2021 Congress of the Schizophrenia International Research Society

ABSTRACT BOOK

Bringing Precision Medicine to Mental Health Services

Workshops

1. THE FUTURE OF SCHIZOPHRENIA RESEARCH: ACADEMIC/PHARM COLLABORATIONS

Nina Schooler

Suny Downstate Health Sciences Center

Overall Abstract: Collaborations between investigators who work in academic and industry settings have a long history in schizophrenia research and have taken many varied forms over the years and across the range of countries represented by SIRS. The goal of the proposed workshop is to bring together investigators who span the current landscape in the field from both the pharmaceutical industry and academic settings. All have a history of successful personal collaborations and can present case examples. The goal of the session will be to consider current opportunities for collaboration, barriers that may exist and strategies for overcoming these barriers.

1.1 FROM MECHANISMS TO NEW TREATMENTS BY USING REPOPOSING

Peter Falkai

Psychiatric University Hospital Munich

Individual Abstract: Most pharmaceutical companies have ceased drug discovery programs for psychiatric diseases given many costly failures in the last decades which followed the classical target-focused approach. Nonetheless, there is still a strong demand in novel pharmaceutical approaches since many symptoms e.g. of schizophrenia (SZ) cannot be targeted adequately. Human genetics has provided a plethora of genetic risk factors for SZ which seem to converge on a set of molecular and cellular pathways including control of gene expression, synapse function and excitation-inhibition (E/I) balance.

To overcome the limitations of the target-driven approaches we have developed a concept for repurposing in SZ that is pathway-oriented. Here, we aim at developing cellular assays that allow to monitor disease-associated pathways. We use these assays to screen collections of approved drugs capable of modulating these pathways in toto rather than focusing on individual protein targets.

In a pilot study, we identified Spironolactone as a modulator of the Neuregulin1-ERBB4 signaling pathway which is implicated in the control of cortical E/I balance. We showed in a pre-clinical study with dedicated transgenic mouse models that Spironolactone ameliorated cognitive deficits likely by rescuing E/I dysbalances. These results led to the initiation of a clinical trial to assess Sprionolactone as a potential add-on therapy for schizophrenia.

We are currently developing additional cellular screening assays to target SZ-associated pathways for repurposing which may hopefully foster more clinical studies for SZ in the future.

1.2 THE FUTURE OF SCHIZOPHRENIA RESEARCH: ACADEMIC/PHARM COLLABORATIONS: COLLABORATIONS BETWEEN JANSSEN AND ACADEMIA

Srihari Gopal

Janssen Research & Development, LLC

Individual Abstract: During this presentation, Dr. Gopal will speak about the efforts within Janssen to partner with academic institutions in the field of schizophrenia research. In particular, he will speak on 3 main aspects:

1) Repurposing of Inactive Compounds: as part of every pharmaceutical pipeline, there are compounds which are longer being developed actively. An example of a Positive Allosteric Modulator (PAM) of Nicotinic Alpha-7 acetylcholine receptors (JNJ-39393406) and its use for smoking cessation in conjunction with the University of Pittsburgh will be discussed.

2) Open Translational Science in Schizophrenia (OPTICS): a collaborative translational science project was initiated between Janssen and several leading universities (Yale, Harvard, Rutgers and the NIH). As part of this, Janssen clinical trial data along with pharmacogenomic data from dbGAP were shared.

3) Yale Open Access Data (YODA): This initiative opened up the vast trove of datasets from Janssen sponsored clinical trials. As part of this, the full datasets, study reports and all accompanying details are provided to researchers to allow independent analyses. A number of important meta-analyses have resulted from these efforts.

References

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3. Ross JS et al. Sci Data 5, 180268 (2018) doi:10.1038/sdata.2018.268

1.3 COLLABORATIONS BETWEEN ACADEMIA AND PHARMACEUTICAL INDUSTRY ARE ESSENTIAL FOR THE SUCCESS OF DRUG DISCOVERY IN NEUROPSYCHIATRIC DISORDERS

Bernd Sommer

Boehringer Ingelheim Pharma GmbH & Co KG

Individual Abstract: The complex nature of Neuropsychiatric Disorders such as Schizophrenia is reflected by the limited pharmacological treatment opportunities and the paucity of therapeutic innovation in the last decades. One important component to overcome the immanent challenges for drug discovery in this area are efficient partnerships between drug makers and academic researchers.

It is Boehringer Ingelheim's strong belief and partnering philosophy that such partnerships can only deliver, when they are founded on genuine mutual interests and are designed to utilize each partners' strengths in a complementary and synergistic way.

In this presentation different types of academia/pharm collaborations will be discussed. These include:

- Multipartner Consortia involving several companies and academic institutions such as the EU's Innovative Medicine Initiative PRISM consortium or the Alzheimer's Research UK Psychiatry consortium addressing fundamental questions in the field in a precompetitive manner.
- Bilateral partnerships with renowned academic centers such as Vanderbilt's VCNDD, which bring in complementary expertise to drive innovative joint drug discovery projects.

o Dependent on the partner's specific know-how and focus these bilateral collaborations may address multiple aspects along the value chain of drug discovery, reaching from target identification to translational research in patients.

• Collaborations with philantrophic non-profit organisations to contribute to the resolution of large open issues in a precompetitive and mutual manner.

The distinct aims, purpose and values of each type of collaboration will be outlined and discussed in an exemplary way.

1.4 THE FUTURE OF SCHIZOPHRENIA RESEARCH: ACADEMIC/PHARM COLLABORATIONS

Andreas Meyer-Lindenberg

Central Institute of Mental Health, University of Heidelberg

Individual Abstract: Recent progress in understanding the genetic and environmental causes and the systems level neural alterations in schizophrenia has been rapid, raising the possibility that 'disease-modifying' strategies could alter the course of this devastating disorder, rather than symptomatic treatment. A promising window for course-altering intervention is around the time of the first episode of psychosis, especially in young people at risk of transition to schizophrenia. Indeed, studies performed in both individuals at risk of developing schizophrenia and rodent models for schizophrenia suggest that pre-diagnostic pharmacotherapy and psychosocial or cognitive-behavioural interventions can delay or moderate the emergence of psychosis. Of particular interest are 'hybrid' strategies that both relieve presenting symptoms and reduce the risk of transition to schizophrenia or another psychiatric disorder. We outline a strategy based on muli-omic analyses of longtudinally followed cohorts to identify treatment targets, and of a new way of interfacing neuroscience with very early phase clinical trial to speed up the human translational phase.

1.5 NOVEL STRATEGIES FOR PROOF-OF-CONCEPT TRIALS IN MOOD AND PSYCHOTICS DISORDERS

Allan Young

Institute of Psychiatry, King's College

Individual Abstract: Drug development in Psychiatry essentially began with the discovery of antipsychotics in the 1950s and Schizophrenia has remained the primary target for much of drug development in psychiatry since then. As Academic Psychiatry has moved to a more transdiagnostic and dimensional approach to help better understand Mood and Psychotic Disorders, drug development appears to be still constrained by the tramlines of DSM. This means that a treatment developed for schizophrenia is delayed in being investigated in related illnesses. A good example is given by the atypical antipsychotics. These drugs were developed in an attempt to replicate clozapine but were subsequently found to be antimanic (as all antipsychotics are, irrespective of the presence of psychotic symptoms) and some were found to be of benefit in bipolar depression and major depressive disorder. Clozapine itself is used in severe mood disorders despite the dearth of trial evidence because of clinician's experience of therapeutic success. A simple reordering of the pathway of clinical drug development might greatly expedite the process. This might involve:

(1) Considering Mood and Psychotic Disorders together at every stage of drug development.

(2) Carrying out initial proof of concept studies in mania.

(3) Depending on the signal from (2), then conducting transdiagnostic studies across the range of Mood and Psychotic Disorders.

Mania is a condition which encompasses manic and frequently depressive symptoms, psychosis as well as anxiety and suicidality. Trials are typically relatively brief and usually not compromised by excessive placebo affects. The time is right for Academics and Industry to adopt such a novel strategy for proof-of-concept trials in Mood and Psychotics Disorders.

2. THE FUTURE OF SCHIZOPHRENIA RESEARCH: OPEN SCIENCE

Deanna Barch

Washington University

Overall Abstract: This workshop will cover current challenges and opportunities in open science and the ways in which it can contribute to our understanding of the causes and treatment of psychosis. This will include discussion and review of options for accessing open science data in psychosis research, examples of novel science that has been enabled through open science practices, and considerations in the development of studies if you plan to engage in open science practices. We will also discuss some of the challenges engendered by open science practices, including credit assignment, considerations for tenure and promotion and confidentiality and privacy issues in regard to participant information. Workshop participants are encouraged to bring questions and to share their own experiences and best practices.

2.1 NIMH, OPEN SCIENCE, AND SCHIZOPHRENIA

Gregory Farber

National Institute of Mental Health

Individual Abstract: This talk will present an overview of how data from large NIMH funded trials related to schizophrenia are used and compare that to data reuse from smaller studies. Efforts to improve the reusability of data will be described. Those efforts involve the NIMH Data Archive as well as new requirements related to data deposition and the use of common data elements.

2.2 USING OPEN DATA AND MAKING DATA AVAILABLE TO ADVANCE SCHIZOPHRENIA RESEARCH

Aristotle Voineskos

Centre for Addiction and Mental Health

Individual Abstract: This talk will review available data and opportunities for schizophrenia research based on a range of initiatives aiming to advance early identification and prevention of illness.

The Philadelphia Neurodevelopmental Cohort (n~1,500) and Adolescent Brain Cognitive Development (n~10,000) studies provide increasingly large catchment and cohort based data in both breadth and depth that may provide useful risk identification mechanisms related to psychosis. These in turn can inform future prevention efforts. Multi-center initiatives to help better understand brain-behavior relationships and enhance treatment efforts in people with

schizophrenia, such as the Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS) (n~500) will be described, including examples of data made publicly available. These will include data made available back to the NIH for further interrogation, as well as efforts to use open science platforms such as OpenNeuro to share datasets. Collectively, these initiatives can help advance our understanding of neurobiological risk factors for schizophrenia, and hopefully accelerate therapeutic advances. Consistent with the theme of this conference, this talk will also describe a health services initiative, known as 'EPI-SET' in Canada, somewhat similar to the U.S. EPI-NET initiative to improve care for younger people dealing with early psychosis. Here, examples will be provided where the course and progress of the study is made available, and where tools are being built that can advance practice and care in the health service across jurisdictions, including in the context of virtual care. Finally, a new large cohort study will be described taking place in Toronto, Canada that aims to bridge neuroscience with the health service to understand novel risk mechanisms and care pathways for people at-risk of developing psychosis.

2.3 RECOGNITION AND REWARD

Neeltje Van Haren

Erasmus Medical Centre, Rotterdam, Netherlands

Individual Abstract: Academia is reconsidering its incentives and reward structure, and this will become relevant for researchers at all levels. In more and more institutions, it is now recognized that the disproportional emphasis on impact factor, h-index, number of publications, citations, patents, and research dollars, alters academic behavior of researchers, reducing scientific progress and increasing unethical actions. The solution appears simple; recognition of an excellent researcher must be based on quality, and not only on quantity. But how?

An alternative approach to bibliometrics is the Rule of Five: present your best five papers over the past five years, accompanied by a description of the research, its impact and your individual contribution. The exact numbers are immaterial: what matters is the focus on quality. Such an approach allows a researcher to highlight a paper that is published in a low-impact journal, but which had enormous impact in clinical care or was the start of a productive new research line.

Other institutions, like the University Medical Centre Utrecht, radically changed the way they evaluated CVs for professional promotions. Candidates must provide a short essay about who they are and what their plans are as faculty members. They must discuss achievements in terms of five domains, only one of which is scientific publications and grants. The other domains are managerial responsibilities and academic duties (e.g. reviewing for journals and contributing to internal and external committees), teaching activities, entrepreneurship and community outreach and, if applicable, clinical work (including participation in organizing clinical trials and research into new treatments and diagnostics) (Benedictus & Miedema, Nature, 2016, 538, 453-455).

Is this the way forward? How to weight accomplishments in the different domains? Are we now looking for a five-legged sheep? How to compare candidates within the same field who during their careers put emphasis on different domains? Moreover, does this solve the problem of comparing between researchers from different academic cultures or research fields?

2.4 PITFALLS OF MACHINE LEARNING IN SCHIZOPHRENIA RESEARCH AND HOW TO ADDRESS THEM USING OPEN SCIENCE APPROACHES

Nikolaos Koutsouleris

Ludwig-Maximilian-University

Individual Abstract: Background: Machine learning approaches are increasingly gaining traction in schizophrenia research as they have demonstrated the power to detect new subtypes of psychotic disorders and to establish prognostic models for individualized prediction of adverse outcomes. However, these promises with regard to disentangling the cross-sectional and longitudinal heterogeneity of psychoses have been paralleled by increased scrutiny and skepticism towards the weaknesses of these techniques. Specifically, these weaknesses may comprise the risk of model overfitting, circularity of analytical strategies, the black-box nature of machine learning and the lack of evidence for clinical applicability.

Methods: My talk will provide a critical review of the current state-of-the-art of machine learning techniques as the key driver of precision psychiatry research in psychotic disorders. I will focus on the methodological and conceptual issues of machine learning / AI, particularly with respect to model generalizability and the utility of these techniques for advancing knowledge compared to classical inferential statistics. Furthermore, I will address topics beyond the question of the feasibility of individualized prediction, such as urgently needed infrastructures for model sharing, methods for establishing model transparency and regulatory action needed to achieve ethical acceptability of machine learning as a critical component of future clinical care.

