was chosen to maximize measurement precision. The YEAH was filled in by 752 patients (ages 13–18) entering adolescent outpatient care and analyzed with exploratory categorical factor analysis using the WLSMV estimator and oblique Varimax rotation. Rank order correlations between factor scores and results from various established mental health self-report scales were investigated.

Results: The response category “Continuously” was very infrequently used and was therefore combined with the next category “Several times per day” in the analyses. A four-factor model had good fit (CFI .97, RMSEA .04, SRMR .03), few cross-loadings, and was clearly interpretable as consisting of Delusions, Hallucinations, Negative Symptoms, and Dissociation, with approximately equal numbers of items.

Delusions were most strongly correlated with self-reported depression (.58), mental well-being (-.50), social phobia (.47), anxiety (.47), loneliness (.40), childhood adversity (.39), internet dependency (.34), insomnia (.34), and school bullying (.33). Hallucinations were mainly associated with anxiety (.27). Negative Symptoms were most strongly correlated with depression (.66), mental well-being (-.57), insomnia (.46), anxiety (.47), social phobia (.40), resilience (-.40), and loneliness (.36). Dissociation was associated with depression (.39), loneliness (.38), mental well-being (-.35), anxiety (.34), internet dependency (.29), and childhood adversity (.27).

Discussion: The novel YEAH questionnaire was informative and well-received in adolescent psychiatric care, a setting where screening for psychotic-like and putative psychosis-risk symptoms may improve detection and help direct interviewing resources. The meaningful differential correlations with other measures supported the interpretation of the factors. The cohort will be followed in comprehensive registers to assess diagnostic test accuracy.

S305. REDUCED OFFLINE MEMORY CONSOLIDATION DURING BRIEF REST PERIODS IN SCHIZOPHRENIA

Dimitrios Mylonas¹, Bailey Driscoll¹, Martin Sjogard¹, Bryan Baxter¹, Robert Stickgold², Dara Manoach*¹

¹*Massachusetts General Hospital*, ²*Harvard Medical School, Beth Israel Deaconess Medical Center*

Background: Research on the role of the hippocampus in memory has generally focused on active learning. But to understand memory, it is at least as important to study learning that happens offline, during both wake and sleep. During active learning, hippocampal firing represents ongoing experience. During the wakeful rest and sleep that follows, the hippocampus replays this pattern of firing during sharp wave ripples, which predict memory improvement. Schizophrenia is characterized by hippocampal abnormalities, including a selective loss of inhibitory interneurons that modulate ripple generation. Abnormal ripples may give rise to the impairments of sleep-dependent memory consolidation seen in schizophrenia. Here we tested the hypothesis that a disruption of ripple-related memory replay also gives rise to impairments in offline learning during wake.

Methods: We used the finger tapping Motor Sequence Task (MST) to probe motor procedural memory. Even though a functional hippocampus is not necessary to learn the MST during training, it is necessary for its offline consolidation during both sleep (Schapiro et al., 2019) and wake (Mylonas et al., 2024). People with schizophrenia (PWS) show intact total learning during MST training but fail to show significant sleep-dependent consolidation (Manoach et al., 2004). To look for a corresponding deficit of offline learning during wake, we divided total learning during training, measured as gains in typing speed, into its Online (during task execution) and Offline (across interleaved 30 s breaks) components.

Results: As expected, PWS (n=41, age 34+/-8, 32M) and demographically matched controls (n=44, age 32+/-7, 33M) did not differ in total MST learning ($F(1,81)=0.50$, $p=.50$), but differed in the pattern of performance improvement (Group X Condition: $F(1,164)=6.54$, $p=.01$). Both groups improved primarily offline, across the rest breaks, but PWS showed reduced offline improvement and higher online gains than controls.

Discussion: Despite intact overall learning of a motor task during training, PWS learned differently than their healthy peers. They show reduced offline learning during wake, which together with their deficit in sleep-dependent memory consolidation, is consistent with the hypothesis of a disruption of hippocampal ripple-related memory replay. Further support for this hypothesis comes from magnetoencephalography findings of reduced memory replay in the context of increased hippocampal ripple power in PWS and a mouse model of schizophrenia that shows increased ripples accompanied by a breakdown of memory replay during awake rest periods. This study adds to the literature showing reduced sleep-dependent memory in schizophrenia by establishing a corollary deficit in offline learning during wake. Deficits in both types of offline learning implicate the hippocampus and can serve as outcome measures in clinical trials of interventions to improve memory in schizophrenia.

S306. EXPLORING THE IMPACT OF ONLINE YOGA ON OUTCOME AND NEGATIVE SYMPTOMS IN PEOPLE WITH PSYCHOSIS

Michael Bodnar*¹

¹*The Royal's IMHR*

Background: Psychosis impacts ~3% of Canadians at any one time. The gold standard for care includes antipsychotics along with therapeutic support. In an ever-changing world, E-mental health, composed of therapy via secure online platforms, web-based self-management and internet forums, is now an option providing support and improving mental health care via increase accessibility. But with these advances, the negative symptoms still remain an unmet need for care. Yoga is a complementary and alternative medicine (CAM) encompassing health modalities of Eastern cultures that involves breathing techniques, relaxation, and bodily postures. Yoga has been found to improve levels of depression and quality of life, and even attenuate negative symptoms. Given the extensive health care expenditures and unmet care needs for negative symptoms, there is a growing need to consider CAMs, such as yoga, and accessibility of CAMs via online methods.

Methods: This pilot study explored the effect of an 8-week (i.e., 8 session) online yoga and mindfulness program on outcome, with a focus on negative symptoms, in people with psychosis. We recruited 10 people with psychosis (yoga=4) and 12 non-clinical people (yoga=6), randomly assigned to each group. Mindfulness is yoga without the physical aspect (i.e., poses). We hypothesized that people in the yoga group would show lower total scores on the CORE10 and people with psychosis would show an attenuation of symptom severity, with a larger effect on negative symptoms. Behavioural data for the CORE10, PANSS-8, and SNS (self-report negative symptom scale) were collected at Baseline, Week 4, and at Week 8; an instructor was present for 4 of the 8 sessions. All sessions were pre-recorded and accessible to the participants at any time.

Results: People with psychosis showed a strong response to the 8-week program as indicated by a large decrease in the CORE10 (Baseline=15.7 vs. Week8=9.8) and PANSS-8 (Baseline=21.6 vs. Week8=15.8). Of note, those in the yoga group showed a significant decrease in the CORE10 (Baseline=15.0 vs. Week8=6.5), SNS (Baseline=20.5 vs. Week8=14.0), and PANSS-8 (Baseline=19.0 vs. Week8=13.0); the mindfulness group did not show the same decrease. Of note, this study was hampered by low recruitment and high drop-out.

Discussion: Online-yoga may prove to be a highly accessible and cost-effective modality for care, with an added benefit for improving negative symptoms. It may prove to be a critical care

option for both mental health care providers and for those with psychosis who cannot readily access care and for those with predominant negative symptoms.

S307. SEXUAL ORIENTATION AND ILLNESS EXPRESSION IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS

Hilmar Luckhoff¹, Anna Margaretha Smit¹, Elisabetta C. del Re², Sanja Kilian¹, Lebogang Phahladira¹, Robin Emsley¹, Laila Asmal*¹

¹*University of Stellenbosch*, ²*Harvard Medical School, Veterans Affairs Boston Healthcare System, Brockton Division and Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School*

Background: Sexual minorities with schizophrenia face discrimination at the intersection of both marginalised identities. Sexual minorities are also at increased risk of psychosis which may be linked to childhood trauma, social adversities and substance use. Sexual orientation might also influence the clinical expression and severity of schizophrenia. No studies have comprehensively examined the association between sexual orientation, and illness expression in people with first episode schizophrenia (FES). Our aim was to examine the associations of sexual orientation with neurodevelopmental compromise and illness presentation in patients with FES compared to matched controls Hypothesis: Higher orientation as lesbian, gay, or bisexual is associated with more severe illness in patients with FES.

Methods: Our sample comprised 77 patients (56 males, 21 females) with FES compared to 64 matched controls. Self-reported sexual attraction and self-identified sexual orientation were measured using the Sexual Orientation and Identity Scale (SOIS). Neurodevelopmental risk markers of interest were schizophrenia family history, obstetric complications, childhood trauma, premorbid functioning, cognition, neurological soft signs, and cannabis use. Clinical measures of interest were psychopathology, depression, insight, functioning, and quality of life. Sexual orientation profiles were compared between cases and controls. Stepwise linear regression models were used to determine predictors of sexual orientation in patients.

Results: FES patients and controls were balanced for age, sex, ethnic background, and cannabis use Sexual orientation profiles were similar in FES patients compared to controls. Higher self-identified LGB orientation was associated with emotional neglect during childhood ($p=0.016$), poorer premorbid functioning during late adolescence (0.010), poorer insight into the need for treatment ($p=0.015$), and worse quality of life ($p=0.012$) Lower self-identified heterosexual orientation was associated with more severe experiential negative symptoms ($p=0.024$) and sensory integration deficits ($p=0.02$)

Discussion: Self-identified sexual orientation may influence illness expression in FES. In sexual minorities with schizophrenia, emotional neglect during childhood may contribute to poor premorbid functioning during adolescence, potentially increasing the risk for substance abuse and more severe psychopathology. Our finding of an association between lower heterosexual orientation and more severe symptoms is consistent with the theory that sexual orientation can become “less defined” in acute schizophrenia. We also propose that patients with more pronounced negative psychopathology and sensory integration deficits have diminished capacities for the self-attribution and expression of their sexuality, as part of a deficit-type presentation. Limitations include a cross-sectional design and the use of a single instrument to measure sexual orientation. Further prospective studies are needed to examine

biological and behavioural factors from childhood through adulthood to observe how these are related to the development of schizophrenia in sexual minorities.

S308. THE EXISTENCE OF A GRADIENT FOR ABERRANT SALIENCE IN SCHIZOPHRENIA

Yinan Li^{*1}, Oishi Naoya¹, Qi Dai¹, Yukako Nakagami¹, Yuko Nakamura², Shinsuke Koike², Toshiya Murai¹, Jun Miyata³

¹Kyoto University, ²University of Tokyo Institute for Diversity and Adaptation of Human Mind (UTIDAHM), ³Aichi Medical University

Background: Schizophrenia spectrum disorder, a prevalent psychiatric condition, is characterized by positive symptoms, such as hallucinations and delusions. Studies in non-human primates have demonstrated a salience gradient in the midbrain-striatum circuitry, shedding light on the role of these altered circuits and their potential contribution to the development of hallucinations or delusions. However, the precise relationship between aberrant salience and the development of delusions and/or hallucinations remains unclear, as no clear salience gradient has been identified in the human midbrain-striatum.

Methods: To address this, we conducted a study using resting-state functional magnetic resonance imaging (rsfMRI) on 124 patients with schizophrenia (SCZ) and 239 healthy controls (HC). We extracted the mean time series data from six striatal subregions and calculated their voxel-based correlations within a mask consisting of the ventral tegmental area (VTA) and substantia nigra (SN). Permutation-based non-parametric inference was performed using PALM in FSL. One-sample t-test, Group comparison, and correlation with the Aberrant Salience Inventory (ASI) were performed. Additionally, we also examined the interaction between the diagnosis and 3 factors of the ASI in the functional connectivity of midbrain-striatum circuit.

Results: Our results revealed a significant positive correlation ($p=0.03$, family-wise error [FWE] corrected) between the left ventral striatum and the ventral midbrain in terms of functional connectivity across the entire group. SCZ showed reduced connectivity between the ventral striatum and the ventromedial part of the VTA-SN mask, and increased connectivity between the right caudal striatum and the dorsolateral part of the VTA-SN, compared to HC ($p=0.02$ and $p=0.04$, FWE adjusted, respectively). While ASI scores varied significantly between groups ($p=0.04$, Welch's T-test), no potential association was found between these scores and midbrain-striatum connectivity in patients. However, an interaction was observed between diagnosis and Factor 3 (Sharpening of Senses) scores of the ASI in relation to connectivity between the midbrain and the left caudal striatum ($p=0.04$, FWE adjusted).

Discussion: These findings underscore a pattern of functional dysconnectivity within the midbrain-striatum circuit, supporting the idea that abnormal connectivity is a key feature of schizophrenia. While the interaction between the diagnosis and Factor 3 (Sharpening of Senses) of the ASI was significantly found in the midbrain-striatum connectivity, the lack of correlation between ASI scores and connectivity challenges assumptions in previous studies about their direct associations. It's crucial to consider factors such as sample size, antipsychotic use, and disease duration. In conclusion, our study elucidates midbrain-striatal dysconnectivity in schizophrenia and highlights the complexity of associations between abnormal salience and the pathophysiology of schizophrenia.

S309. MULTIMODAL NORMATIVE MODELLING IN ANTIPSYCHOTIC MEDIATION-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

Rhea Thukral*¹, Natalie Remiszewski², Jose Maximo³, Adrienne Lahti², Saige Rutherford⁴, Andre Marquand⁴, Nina Kraguljac¹

¹The Ohio State University, ²University of Alabama at Birmingham, ³University of Alabama At Birmingham, ⁴Donders Centre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition and Behavior, Radboud University

Background: Given the known clinical heterogeneity in psychosis spectrum disorders, it has become increasingly important to map these individual differences to establish a better understanding of psychosis spectrum disorders. To this end, normative modeling ('brain growth charting'), a novel analytical technique, has been established to understand variations in brain structure and function at the individual level (Rutherford et al., 2022). This method allows us to characterize the extent of the individual-level heterogeneity present in patients with psychosis.

Most research on the structural and functional distinctions among people with psychosis have been done, primarily, independently. However, if we are to understand psychosis on a more comprehensive basis, it is important to understand structural and functional abnormalities in context of each other.

Methods: We analyzed structural data from 114 antipsychotic, medication-naïve first-episode psychosis patients and 113 matched controls and resting-state functional connectivity data from 117 patients and 125 matched controls. Cortical thickness and functional network connectivity were assessed for each patient using the Destrieux and Yeo-17 parcellations, respectively. The PCN toolkit was used as a normative reference model to determine the number of deviations (± 2 standard deviations) in patients for cortical thickness and functional connectivity. Positive and negative deviations were determined for both modalities using a z-score threshold of +2 and -2, respectively. Patients were then sorted into one of 4 groups (no significant deviations, primarily positive, primarily negative, and a mix) using a false discovery rate significance threshold of 0.05.

Patients included in both analyses were then combined to compare the deviation loads between imaging modalities resulting in a total of 108 patients included in this analysis.

Results: χ^2 analysis was conducted on the combined groups ($p = 0.038$). Overall 23 out of the 108 patients included remained within the same group across modalities. A correlation was found between the three deviation load ratings across modalities when the patients who changed groups were separated from the patients who remained in the same group. In the group of patients who changed groups, the absolute, positive, and negative deviation loads across modalities were all found to be negatively correlated after Benajmini-Hochberg corrections (Absolute: $r = 0.22$, $p = 0.04$; Positive: $r = -0.28$, $p = 0.01$; Negative: $r = -0.28$, $p = 0.01$). Furthermore, the patients who stayed in the same group were also found to have significant correlations between the modalities and their deviation loads (Absolute: $r = 0.56$, $p < 0.01$; Positive: $r = 0.49$, $p = 0.02$; Negative: $r = 0.42$, $p = 0.04$).

Discussion: This data suggests that a significant degree of individual-level heterogeneity is present across modalities, and that there is a relationship between structural and functional pathology in patients suffering from a psychosis spectrum disorder.

These findings suggest that normative modeling is a promising method to relate different imaging modalities and create a holistic patient profile. This holds great promise for precision psychiatry, where inferences are made at the individual level.

S310. ELUCIDATING THE POTENTIAL ROLE OF OBSTETRIC COMPLICATIONS ON PSYCHOPATHOLOGY IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Gisela Mezquida*¹, M Florencia Forte², Michele De Prisco³, Vincenzo Oliva³, Byron Bitanhirwe⁴, Marina Garriga⁵, Sergi Mas⁶, Patricia Gassó⁷, Eduard Parellada⁸, Miguel Bernardo⁹, Eduard Vieta¹⁰, Silvia Amoretti¹¹, Clemente Garcia-Rizo¹²

¹Department of Clinical Foundations, University of Barcelona, ²Bipolar and Depressive Disorders Unit; Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Institute of Neurosciences, August Pi I Sunyer Biomedical Research Institute (IDIBAPS); University of Barcelona, ³Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Institute of Neurosciences (UBNeuro); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, ⁴Centre for Global Health, Trinity College, Department of Psychology, Trinity College, Dublin; School of Medicine, Trinity College, ⁵Bipolar and Depressive Disorders Unit. Institute Neuroscience. Hospital Clinic Barcelona, ⁶Department of Basic Clinical Practice, University of Barcelona, IDIBAPS, CIBERSAM, ⁷Department of Clinical Foundations, Pharmacology Unit, University of Barcelona, ⁸Child and Adolescent Psychiatry and Psychology Department; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), ⁹Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. University of Barcelona. CIBERSAM, IDIBAPS, ¹⁰Barcelona Clinic Schizophrenia Unit (BCSU). Hospital Clinic Barcelona. Universitat Barcelona. IDIBAPS. CIBERSAM.; UBNeuro, Institut de Neurociències de la UB, ¹¹Bipolar Disorder Program, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, ¹²Department of Psychiatry, Hospital Universitari Vall d'Hebron, Group of Psychiatry, Mental Health and Addictions, Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), ¹²Barcelona Clinic Schizophrenia Unit (BCSU). Neurosciences Institute. Hospital Clinic of Barcelona. CIBERSAM, IDIBAPS

Background: Schizophrenia (SZ) is a complex and systemic brain disorder characterized by a myriad of symptomatology, such as positive, negative and cognitive, associated with functional and neuro-structural abnormalities. Its aetiology comprehends a gene, epigenetic, plus environment interaction (1,2). Among the latter, obstetric complications (OCs) have been widely considered key contributors to psychosis risk, but how OCs relate to different clinical phenotypes still remains unclear (3,4,5).

Aims: 1) to review and describe the potential association of OCs with clinical symptomatology in SZ patients, and 2) to analyse whether SZ patients with OCs present a specific clinical profile worsening in comparison to those patients without OCs.

Methods: A systematic review and meta-analysis describing clinical psychopathology and OCs in patients with SZ and related disorders were conducted. It was registered on PROSPERO (CRD42022316655). PubMed/MEDLINE, PsychINFO, and Scopus were systematically searched to identify eligible studies up to November 8, 2023.