Conclusions: The pitfalls of machine learning in schizophrenia research need to be addressed before the field can enter the next stage, which is the assessment of models' clinical utility in stratified clinical trials.

Opening Keynote

3. CHOOSING A VIBRANT FUTURE

Til Wykes

Institute of Psychiatry, Psychology & Neuroscience

Overall Abstract: We are delighted to welcome Margaret Trudeau as our keynote speaker. She is celebrated as a respected mental-health issues advocate which results from an understanding of public pressures and her experience of living with bipolar disorder. Margaret Trudeau has a well-known family name and yes she is the proud mother to Prime Minister Justin Trudeau but we have invited her to share her personal stories to remind us of what people with mental health diagnoses want from life and how our work may sustain their recovery.

Margaret is also a bestselling author of four books, including Changing My Mind, which charts her life's ups and downs, and her latest title, The Time of Your Life, which offers women an inspirational and practical approach to creating a healthy, happy, secure, and satisfying future. The stage show, A Woman of a Certain Age that she co-wrote is partly an exploration of mental illness and partly based on her public and private journeys. The live recording of a performance is available via audible.ca. So we are all moving into the internet age.

Margaret also contributes as a community advocate to the Executive Advisory Board of the UBC Mental Health Institute and is an active Charity ambassador and she was the honorary president of WaterAid, a charitable Canadian non-governmental agency that helps communities in developing countries build sustainable water-supply and sanitation services. So, she is a woman of many talents.

The themes of her first and most recent volumes, on mental health and women, make her an excellent speaker for the SIRS journey with our objective of increasing and promoting diversity, particularly women, in our research, our membership and our leadership as well as our commitment to translating and implementing research evidence to help people with a diagnosis of schizophrenia.

3.1 CHOOSING A VIBRANT FUTURE

Margaret Trudeau

Individual Abstract: Canadians fell in love with Pierre Elliott Trudeau's beautiful bride when he brought her to the world stage as the youngest First Lady in the history of the country. Yet, as time went by, Margaret was unprepared for public life, and plagued by mood swings. After three sons with Pierre, the marriage ended. She then remarried and had two more children. But the tragic loss of her son, Michel, in a skiing accident and the passing of Pierre Trudeau a few years later, were too much to bear, and she became severely ill.

Today, Margaret has rebuilt her life once again. Now, she brings her formidable life story to the stage in her quest to help others, sharing her message of resilience with the goal of helping to inspire others and to erase the stigma surrounding mental health issues.

Plenary Session

4. HOW TO TRANSLATE SCIENTIFIC FINDINGS ON EMOTIONAL INFORMATION PROCESSING TO PSYCHOLOGICAL INTERVENTIONS FOR PEOPLE WITH PSYCHOTIC DISORDERS

Nicole Kozloff

Centre for Addiction and Mental Health

Overall Abstract: This plenary session will explore the link between emotion processing and delusions in psychosis and implications for psychological interventions. Dr. Lincoln will review research suggesting that negative affect has a causal role in the formation and maintenance of delusions, possibly through a failure to downregulate negative affect or impaired emotional learning. Dr. Lincoln will then discuss implications for treatment that teaches specific affect regulation strategies or enables corrective social experiences, approaches that may be enhanced by technology.

4.1 HOW TO TRANSLATE SCIENTIFIC FINDINGS ON EMOTIONAL INFORMATION PROCESSING TO PSYCHOLOGICAL INTERVENTIONS FOR PEOPLE WITH PSYCHOTIC DISORDERS

Tania Lincoln

University of Hamburg, Institute of Psychology

Individual Abstract: The last decades of research have revolutionized the understanding of psychosis. We now have an increasingly clearer picture of the psychological mechanisms that drive the formation and maintenance of psychotic symptoms and are beginning to translate this knowledge into targeted interventions. Within this broader context, this talk will spotlight the link between emotion processing and delusions and its implications for psychological interventions.

The first part of the talk will cover research on the link between negative affect and delusions. Using a variety of designs, including longitudinal surveys, experimental and experience-sampling methods this research clearly demonstrates that negative affect precedes, accompanies and follows delusions. It has also shown that interventions that are successful in reducing negative affect tend to attenuate delusions as well. Taken together, this research renders support to the notion of a causal role of negative affect for delusion formation and maintenance.

The second part will introduce two lines of research that are exploring the exact mechanisms that link negative affect to delusions. One possibility is that delusions arise from a failure to downregulate negative affect. Indeed, patients with delusions report to use fewer 'functional' affect regulation strategies (e.g., reappraisal). They also show a lower heart rate variability, a physiological indicator of affect regulation difficulties. Another possibility is that delusions stem from difficulties in emotional learning. This view is indirectly supported by experimental studies showing heightened fear responses to neutral faces in patients with delusions, indicating a tendency to overgeneralize and by self-reported safety behaviour, pointing to a maintaining role of avoidance.

Although these lines of research are still in their early stages, they already promise novel opportunities for intervention. These will be discussed in the last part of the talk. They include training of specific affect regulation strategies or enabling corrective social experiences. Novel technology could be used to enhance the effectiveness of this approaches, for example by prompting the use of emotion regulation strategies in daily life or by creating virtual social learning environments to promote emotional learning.

Concurrent Symposia

5. SULFORAPHANE AS A POTENTIAL ADD-ON TREATMENT STRATEGY FOR SCHIZOPHRENIA AND AUTISM: BASIC AND CLINICAL EXPERIMENTAL FINDINGS

John Davis
University of Illinois at Chicago

Overall Symposia Abstract: Autism: Basic and Clinical Experimental Findings.

There is evidence that biochemical abnormalities associated with oxidative stress, reduced ani-oxidant capacity, overactivity of inflammatory markers and abnormalities in HDAC activity and overactivity in methylation of some promotor genes, such GAD67, may be involved in the underlying pathophysiology of schizophrenia and autism. Sulforaphane (SFN: 1-isothiocyanato-4-methylsulfinylbutane) is an organosulfur isothiocyanate derived from a

glucosinolate precursor (glucoraphanin) found primarily in the cruciferous vegetable broccoli, which has chemical properties both as an antioxidant and an HDAC inhibitor, and some of its epigenetic effects also resulted in decreasing the expression of several methylation enzymes DNMT1 and DNMT3a and DNMT3b. There are some studies in mice showing that treatment with sulforaphane can ameliorate or reverse cognitive deficits and histological changes induced by phencyclidine, which has been used as an animal model for schizophrenia. Although one small open label trial in 7 patients with schizophrenia suggested that sulforaphane may improve these subject's performance on some cognitive tests, there have been no double-blind studies of the potential efficacy of add-on treatment with sulforaphane for schizophrenia. One double-blind clinical study involving 44 subjects with autism showed that sulforaphane significantly improved patient's scores on 2 autism behavioral scales. In the proposed symposium we will review the biochemical and pharmacokinetic properties of sulforaphane and its sources, and present results from three double-blind placebo controlled studies of sulforaphane effects in patients with schizophrenia and autism. John Fahey will discuss the biochemical properties of sulforaphane and his studies of pharmacokinetics, absorption and bioavailability along with biochemical correlates of efficacy from preliminary studies. Renrong Wu will present results from a study of sulforaphane done with 151 subjects in china diagnosed with first-episode schizophrenia. In that study we found statistically significant effects of sulforaphane on reducing cognitive deficits schizophrenia on several domains measured on the MATRICS Battery- Spatial Working Memory, Reasoning and Problem Solving, and Verbal Learning. Faith Dickerson will present results from a study of sulforaphane patients with chronic schizophrenia, where preliminary results show effects of the treatment on working memory. Since there are no generally effective add-on drugs for treating cognitive deficits in schizophrenia, these results with sulforaphane may have clinical significance if additional studies confirm our findings. Robert Smith will present the results form a study of 110 subjects with autism in China who received sulforaphane or placebo for 12 weeks; the sulforaphane subjects showed significant improvement on the OSU autism rating scale (OASR) on both total scores and several of the subscale scores as well as overall global improvement on CGI scale. Side effects of sulforaphane in all the studies were minimal. Sulforaphane has already been investigated as a potential efficacious nutrachemcial for treating some cancers with potential for possible approval as a drug formulation in the future. This symposium will show its potential for treatment of neuropsychiatric diseases and encourage further research in this area.

5.1 SULFORAPHANE FROM BROCCOLI FOR NEUROPSYCHIATRIC DISORDERS: OVERVIEW OF BIOCHEMISTRY, SAFETY, BIOAVAILABILITY, AND MECHANISMS OF EFFICACY

Jed Fahey

Johns Hopkins University Medical School

Background: Sulforaphane (SF) is a phytochemical from broccoli, derived from a stable and abundant precursor glucoraphanin (GR) and. It is an isothiocyanate with over 3000 published studies that examine its efficacy in rodent and other mechanistic disease models. SF is known in particular for its antibacterial, antifungal, antioxidant, and cytoprotective properties. SF is formed by the conversion of the vacuole-entrained precursor GR, to SF, mediated by myrosinase, an enzyme that is compartmentalized and sequestered in the cell, until released

upon cell lysis. GR is also converted to SF by the microbiota in the gastrointestinal tract. SF is rapidly absorbed by the GI tract and it rapidly distributes to cells throughout the body. It is a highly promising agent currently under preclinical and clinical evaluation for disease prevention. Depending on its use, SF (and GR) can be considered foods, dietary supplements, or natural product-based drugs. We and others have generated extensive animal and human clinical evidence on the bioavailability of both GR and SF.

Methods: We will review studies from our own and other groups exploring the underlying biochemical abnormalities associated with neurodevelopmental illness, and discuss how the underlying biochemical effects of sulforaphane that may counteract these deficits, and which types of markers may be useful in monitoring in treatment strategies and clinical trials.

Results: Several basic physiological pathways have been associated with neurodevelopmental and/or neurodegenerative conditions. To name a few, they include: redox metabolism/oxidative stress including reduced glutathione synthesis, mitochondrial dysfunction and low oxidative phosphorylation, increased lipid peroxidation, immune dysregulation, neuroinflammation, febrile illness associated with the heat shock response, and synaptic dysfunction. There is extensive evidence from in vitro and clinical studies, that SF counteracts many of these same biochemical and molecular abnormalities. Importantly, SF is a food-sourced small molecule that can cross the blood-brain-barrier and quickly reach the CNS to exert its protective effects. There have been over 50 clinical trials to date examining pharmacokinetics, pharmacodynamics, and disease mitigation of SF.

We have identified biomarkers that can be used to assess the functioning of these pathways that could even guide novel treatment strategies to correct these biochemical abnormalities or to improve core and associated symptoms of some of these conditions. A key mechanism of action of SF is the activation of the transcription factor Nrf2, which regulates the expression of at least 2% of the coding human genome, inducing an extensive array of cytoprotective responses. Upon its interaction with specific cysteine residue sensors on the cytoplasmic tether peptide Keap1, SF frees Nrf2 to translocate to the nucleus and activate transcription of a coordinate set of genes coding for phase 2 detoxification enzymes. Separately, SF also has potent anti-inflammatory, heat shock-response-inducing, and histone deacetylase (HDAC) inhibiting properties.

Conclusions: Sulforaphane may have a broad range of potential uses in treating many medical conditions. The information on sulforaphane's pharmacokinetics and biochemistry, and the biochemical markers that may be utilized in future clinical studies, provide basic information which will help participants better understand and interpret the potential mechanisms underlying sulforpahane's clinical effects in studies reported in this symposium.

Sulforaphane is a compound- whether classified as a food, nutritional chemical supplement, or potential drug—which has mechanisms of action which may be useful in treating several types of illness, including psychiatric neurodevelopmental illnesses. The biological and pharmacokinetic background presented will help in furthering clinical trials

5.2 EFFICACY OF ADD-ON SULFORAPHANE FOR IMPROVING COGNITION AND SYMPTOMS IN FRIST-EPISODE SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND STUDY

Renrong Wu*[1], Robert C. Smith[2], Gangrui Hei[1], Ranran Li[1], Jianjun Ou[1], Xueqing Song[3], Yinjun Zheng[4], Yiqun He[5], Jen Arriaza[6], Jed W Fahey[7], Brian Cornblatt[8], Dongyu Kang[1], Ye Yang[1], Jing Huang[1], Xiaoyi Wang[1], Kristin Cadenhead[9], John M. Davis[10], Hua Jin[11], Jingping Zhao[1]

[1]*The Second Xiangya Hospital of Central South University,* [2]*NYU Medical School, NKI, ,* [3]*The First Affiliated Hospital of Zhengzhou University,* [4]*The Affiliated Brain Hospital of Guangzhou Medical University,* [5]*The Second Affiliated Hospital of Xinxiang Medical University,* [6]*School of Professional Studies, New York University,* [7]*Center for Human Nutrition, International Health,* [8]*Nutramax Laboratories,* [9]*University of California, San Diego,* [10]*Univ of Illinois, Chicago,* [11]*University of California San Diego and Psychiatric Service*

Background: Cognitive symptoms are common and associated with significant dysfunction in schizophrenia. Oxidative stress, inflammation and epigenetic modifications involving HDAC and methylating enzymes have been implicated in some of the risk factors or underlying pathophysiology of schizophrenia. Sulforaphane has chemical properties both as an antioxidant and an HDAC inhibitor. One published study suggests it have beneficial effects in autism. Studies in PCP animal models of schizophrenia suggest it may be effective on improving some of the cognitive deficits and underlying pathophysiological abnormalities in schizophrenia. However, no large sample trials have been done to examine the efficacy of sulforaphane in treating cognitive and psychotic symptoms in schizophrenia. The objective of the current study was to determine the efficacy and safety of sulforaphane as an add-on treatment for patients with first episode schizophrenia and particularly its effects on cognitive symptoms.
Methods: This double-blind randomized trial was conducted from November 2016 to June 2019 in 4 psychiatric institutions in China. Patients with first-episode schizophrenia with minimum PANSS >75 were enrolled and followed for 22 weeks. The patients were randomized to 3 groups (low and high doses of sulforaphane vs placebo) and symptomatic and cognitive assessments were done at multiple time points. The Avmacol® tables contained glucoraphanin and active myrosinase which converted to sulforaphane with the estimated delivery of approximately 48 and 72 umol of sulforaphane daily in the low and high dose group. The primary outcome was change in the MATRICS Composite score and secondary outcome changes in MATRICS Domain scores. Additional secondary outcomes were change PANNS Total score PANSS 5-factor scores, and change in side-effect scales scores.
Results: A total of 172 patients with first-episode of schizophrenia were enrolled and randomized into 3 study groups and 151 patients had at least 1 follow up evaluation. In the mixed -model intention-to-treat analysis, sulforaphane significantly improved performance scores on several Domains of the MATRICS battery, spatial working memory (P= 0.004), reasoning-problem solving (P= 0.063), and verbal learning (P= 0.031) (Overall effect sizes d=.26-.35). It did not improve global cognitive function as measured by the MATRICS overall composite score. There were no effects on PANSS symptom scores. Sulforaphane was well tolerated and side effects were very low and infrequent.
Conclusions: If these positive effects of sulforaphane on selected aspects of cognitive function in schizophrenia can be replicated, it may be useful as an add-on treatment for reducing cognitive deficits in schizophrenia. Cognition is a different aspect of schizophrenia than symptoms, and it's possible that even a small benefit in cognition, added to that produced by standard treatment, could make a clinical important difference, if these findings replicate in additional studies.