Meta-analyses were conducted using a random-effect model, using RStudio version 4.1.2. Standardized mean differences (SMD) with their confidence intervals (CI) were used as effect sizes and represented by Hedge's *g*. Homogeneity was assessed using the Q-statistic (χ^2).

Results: A total of 4,088 records were retrieved. After duplicate removal 2,683 studies were screened. Among these, 2,597 were excluded at the title/abstract level and 75 after the full-text evaluation. Finally, 13 studies were included, 12 of them provided enough data to perform a meta-analysis.

SZ patients with positive lifetime history of OCs presented higher total scores at psychotic symptoms scales (SMD=0.44, 95%CI=0.24, 0.64; p -value=1.45e-05) when compared to patients without history of OCs. When looking at different subscales, the first showed higher scores at positive (SMD=0.10, 95%CI=0.01, 0.20; p -value=0.03) and general (SMD=0.37, 95%CI=0.22, 0.52; p -value=1.29e-06) symptoms scales. No differences were found between the two groups in terms of negative symptoms scales (SMD=0.19, 95%CI=-0.01, 0.38; p -value=0.05). SZ patients with OCs also presented worse depressive symptoms (SMD=0.47, 95%CI=0.09, 0.84; p -value=0.01). No differences were found between the two groups in terms of functioning (SMD=-0.01, 95%CI=-0.35, 0.34; p -value=0.95).

Discussion: OCs appear to have an impact on specific clinical profiles in SZ patients. Specifically, in comparison to patients without OCs, those with OCs presented greater severity in positive, depressive, and general symptomatology, but not in the negative and functional outcomes. Our findings suggest the sociosanitary need to detect OCs in SZ samples and in early stages of the illness, such as first-episode psychoses.

Future studies should have into consideration the timing and type of the obstetric complication during the perinatal period in order to better understand its potential impact on the clinical presentation in the early stages of schizophrenia. This could help to better understand its association on long-term clinical and functional outcomes, reflecting the need for earlier and personalised interventions.

S311. SEX-SPECIFIC IMPACT OF PERIPUBERTAL STRESSORS ON THE ACTIVITY OF THE THALAMIC RETICULAR AND REUNIENS NUCLEUS IN RATS

Daniela Uliana^{*1}, Anthony Grace¹

¹*University of Pittsburgh Dept. of Neuroscience*

Background: Stress is a socio-environmental risk factor for schizophrenia with the age of exposure potentially determining the outcome. Early life adversity has a significant impact on the development of neuropathological states with males and females having different vulnerability periods. Males rats are sensitive to peripuberty stress (PeriP; postnatal days, PD31-40) and females to postpubertal stress (PostP; PD41-50) in inducing adult hyperdopaminergic state and deficits in cognition. The neurobiological mechanisms contributing to sex-specific stress susceptibility remain understudied. We explore the

involvement of the nucleus reuniens of thalamus (RE) and thalamic reticular nucleus (TRN) in the observed differences, as these regions are linked to dopaminergic activity and cognitive regulation. TRN has extensive expression of parvalbumin (PV) interneurons and their perineuronal nets (PNN) which is implicated in thalamic relay neuron inhibition. Here we investigated the impact of PeriP and PostP stress on adult RE activity, TRN gamma oscillations, and PV/PNN staining.

Methods: Male and female Sprague-Dawley rats were subjected to footshock/restraint stress during PeriP (PD31-40) and PostP (PD41-50). The rats were tested for single-unit extracellular electrophysiology recording of RE neurons 5-6 weeks after stress (PeriP, PD75-82; PostP, PD85-92). Independent groups of animals were subjected or not to stress and recorded in the TRN for local field potentials at PD31, PD41, PD51, and PD75 for PeriP stress and at PD41, PD51, PD61, and PD85 for PostP stress. Low (30-50Hz) and high (60-120Hz) gamma were analyzed. Posterior immunohistochemistry assessed PV/PNN content one week after PostP stress (PD61). All procedures were conducted in compliance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh.

Results: Sex differences were observed with males having more active RE neurons at baseline (PeriP, $F_{1,20}=21.56$, $p < 0.05$; PostP, $F_{1,36}=5.28$, $p < 0.05$; ANOVA). PostP stress increased the number of active RE neurons only in females after 5-6 weeks of stress ($n=6$; Sex-Stress, $F_{1,36}=16.74$, $p < 0.05$, ANOVA) with no effect of PeriP stress on either sex ($n=8-12$). PeriP stress increased low gamma power only in females ($n=5-9$) at PD51 ($F_{1,35}=5.48$, $p < 0.05$, ANOVA) and PostP stress ($n=3-8$) increased low gamma at PD51 (Stress-age interaction, $F_{2,29}=6.10$, $p < 0.05$, ANOVA). High gamma was not changed in females after PeriP and PostP stress. No effect was observed in males for all time points (PeriP, $n=6-7$; PostP, $n=3-7$). For PV/PNN staining, PostP stress decreased the number of PV in the TRN at PD61 only in females ($n=2-9$; sex-stress interaction, $F_{1,16}=7.53$, $p < 0.05$, ANOVA). Females were found to have more PV+ interneurons than males (sex, $F_{1,16}=5.94$, $p < 0.05$, ANOVA).

Discussion: Females exhibit sensitivity to PostP stress, potentially mediated by RE and TRN activity. PostP stress increased the adult RE activity, increased low and high gamma immediately after stress, and decreased PV+ cells one week after stress. Stress affects PV-TRN transmission during PostP stress, leading to impaired PV content and disrupted inhibitory drive to RE, resulting in increased RE activity. TRN gamma oscillations and RE activity were unaffected by PeriP or PostP stress, suggesting that they do not underlie male vulnerability. Therefore, TRN and RE seem to be involved in the sex-dependent neurobiological circuit disruption underlying early-life stress vulnerability, especially in females.

S312. A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE IMPACT OF COMMUNITY-BASED INTERVENTIONS FOR IMPROVING MENTAL HEALTH OUTCOMES IN DEPRIVED NEIGHBOURHOODS

Sheri Oduola*¹, Charlottee Humphreys¹

¹*University of East Anglia*

Background: Residents of deprived areas face inequalities in their mental health and access to treatment. Many of the stressors these residents face often lie outside the remit of mental health services. Health policy in England, UK has highlighted the importance of community engagement to ensure sustainable gains in health at the population level, e.g., community-based

interventions which attempt to situate treatment in a person's social context. Previous reviews examined the impact of community-based interventions on marginalized groups facing similar challenges to deprived area residents. This review considers the impact of community-based interventions on mental health specifically in deprived areas.

Methods: This review included a narrative synthesis of 26 studies and meta-analyses of six eligible studies. A harvest plot approach to narrative synthesis based on the direction of change and not statistical significance was taken as this is suited to combining research with different study designs and outcomes. Two meta-analyses were completed - one on eligible papers with all mental health outcomes and another on interventions using postnatal depression measures.

Results: 7 categories of community-based interventions were identified in this review, with mixed findings found for their impact. Meta-analysis showed a significant difference in mental health outcomes, favouring the control group (Hedge's $g = 0.12$, 95% CI 0.04 to 0.19, $p < 0.005$). Training-based interventions (e.g. exercise consultation and parenting training courses), shorter interventions, and those with fewer components appeared most promising. Interventions targeting post-natal depression showed more promise than general mental health interventions in new mothers. No interventions focused on the mental health outcomes of residents with severe mental illness were identified.

Discussion: More high-quality randomised trials are needed to build confidence in community-based interventions. Shorter, skills-based, single-component interventions seem most promising for residents who can participate. However, interventions must be accessible to deprived areas, where engagement barriers may be higher.

S313. AN EXPLORATORY STUDY OF THE RELATIONSHIP BETWEEN PREMATURE TERMINATION OF MENTAL HEALTH SERVICES IN EARLY PSYCHOSIS CLINICS AND SELF-REPORTED FAMILY FUNCTIONING AND SUPPORT, AND SHARED DECISION MAKING WITH A DOCTOR

Susie Xiong^{*1}, Yen-Ling Chen², Tzuahzia Lee³, Kathleen Nye⁴, Valerie Tryon⁵, Laura M. Tully⁶, Stephanie Hayes⁶, Mark Savill³, Sabrina Ereshefsky³, Katherine Pierce⁷, Madison Miles⁵, Merissa Kado-Walton⁸, Katherine Nguyen⁶, Nitasha Sharma⁶, Amanda McNamara⁸, Christopher Hakusui⁶, Maliha Safdar⁸, Rachel Loewy⁹, Daniel I. Shapiro³, Khalima A. Bolden³, Karina Muro³, Yi Zhang¹⁰, Leigh Smith³, Adam B Wilcox¹¹, Rebecca Grattan³, Tara A. Niendam³, Cameron S. Carter³, Joy Melnikow¹², Daniel Tancredi¹³, For the EPI-CAL Group For the EPI-CAL Group¹⁴

¹University of California, Davis, ²UC Davis Dept. Psychiatry and Behavioral Sciences; Early Psychosis Programs, ³Department of Psychiatry and Behavioral Sciences, University of California Davis, ⁴Department of Psychiatry, University of California, Davis, ⁵Department of Psychiatry and Behavioral Sciences, University of California, Davis, School of Medicine, ⁶Department of Psychiatry and Behavioral Sciences, University of California-Davis, ⁷Department of Psychiatry and Behavioral Sciences, University of California, Davis, ⁸Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, ⁹Department of Psychiatry, University of California San Francisco, ¹⁰Center for Healthcare Policy and Research, University of California-Davis, ¹¹Washington University St. Louis, ¹²University of California, Davis, ¹³University of California Davis, ¹⁴For the EPI-CAL Group

Background: Research shows Asian Americans (AA) are 50% less likely than other ethnic groups to employ mental health services and have a higher percentage of unmet mental health treatment needs. Those connected to services have been reported as challenging, complex, or difficult to connect with, by their therapists. To add, American Psychological Association (APA) reported high premature termination of mental health services for AA. Some reasons for premature termination include discomfort with emotional display and personal disclosures that may be perceived as disloyal to the family, filial piety, lack of cultural understanding and communication and discussion by the therapist, and language barriers. Also, the family is an integral role within AA values and cultural systems and may impact individual's mental health service utilization. This pilot study aims to explore whether family functioning/support, and perceived shared treatment decision-making with a provider were related to AA premature termination in early psychosis (EP) clinics.