5.3 EFFICACY OF ADD-ON SULFORAPHANE FOR IMPROVING SYMPTOMS AND COGNITION IN SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND STUDY

Faith Dickerson*[1], Robert Yolken[2]

[1]*Sheppard Pratt,* [2]*Johns Hopkins University School of Medicine*

Background: The consumption of cruciferous plants such as broccoli and cauliflower has been associated with a reduced risk of cancer and other chronic diseases. This beneficial effect has been ascribed largely to the plants' high content of glucosinolates which are converted to isothiocyanates such as sulforaphane. Sulforaphane crosses the blood brain barrier and has antioxidant and anti-inflammatory activities. A previous trial in males with autism found that adjunctive sulforaphane was associated with improvements in some indicators of social functioning and aberrant behavior. The primary aim of the current study was to evaluate the safety and efficacy of an adjunctive sulforaphane nutraceutical for individuals with schizophrenia in a placebo-controlled, randomized double blind trial.
Methods: : Individuals with schizophrenia or schizoaffective disorder, most of whom had long-standing illness and who had residual psychotic symptoms of at least moderate severity were randomized to receive 6 tablets per day of 16 mg of glucoraphanin, which is metabolized following ingestion yielding approximately 100 micromoles of sulforaphane, or identical-appearing placebo added to usual psychiatric medications. The study duration was 16 weeks following a 2 week placebo run-in. The primary outcome was change in the severity of psychiatric symptoms, measured biweekly by the Positive and Negative Syndrome Scale (PANSS) over the double-blind phase. The secondary outcome was change in cognitive functioning, measured by the MATRICS Consensus Cognitive Battery (MCCB), from the beginning to the end of the trial. Mixed effects models were used to evaluate the relationship between the administration of the sulforaphane precursor and change in symptoms or cognitive functioning during the study period. Exploratory analyses were performed to examine the association between levels of the sulforaphane metabolite, dithiocarbamate, in urinary samples and changes in the outcome measures.
Results: A total of 64 participants were randomized (mean age 44.0 (±12.0) years); 58 participants, 29 in the active arm and 29 in the placebo arm, completed the 18 weeks of the trial. There were no significant differences in the change of positive, negative, general, or total PANSS symptom scores between groups including all of the randomized participants or the subgroup of individuals who completed the study. There was also no significant improvement in MCCB total or domain scores by treatment group in the entire cohort. However, there was a significant association between glycophorin treatment and improvement in the MCCB working memory domain in individuals with urine concentrations of dithiocarbamate of > 1 mmol/L . Reasons for the differences in sulforaphane metabolism are not known with certainty but may be related to host genetics, the composition of the gastrointestinal microbiome, or medication compliance. The study medication was well tolerated with no significant difference in the number of adverse events between groups.
Conclusions: The trial did not demonstrate an overall benefit of adjunctive sulforaphane for psychiatric symptoms or cognition in schizophrenia. Sulforaphane may result in improvement in working memory for the subset of persons who generate dithiocarbamate following treatment

5.4 SULFORAPHANE AS A TREATMENT FOR AUTISM: REPORT OF A RANDOMIZED DOUBLE-BLIND STUDY

Robert Smith*[1], JanJun Ou[2], Russel Tobe[3], Jen Arriaza[4], Hua Jin[5], John M. Davis[6], Renrong Wu[7], Jingping Zhao[7]

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Background: Some underlying biochemical abnormalities in Autism Spectrum Disorder (ASD) may be associated with oxidative stress and lower antioxidant capacity, depressed glutathione synthesis, reduced mitochondrial function and oxidative phosphorylation, increased lipid peroxidation, and increased neuroinflammation. Sulforaphane (SNF) has chemical properties which may counteract some of these deficits. A double-blind study in the US found that sulforaphane ameliorated several measures of ASD symptoms, a finding supported by some open trials. We present results from a larger double-blind study of sulforaphane effects on children with ASD in China.

Methods: 110 children, ages 5-15, with a diagnosis of ASD, were enrolled in a 12 week randomized double blind study of sulforaphane or matched placebo, using Avmacol® tablets (Nutrimix Laboratories). Dosage was based on weight ranging from 2 ,4, 6 or 8 tablets /day. Outcomes measures, evaluated at bassline and weeks 4, 8 and 12, included a clinician rated scale, Ohio State Autism Rating Scale (OARS-4),Clinical global Improvement (CGI-I) and several caregiver rated scales- Social Responsiveness Scale (SRS), Repetitive Behavior Scale – Revised (RBS-R), and social relatedness sub-scale from the Autism Behavior checklist. Side-effects were rated using the SAFTEE scale and laboratory measures collected at baseline and 12 weeks. Statistical analysis used intent to treat mixed model analysis of covariance, using both differences score from baseline and actual scores at each time point.

Results: 94 patients were available for analysis of treatment effects if they had at least one post drug treatment study evaluation. The intent to treat mixed model analysis showed that sulforaphane improved ratings more than placebo on the clinician rated CGI-I ($P<.0001$) and on the OARS with significant decreases on OARS total average scores ($P=0.002$) and sub-scores of impaired social interaction ($P=.0006$) and communication barriers ($P=.003$) but not stereotyped behaviors ($P=0.300$). 90% of SFN treated subjects showed at least mild improvement or better (score 3 or less) on the CGI-I by week 12 compared to 41% of PLO subjects. However, there were no significant changes in scores on the caregiver rated scales (SRS, RSR, Autism Checklist (social relating behavior sub-scale). For OARS total average difference scores, and impaired social interaction scores, patients over 10 yrs. of age showed a greater decrease than younger patients. For OARS scores patients with lower surrogate IQ scores ($IQ<60$ score) showed a greater improvement that patients with higher scores ($IQ\geq60$ score) although the interaction effects of IQ and treatment effect were not statistically significant. Side effects were low; there were few difference between placebo and sulforaphane groups on SAFTEE scale and no clinically significant difference between the groups on changes in routine laboratory values.

Conclusions: Sulforaphane produced significant decrease in autism scores on a clinician rated scale with some significant reductions in symptoms occurring as early as 8 weeks of treatment. The SNF treatment was safe and well tolerated. We cannot fully assess reasons for the lack of changes in parent-caregiver rated scores. However, it may be due to the (a)relatively short length of treatment, since the initial Zimmerman study reported maximum changes in some of these scales at 18 weeks' treatment, and/or (b) our ASD subjects were in a highly supportive educational placement that facilitated robust observations of professional staff that were elicited during clinician administered ratings with input from other support providers beyond family.

6. CURRENT ADVANCES IN DIGITAL COGNITIVE ASSESSMENT AND INTERVENTION FOR PSYCHOSIS

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Overall Symposia Abstract: Cognitive impairments are a hallmark feature of psychosis and include deficits in traditional cognitive domains (e.g., memory, attention, executive function) as well as cognitive biases (e.g., jumping to conclusions, belief inflexibility). These significantly impact both clinical and functional outcomes in psychosis and are a prime target for psychosocial interventions. Cognitive assessment often involves performance of experimental tasks while many psychosocial interventions are conducted in group settings, both of which have become challenging in the context of the current COVID-19 pandemic. Restrictions to in-person contact have led many researchers to postpone research studies or consider other alternatives. Individuals with psychosis have also seen reduced access to mental health services, particularly psychosocial interventions. These restrictive measures can have direct negative effects on patient outcomes, including increased risk for relapse and hospitalization. The growing field of digital mental health has been propelled to the forefront as researchers and clinicians move towards virtual research and intervention. Digital technologies have the potential to lead to more standardized measures of cognition, recruit larger samples from broader communities, and take advantage of the opportunity for automated and more frequent data capture. Despite this, there is no "gold standard" digital cognitive assessment battery for schizophrenia and the efficacy of virtual psychosocial interventions has yet to be established.

This symposium describes the current state of digital cognitive assessments and interventions for psychosis, probes into their efficacy, and highlights promising future directions. Dr. Lavigne will provide a scoping review of the literature on digital cognitive assessment in severe mental illness and introduce two novel web-based assessments of cognitive biases in psychosis. Dr. Guimond will present recent work on acceptability, validity, and reliability of smartphone-based assessment of cognition. Dr. Torous will discuss digital phenotyping methods to identify patient clusters based on cognition and clinical course in schizophrenia. Finally, Dr. Best will present a systematic review and meta-analysis on evidence-based cognitive and psychosocial interventions for schizophrenia-spectrum disorders delivered through virtual care.

Digital mental health research has taken the spotlight in recent months in light of the worldwide COVID-19 pandemic. This symposium will provide researchers and clinicians alike with a better understanding of the currently available tools and of the important considerations for digital cognitive assessment and treatment in psychosis. The advancement of digital technology solutions for psychosis will benefit schizophrenia research well-beyond current events, as it encourages standardization, improved accessibility to research and treatment, and recruitment of larger and more widespread samples. We hope that this overview of current directions encourages further studies in digital mental health to improve the quality of digital research and clinical practice surrounding cognitive impairments in psychosis.

6.1 REMOTE COGNITIVE ASSESSMENT IN SEVERE MENTAL ILLNESS: OVERVIEW OF CURRENT TRENDS AND AN ONLINE OPEN SOURCE IMPLEMENTATION

Katie Lavigne*[1], Genevieve Sauve[2], Delphine Raucher-Chéné[1], Martin Lepage[1]

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Background: Many individuals diagnosed with severe mental illness (e.g., schizophrenia) experience cognitive deficits and biases in decision-making that negatively impact clinical and functional trajectories. Within the context of the current COVID-19 pandemic, both clinicians and researchers must adapt traditional in-person assessment methods for remote delivery. However, while many cognitive tests can be easily administered via these methods, others may not be so easily translatable to the digital world. Moreover, the validity of remotely supervised or unsupervised cognitive tests remains in question, particularly for vulnerable populations, such as schizophrenia. We conducted a systematic review of the literature on digital assessment of cognition and cognitive biases in severe mental illness to (1) map currently available measures and their psychometric properties, (2) identify facilitators and barriers to remote assessment, and (3) highlight directions for future research. Based on our findings, we then developed two open-source cognitive bias tasks (jumping to conclusions, bias against disconfirmatory evidence) for remote delivery.
Methods: Our systematic review was preregistered on the Open Science Framework (https://osf.io/cbzq8) and was based on the following criteria: (a) peer-reviewed articles; (b) include individuals with a diagnosis involving severe mental illness (e.g., schizophrenia, bipolar disorder); and (c) report on remote assessment of cognitive capacity and/or cognitive biases. Articles were screened and data extraction was performed according to predetermined variables, including study design, study population, remote measure, psychometric properties assessed, facilitators, barriers, and future directions. Extracted data were synthesized and illustrated using the logic models methodology.
Results: Of the 24,519 retrieved articles, 29 were included in our review. We categorized cognitive measures into the 7 MATRICS consensus domains (speed of processing, attention, working memory, verbal memory, visual memory, reasoning, and social cognition) with the addition of a cognitive bias domain. Remote assessment measures were available for all domains across several platforms (web, tablet, smartphone), though few were open source and remote norms were not available. Psychometric properties were rarely assessed but those that were generally showed good correspondence with traditional assessments. Facilitators included test standardization and authentic adaptation of traditional tests, whereas barriers included device variability, user digital competence and illness severity.
Conclusions: While many digital cognitive assessments exist across a variety of platforms, there is currently no gold standard for remote cognitive assessment in severe mental illness. Currently available measures show promise but have not been systematically tested in remote settings. Future directions include further psychometric validation, implementation of additional measures, development of norms, and utilization of open source resources. As a first step, we will introduce two open source implementations of cognitive bias tasks (jumping to conclusions,, bias against disconfirmatory evidence) and preliminary psychometric properties in a remotely assessed schizophrenia sample.