Methods: The pilot sample is from the EPI-CAL project and data was collected with Beehive. The sample included 8 individuals who were enrolled and discharged in EP clinics. Of the sample, 75% were female ($M = 19$ years old, $SD = 3.46$ years old). Additionally, 25% identified as AA only and 75% identified as biracial/multiracial. Premature termination of service was clinician-reported with Beehive. Family functioning/support was captured through self-report on beehive and with

The Systemic Clinical Outcome and Routine Evaluation (SCORE-15), which is 15-item on a 5-point Likert Scale (1=describes us very well, 5=describes us not well at all). Items that assessed self-reported shared decision-making were scored on a 6-point Likert scale (1=completely disagree, 6=completely agree). Descriptive statistics were reported for demographic and study variables. The active EPI-CAL project is continuously collecting data and anticipates an increase in sample size for additional analysis to examine the relationship between family functioning/family support, shared decision-making, and premature termination of services.

Results: The pilot sample indicated 25% did not complete the program. The SCORE-15 sum resulted a $M = 2.79$, $SD = 1.18$. Self-report of family support, "I feel like at least one of my parents/guardians understands or tried to understand my mental health" scored a $M = 3.85$, $SD = 1.34$. Among the shared decision-making items, the item "my doctor and I selected a treatment option together" yielded the highest score ($M = 5.4$; $SD = .89$); while participants scored lowest on the item "my doctor and I thoroughly weighed the different treatment options" ($M = 4.0$, $SD = 1.87$). The other shared decision-making items have the following scores: "my doctor told me that there are different options for treating my medical condition" $M = 4.80$, $SD = 1.30$, and "my doctor asked me which treatment option I prefer" $M = 4.6$, $SD = 1.67$.

Discussion: Participants mostly completed EP clinic services and 25% prematurely terminated. Participants reported they neither agree or disagree that they felt supported by at least one of their guardian and their family functioned well. Also, participants scored lower on thoroughly weighing in different treatment options with their doctor ("somewhat agree") when compared to selecting a treatment option together with their doctor ("completely agree"). This deserves further investigation to understand why participants felt that they selected a treatment with their doctor while they only somewhat agree that they engaged in a conversation with their doctor about different treatment options. Results produced show a trend shift in AA mental health data. Future directions include increasing the sample size to better understand the data results for a historically underserved population. Additionally, results emphasized the need for quality outreach within the AANHPI community given a significantly small sample size within the EPI-CAL project data.

Acknowledgment: Contributing Authors are listed at EPI-CAL Website (<https://epical.ucdavis.edu>)

S314. INTERPERSONAL DISTANCE IN SCHIZOPHRENIA

Natália Čavojská^{*1}, Vladimír Ivančík¹, Alexandra Straková¹, Jakub Januška¹, Jakub Kraus¹, Hana Hollá Kutlíková¹, Vanda Valkučáková¹, Anton Heretik¹, Ján Pečeňák¹, Michal Hajdúk¹

¹*Comenius University in Bratislava*

Background: Interpersonal distance (ID) refers to the physical space surrounding an individual during social interactions, describing the boundaries of intimacy. Research indicates that individuals with schizophrenia tend to prefer greater ID than those in the control group and the relationship between ID and severity of positive and negative symptoms was found. The present study aims to evaluate preferred ID in individuals with schizophrenia and its association with symptomatology.

Methods: The sample consisted of 40 patients (55 % females; age $M = 41.63$) diagnosed with schizophrenia spectrum disorders and 31 healthy controls (68 % females; age $M = 32.42$). Participants engaged with a same-sex researcher in two versions (approach and avoidance) of the Behavioral Approach Task. In the approach condition, participants were instructed to approach the researcher positioned 5 meters away and stop at a distance they found comfortable. Conversely, in the avoidance condition, the researcher approached the participant, who was asked to signal them to stop at a comfortable distance. Subsequently, participants rated the perceived pleasantness of each condition on the Visual analog scale. Psychopathological symptoms were assessed using the Brief Psychiatric Rating Scale and Community Assessment of Psychic Experiences. Group differences (HC vs SCH) across conditions (approach vs avoidance) for distance and pleasantness were evaluated using mixed repeated measures ANOVA. Associations with symptoms were assessed using Spearman Rank correlations.

Results: Repeated measures ANOVA for distances revealed a significant effect of condition ($F=17.05$, $p < .001$) and group ($F=15.31$, $p < .001$), while their interaction was nonsignificant ($F=1.04$, $p=.31$). Results from the subjective evaluation of pleasantness indicated a significant effect of condition ($F=14.74$, $p < .001$), a nonsignificant effect of group ($F=2.88$, $p=.09$), and a non-significant effect of the interaction ($F=.52$, $p=.47$). Participants demonstrated a preference for a lower ID when initiating contact ($1.02 \text{ m} \pm .54$) compared to being approached ($1.19 \text{ m} \pm .71$, $p < .001$). Additionally, they rated the approach condition as more pleasant (77.73 ± 20.28) than when the researcher was approaching them (72.09 ± 23.36 ; $p < .001$). Patients with SCH favored a larger ID than HC ($p=.001$). Notably, subjective assessments of pleasantness and interpersonal distances exhibited no significant correlations across groups. In individuals with SCH, ratings of pleasantness negatively correlated with self-reported positive ($r=-.35$; $p=.03$), negative ($r=-.36$; $p=.03$), and depressive symptoms ($r=-.35$; $p=.03$), as well as clinician-rated negative symptoms ($r=-.38$; $p=.02$). No significant associations between symptoms and measured ID were found.

Discussion: The present findings underline a preference for smaller interpersonal distances when initiating contact, aligning with the protective function traditionally associated with maintaining personal space. However, the perceived level of pleasantness did not directly influence individuals' preferred interpersonal distances. Patients with schizophrenia favored

larger interpersonal distances compared to healthy controls. Contrary to previous research, our study did not reveal a significant relationship between symptomatology and the actual preferred interpersonal distance across the groups. A possible explanation is that symptoms, such as social anhedonia and paranoia, may independently contribute to higher discomfort experienced during social situations and therefore the perception of interaction might be more important than the objective distance.

Funded by: APVV 20-0185

S315. INVESTIGATION OF SELF-DISTURBANCES WITH THE BODY DISTURBANCE INVENTORY (B-BODI) IN BRAZIL; A FEASIBILITY STUDY OF CULTURAL ADAPTATION.

Mariana da Silva¹, Renan Moreira Biokino², André Fernandes², Tatiana Baxter³, Sohee Park³, Ary Gadelha², Ary Gadelha de Alencar Araripe Neto*⁴

¹*Federal University of Sao Paulo/Univ. of Sao Paulo Medical School*, ²*Federal University of São Paulo*, ³*Vanderbilt University*, ⁴*PROESQ - EPM/UNIFESP*

Background: A central feature of schizophrenia is the alteration of the perception of boundaries between the body and the external environment, marked by symptoms of somatic passivity and opposition between "self and the world." Difficulties in integrating bodily sensations in individuals with schizophrenia (SZ) could lead to the emergence of anomalous affect, dissociated from cognitive contexts, and a disconnection of the self from the social world. However, there is a lack of culturally-valid methods to assess body disturbances. The goal of this pilot study was to translate and validate the B-BODI (Benson et al. Body Disturbances Inventory) into Brazilian Portuguese to investigate bodily disturbances including loss of self-other boundaries, agency and related impairments. We also examined the feasibility and acceptability of B-BODI in the context of culture.

Methods: This pilot study was part of the project for the translation and validation of the B-BODI Protocol in Brazil. The final version of the Brazilian version of the B-BODI protocol consisted of 7 images (6 depicting bodily disturbances and 1 control image). SZ outpatients with a stable dose of medication during the previous 4 week were recruited (mean age, 37.8 years; 80% male). Content analysis was conducted with 10 individuals regarding the B-BODI. They were asked about their personal impressions while answering B-BODI. B-BODI generated specific scores for frequency, vividness, distress, and positivity per each picture.

Results: Respondents reported having a good understanding of the images and captions. All participants completed the entire protocol and reported at least one anomalous bodily self-experiences. When asked further, SZ participants presented an adequate understanding of the experience depicted in the B-BODI image. Each item was endorsed by at least one respondent. Frequency and vividness of these experiences were mostly endorsed. Positivity was the least endorsed.