6.2 ASSESSING COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA WITH A SMARTPHONE APP

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Background: Processing speed and cognitive flexibility are two cognitive domains that are frequently impaired in schizophrenia. However, it remains challenging to evaluate these

impairments in clinical settings. Smartphone applications (apps) could provide the opportunity to assess cognitive impairments in a more accessible way. Yet, no smartphone-based cognitive assessments have been validated for schizophrenia. In this study we assessed the acceptability, validity, and reliability of the Jewels Trail Tests to assess cognition in schizophrenia.
Methods: All participants completed the standard pen-and-paper Trail Making Tests and smartphone-based versions, named the Jewels Trail Tests, in-lab at baseline and remotely on a weekly basis for three months. After quality control of the data, a total of 26 individuals with schizophrenia and 34 healthy controls was kept in our analyses. We investigated the convergent validity and test-retest reliability of the Jewels Trail Tests. We also investigated how variables such as symptom severity and screen size may affect cognitive performance at baseline, and how practice effects and self-reported mood and sleep may affect cognitive performance longitudinally.
Results: Cognitive performances from the Jewels Trail Tests significantly and moderately correlated with those from the Trail Making Tests (Parts A: $r = 0.57$, $p < .001$; Parts B: $r = 0.58$, $p < .001$). Moderate test-retest reliability and low percentages of variance were observed between the first and second completion time of the Jewels Trail Tests (Jewels A: $r = .63$, $p < .001$, $s2 = 0.03\%$; Jewels B: $r = .53$, $p < .001$, $s2 = 0.12\%$). We found no significant effects of symptom severity nor screen size at baseline ($p > .05$). Over the three-month study period, participants completed the Jewels A on average 6.7 times (SD = 5.5, range = 1, 24) and the Jewels B on average of 5.6 times (SD = 4.9, range = 1, 21). No practice effects were observed during the 3-month period ($p > .05$). Self-reported mood and sleep over the weeks showed a significant effect on cognitive performance on the Jewels A (mood: $F(9, 234) = 4.89$, $p < .001$; sleep: $F(9, 196) = 3.10$, $p < .001$), but not Jewels B ($p > .05$).
Conclusions: Our results support the preliminary validity and reliability of using the smartphone-based Jewels Trail Tests to measure processing speed and executive functioning in schizophrenia. Our findings also suggest that smartphone-based cognitive assessments are a promising tool for people with a mental health disorder, such as schizophrenia. Future research to develop additional cognitive tests for cognitive domains impacted in schizophrenia as well as other mental illnesses are warranted.

6.3 CHARACTERIZING THE CLINICAL COURSE AND COGNITION IN SCHIZOPHRENIA WITH DIGITAL PHENOTYPING

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Background: Digital phenotyping methods offer the potential to better understand the lived experiences of patients with serious mental illnesses like schizophrenia. Yet to date it is unclear if the digital biomarkers offered from this method are unique to certain conditions like schizophrenia, or rather are shared by diverse populations, and to what degree digital phenotyping data are correlated with patient and clinician assessments.
Methods: 60 patients with schizophrenia and 48 healthy controls collected smartphone digital phenotyping data for a three month duration including measures of geolocation, physical activity, screen use, cognition, and self reported surveys. In-clinic assessments at study start and at three months assessed cognition (Brief Assessment of Cognition in Schizophrenia), psychosis symptoms (Positive and Negative Symptom Scale; PANSS) and other measures. Clustering and correlational methods were utilized to compare active and passive data streams both within and across groups.

Results: Adherence to active data (surveys and cognitive assessments) on the phone was roughly 50%, both for those with schizophrenia as well as for the healthy controls. Four unique clusters that included both active and passive data emerged for each group and the clusters were distinct with unique symptoms, cognition, and passive data metrics. Each group also possessed distinct correlations between active and passive data, with the schizophrenia group having more statistically significant findings especially around sleep.
Conclusions: Digital phenotyping methods offer the potential to identify unique clusters of patients based on both their self-reported as well as passive data. Future research will explore the utility of these clusters in predicting functional outcomes and offering personalized treatment.

6.4 EXAMINING THE EFFICACY OF EVIDENCE-BASED PSYCHOSOCIAL INTERVENTIONS FOR SCHIZOPHRENIA-SPECTRUM DISORDERS DELIVERED THROUGH VIRTUAL CARE

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Background: Schizophrenia-spectrum disorders are among the most persistent and debilitating mental illnesses worldwide, and most treatment options are delivered in person. Individuals with severe mental illnesses such as schizophrenia-spectrum disorders are projected to be among the most affected by the COVID-19 pandemic, and associated social restrictions, however, most treatments for schizophrenia-spectrum disorders are offered in-person. Social restrictions associated with COVID-19 have made delivering in-person treatment problematic, and many services have either been delayed or moved to virtual delivery. However, it is unclear what interventions have an evidence-base for virtual delivery. Objectives: The objectives of the current knowledge synthesis were to:

1) Determine which evidence-based interventions for schizophrenia-spectrum disorders have been empirically examined for virtual delivery

2) For any interventions that have been studied for virtual delivery, determine the efficacy of virtual delivery through meta-analysis

Methods: Ten separate systematic reviews were conducted to examine virtual delivery for each of the ten evidence-based psychological interventions for schizophrenia-spectrum disorders recommended by the American Psychological Association: assertive community treatment, cognitive adaptation training, cognitive behavioural therapy, cognitive remediation, family psychoeducation, illness management and recovery, social learning / token economy, social skills training, supported employment, and acceptance commitment therapy.
Results: Only cognitive remediation, cognitive-behavioural therapy, and family psychoeducation have more than two studies examining their efficacy through virtual care. Virtual delivery of cognitive remediation produced moderate effects on neurocognition ($g = 0.35$) and functioning ($g = 0.33$). Virtual delivery of cognitive behavioural therapy produced moderate effects on symptoms ($g = 0.39$) and small effects on functioning ($g = 0.18$). There were insufficient studies of family psychoeducation with equivalent outcome measures to assess quantitatively, however, studies of virtually delivered family psychoeducation suggested that it is feasible, acceptable, and potentially effective. Delivery through mobile applications was the most common virtual delivery method and few studies compared in-person to remote delivery of the same intervention.
Conclusions: Overall there is a clear lack of evidence for the virtual delivery of evidence-based interventions for schizophrenia. The studies that have been conducted are promising,

however, further research is required to determine how to make remote delivery most effective. Of the examined interventions, cognitive remediation has the most evidence for virtual delivery, with effect sizes similar to those observed in meta-analyses of the intervention. Cognitive behavioural therapy and family psychoeducation have also demonstrated some promising studies of virtual delivery, however, future research is required. Examining the virtual delivery of psychological interventions for schizophrenia should be a critical research priority to ensure this population has access to services when in-person services are not possible.

7. PSYCHOSIS AROUND THE GLOBE: NOVEL INSIGHTS FROM A 3 COUNTRY PROGRAMME IN THE GLOBAL SOUTH (INTREPID)

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Overall Symposia Abstract: There are striking global inequities in our knowledge and treatment of psychotic disorders. Over 80% of the world's population live in the global South, but less than 10% of research on psychotic disorders is done in these settings. This has two important implications. First, our knowledge of psychotic disorders, especially of the basic epidemiology, of associated risk factors, and of course and outcome, is incomplete and may be distorted. We simply do not know whether psychoses manifest, occur, and develop in the same ways around the world: there is some evidence to suggest not, but the data are not robust and myths abound. Second, we do not have robust and replicated findings on which to base the development of accessible, humane, and effective services in low resource settings.

INTREPID (International Programme for Research on Psychotic Disorders) is a multi-country programme of research in 3 settings in the global South: India (Tamil Nadu), Nigeria (Oyo State), and Trinidad. The aims of the programme are to investigate the incidence, aetiology, course and outcome, and treatment of psychotic disorders, using population-based cohorts of cases with an untreated psychotic disorder (~ 220 per site; ~ 660 total) and controls with no history of psychotic disorder (~ 220 per site; ~ 660 total). The programme comprises four interconnected studies focusing on: (1) incidence and presentation; (2) 2 year course and outcome; (3) help-seeking by and impacts on individuals and families; and (4) the co-occurrence of physical health problems.

This is the first multi-country programme in the global South in 40 years. This symposium brings together four sets of analyses form the programme that provide novel insights on incidence, presentation, risks, and help-seeking. In the first, Roberts et al compared incidence rates between sites and by core demographics, finding especially high rates in Trinidad and notable variations in incidence by gender and age. In the second, Ayinde et al compared neurodevelopmental markers between cases and controls across all sites, finding evidence that, across sites, those with a psychotic disorder were more likely to have a family history of mental illness and to score lower in all domains on cognitive tests than age- and sex-matched controls without psychosis. In the third, Lee Pow et al compared cannabis use between cases and controls across all sites, finding strong evidence that, overall, cannabis use was associated with psychotic disorder, but that this varied greatly by site, suggesting that cannabis use may be a more important target for intervention in Trinidad and Nigeria than India. Finally, Raghavan et al examined patterns of help-seeking, finding that use of professional mental health services and traditional practitioners for psychosis varied considerably between settings, suggesting

context-specific approaches are needed to identify, engage, and treat those with a psychotic disorder.

Together, these findings point to both similarities (e.g., in associations with neurodevelopmental markers) and differences (e.g., incidence, cannabis use, help-seeking) across sites, with important implications for our understanding of psychoses and for the development of effective services.

7.1 RATES OF UNTREATED AND FIRST EPISODE PSYCHOSIS IN THREE DIVERSE SETTINGS

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Background: There are striking global inequities in our knowledge of the incidence, aetiology, and outcome of psychotic disorders. We do not know, for example, whether findings from the global North on variations in incidence and presentation generalise to low resource settings. Extending research to consider more diverse settings has the potential to provide important new insights into the nature, aetiology, and outcome of psychoses. We established the INTREPID programme to investigating these aspects of psychotic disorders in 3 sites in the global South – in India (Tamil Nadu), Nigeria (Oyo State), and Trinidad. In this paper, we compare demographic characteristics and incidence rates across the sites.

Methods: In each site, to identify untreated cases of psychoses aged 18 to 64 years in defined catchment areas (comprising around ~ 600,000 people at risk in each) we established case detection systems comprising mental health services, traditional and spiritual healers, and key informants. Inclusion criteria were age of 18-64, resident in catchment area, presence of a ICD-10 psychotic disorder, and no more than one continuous month of treatment with antipsychotic medication prior to the start of case identification. Researchers in each site routinely monitored all components of the detection system to identify new cases over a two-year period. Information on clinical presentation and demographic characteristics was collated from interviews and clinical notes for all cases identified.

Results: In the two year period of case identification, we identified 259 cases in India, 128 in Nigeria, and 578 in Trinidad. Age and sex standardised incidence rates were markedly higher in Trinidad (51.6 [per 100,000 person years], 95% CI 47.4-55.8) than in India (20.8, 95% CI 18.3-23.4) and Nigeria (10.8, 8.9-12.8). There were also differences in the age and sex profiles of cases in each site. In Trinidad, cases tended to be younger (mean age 32 years vs. 42 in India and 36 in Nigeria), more were men (59% vs.42% in India and 51% in Nigeria), and more had a diagnosis of an affective psychotic disorder (32% vs. 5% in India and 8% in Nigeria).

Conclusions: Our findings suggest there may be differences in rates of psychoses and in the clinical and demographic profiles of cases across economically and socially distinct settings.

7.2 NEURODEVELOPMENTAL MARKERS AND PSYCHOTIC DISORDERS IN INDIA, NIGERIA, AND TRINIDAD

Olatunde Ayinde*[1], Olufemi Philippe Idowu[1], Tessa Roberts[2], Georgina Miguel Esponda[3], Alex Cohen[4], Helen Weiss[5], John Sujit[6], Joni Lee Pow[7], Casswina Donald[8], Bola Olley[1], Robin M. Murray[2], Rangaswamy Thara[6], Gerard Hutchinson[9], Craig Morgan[10], Oye Gureje[11]

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Background: Evidence suggests that psychotic disorders, particularly schizophrenia, neurodevelopmental markers, such as cognitive impairments of developmental origin. However, to date, the vast majority of evidence on this originates from a small number of settings in North America, Western Europe and Australasia. Robust population-based data from more diverse contexts are needed to further examine the contribution of neurodevelopmental risk factors to the emergence of psychotic disorders, where the prevalence of neurodevelopmental risk factors may vary. In this paper, we present an analysis of data from three diverse catchment areas, with populations at risk of ~ 600,000 in Tamil Nadu (India), Oyo state (Nigeria), and northern Trinidad, on neurodevelopmental risk factors for psychosis.
Methods: In each site, individuals with an untreated psychotic disorder were identified through a comprehensive case detection system that included professional, folk, and popular sectors. During a two-year period, we recruited and assessed 220 cases in India, 210 in Nigeria, and 212 in Trinidad. Inclusion criteria were age of 18-64, resident in catchment area, presence of a ICD-10 psychotic disorder, and no more than one continuous month of treatment with antipsychotic medication prior to the start of case identification. Diagnoses were confirmed through a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, administered by a trained researcher and reviewed by a psychiatrist. Controls matched for age, sex and neighbourhood were also recruited in each site. Detailed data on demographic characteristics, cognitive functioning, family history of mental illness, and premorbid adjustment were collected using validated measures.
Results: Parental history of psychosis was more common among cases compared with controls both overall and across the sites (e.g., all sites: cases 32/588 (5.4%) vs. controls 7/589 (1.2%), $X2 = 16.6$, $p < 0.001$). Cases scored consistently lower than controls overall on all the domains of BACS (verbal memory: $z = -8.0$, $p < 0.001$; digit sequence: $z = -8.6$, $p < 0.001$; motor function: $z = -11.1$, $p < 0.001$; verbal fluency, animal score: $z = -8.9$, $p < 0.001$; verbal fluency, A score: $z = -7.3$, $p < 0.001$; verbal fluency, B score: $z = -6.8$, $p < 0.001$; symbol coding: $z = -8.5$, $p < 0.001$; tower of London score: $z = -9.2$, $p < 0.001$). However, cases in India scored lower than controls only on motor function ($z = -3.4$, $p = 0.001$) while cases in Nigeria and Trinidad scored lower than controls on all the domains.
With regard to premorbid adjustment, cases in Trinidad scored higher than their counterparts in both Nigeria and India on sociability and withdrawal ($X2 = 19.6$, $p < 0.001$) and peer relationships ($X2 = 27.4$, $p < 0.001$). On early adolescent adjustment, cases in Trinidad scored higher than cases in Nigeria and India on sociability and withdrawal ($X2 = 59.4$, $p < 0.001$), peer relationships ($X2 = 48.1$, $p < 0.001$), academic performance ($X2 = 52.6$, $p < 0.001$), and adaptation to school ($X2 = 42.4$, $p < 0.001$). Nigerian cases scored higher than Indian cases on

sociability and withdrawal and scholastic domains. However, Indian cases scored higher than both Nigerian and Trinidadian cases on social and sexual domains ($X2 = 214.5$, $p < 0.001$).

Conclusions: We found evidence that, across sites, people with a psychotic disorder were more likely to have a family history of mental illness and to score lower in all domains on cognitive tests than age- and sex-matched controls without psychosis. These findings support the relevance of neurodevelopmental pathways to psychosis across diverse populations.

7.3 CANNABIS USE AND PSYCHOTIC DISORDERS IN INDIA, NIGERIA AND TRINIDAD

Joni Lee Pow*[1], Tessa Roberts[2], Casswina Donald[3], Georgina Miguel Esponda[4], Gerard Hutchinson[5], Craig Morgan[6], Helen Weiss[7], Robin Murray[8], Oye Gureje[9], Rangaswamy Thara[10], Alex Cohen[11], Sujit John[12], Olatunde Ayinde[13], Bola Olley[13]

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Background: Recent meta-analyses have confirmed a strong dose-response relationship between cannabis use and risk of psychotic disorders. However, to date this research comes almost exclusively from North America, Western Europe, and Australasia. The association between cannabis use and psychosis has not been examined across more diverse populations, despite the fact that around 85% of the world's population lives in the global South (Africa, Asia, Latin America and the Caribbean). Robust population-based data from these contexts are needed to better understand the contribution of cannabis use to psychotic disorders across diverse settings. In this paper, we analyse data from the INTREPID Programme, conducted in three diverse catchment areas with populations at risk of ~ 600,000 in Tamil Nadu (India), Oyo state (Nigeria), and northern Trinidad, on cannabis use and psychotic disorders.

Methods: In each site, individuals with an untreated psychotic disorder were identified through a comprehensive case detection system that included professional, folk, and popular sectors. During a two-year period, we recruited and assessed 220 cases in India, 210 in Nigeria, and 212 in Trinidad. Inclusion criteria were age of 18-64, resident in catchment area, presence of a ICD-10 psychotic disorder, and no more than one continuous month of treatment with antipsychotic medication prior to the start of case identification. Diagnoses were confirmed through a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, administered by a trained researcher and reviewed by a psychiatrist. Controls matched for age, sex and neighbourhood were also recruited in each site. Detailed data on demographic details and substance use were collected using the MRC Sociodemographic Schedule and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).

Results: Cannabis use varied greatly by country (70% of cases and 85% of controls had used cannabis in Trinidad, compared with 25% of cases and 14% of controls in Nigeria, and 4% of cases and 1% of controls in India). After adjusting for country, there was evidence of a strong association between psychosis and having ever used cannabis (OR=1.94, 95%CI 1.40-2.68). This association was stronger for men (OR=2.35 95%CI 1.60-3.46) than women (OR 1.58,

95%CI 0.95-2.64). There was no evidence of a strong association between psychosis and frequency of cannabis use during the past 3 months.
The odds of psychotic disorder were higher for those who first used cannabis at age 15 years or younger (OR 1.6 95% CI 1.07-2.39, adjusting for country). Having a higher level of dependency, as measured by the ASSIST substance involvement score, for cannabis was associated with increased odds of psychotic disorder (e.g., high dependency: OR 3.73, 95% CI 1.16-11.9).

Conclusions: We found evidence that cannabis use is associated with psychosis and varies greatly by site, suggesting that this may be a more important target for intervention in Trinidad and Nigeria than India. A limitation of this research is that cannabis use was measured after the onset of psychosis, so the direction of causation cannot be established. Services that address substance use among those with psychoses may be particularly warranted in Trinidad. We recommend further research into variation in types of cannabis and the subjective experience of cannabis use.

7.4 A COMPARISON OF HELP-SEEKING FOR PSYCHOTIC DISORDERS IN INDIA, NIGERIA AND TRINIDAD

Vijaya Raghavan[1], Sujit John[1], Tessa Roberts[2], Georgina Miguel Esponda[2], Alex Cohen[3], Helen Weiss[4], Joni Lee Pow[5], Casswina Donald[5], Bola Olley[7], Olatunde Ayinde[7], Robin Murray[2], Oye Gureje[8], Gerard Hutchinson[9], Craig Morgan[10], Rangaswamy Thara[11], Vijaya Dhandapani*[1]

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Background: Help-seeking patterns for psychotic disorders are highly variable across and within populations. Effective service design and delivery requires an understanding of existing services and patterns of help-seeking, which are likely to be setting-specific. In this paper, we present findings from the INTREPID programme on variations in help-seeking between participating sites India, Nigeria, and Trinidad.
Methods: In each site individuals with an untreated psychotic disorder were identified through a comprehensive case detection system that included professional, folk, and popular sectors. During a two-year period, we recruited and assessed 220 cases in India, 210 in Nigeria, and 212 in Trinidad. Inclusion criteria were age of 18-64, resident in catchment area, presence of a ICD-10 psychotic disorder, and no more than one continuous month of treatment with antipsychotic medication prior to the start of case identification. Diagnoses were confirmed through a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, administered by a trained researcher and reviewed by a psychiatrist. Detailed data on demographic details and were collected using the MRC Sociodemographic Schedule and the Personal and Psychiatry History Schedule (PPHS).
Results: The proportion of cases who sought any help for psychosis was lower in India (77.9%) compared with Nigeria (93.9%) and Trinidad (97.7%). While only 11.0% of cases had hospital admission in India and Nigeria, 61.6% were admitted to hospital in Trinidad. Most hospital admissions were compulsory: 91.7% in India, 77.3% in Nigeria and 76.9% in Trinidad. In

Nigeria, a high rate of admission to healers' facilities was observed (59.3%), while it was low in India (6.1%) and Trinidad (1%). The use of restraint was found to be 1.4% in Trinidad, 9.7% in India and 21.1% in Nigeria. The most common first contact for cases in India was priests (35.3%) followed by faith healers (33.5%), while in Nigeria, it was faith healers (57.9%) and mental health professionals (16.6%). Mental health professionals (23.1%) and emergency services (19.2%) were the most common first contact for cases in Trinidad. While no contact with the police or justice system was observed among cases during first contact in India or Nigeria, 11.1% of cases had their first contact with police in Trinidad.
When compared with India, the number of cases who ever contacted mental health services was lower in Nigeria (OR=0.48, 95%CI= 0.32-0.73) and higher in Trinidad (OR=8.52, 95%CI=5.25-13.83). After adjusting for country, there was some evidence of differences in having ever contacted mental health services by age (OR=0.98, 95%CI=0.96-0.99), being self-employed at onset (OR=2.93, 95%CI=1.49-5.75), living with partner/spouse and children at onset (OR=3.40, 95%CI=1.16-9.94) and having more than secondary education (OR=3.18, 95%CI=1.33-7.60), but not gender.

Conclusions: We found evidence that help-seeking for psychosis varies considerably between settings, necessitating context-specific approaches to outreach and case detection. Our findings suggest a need for collaboration between health services and traditional and religious providers in India and Nigeria and between health services and police and judicial services in Trinidad. Our findings also show that many people with psychotic disorders in rural India currently receive no care, indicating an urgent need to develop more accessible services with proactive outreach programmes.

8. SUICIDAL THOUGHTS AND BEHAVIORS IN PEOPLE WITH FIRST-EPISODE PSYCHOSIS

Srividya Iyer
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Overall Symposia Abstract: Suicide is an important cause of premature death among persons with first-episode psychosis (FEP). Among FEP patients, the 10-year suicide rate is 2.6%, more than 18 times higher than that of the general population. There are critical gaps in the literature on suicide in FEP. Little is known about the evolution of suicidal thoughts and behaviors and the factors associated therewith. While many predictors of suicidal behaviors have been examined, these investigations have not been informed by coherent hypotheses about how various predictors act together. Finally, too few intervention studies have addressed suicidal thoughts and behaviors in early psychosis. Our symposium (chaired by Srividya N. Iyer and Amal Abdel-Baki, leading Canadian experts in early intervention for psychosis) addresses these gaps. First, Roxanne Sicotte (Canada), will present the results of her systematic review of longitudinal studies that found high rates of suicidal thoughts and behaviors among persons with FEP before their first contact with the psychiatric services, at entry into treatment and throughout follow-up. Suicidal thoughts and behaviors generally declined during follow-up. Roxanne Sicotte will also discuss the risk factors that were associated with suicidal thoughts and behaviors and death by suicide, and that could serve to assess suicidal risk. Next, Merete Nordentoft (Denmark) will present her unique longitudinal study of the three-year trajectories of suicidal ideation among 521 FEP patients. This study revealed three distinct trajectories characterized by the decrease, persistence and aggravation of suicidal ideation. Up to 40% of persons with FEP had persistent or increasing suicidal ideation. Merete Nordentoft will also

present clinical markers that distinguished these trajectories. Lindsay Bornheimer (USA) will address the little-studied, complex relationships in FEP between symptoms, clinical insight, cognition and suicide ideation over time. She will present data indicating that clinical insight and working memory serve as mechanisms in the relationships between depression, positive symptoms, negative symptoms, and suicide ideation. Her results underline the importance of addressing cognitive functioning in order to reduce suicidal ideation. Her finding that suicidal ideation seems to decrease when clinical insight is poorer poses a paradox, since the treatment of psychosis has tended to seek to improve insight among patients. While broader studies of risk factors and trajectories can inform efforts to reduce the risk for suicide in FEP, examinations of specific interventions are also important. Christopher Bowie (Canada) will present data from his ongoing study of a treatment for internalized stigma in early psychosis that seeks to reduce suicidal thoughts and behaviors. The treatment, Be Outspoken and Overcome Stigmatizing Thoughts (BOOST), is co-facilitated by persons with lived experience. Results from a pilot study have shown that BOOST reduces internalized stigma more than all existing interventions. Preliminary data will also be presented from a larger ongoing study (N=100) that seeks to verify the results of the pilot study and clarify the pathways by which reductions in internalized stigma can reduce suicidal thoughts and behaviors in FEP. Finally, as the discussant, Ingrid Melle (Norway) will synthesize the results from the four presentations. She will also lead a discussion on the clinical and research implications of the presented findings. Overall, this symposium will generate a better understanding of suicidal thoughts and behaviors in FEP, and of strategies to better support patients at risk of suicide and reduce mortality by suicide.

8.1 FACTORS ASSOCIATED WITH SUICIDAL THOUGHTS AND BEHAVIORS AMONG FIRST-EPISODE PSYCHOSIS PATIENTS: A SYSTEMATIC REVIEW OF LONGITUDINAL STUDIES

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Background: People with psychotic disorders are at high risk for suicide, especially in the early stages of the illness. A better understanding of the evolution of suicidal thoughts and behaviors and factors associated therewith could help to assess the suicidal risk of patients with first-episode psychosis (FEP) more accurately, and to address modifiable factors to mitigate their effect and thus reduce the risk of suicide. This study aims to investigate the evolution of suicidal thoughts and behaviors in people with FEP and identify the factors associated with suicidal ideation, suicidal attempts and death by suicide in FEP patients.

Methods: The protocol for the systematic review was registered in PROSPERO (CRD42020168050) and meets PRISMA reporting guidelines. Longitudinal studies assessing factors associated with the evolution of suicidal ideation, suicidal attempts or death by suicide in all FEP patients (including affective or non-affective FEP) were included. Relevant articles were identified through a search of databases (PubMed, Medline, PsycINFO, Embase and EBM Reviews) and a review of the references lists of relevant articles. Screening of articles, data extraction and quality assessment was carried out by two independent reviewers and disagreements were resolved by consensus. Study quality was assessed using an adaptation of the Newcastle-Ottawa scale.

Results: Out of 3177 articles, 11 studies were included with lengths of follow-up varying between 1 and 13.5 years. Nine studies were rated as being of good methodological quality.