Discussion: The Brazilian version of the B-BODI was well tolerated and was completed by all participants. The B-BODI pictures were understood and evoked recognizable sensations by the Brazilian patient sample. Thus, there was no further need for a specific cultural adaptation. The next step is conduct a large-scale study to investigate dissociations body in schizophrenia in relation to symptoms, functional outcome and neural correlates.

S316. IMPLEMENTATION OF A COMMUNITY INTENSIVE TREATMENT TEAM: FLEXIBILITY IS THE ANSWER

Fernando Vílchez Español*¹, Rafael José Carrillo Molina¹, Sheila Cruz Bailén², Mirta Olga Solís³, Mercedes Valverde Barea¹

¹*Complejo Hospitalario de Jaén*, ²*Hospital San Agustín, Linares*, ³*Unidad de Salud Mental Comunitaria Baza*

Background: The Community Intensive Treatment Team (in spanish, ETIC) is an innovative model, based on flexible assertive community treatment (FACT), which seeks to provide a multidisciplinary service to achieve comprehensive care in people with serious mental illness at risk of abandonment of treatment or follow-up by Mental Health. The efficacy of people in treatment and follow-up by the ETIC of Jaen Sur is evaluated from its implantation until the first five months.

Methods: 27 patients were evaluated. Their diagnoses are described and a comparison is made of both adherence to treatment and follow-up from device implantation up to five months later, using the McNemar test to evaluate the relationship between the two variables.

Results: Of the 27 patients treated, 14 (52%) were diagnosed with schizophrenia spectrum disorders. 6 (22%) of bipolar disorder. 3 (11%) of affective psychosis. 2 (7%) of personality disorder. 1 (4%) of obsessive-compulsive disorder and 1 (4%) of anxiety disorder with agoraphobia. As regards adherence to treatment, 16 of the patients treated were not receiving treatment. 4 of them took it wrong and 7 took it right. At five months, only 4 people did not take treatment and 23 took it properly.

In terms of follow-up, 19 of them did not perform. 5 were attended only by nurses and 3 performed adequate follow-up. After five months, 3 patients did not follow up, 1 was attended only by nursing and 23 performed adequate follow-up. The results were statistically significant for both follow-up and treatment.

Discussion: Our experience in these first five months at the ETIC is that this model can address unmet needs in people with severe mental disorder.

S317. WHAT THE NOSE KNOWS: THE RELATIONSHIP OF OLFACTORY HEDONIC CAPACITY TO NEGATIVE SYMPTOMS AND INDICES OF REWARD IN SCHIZOPHRENIA

Seo Yeon Lee¹, Tabinda Khan¹, Gautami Shashidhar¹, Youjin Jang¹, Diane Beckman¹, Deanna Barch², Kathryn Lewandowski³, Diego Pizzagalli³, Bruce Turetsky⁴, Matthew Killam¹, Russell Schutt⁵, Matcheri Keshavan⁵, Raquelle Mesholam-Gately⁵, Matcheri Keshavan*⁶

¹*Beth Israel Deaconess Medical Center*, ²*Washington University*, ³*Harvard Medical School/McLean Hospital*, ⁴*University of Pennsylvania*, ⁵*Beth Israel Deaconess Medical Center/Harvard Medical School*, ⁶*Harvard University*

Background: The relationship between reward circuitry and the cognitive, emotional and behavioral deficits of schizophrenia (SZ) has garnered increasing attention in recent years, particularly given the vital role of reward in learning and social interactions and the considerable public health importance of its potential association with better cognitive and

social outcomes. Although various measures assess reward system processes, an increasing number of studies leverage the olfactory system to assess hedonic capacity across the psychosis spectrum. Amongst other benefits, standardized olfactory probes are reliable and easy to administer, and olfactory hedonic ratings often correlate with negative symptoms. In these analyses, we further explore the relationship between olfactory hedonic judgments and specific components of negative symptoms and other indices of reward.

Methods: Seventy-six participants (aged 19 - 74) diagnosed with SZ-spectrum disorders provided baseline data for these analyses as part of an ongoing clinical trial examining olfactory hedonic capacity (OHC) as a moderator of psychosocial intervention effectiveness. The NIH Toolbox Odor Identification Test was administered to examine olfactory identification abilities. Data from two participants with scores in the anosmic range were excluded from analyses, resulting in a final N of 74. Participants rated the hedonic valence of each odor by indicating specific values on a visual analog scale. Negative symptoms were evaluated with the Clinical Assessment Interview for Negative Symptoms (CAINS) and Positive and Negative Symptom Scale-6 (PANSS-6). Additional reward-related processes were assessed with the Temporal Experience of Pleasure Scale (TEPS), the Snaith-Hamilton Pleasure Scale, and the Behavioral Inhibition/Behavioral Activation System Scale (BIS/BAS). Associations between olfactory hedonic ratings and scores on symptom/reward indices were measured with Spearman's correlations.

Results: The results showed that the highest hedonic valence rating, lowest hedonic valence rating, and the average hedonic valence rating correlated significantly with negative symptomology and other indices of reward, namely anticipatory and consummatory pleasure. Several significant correlations were observed between olfactory hedonic ratings and measures of negative symptoms and reward processes. Most notably, average hedonic valence was inversely correlated with total negative symptoms from the PANSS-6 ($r_s = -.26$, $p < .05$), largely driven by the N1 item of blunted affect ($r_s = -.24$, $p < .05$) and N4 item of social withdrawal ($r_s = -.27$, $p < .05$). Additionally, average hedonic valence positively correlated with anticipatory pleasure ($r_s = .39$, $p < .001$) and consummatory pleasure ($r_s = .34$, $p < .01$) from the TEPS.

Discussion: The results showcased the relationship between OHC, negative symptoms and other indices of reward, providing further support for the use of olfactory hedonic probes as translational correlates of reward circuitry dysfunction. These preliminary data are expected to inform a highly promising line of research, including examining the predictive utility of OHC measurement for targeted psychosocial rehabilitation, that is critical for advancing the treatment of functional impairment in schizophrenia.

S318. READMISSIONS OF PSYCHOTIC DISORDERS IN A BRIEF HOSPITALIZATION PSYCHIATRIC UNIT FROM 2019 TO 2022: THE ROLE OF ADHERENCE TO SERVICES AND LONG ACTING INJECTABLES FOR PREVENTIVE APPROACHES

Sara Vega-García^{*1}, José María Pelayo-Terán², María Camino Fernández-Borregán², Mario Manuel Martínez-Pérez², Marcos Gómez-Revuelta³, Ruth Landera-Rodríguez², María Estrella García-Llamas², Zaida Gutierrez-Hervás², Raquel Martín-Gutierrez², Elena Martín-Gil², Nicolás Martín-Navarro², Flora María Vega-Fernández², Eva María Romero-Gómez², Yolanda Zapico-Merayo²

¹Hospital el bierzo, ²Servicio de Psiquiatría y Salud Mental. Hospital el Bierzo. GASBI. SACYL, ³Servicio de Psiquiatría y Salud Mental. Hospital Universitario Marqués de Valdecilla

Background: Psychosis causing great disability to the patients' normal function and burden to families, particularly during admissions.

One challenge is to improve adherence to treatments and to prevent rehospitalizations.

This study evaluates patients with psychotic disorders admitted to treatment in a hospital inpatient unit for a 4 year period to evaluate the risk of rehospitalizations and the clinical factors associated.

Methods: We evaluated the hospitalizations in the acute psychiatric Unit of Hospital El Bierzo (Spain, Catchment area of 131646 hab) with an ICD-10 Psychotic disorder diagnosis (F20-29) between 2019 and 2022.

Time to rehospitalization was evaluated with a Kaplan-Meier survival analysis. Predictors were included in a cox regression analysis with a backward-Wald model. Finally, we analyzed the factors that predict the use of LAI antipsychotics, with a logistic regression analysis (backward-Wald model).

Results: 1322 subjects were admitted from 2019 to 2022. 491 (37.1%) had a diagnosis of psychosis, the most frequent diagnosis. 57.8% were males, mean age: 45.87 ± 14.69 years. The rates increased from 115 in 2019 (8.73/10000hab) to 116 in 2020 (rate: 9.85), 126 in 2021 (9.82) and 134 in 2022 (10.50). The differences were not significant ($p=0.670$).

208 (42.4%) rehospitalized. Hospitalizations during pandemics (2020-2021) had a higher probability of rehospitalization within the year (41.3%) compared to post pandemic year (25.42; χ^2 : 9.617; $p=0.008$). The survival analysis showed a mean survival of 817.42 days (IC95% 755.11-874.74) and a median survival of 1037 days (IC95% 676.03-1397.97). Those patients with a partial adherence showed a inferior mean survival of 645 days and a median of 335 days (Log Rank of Mantel-Cox χ^2 : 6.247; p is 0.044).

Rehospitalized subjects were younger (43.8 years vs 47.4; T :-2.702; $p=0.008$), have more previous hospitalizations (54.1% vs 33%; χ^2 : 22.230; p LESS THAN 0.001), were more frequently from prepandemic period (p LESS THAN 0.001), less adherent (40.9% vs 59.6%; χ^2 : 9.334; $p=0.009$), had more suicide behavior (52.9% vs 40.7%; χ^2 : 3.618; $p=0.057$). The Cox regression model included age (ExpB: 0.987; $p=0.013$), previous hospitalization (ExpB: 0.551; p LESS THAN 0.001), substances (ExpB: 1.397; $p=0.043$, adherence (ExpB: 0.729; $p=0.038$) and suicide behavior (ExpB: 0.716; $p=0.077$) in the model (χ^2 : 35.667; p LESS THAN 0.001)

The logistic regression used to predict the indication of LAIs to improve the adherence at discharge was significant; χ^2 : 47.273; p LESS THAN 0.001 χ^2 : 47.273; p LESS THAN 0.001 and classified correctly 62.7% of the subjects.