Up to a third of FEP patients had a history of both suicidal ideation and suicide attempts prior to their first contact with psychiatric services. There was a general decrease in the prevalence of suicidal thoughts and behaviors during follow-up. However, up to 18% of patients with FEP made at least one suicidal attempt and 28% had suicidal ideation during follow-up. The rate of deaths by suicide varied between 1% and 4.2%. No factors were assessed exclusively for their association with suicidal ideation. Forty-five distinct factors were assessed for their association with suicide attempts or death by suicide. Of these, 15 were assessed by a single study. Previous suicidal behaviors (n=5 studies) and depressive symptoms (n=4 studies) were associated with an increased risk of suicidal attempts during follow-up. Males (n=2 studies) and FEP patients having more psychotic symptoms during follow-up (n=1 study) were at increased risk of death by suicide. The risk of suicide was significantly lower among people with FEP who received early intervention compared to those who received regular mental health services during the first three years of follow-up (n=2 studies).
Conclusions: Suicidal thoughts and behaviors are frequent throughout the critical period of the first five years of psychotic disorders before contact with services, at entry into services and during follow-up. Early detection and early intervention are of major importance given the high rates of suicidal thoughts and behaviors in psychosis during the period before first contact with psychiatric services. Among individuals with FEP, suicidal risk should be assessed on an ongoing basis throughout follow-up, with particular attention given to identified risk factors. Overall, the literature base is limited albeit of acceptable quality. Thus, additional well-designed longitudinal studies including all factors that may influence both suicidal ideation and behaviors are needed.

8.2 TRAJECTORIES OF SUICIDAL IDEATION IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS - SECONDARY ANALYSES FROM THE OPUS TRIAL

Merete Nordentoft[1], Karen-Inge Karstoft[2], Trine Madsen[1], Trine Madsen*[1]

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Background: Heterogeneity of suicidal ideation (SI) over time amongst patients with first-episode psychosis is expected, but prototypical trajectories of SI has not yet been established. The primary aim was to identify three-year trajectories of suicidal ideation and to examine if and how these trajectories relate to subsequent suicidality and mortality. Furthermore, we explored predictors of trajectory group membership.
Methods: Longitudinal data on 521 patients with FEP from the Danish OPUS trial was applied. Patients were assessed at treatment initiation, and after one, two, five and ten years. Data on SI from the first three assessments were included in a Latent Growth Mixture Modeling analysis to empirically identify trajectories of SI. Predictors and distal outcomes of the trajectories were estimated subsequently
Results: : Three trajectories of SI were identified. The largest class (60.7%) 'Low-decreasing', was described by patients who at treatment initiation reported SI once or a few times last year followed by a decrease to almost no SI after two years of treatment. A second trajectory 'frequent-stable' reported SI sometimes-to-frequent which remained stable over time (33.1%) and finally the last class 'frequent-increasing' represented patients reporting frequent SI at treatment initiation followed by aggravation of SI (6.2%). Compared to the low-decreasing class, the risk of persistent SI at five and ten years was significantly higher in patients from the frequent-stable and frequent-increasing classes. Further, there was a tendency towards significant differences between classes in risk of suicide at the 10 year follow-up. Clinical markers significantly predicted membership of SI trajectories.

Conclusions: Three prototypical trajectories of SI were established. Importantly the largest class consisted of patients, who over time had fewer and fewer SI , but of clinically relevance we found that having relatively frequent suicidal ideations persisted or increase in up to 40% of patients over the first couple of years in treatment.

8.3 CLINICAL INSIGHT AND COGNITIVE FUNCTIONING AS MECHANISMS IN THE RELATIONSHIPS BETWEEN PSYCHOSIS SYMPTOMATOLOGY, DEPRESSION, AND SUICIDE IDEATION AMONG INDIVIDUALS IN A FIRST EPISODE OF PSYCHOSIS

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Background: First-episode psychosis (FEP) is a particularly high-risk period in which risk for suicide death is elevated by 60% as compared to individuals in later stages of psychotic illness. Literature demonstrate poorer cognitive functioning may serve as a protective factor, and investigations of clinical insight reveal a complex relationship between suicide outcomes and increased awareness of illness or need for treatment. Clinical insight and cognition have been studied in more chronic stages of illness (e.g., schizophrenia) in relation to suicide ideation and attempt, yet, less is understood within the context of FEP. This study examined whether clinical insight and cognitive functioning served as a mechanism in the relationships between depression, positive symptoms, negative symptoms, and suicide ideation over time among individuals in FEP.

Methods: Data were obtained from the Recovery After an Initial Schizophrenia Episode (RAISE) project. Participants (n=404) included adults in FEP between ages 15 and 40. Suicide ideation was measured by the Calgary Depression Rating Scale across the full study period. Positive and negative symptoms and clinical insight were measured at baseline using the Positive and Negative Syndrome Scale. Cognitive functioning variables included working memory, attention and speed of information processing, executive functioning, verbal memory, verbal fluency, and motor speed, all of which were measured by the Brief Assessment of Cognition in Schizophrenia at baseline. Structural equation modeling was used in Mplus8 to examine the proposed mediation model.

Results: The likelihood of experiencing suicide ideation was significantly increased when positive symptoms (b=.011, SE=.01, $p < .05$) and depressive symptoms (b=.042, SE=.01, $p < .001$) were independently worse, and significantly decreased when clinical insight (b=-.048, SE=.02, $p < .05$) was poorer and working memory (b=-.011, SE=.01, $p < .05$) stronger. Greater depression related to poorer clinical insight and stronger attention and speed of information processing. Greater positive symptoms related to poorer clinical insight, stronger working memory, stronger attention and speed of information processing, and stronger verbal fluency. Greater negative symptoms related to poorer clinical insight and weaker working memory, attention and speed of information processing, executive functioning, verbal memory, verbal fluency, and motor speed.

Conclusions: Clinical insight and working memory functioned as mechanisms in the relationships between depression, positive symptoms, negative symptoms, and suicide ideation. As depression decreased and positive and negative symptoms increased, clinical insight was shown to be poorer, which in turn related to decreased suicide ideation. As positive symptoms increased and negative symptoms decreased, working memory was shown to be stronger, which in turn related to decreased suicide ideation. Implications surround the importance of approaches aiming to strengthen cognitive functioning given the relationships between cognition and suicide ideation in FEP. Also, of importance, practitioners should have

awareness of the insight paradox in practice given the complex and dynamic relationships between clinical insight and suicide thoughts and behaviors.

8.4 PREVENTION OF INTERNALIZED STIGMA TO REDUCE SUICIDAL THOUGHTS AND BEHAVIORS IN EARLY PSYCHOSIS

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Background: Internalized stigma, defined as the application of negative stereotypes about a diagnostic group to one's self, is the strongest predictor of the extraordinarily high rates of suicidal thoughts and behaviors in schizophrenia and other psychoses, accounting for over half the variance. Recent evidence has suggested that interventions targeting internalized stigma may be of critical importance to reducing suicide in this population, however, few effective interventions have been developed and even fewer individuals have access to these services.
Methods: Be Outspoken and Overcome Stigmatizing Thoughts (BOOST) is a treatment for internalized stigma in early psychosis, co-created and co-facilitated by those with lived experience. We will present results of an initial pilot study as well as interim analyses of an ongoing study aimed at reducing suicidal thoughts and behaviors.
Results: In our initial pilot study, BOOST demonstrated significant improvements in internalized stigma, self-esteem, and quality of life. Despite BOOST demonstrating the largest effect size improvement on internalized stigma of any intervention currently evaluated (Cohen's d = 0.76), the small sample size limits generalization. Our ongoing study is collecting data on 100 people with early episode psychosis and delivering the intervention remotely.
Conclusions: This study and its findings have implications for clarifying the pathway from internalized stigma and associated symptoms to suicidal thoughts and behaviors. Targeting negative self-beliefs early in illness course to prevent internalized stigma is proposed as a model for reducing suicidal thoughts and behaviors.

9. EFFECTS OF THE COVID-19 PANDEMIC ON CLINICAL OUTCOMES IN THE PSYCHOSIS SPECTRUM

Jonathan Wynn

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Overall Symposia Abstract: The COVID-19 pandemic has negatively impacted the lives of nearly every person worldwide. Social and financial disruptions due to social distancing mandates and anxiety about virus exposure have negatively affected mental health and social functioning. People on the psychosis continuum may be particularly impacted due to already having poorer mental health and community functioning. This panel will present data on pandemic effects in people on the psychosis continuum. Dr. Anne Giersch (France) will present data collected from participants in the community who self-report prodromal psychosis symptoms induced or increased by the pandemic. Dr. Giersch will show that prodromal psychotic symptoms decreased over time and that urbanicity impacted the decline in symptoms due to a subjective decrease in environmental noise during confinement. Moreover, decreases in prodromal symptoms were associated with increased family contacts during confinement. Dr. Gregory Strauss (Georgia, USA) explored how negative symptoms were impacted by the pandemic in samples of people at clinical high risk (CHR), chronic schizophrenia (SZ), and

matched healthy controls. Different pattern of effects relative to pre-pandemic ratings emerged in the two psychosis groups: CHR only had increased anhedonia while chronic SZ showed increases in several domains (both expressive and experiential negative symptoms). Moreover, across groups, negative symptom severity was predicted by exacerbations in defeatist, asocial, and low pleasure beliefs. Finally, Dr. Amanda McCleery (Iowa, USA) will present data from an ongoing longitudinal study in Veterans with a chronic psychotic disorder and healthy control Veterans on the impact on clinical and community integration factors. Both groups exhibited negative impacts on mental health, including depression, anxiety, and loneliness, and decreased community integration (e.g., social network engagement, family relationship functioning, role functioning) during the initial stages of the pandemic relative to pre-pandemic levels. Contrary to expectations, those with a psychotic disorder did not report disproportionate worsening of outcomes compared to healthy controls. Finally, Dr. Monica Calkins (Pennsylvania, USA) assessed self-reported worries about the COVID pandemic in community ascertained youth with and without psychosis spectrum symptoms, youth with early psychosis enrolled in coordinated specialty care clinics (CSC), and CSC care providers. Across all groups, many participants expressed concerns about family contracting the virus, personally infecting others, or contracting and dying from COVID, and the financial consequences of the pandemic. Community youth with psychosis spectrum symptoms exhibited the most worry, while CSC early psychosis clients endorsed the least. Additionally, in all groups Black participants expressed more concern about contracting and dying from the virus than White participants. Collectively, these data demonstrate that the COVID-19 pandemic has negatively impacted the social functioning and mental health of those along the psychosis continuum. The data from the presenters demonstrate a complex pattern of effects associated with positioning on the psychosis continuum: those with prodromal symptoms show decreased symptoms over time, those at high-risk showed less impact compared to chronic psychosis, and those with early or chronic psychosis showed similar negative impacts as healthy controls. However, community youth with psychosis spectrum symptoms appear especially vulnerable to COVID specific worries. Importantly, these patterns are affected by various factors, such as environmental factors, race, and setting.

9.1 IMPACT OF THE COVID-19 PANDEMIC AND SOCIAL DISTANCING ON VETERANS WITH PSYCHOSIS: FINDINGS FROM AN ONGOING LONGITUDINAL STUDY

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Background: The COVID-19 pandemic and social distancing has impacted nearly every American, and it has disrupted many aspects of daily life. Within the Veterans Affairs (VA) system one of the most vulnerable populations to disruptions in daily and social routines are those who have a psychotic disorder (PD). In this ongoing longitudinal study, we aim to determine the impact of the COVID-19 pandemic and social distancing on clinical symptoms and community integration, and explore potential vulnerability and protective factors, in Veterans with PD and Veterans without history of psychosis (healthy controls or HC), and to study trajectories for recovery.

Methods: Eighty-one PD and 74 HC participated in the study. Data collection for the initial study visit started in May 2020 via telephone interview with trained assessors. Questionnaires assessing clinical symptoms (depressed mood, anxiety, loneliness, suspiciousness), community

integration (social network engagement, role functioning, relationship functioning), and vulnerability and protective factors (tolerance of uncertainty, perceived stress, defeatist beliefs, resilience, and coping strategies) were administered. Rating periods for all questionnaires were past 30 days (i.e., "current"). In addition, for the clinical and community integration measures, participants were also asked to retrospectively evaluate their functioning during the month of January 2020, prior to the COVID-19 pandemic (i.e., "pre-COVID"). Data were analyzed using MANOVA.

Results: For the clinical factors, there was an overall main effect of group (i.e., PD more symptomatic) [$F(5, 140) = 4.86$, $p < 0.001$], and a main effect of rating period (i.e., higher levels of current symptoms vs. pre-COVID period) [$F(5, 140) = 37.93$, $p < 0.001$]. The group x rating period interaction was not significant [$p = 0.46$]. For the community integration factors, there was a main effect of group (i.e., lower community integration in PD) [$F(5, 138) = 23.90$, $p < 0.001$], and a main effect of rating period (i.e., lower community integration in current vs. pre-COVID period) [$F(5, 138) = 2.53$, $p = 0.03$]. The group x rating period interaction effect was not significant [$p = 0.48$]. The two groups did not significantly differ on the vulnerability and protective factors [$p = 0.39$]. Data collection and analyses for the follow-up assessments are currently underway, and the available results will be presented.

Conclusions: Following the onset of the COVID-19 pandemic and social distancing, Veterans with and without PD report significant impact and disruption to their daily lives. This was reflected by an increase in self-reported severity of clinical symptoms and a lower level of community integration compared to the pre-COVID rating period. As expected, Veterans with PD exhibited higher levels of clinical symptoms and were less integrated into the community. However, contrary to expectations, Veterans with PD did not report a disproportionate worsening of these factors. This may be reflect availability and utilization of comprehensive VA services available to Veterans with PD (e.g., housing and financial support, medical and mental health services), which may help to mitigate the impact of the pandemic. The two groups did not differ on the vulnerability and protective factors. It is possible that individual differences on these factors will predict which individuals are less impacted and can adapt more readily to pandemic-related disruption to their daily and social routines. Longitudinal follow-up is currently underway. We will examine trajectories for clinical recovery and community integration, and their predictors, as Veterans adapt to the COVID-19 pandemic and social distancing.

9.2 LONGITUDINAL IMPACT OF THE PANDEMIC AND CONFINEMENT ON PRODROMAL PSYCHOTIC SYMPTOMS IN THE GENERAL POPULATION

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Background: Anxiety and stress, loneliness, and the urban environment are factors that have all been associated with prodromal psychotic experiences. The pandemic and resulting confinement orders, associated with social distancing, can be expected to affect all these factors, which may in turn impact prodromal psychotic symptoms. We aimed to explore whether one or several of the factors associated with psychosis induced or increased psychosis-like symptoms in the general population during the pandemic. Additionally, we examined if communication skills and the ability to express oneself through daily narratives or social connections helped alleviate any of the effects of the pandemic on psychosis-like symptoms.

Methods: We explored prodromal psychosis, symptoms in a longitudinal study by means of the 16-Item Prodromal Questionnaire (PQ-16). One hundred fifty unselected French

participants contacted through the internet filled in questionnaires at 4 different time points: before, during, at the end, and after confinement orders. We additionally evaluated anxiety, stress and depression, loneliness, the frequency of social contacts with e.g. family, the subjective experience of noise and social competition, access to nature, and demographic variables. Participants were asked to write a narrative daily about what happened to them that day. Narratives were analyzed with the software Tropes. We analyzed how the different factors mediated the change in symptoms over time by means of mediation analyses.
Results: Overall, psychosis scores were maximal before the confinement started, with 18% of the participants with prodromal psychotic symptoms. Scores then decreased across the 4 successive time points (4% of the participants with prodromal symptoms in the last questionnaire), which mirrored a decline over time with the concern about the pandemic. Initial psychosis scores were correlated with depression, anxiety and stress scores, such that those self-reporting larger prodromal psychotic symptoms reported greater symptomatology. At the environmental level, unusual thought content was largest in big cities relative to smaller cities. Mediation analyses revealed that several factors predicted the decrease in psychosis-like symptoms. The decrease was especially marked in large, urban cities relative to small, suburban cities and was predicted by the subjective decrease of environmental noise levels during confinement. The link with environmental noise decrease was largest for unusual perceptions. Regarding daily narratives, several factors suggested an additional influence of communication skills in mediating the effects of the pandemic on psychosis-like symptoms. The distress associated with psychosis prodromal symptoms was largest in those participants who provided the smallest number of narrations, and was reflected in the narrations. The proportion of emotional words in the initial narrations was indeed highest in participants reporting more severe symptoms on the PQ-16. Finally, contacts with family increased during the confinement and this increase was found to be associated with a decrease in prodromal psychosis symptoms.
Conclusions: The results confirm that the general public endorsed distressing prodromal psychosis symptoms associated with the pandemic. In the present study, prodromal symptoms unexpectedly decreased rather than increased during the course of confinement orders. Mediation analyses suggested that environmental factors (i.e., noise levels in large urban areas) are related to prodromal psychosis symptoms. The results also revealed that social contact and communication skills are protective factors against reporting psychotic symptoms.

9.3 THE IMPACT OF THE COVID-19 PANDEMIC ON NEGATIVE SYMPTOMS IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS AND OUTPATIENTS WITH CHRONIC SCHIZOPHRENIA

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[1]*University of Georgia*

Background: Negative symptoms are core features of schizophrenia-spectrum disorders that are frequently observed across all phases of illness. By their nature, COVID-19 social isolation, physical distancing, and health precautions induce behavioral aspects of negative symptoms. However, it is unclear whether these prevention measures also lead to increases in experiential negative symptoms, whether such effects are equivalent across individual negative symptom domains, and if exacerbations occur equivalently across phases of illness.
Methods: The current study compared negative symptom severity scores obtained during the pandemic to pre-pandemic assessments in two samples: 1) outpatients with chronic schizophrenia (SZ: n = 32) and matched healthy controls (CN: n = 32); 2) individuals at clinical high-risk for psychosis (CHR: n = 25) and matched CN (n = 30).

Results: Pre-pandemic ratings of negative symptoms were clinically elevated in SZ and CHR groups, which did not differ from each other in severity. In SZ, ratings obtained during the pandemic were significantly higher than pre-pandemic ratings for all 5 domains (alogia, blunted affect, anhedonia, avolition, asociality) and item-level analyses indicated that exacerbations occurred on both experiential and behavioral symptoms of anhedonia, avolition, and asociality. In contrast, in CHR only anhedonia increased during the pandemic compared to pre-ratings, and item level analyses indicated that behavioral scores for avolition and asociality increased, whereas experiential did not. Furthermore, exacerbations in defeatist beliefs, asocial beliefs, and low pleasure beliefs predicted increases in negative symptom severity across groups.
Conclusions: Findings suggest that negative symptoms worsened in both SZ and CHR during the pandemic. Negative symptoms should be a critical treatment target during and after the pandemic in both SZ and CHR populations given that they are critically related to poor functional outcome, low rates of recovery, and risk for conversion. During the current pandemic, or in future pandemics, psychosocial interventions (e.g., CBT) can be effectively delivered via teletherapy to target the psychological mechanisms (e.g., defeatist beliefs, asocial beliefs, low pleasure beliefs) associated with negative symptoms in SZ and CHR populations.

9.4 COVID-19-RELATED STRESS IN YOUTH WITH PSYCHOSIS SPECTRUM SYMPTOMS DURING THE PANDEMIC

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Background: There is urgent global concern about the mental health impact of the COVID-19 pandemic on individuals experiencing or at-risk for psychosis. Emerging research suggests a range of pandemic impacts to which youth with psychosis may be exposed, including increased infection risks, exacerbation of psychosis and associated symptoms (e.g. anxiety, depression, suicidality, substance use), social isolation, occupational dysfunction, and alterations or interruptions in mental health treatment access and delivery. However, little research has examined worries specifically associated with COVID-19 and its sequelae. Recent findings suggest that the general population experiences more distress about family contracting COVID and unknowingly infecting others, than of themselves contracting COVID (Barzilay et al. 2020). Given the vulnerability of individuals with psychosis and opportunity to inform interventions, we sought to evaluate specific aspects of COVID related worries in youth with psychosis spectrum (PS) symptoms.
Methods: Participants (n=158; 55% female; age 22% 13-17, 60% 18-29, 18% 30+; 34% Black, 52% White, 11% Other) included clients with early psychosis enrolled in Pennsylvania (PA) coordinated specialty care clinics (CSC; n=32; headsup-pa.org) and community youth previously ascertained and evaluated through the Lifespan Brain Institute as having (n=48) or not having (n=45) PS symptoms. Mental health providers (n=33) from PA CSC programs were also surveyed. Following the PA state-wide shut down and between May and August 2020, participants completed remote self-report surveys regarding personal and family COVID exposure and financial consequences. They were asked to rate worries about: (1) contracting, (2) dying from, (3) currently having, (4) family member contracting, (5) unknowingly infecting others with, and (6) experiencing significant financial burden following COVID, on a 5-point scale (0=not at all to 4=a great deal).

Results: Across the four groups, many participants were at least moderately (>=3) worried about family contracting (67%); themselves unknowingly infecting others (59%), contracting (43%) or dying from (24%); and financial consequences of (35%) COVID. Black participants reported comparatively more moderate to high worries about dying from (30%) and currently having (28%) COVID than White participants (19%, 12% respectively). Among all four groups (ANOVA), community youth with PS symptoms endorsed the highest total level of COVID related worries (M=16.7, SD=6.7; p's <0.05), while early psychosis CSC clients endorsed the lowest (M=11.9, SD=5.19). Community ascertained youth with PS symptoms particularly worried about having or dying from COVID more than all other groups (MANOVA, p's <0.05). A minority of participants (11%) reported having been tested for COVID (2% tested positive); the majority (81%) reported no COVID symptoms.
Conclusions: Stress and worry associated with the COVID-19 pandemic are experienced by a majority of respondents, including those with and without PS symptoms, and especially by Black individuals. Community youth with PS symptoms appear especially vulnerable to COVID related stress, highlighting the need for screening and outreach. Our small sample of early psychosis CSC ascertained clients endorsed comparatively fewer worries; this could reflect protective benefits of program participation, but requires future examination of alternative explanations (e.g., socioeconomic differences among respondents). Complementary survey data obtained from CSC clients and providers will inform how implementation and perceptions of treatment (e.g., telehealth) during the pandemic are related to COVID stress levels.

10. MUSCARINIC CHOLINERGIC RECEPTOR AGONISTS AND ALLOSTERIC MODULATORS AS NEXT-GENERATION ANTIPSYCHOTICS

Steven Paul
Karuna Therapeutics

Overall Symposia Abstract: Muscarinic cholinergic receptors are G-protein coupled receptors that mediate the physiological actions of the neurotransmitter acetylcholine. Preclinical and clinical studies have implicated cholinergic neurotransmission, and M1 and M4 muscarinic receptors in particular, in the pathophysiology of schizophrenia and other psychotic disorders. As such, muscarinic receptors represent novel, non-dopamine receptor-blocking targets for antipsychotic drug development. This panel will cover: 1) foundational research that established muscarinic receptors as novel drug targets for antipsychotic drugs and the recent discovery of M1 and M4 orthosteric and allosteric muscarinic receptor agonists, 2) the development of a M4 PET radiotracer for clinical research, 3) recent gene expression and GWA studies directly implicating M4 muscarinic receptors in the pathophysiology of schizophrenia and, 4) recent phase 2 clinical data demonstrating robust antipsychotic effects of the muscarinic agonist xanomeline-trospium in patients with schizophrenia. Jeff Conn (Vanderbilt) will describe the role of M1 and M4 muscarinic receptors as drug targets in schizophrenia and his team's recent progress developing selective M1, M4 and M5 positive allosteric modulators (PAMs). Jason Uslaner (Merck) will describe recent work on M4 PAMs and the successful development of the first M4 PAM PET radiotracer 11C-MK-6884, a unique translational neuroimaging tool to determine receptor occupancy and changes in cholinergic neurotransmission in various neuropsychiatric diseases. Tony Altar (Splice Therapeutics) will present gene expression data in hippocampal dentate granule neurons from patients with schizophrenia, which are reversed by muscarinic agonists in an in vitro model. Dr. Altar will also present new GWAS data demonstrating that the CHRM4 locus encoding M4 muscarinic

receptors is associated with schizophrenia risk, supporting this receptor's role in schizophrenia pathophysiology. Steve Brannan (Karuna) will present recent data from a large, placebo controlled phase 2 clinical trial of xanomeline-trospium, a M1/M4-preferring muscarinic agonist, in acutely psychotic patients with schizophrenia, demonstrating marked antipsychotic effects on both positive and negative symptoms. Collectively, these diverse sets of data strongly suggest that M1 and M4 receptors are particularly compelling novel class of drug targets for the treatment of psychotic disorders like schizophrenia.

10.1 ALLOSTERIC MODULATORS OF MUSCARINIC RECEPTORS FOR TREATMENT OF MULTIPLE SYMPTOM DOMAINS IN SCHIZOPHRENIA

P. Jeffrey Conn*[1]

[1]*Vanderbilt University School of Medicine*

Background: Exciting new clinical and preclinical studies suggest that activators of M1 and/or M4 subtypes of muscarinic acetylcholine receptors (mAChRs) could provide a novel approach for improving psychotic symptoms, as well as cognitive deficits and negative symptoms in patients suffering from schizophrenia. However, a lack of highly selective molecular and genetic probes for each of the individual mAChR subtypes have made it difficult to understand the roles of these two muscarinic subtypes in modulating brain circuits and symptom domains that are relevant for schizophrenia. Also, non-selective mAChR agonists suffer from adverse effects due to activation of peripheral mAChR subtypes. We discovered and advanced highly selective positive allosteric modulators (PAMs) as well as the first highly selective agonists for M1 and M4 receptors and have also developed genetic mouse models that allow us to selectively manipulate M1 and M4 signaling in specific brain circuits. These new molecular and genetic probes are allowing us to make unprecedented advances in our understanding of the specific roles of each receptor in brain circuits that are relevant for schizophrenia, and highly optimized M1 and M4 PAMs are now advancing to clinical testing for potential efficacy in treatment of different symptom domains in schizophrenia patients.

Methods: We have focused our efforts on developing highly selective positive allosteric modulators (PAMs) of both M1 and M4 that have excellent properties for in vivo studies and as drug candidates that can be advanced to clinical testing. In addition, we have developed highly selective antagonists for M1, M4, and M5 mAChR subtypes, and have established genetic mouse lines that allow selective deletion of these receptors from individual neuronal populations. We have used these novel molecular and genetic tools in combination with electrophysiology, fast scan cyclic voltammetry (FSCV), photometry, optogenetic, in vivo imaging , and behavioral approaches to develop an understanding of the specific roles of M1 and M4 in brain circuits involved in the pathophysiology underlying schizophrenia.