The factors included by the model were involuntary hospitalization, tobacco abuse, substance use, length of hospitalization and the concomitant use of antidepressants.

Discussion: Maintaining adherence appears to be the one of the keys in preventing relapse. LAI may be a useful treatment to patients with psychotic disorders that may help to improve adherence taking into consideration other relevant factors.

S319. SCHIZOPHRENIA AND AUTISM: NOT THE SAME

Rafael Rodriguez-Garcia*¹, Nuria Planet Nielsen², Montse Roquer³, Maria Teresa Burguete⁴, Eva Faure³, Sira Diaz Moran³

¹CAS Delta, ²CAS Delta, badalona, ³CAS Delta, Badalona, ⁴CAS Delta Badalona

Background: Autism spectrum disorder (ASD) and schizophrenia are distinct psychiatric conditions with different features and diagnostic criteria. We present a clinical case with a new diagnostic approach after not meeting criteria for schizophrenia.

Methods: 45-year-old patient referred for alterations in thought content and cocaine use. This is a woman, transsexual since adolescence, with a single psychotic episode in 2012. Born in Brazil, resident in Spain since she was 18 years old. He presents alterations in sociability since childhood, he presented selective mutism until the age of 7, repetitive and stereotyped behaviors. Parental rejection due to sex change in a religious family. Oriented as schizophrenia after a psychotic episode in 2012 after cocaine consumption. Subsequent remission ad integrum of the symptoms. Maintains unusual beliefs during adulthood secondary to alterations in sociability, perception of the world, and social rejection. Schizophrenia is ruled out because there are no positive or negative symptoms during the course and the diagnosis is oriented toward autism spectrum disorder.

Results: ASD is a neurodevelopmental disorder that typically manifests in early childhood. It is characterized by challenges in social communication and interaction, as well as restricted and repetitive behaviors. Individuals with ASD may have difficulties in socializing, forming relationships, and communicating effectively. Core symptoms of ASD include challenges in social communication and the presence of repetitive behaviors or interests. Signs of ASD are typically present in early childhood, often before the age of three. The symptoms may become more apparent as a child grows and interacts with others. Individuals with ASD may exhibit variations in cognitive abilities, with some having intellectual disabilities and others having average or above-average intelligence. Schizophrenia is a psychotic disorder that usually emerges in late adolescence or early adulthood. It involves a range of symptoms, such as hallucinations, delusions, disorganized thinking, and impaired emotional regulation. People with schizophrenia may experience a disconnect from reality, affecting their perception of the world. Symptoms of schizophrenia include positive symptoms (hallucinations, delusions), negative symptoms (diminished emotional expression, reduced motivation), and cognitive symptoms (impaired executive function, memory deficits). Onset usually occurs in late adolescence or early adulthood. The symptoms of schizophrenia may develop gradually or suddenly, and the course of the disorder can vary widely among individuals. Cognitive impairments are often observed in individuals with schizophrenia, affecting memory, attention, and problem-solving skills.

Discussion: It's important to note that while these conditions are distinct, comorbidity (the presence of both conditions in the same individual) can occur. Additionally, advances in research may lead to updates in our understanding of these disorders over time. Seeking professional advice and evaluation is crucial for accurate diagnosis and appropriate intervention.

S320. HYPOTHALAMIC-PITUITARY-ADRENAL AXIS GENES AND COGNITION IN SCHIZOPHRENIA SPECTRUM DISORDERS: A SYSTEMATIC REVIEW

Alex Ferrer*¹, Anna Barnes¹, Ariadna Pelegrí¹, Victor Del Rio¹, Siddarta Acebillo¹, Javier Labad², Diego Palao¹, Virginia Soria¹

Background: Schizophrenia (SCZ) and other psychotic disorders are highly heritable, however results from genetic association studies are highly inconsistent. For this reason, the endophenotype approach has been increasingly used, in which association between genetic factors and quantitative traits associated to core elements of genetically complex diseases has been studied. Two well characterized endophenotypes in patients suffering from psychotic disorders are dysregulations in hypothalamic-pituitary-adrenal (HPA) axis activity and cognitive impairment, which is considered one of the core features of the disease. We hypothesized that genetic variations in HPA related genes would have an influence on cognition in patients with SCZ spectrum disorders. Our objective was to perform a systematic review dealing with the involvement of genetic and epigenetic variations in HPA axis related genes on cognitive performance in patients with SCZ and other psychotic disorders.

Methods: A systematic search was performed using PubMed, PsychInfo and Scopus databases. Studies were included only if they obtained data on genes related to the HPA axis including CRH, CRHR1, CRHR2, CRHBP, NR3C1, NR3C2 or FKBP5, assessed the association between genetic data with measured neurocognitive variables and the sample included patients with diagnosed SCZ spectrum disorders.

Results: Seven studies were identified focusing in the association between variations in HPA axis related genes and cognition in patients with psychotic disorders.

Five of the identified publications were centered on single nucleotide polymorphisms (SNPs) in the FKBP5 gene. Among them, only one study analyzed measures of “hot” cognition and found an association between rs1360780 and attention bias for threat and hippocampal morphology. The other four works pointed out measures of “cold” cognition and some positive and negative findings were found. Two studies found significant associations between FKBP5 SNPs and several cognitive measures including global cognitive performance, attentional capacity, language ability and global IQ estimates. The remaining two studies could not identify any significant associations.

The last two studies analyzed methylation levels in the FKBP5 and NR3C1 promoter regions respectively. The first work showed that in patients with first episode psychosis and relapsed schizophrenia, lower FKBP5 methylation might be associated with better cognitive performance. The second study demonstrated that higher NR3C1 methylation was associated to worse delayed memory, attention and general functioning in patients with psychosis and not in other groups.

Discussion: This review supports the hypothesis that both genetic and epigenetic variations within HPA axis related genes might influence cognition in patients suffering from psychotic disorders. The influence of FKBP5 and NR3C1 variants on cognition has also been reported in samples of healthy individuals and individuals suffering from different mental disorders. However, available data is scarce, future research in samples including SCZ spectrum disorders and HPA axis variants would be of great interest to help generate a genetic profile associated to increased cognitive dysfunction, which could be used to select subjects whom might benefit from specific interventions targeting cognition.

S321. LONELINESS IN CHILDHOOD AND FIRST-EPISODE PSYCHOSIS

Covadonga Díaz-Caneja*¹, Vito Cavone², Álvaro Andreu-Bernabeu², Javier González-Peñas², Leonor Donaire², Marina Díaz-Marsá³, Roberto Rodríguez-Jiménez⁴, Ángela Ibáñez⁵, Enrique Baca-García⁶, Juan Carlos Leza⁷, María Fé Bravo-Ortiz⁸, José Luis Ayuso-Mateos⁹, Celso Arango²

¹*Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense,* ²*Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense,* ³*Department of Psychiatry, Instituto de Investigación Hospital Clínico San Carlos (IdISSC), CIBERSAM, ISCIII, School of Medicine, Universidad Complutense,* ⁴*Department of Psychiatry, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas 12), CIBERSAM, ISCIII, School of Medicine, Universidad Complutense,* ⁵*Department of Psychiatry, Hospital Universitario Ramón y Cajal, IRYCIS, CIBERSAM, ISCIII, Universidad de Alcalá,* ⁶*Department of Psychiatry, Hospital Fundación Jiménez Díaz, Hospital Rey Juan Carlos, Hospital General de Villalba, Hospital Infanta Elena, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, CIBERSAM, ISCIII, Universidad Autónoma de Madrid; Universidad Catolica del Maule, Talca, Chile; Department of Psychiatry, Centre Hospitalier Universitaire,* ⁷*Department of Pharmacology and Toxicology, School of Medicine, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas 12), IUIN,* ⁸*Department of Psychiatry, Clinical Psychology and Mental Health, Instituto de Investigación Hospital Universitario La Paz, IdiPaz, Hospital Universitario La Paz, CIBERSAM, ISCIII, Department of Psychiatry, Universidad Autónoma de Madrid,* ⁹*Department of Psychiatry, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria del Hospital Universitario de La Princesa, IIS Princesa, CIBERSAM, ISCIII, School of Medicine, Universidad Autónoma de Madrid*

Background: Loneliness or perceived social isolation refers to the subjective feeling of distress associated with a lack of meaningful relationships, irrespective of the quantity of social contact. This is in contrast to objective social isolation, which is defined as an actual lack of social connections, including interactions, contacts, or relationships. Evidence from observational and genetic studies suggests a bidirectional relationship between loneliness and psychosis. Loneliness in childhood is associated with increased odds of anxiety and depressive disorders in young adults, thus suggesting its potential as an early risk marker for mental disorders. To our knowledge, no previous study has examined the association between loneliness in childhood and first-episode psychosis (FEP).

In this study, we aimed to assess the association between loneliness in childhood and the odds of FEP and to explore gender differences in this association.

Methods: This was an observational, cross-sectional, case-control study, based on the AGES-CM cohort, a longitudinal prospective study including patients with FEP ages 7-40 and an age- and sex-matched sample of controls in seven university hospitals in the region of Madrid, Spain.

We assessed loneliness in childhood with the question "Have you ever felt lonely for more than 6 months before the age of 12" and objective social isolation with the peer relationships item from the childhood subscale of the Premorbid Adjustment Scale.

We conducted logistic and linear regression analyses to assess the association between childhood loneliness and i) the odds of presenting a FEP and ii) clinical variables of interest,

including diagnosis and scores on positive, negative, and general symptoms measured by the Positive and Negative Syndrome Scale, as well as global functioning measured by the Global Assessment of Functioning Scale. These analyses were adjusted for demographic variables.

Results: The study sample comprised 285 patients with FEP (32.6% female, age 24.50 ± 6.2 years) and 261 controls (48.7% female, age 25.93 ± 5.5 years). Objective social isolation and loneliness in childhood were associated with increased odds of FEP (adjusted odds ratio; aOR: 2.87, 95% CI [1.16-7.09], $p=.022$ and aOR: 2.17, 95% CI [1.40-3.51], $p=.002$, respectively). The association between loneliness in childhood and FEP remained significant after controlling for objective social isolation in childhood (aOR: 2.70, 95% CI [1.58-4.62], p LESS THAN .001). We found opposite effects of childhood loneliness in participants not presenting objective social isolation during childhood (aOR: 2.68, 95% CI [1.56-4.60], p LESS THAN .001) relative to those presenting objective social isolation (aOR: 0.33, 95% CI [0.08-1.45], $p=.142$).

The effect of the association between loneliness in childhood and FEP was stronger in females (aOR: 4.74, 95% CI [2.23-10.05], p LESS THAN .001) than in males (aOR: 1.17, 95% CI [0.63-2.19], $p=.623$). In females with FEP, loneliness in childhood was significantly associated with reduced odds of receiving a schizophrenia spectrum disorder diagnosis relative to other diagnoses (aOR: 0.155, 95% CI [0.048-0.506], $p=.002$). In the FEP sample, loneliness in childhood was associated with greater severity of positive and general symptoms, as well as poorer global functioning.

Discussion: Loneliness in childhood is associated with increased odds of first-episode psychosis and clinical variables of interest. This association appears to extend beyond the effects of objective social isolation and is particularly pronounced in females. These findings suggest the potential of this phenotype as an early risk marker for psychosis that could help guide targeted interventions.

S322. ILLNESS-RELATED VARIABLES AND ABNORMALITIES OF RESTING-STATE BRAIN ACTIVITY IN SCHIZOPHRENIA

Giulia Giordano*¹, Pasquale Pezzella², Luigi Giuliani², Leonardo Fazio³, Armida Mucci², Andrea Perrottelli², Giuseppe Blasi⁴, Mario Amore⁵, Paola Rocca⁶, Alessandro Rossi⁷, Alessandro Bertolino⁴, Silvana Galderisi²

¹University of Campania "Luigi Vanvitelli", ²Department of Psychiatry, University of Campania "Luigi Vanvitelli", ³Department of Medicine and Surgery, LUM University, ⁴Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', ⁵Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, Section of Psychiatry, University of Genoa, ⁶Department of Neuroscience, Section of Psychiatry, University of Turin, ⁷Department of Biotechnological and Applied Clinical Sciences, Section of Psychiatry, University of L'Aquila

Background: Schizophrenia is a complex mental disorder characterized by a large heterogeneity in terms of risk factors, pathophysiology, clinical presentation, and functional outcome. A huge number of illness-related variables, such as positive symptoms, disorganization, depression, negative symptoms and cognitive impairment has a great impact on functioning of people affected from this disorder. Among these variables, cognitive deficits and negative symptoms seem to be the most important predictors of a poor functional outcome.

In order to disentangle the pathophysiological heterogeneity of schizophrenia, the aim of the present study was to investigate the relationships between clinical features and abnormalities in resting-state brain activity in people with schizophrenia.

Methods: Resting-state (rs) functional MRI data were analyzed in 62 subjects with schizophrenia (SZs) and 46 healthy controls (HCs), as part of the add-on brain imaging study of the Italian Network for Research on Psychoses. The selected ROIs were the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), the orbitofrontal cortex (OFC), the precuneus (PCun), the inferior parietal lobule (IPL), the temporo-parietal junction (TPJ), the superior temporal gyrus (STG), the ventral anterior insula (vaIC), the dorsal anterior insula (daIC), the posterior insula (pIC), the lateral occipital cortex (LOC), the dorsal anterior cingulate cortex (dACC), the amygdala (Amy), the nucleus accumbens (NaC), the ventral caudate (vCa), the dorsal caudate (dCa), and the putamen (Pu).

The Positive and Negative Syndrome scale was used to measure positive symptoms and disorganization, the Calgary Depression Scale for Schizophrenia to assess depression, the Brief Negative Symptom Scale for negative symptoms and the MATRICS Consensus Cognitive Battery to assess six neurocognitive domains.

Between-group comparisons were performed with χ^2 and one-way analysis of variance (ANOVA) tests, according to the type of variable. In addition, we performed regression analyses using the cognitive performance and the psychopathology as predictors, and the resting-state data as the explained variable.

Results: The SZs, compared to the HCs, showed higher rs functional activity of the right IPL and right TPJ junction, and lower rs activity of the right DLPFC, the bilateral dACC, and the ventral and dorsal caudate. Furthermore, deficits in the attention and vigilance (AV) and in reasoning and problem solving together with conceptual disorganization were associated with the rs activity of the right IPL and right TPJ. Deficits in AV together with depression were associated with the rs functional activity of the right DLPFC while, independently from psychopathology and other cognitive functions, these deficits in AV predicted the rs activity of the right and left dACC. The Expressive Deficit domain of negative symptoms was associated with the rs activity of the left vCa, while the Motivational Deficit with that of the right and left dCa.

Discussion: Our results suggested that neurocognitive functions (in particular attention and vigilance) and the two negative symptom domains were independently associated with the rs activity of different brain regions. Furthermore, in line with the literature, we demonstrated how the two domains of negative symptoms are subtended by different pathophysiological mechanisms. A better understanding of the neurobiology of cognitive deficits and negative symptoms could foster the development of innovative treatment strategies targeting these aspects that still represent an unmet need in the care of schizophrenia.

Disclosure of Interest: None Declared

S323. HOW DO AFFECT AND MEMORY FOR SOCIAL APPROVAL IN SCHIZOPHRENIA RELATE TO DAILY SOCIALIZATION: LINKING EVIDENCE FROM A NOVEL BEHAVIORAL TASK TO REAL-WORLD REPORTS OF SOCIAL BEHAVIOR

Jaisal Merchant^{*1}, Erin Moran¹, Deanna Barch¹

¹Washington University in St. Louis

Background: Despite evidence that individuals with schizophrenia (SZ) and healthy individuals (HC) have a similar desire for social relationships and experience similar momentary pleasure from socialization, SZ report smaller social networks and may have reduced motivation for daily social goals. Literature on reward and motivation suggests that SZ have a disruption in the ability to translate intact momentary pleasure to motivated behavior for positive outcomes. This could stem, in part, from difficulty maintaining emotional memory of positive experiences, which may inhibit SZ from predicting that certain behaviors could lead to similar pleasurable outcomes. It is important to further explore this link and examine whether this process extends to the social domain of reward and motivation in SZ. The current project examines the relationship between affective responses to positive vs. negative social experiences, implicit memory for these experiences, and real-world social behavior in SZ vs. HC.

Methods: SZ (n=32) and HC (n=44) completed a novel Prediction of Social Liking Task (PoSLiT) (developed by the presenter) and one week of ecological momentary assessment (EMA). In the PoSLiT participants are shown photos of “peers” who are said to be other study participants who have previously seen their photo (taking of said photo was mimicked at a prior session) and determined whether they thought they would like them. For the first half of the task, participants are presented with a peer photo, asked to indicate whether they think they would like the person pictured, and then presented with that peer’s positive or negative opinion of them: “This person thought they would like you” (social approval- 50% of opinions) vs. “This person thought they would not like you” (social disapproval- 50% of opinions). Participants then indicate their momentary affective response to that opinion on a 5-point Likert scale (“extremely upset” - “extremely happy”). In the second half, the same peer photos are presented in randomized order and participants are asked whether they think the person pictured would like them. Accuracy on this response indicates implicit social memory. The EMA portion of the study involves answering questions about current and planned activities in real-time in participants’ daily lives.

Results: SZ and HC did not differ in their affective responses to peers’ reported positive or negative opinions of them on the PoSLiT ($\beta = 0.11$, $p = .17$). Implicit memory for these opinions showed a trend-level group X opinion interaction with follow-up analyses demonstrating that HC were significantly more accurate in their memory for social approval than disapproval (OR= 5.91, $p = .00$), while this positive vs. negative nature of peer opinions did not differentially relate to implicit memory in SZ (OR= 1.76, $p = .31$). Though not significant, SZ were marginally worse than HC at remembering social approval (63% vs. 73%, $p = .06$), while HC were numerically less likely than SZ to remember social disapproval (46% vs. 55%, $p = .17$). Across participants, EMA reports of frequency of real-world current and planned socialization were positively related to memory for social approval (current: OR= 1.02, $p = .02$, planned: OR= 1.01, $p = .04$), but not to memory for social disapproval, nor to affective response to social approval or disapproval. The main effect of current socialization on memory for social approval was modified by a group X current socialization interaction, with follow-up analyses indicating that frequency of current socialization was related to memory for social approval in HC (OR= 1.10, $p = 0.01$) but not in SZ. Groups did not significantly differ in the relationship between planned socialization and memory for social approval.

Discussion: Results from the PoSLiT indicate that SZ and HC had similar momentary affect in response to positive and negative social experiences (i.e., social approval vs. disapproval). However, unlike SZ, HC demonstrated differentially better memory for social approval than disapproval. Thus, SZ may be specifically impaired in their memory for positive social outcomes. Unlike momentary affect, increased memory for positive (but not negative) peer opinions was related to more real-world plans for socialization across groups, and to more

experienced socialization in HC. This aligns with suggestions that maintenance of emotional memory for positive outcomes may play a role in driving motivated behavior for these experiences. It could also indicate that the positively biased memory for peer opinions in HC could be protective for the pursuit of social activities.

S324. THE EVOLUTION OF CONTROL OVER VOICE HEARING EXPERIENCES

Silmilly Toribio*¹, Catalina Mourgues-Codern¹, Albert Powers III²

¹*Yale University*, ²*Yale University School of Medicine*

Background: Auditory verbal hallucinations are a common symptom of psychosis, often debilitating and interfering significantly with daily life. Nevertheless, some individuals can exert voluntary control over these voices. Qualitative studies have revealed that this control is cultivated over time, with individuals adopting a variety of strategies to manage their voices. The specific factors that may facilitate the development of such control remain uncertain. This study investigates the potential roles of intrusive thoughts, a predisposition towards hallucinations and delusions, diagnoses within the psychosis spectrum, depression, and beliefs about the voices as factors that could influence the acquisition of control over time.

In this study, we investigated the evolution of control over auditory hallucinations over time, using a self-report questionnaire to assess changes from the onset of the voices to the current level of control.

Methods: We selected 632 participants from the Yale Control Over Perceptual Experiences (COPE) study who experienced auditory hallucinations at least once a week for the past month. A stepwise regression analysis was performed, with the change in the degree of control over the hallucinations as the dependent variable, and as independent variables, sex and gender were included as well as the presence of psychosis spectrum diagnosis, then the self-report questionnaires were included, White Bear Suppression Inventory (WBSI), Launay-Slade Hallucination Scale (LSHS), Auditory Hallucinations Rating Scale (AHRS), COPE scale, Patient Health Questionnaire (PHQ) and Peters et al. Delusions Inventory (PDI) to understand the dynamics of this control over time.

Results: The final model explained 25% of the change of control over the voices. These preliminary findings suggest that contrary to expectations, neither a diagnosis within the psychosis spectrum ($B = -.021$) nor symptom-related measures such as the PDI ($B = -.028$), LSHS ($B = .064$), WBSI ($B = -.048$) significantly predicted changes in control over time. Instead, individuals' beliefs about their voices emerged as significant predictors of change in control (Malevolent voices $B = .210$, benevolent voices, $B = .358$ and Omnipotence, $B = -.403$, $P < .05$), along with levels of depression (PHQ, $B = -.126$, $P = .029$) and severity of verbal hallucinations ($B = .101$, $P = .026$). Specifically, the belief in the omnipotence of voices was associated with less change in control, while perceptions of malevolent or benevolent voices correlated with increased control.

Discussion: Understanding the connection between one's beliefs regarding the content and significance of auditory hallucinations and the level of control over these experiences is crucial. A higher level of power associated with the voices seems to correspond with a diminished ability to control them over time, implying a potential decline in the individual's sense of agency.

An exploration of the perceptions surrounding the content of auditory hallucinations emerges as a promising avenue for developing control. Notably, the content of the voices is linked to a

heightened degree of control, whether perceived as malevolent or benevolent. Moreover, this implies that the affective responses elicited by the auditory hallucination content may exert a limited influence on the individual's ability to regulate the voice-hearing experience.

Examining therapeutic interventions targeting these beliefs is crucial. Shaping early beliefs about voices may enhance the likelihood of engaging with them and developing control. A longitudinal study in the same cohort is ongoing, offering a chance for a comprehensive analysis of psychosis symptom management dynamics, potentially identifying more effective treatments.

S325. METABOLIC SYNDROME AND NEUROCOGNITIVE IMPAIRMENT IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS

Lebogang Phahladira*¹, Hilmar Luckhoff¹, Leigh Van Den Heuvel¹, Retha Smit¹, Bröcker Erine¹, Laila Asmal¹, Robin Emsley¹, Soraya Seedat¹

¹*Stellenbosch University*

Background: First-episode schizophrenia spectrum disorders (FES) are associated with subclinical metabolic abnormalities. The relationship between metabolic features and cognitive impairments is not clear cut.

Methods: We examined the associations between metabolic syndrome (MetS) and neurocognitive function in patients with first-episode schizophrenia spectrum disorders (FES) compared to controls assessed using the Repeatable Battery for the Assessment of Neuropsychological Status. In patients, psychopathology was assessed using the Positive and Negative Syndrome Scale and Calgary Depression Scale for Schizophrenia.

Results: First, we found illness- and domain-specific associations between the individual MetS features and neurocognitive performance in patients, but not in controls. Second, body mass index and total cholesterol levels were lower in patients than controls, which in turn correlated with increased global psychopathology severity and cognitive deficits. Third, negative symptoms moderated the association between low HDL cholesterol and poorer immediate verbal memory performance in patients.

Discussion: Our findings suggest that distinct lipid profile alterations are associated with cognitive performance and psychopathology severity in patients with FES. Further studies are needed to explore the associations of MetS with neurocognition over time, as well as how these relationships are affected by socio-demographic and clinical factors, including depression, anxiety, and related psychopathology.

S326. AN EVALUATION OF MEDICATION PRESCRIBING PRACTICES IN EARLY PSYCHOSIS PROGRAMS IN CALIFORNIA, USA

Apurva Bhatt*¹, Mark Savill², Katherine Pierce³, Briana Sepulveda², Kate Hardy⁴, Regina Graham², Kathleen E. Nye⁵, Valerie Tryon⁶, Lindsay Banks⁷, Kristin LaCross⁸, Christopher Blay⁸, Stephania Hayes⁹, Sabrina Ereshefsky⁹, Adrian F. Asbun⁹, Daniel Shapiro¹⁰, Katherine Eisen⁴, Misha Carlson⁸, Tara Niendam⁹

¹Stanford University School of Medicine, ²University of California Davis, ³Department of Psychiatry and Behavioral Sciences, University of California, Davis⁴Stanford University, ⁵University of California, Davis, School of Medicine, ⁶UC Davis Medical Center, ⁷Case Western Reserve University, ⁸University of California San Francisco, ⁹University of California, Davis, ¹⁰UC Davis Dept. Psychiatry and Behavioral Sciences; Early Psychosis Programs

Background: Coordinated Specialty care programs for early psychosis are multidisciplinary teams that include psychiatric providers (psychiatrists and nurse practitioners) who participate in assessment, offer physical health services and medication management. These programs work with individuals experiencing a first episode of psychosis (FEP) and/or clinical high risk psychosis syndrome (CHRP). EPI-CAL is a statewide effort in California, USA to support a learning healthcare network approach to early psychosis care. The objective of this study was to evaluate prescribing patterns in early psychosis programs across EPI-CAL.

Methods: We evaluated data from the EPI-CAL Fidelity Assessment. Each fidelity assessment was conducted using the First Episode Psychosis Services - Fidelity Scale, which involved interviewing key providers, program administrative data, and health record data from a randomized sample of 10 service users. We evaluated data regarding prescribing practices by licensure type, and assessed antipsychotic medication prescribing patterns (polypharmacy, use of clozapine for treatment-resistant psychosis, adherence to evidence-based dosing guidelines for first episode psychosis, and use of antipsychotic medication for CHRP).

Results: Of the 22 participating early psychosis programs, 9 programs had psychiatrists in the psychiatric provider role, 6 had nurse practitioners, 6 had both psychiatrists and nurse practitioners, and one program had an unknown psychiatric provider. Of the 43 service users served just by nurse practitioners, 20.9% received more than one antipsychotic, as compared to 9.7% amongst who were served just by psychiatrists (3/31 service users). 10 programs had prescribing practices where GREATER THAN 60% of service users assessed received antipsychotic doses within recommended guidelines, while 4 programs had prescribing practices with LESS THAN 59% of individuals receiving medication within recommended guidelines. Only 9/16 (56.3%) programs prescribed Clozapine, presumably for treatment-resistant psychosis. Of 15 programs assessed that provided services to individuals with CHRP, 9 were prescribing antipsychotics to GREATER THAN 20% of clients diagnosed with CHRP, contrary to best practice guidelines.

Discussion: Antipsychotic polypharmacy amongst individuals with FEP, and the prescription of antipsychotics to individuals with CHRP was found to be relatively common across the EPI-CAL network. This is concerning, as both practices are inconsistent with current best practices guidelines. Nurse practitioners, who as of 2023 in California can prescribe independently, demonstrated greater polypharmacy prescribing patterns compared to psychiatrists. Almost half of programs assessed were found not to be prescribing Clozapine, which is indicated after a service user does not experience a favorable response to two prior adequate trials of antipsychotic medication. These findings highlight the need for increased support and education around best practices for medication management of early psychosis in community programs.