Results: We have reported studies suggesting that M4 PAMs have potential efficacy in reducing positive symptoms of schizophrenia and have established a novel mechanism by which M4 interacts with the metabotropic glutamate (mGlu) receptor mGlu1 to selectively inhibit dopamine release in the dorsal striatum. Interestingly, we have now found that activation of M4 does not inhibit DA release in the ventral striatum (i.e. nucleus accumbens; NAc), but that activation of M5 induces a profound increase in DA release in this region. In addition, we now report that activation of the M1 receptor activation induces a robust and long-lasting increase in excitability of somatostatin (SST)-expressing inhibitory interneurons (SST-INs) in the prefrontal cortex (PFC). Multiple studies suggest that pathophysiological loss of GABAergic inhibitory transmission in the prefrontal cortex (PFC) and other forebrain regions is important for some of the cognitive deficits in schizophrenia patients. Thus, the ability of

M1 PAMs to increase inhibitory transmission in the PFC could contribute to the beneficial effects of mAChR agonists. We are now advancing highly optimized M1 and M4 PAMs in development and have recently completed a phase I SAD study of novel M1 PAMs that generated exciting new clinical data and help validate this approach for selectively targeting specific mAChR subtypes as potential therapeutic agents.
Conclusions: Highly selective M1 and M4 PAMS have emerged as a novel approach for activation of individual muscarinic receptor subtypes and preclinical studies suggest that these two receptor subtypes may contribute to the efficacy of mAChR agonists in treatment of different symptom domains in schizophrenia patients. M1 PAMs are now in phase I clinical development and M4 PAM clinical candidates are advancing to allow studies to assess potential efficacy in reducing symptoms in schizophrenia patients. Our new data reported here provide exciting new insights into the cellular effects M4 PAMs on dopamine signaling and provide new data suggesting that M5 activation may increase DA release in NAc. Furthermore, our studies reveal novel actions of M1 PAMs in PFC that may contribute to the broad efficacy of mAChR agonists in reducing different symptom domains in schizophrenia patients.

10.2 SCHIZOPHRENIA GENE EXPRESSION, INSULIN SIGNALING DEFICITS, AND GWAS ALL IDENTIFY MUSCARINIC M4 AGONISM FOR ANTIPSYCHOTIC EFFICACY

C. Anthony Altar*[1], Swapnil Awasth[2], Ripke Stephan[3]

[1]*Splice Therapeutics,* [2]*Charité - Universitätsmedizin,* [3]*Charité - Universitätsmedizin and Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard*

Background: We found decreased mRNA expression of genes involved in mitochondrial functions and glucose and energy metabolism in schizophrenia hippocampal dentate granule neurons. Similar changes have been reported in diabetic skeletal muscle. When we treated cultured neuroblastoma cells with proteins or hormones, only insulin or IGF-1 changed gene expression opposite to the changes we found in schizophrenia. We exposed the cells to GPCR-interacting small molecules, yet only muscarinic agonists mimicked the insulin and IGF-1 effects.
Methods: Using combined data from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) and those of a large, phenotypically homogeneous GWAS of schizophrenia, we find that CHRM4 ($p = 10\text{-}16$), DRD2 ($p = 1.4 \times 10\text{-}16$), and HTR1A ($p = 4 \times 10\text{-}8$) are associated with schizophrenia, while neither CHRM1, 2, 3 or 5 nor HTR2A were.
Results: These results suggest that schizophrenia is due to a brain insulin or IGF-1 signaling deficiency and that it might be ameliorated with muscarinic agonism. The antipsychotic efficacy of xanomeline suggests muscarinic agonism as the first validated target for treating schizophrenia in 70 years since the D2 dopamine receptor, whose antagonism or stabilization through partial agonism has been common to all antipsychotic drugs.
Conclusions: Dr. Altar will describe gene expression studies in schizophrenia brain that revealed an insulin / IGF-1 signaling deficiency, consistent with a diabetes-like condition in schizophrenia brain. Insulin, IGF-1, and, uniquely among small molecules, muscarinic agonists, changed neuronal gene expression opposite to their changes in schizophrenia. These results, and GWAS association of CHRM4 ($p = 10\text{-}16$) but not CHRM1, 2, 3 or 5 with schizophrenia, identify muscarinic M4 agonism for antipsychotic efficacy.
Consent of Release of Rights I have read and agree to the above terms and conditions.

10.3 A PHASE 2 TRIAL OF XANOMELINE-TROSPIUM, A MUSCARINIC CHOLINERGIC RECEPTOR AGONIST FOR THE TREATMENT OF SCHIZOPHRENIA

Stephen Brannan*[1], Sharon Sawchak[1], Andrew Miller[1], Steven Paul[1], Alan Breier[2]

[1]*Karuna Therapeutics,* [2]*Indiana University School of Medicine*

Background: Xanomeline, an M1/M4-preferring muscarinic receptor agonist, has shown antipsychotic activity in previous clinical trials in Alzheimer's disease and schizophrenia. High dropout rates due to pro-cholinergic adverse events (ChAEs; e.g., nausea and vomiting) led to termination of xanomeline development. The combination of xanomeline with trospium, a generic anticholinergic drug that does not cross the blood-brain barrier, was developed to extract the antipsychotic efficacy of xanomeline while mitigating its associated ChAEs. A previous Phase 1 trial demonstrated that rates of ChAEs were lower in participants treated with xanomeline-trospium compared with xanomeline alone.

Methods: We conducted a 5-week, inpatient, double-blind Phase 2 RCT at 12 US sites to test the efficacy and safety/tolerability of xanomeline-trospium compared with placebo in patients with schizophrenia experiencing acute psychosis (ClinicalTrials.gov number, NCT03697252). After screening and antipsychotic washout, patients received matched capsules of either placebo capsules or flexibly dosed xanomeline-trospium, titrated based on tolerability from a starting dose of 50mg/20mg xanomeline/trospium BID to a maximum dose of 125mg/30mg BID. The primary endpoint was the least-squares mean (LSM) change in PANSS total (PANSST) score from baseline at week 5. Secondary endpoints included the LSM change from baseline at week 5 on the PANSS positive symptom subscore, PANSS negative symptom subscore, PANSS Marder negative factor score, and shifts in CGI-S score frequency counts and CGI-S responders with scores of 1 or 2 at week 5. Safety and tolerability assessments included standard AE rates, labs, and EPS rating scales.

Results: 182 patients were randomized to receive either xanomeline-trospium (N=90) or placebo (N = 92). The trial met its primary endpoint, with the xanomeline-trospium arm showing a statistically significant 11.6-point LSM change in PANSST score from baseline to week 5 compared to placebo (-17.4 vs. -5.9 points; $P < 0.0001$; effect size: 0.75). Xanomeline-trospium treatment also led to statistically significant LSM change from baseline to week 5 in PANSS positive subscore, PANSS negative subscore, PANSS Marder factor score, and CGI-S score frequency count compared with placebo (all $P < 0.0001$). Two participants in each arm discontinued treatment due to treatment-emergent AEs (TEAEs). The most common AEs associated with xanomeline-trospium treatment (≥5%) were constipation, nausea, dry mouth, dyspepsia, and vomiting. These AEs were rated as mild or moderate in severity and did not lead to treatment discontinuation. Rates of somnolence, weight gain, restlessness, and extrapyramidal symptoms (EPS) were similar in the xanomeline-trospium and placebo arms.

Conclusions: Xanomeline-trospium treatment for 5 weeks led to statistically significant, clinically meaningful differences in positive and negative symptoms compared to placebo in acutely psychotic patients with schizophrenia. In addition, xanomeline-trospium treatment was associated a low TEAE-related discontinuation rate, no discontinuations due to mild-to-moderate pro-cholinergic AEs, and little or no association with sedation, weight gain, or EPS. These data support Phase 3 development of xanomeline-trospium for the treatment of schizophrenia and suggest that M1/M4-preferring muscarinic agonists may represent a promising new class of antipsychotic drug.

10.4 A TRANSLATIONAL STRATEGY TO EXPLORE THE POTENTIAL FOR MUSCARINIC M4 POSITIVE ALLOSTERIC MODULATORS (PAMS) IN THE

TREATMENT OF CNS DISEASE: UTILITY OF THE NOVEL M4 PAM PET TRACER [11C] MK-6884

Wenping Li[1], Eric Hostetler[1], Jason Uslaner*[1], Fiona Marshall[1]

[1]*Merck Research Laboratories*

Background: We have investigated the potential of muscarinic acetylcholine receptor 4 (M4) positive allosteric modulators (PAMs) for the treatment of neuropsychiatric disorders. Novel M4 PAMs were identified and demonstrated efficacy in preclinical models predictive of antipsychotic effects at plasma concentrations that produced fewer adverse effects than observed with less selective agonists. An M4 PAM PET tracer suitable for measuring central receptor occupancy (RO) was discovered. [11C]MK-6884 was designed to bind with high affinity and selectivity to the allosteric site on the M4 receptor. The affinity of [11C]MK-6884 was found to be modulated by the presence of orthosteric agonist in vitro and in vivo. We evaluated the ability of [11C]MK-6884 to quantify M4 target engagement by therapeutic PAMs in both monkey and human. We performed PET studies in monkey, human volunteers and AD patients in the presence of the acetylcholinesterase inhibitor donepezil in order to evaluate the sensitivity of tracer binding to changes in synaptic acetylcholine (agonist) levels.
Methods: In vivo imaging studies of [11C]MK-6884 were performed in rhesus monkeys in the absence and presence of M4 PAMs to assess RO. PET scans were collected for 90 min and striatal non displaceable binding potential was determined. Clinical PET scans were performed to determine PET tracer binding potential in healthy elderly (HE) and determine target engagement of an M4 PAM therapeutic candidate in healthy subjects. Additional HE received a titration regimen of oral donepezil and PET scans were performed to determine changes in striatal binding potential. Finally, PET studies were performed to evaluate the utility of [11C]MK-6884 in AD patients.
Results: [11C]MK-6884 showed promising imaging characteristics in monkey and human with a large displaceable M4-specific signal and low test-retest variability. PET studies were successful in determining the RO of PAM molecules for the purpose of modeling the relationships between drug plasma exposure, RO, and efficacy. [11C]MK-6884 PET studies conducted in the presence of Donepezil in Rhesus and healthy human subjects increased the tracer binding potential confirming the influence of cholinergic tone on [11C]MK-6884 binding . Consistent with a presumed cortical deficit in synaptic acetylcholine, [11C]MK-6884 PET studies in AD patients showed lower cortical binding potential values compared to HE.
Conclusions: We conclude that modulation of M4 receptor pharmacology provides a promising strategy for the treatment of psychiatric disorders. The development of the M4 PAM PET tracer [11C]MK-6884 provides a useful tool to determine the receptor occupancy of M4 PAM candidates during clinical development and can be used as a probe to study changes in cholinergic neurotransmission in disease. Enigma Biomedical Group have an exclusive license agreement with Merck & Co., Inc., for the global development and commercialization of MK-6884. This allows Enigma and its partner, Cerveau Technologies Inc. to provide biomarkers to industry and academia to accelerate research in the field of neurodegenerative diseases

11. TRANSLATING THE BIOMARKERS OF SCHIZOPHRENIA TO CLINICAL SETTING: A PRECISION PSYCHIATRY APPROACH

Raymond Chan

Institute of Psychology, Chinese Academy of Sciences

Overall Symposia Abstract: One of the challenges for the global mental health in the past decade is to identify effective biomarkers for early identification and intervention of psychosis. Despite this growing focus, much remains unknown regarding the mechanisms underlying the development of psychosis and the sensitivity and specificity of these potential biomarkers. This symposium will focus on the clinical utility of some promising biomarkers and their applications to facilitate the precision approach of schizophrenia to clinical settings. Four speakers will present work on this issue.
Prof. James Waltz (Maryland Psychiatric Research Centre) will adopt a computational psychiatry approach to support measures pertaining to the representation and use of uncertainty in learning and decision-making are predictive of severity of positive symptoms in schizophrenia. Prof. Raymond Chan (Institute of Psychology, Chinese Academy of Sciences) will provide up-to-date findings to re-orientate the important roles of neurological soft signs in precision psychiatry for psychosis. Prof. Vijay Mittal (Northwestern University) will evaluate three novel types of biomarkers assessment (language features, automated facial emotion analysis and instrumental motor function) for clinical high-risk youth. His findings show that use of automated analyses and standardized assessments have potential clinical application. Prof. Kathryn Eve Lewandowski (McLean Hospital, Harvard Medical School) will adopt a hierarchical cluster analysis to identify subgroups of psychotic disorders with similar motivational profiles. Her findings highlight 4 subgroups of patients with distinct patterns of motivational impairments.

Finally, Prof. William Carpenter (Maryland Psychiatric Research Centre) will integrate the above findings into a precision psychiatry framework and facilitate a discussion of them. Overall, this symposium will provide attendees with an up-to-date perspective on precision approach to psychosis.

11.1 COMPUTATIONAL PHENOTYPING FOR PSYCHOSIS: EXAMPLES FROM ANALYSES OF REINFORCEMENT LEARNING AND DECISION-MAKING

James Waltz*[1]

[1]*Maryland Psychiatric Research Center*

Background: Behavioral, computational, and neural variables assessing constructs from Reinforcement Learning (RL) and Decision-making (DM) paradigms have frequently been shown to correlate with measures of symptom severity, cognitive impairment, and functional outcome, in psychotic illness. Such constructs include the strength of reward prediction error (PE) signals. While quantifications of these constructs have generally been found to relate to deficits in cognition and motivation, other subprocesses of learning and DM, such as the signaling of unvalenced PEs and the ability of uncertainty about value to drive adaptive fluctuations in learning rates (the ability of positive and negative PEs to drive learning) and decisions to explore lesser-known reward contingencies in the service of obtaining information, have been found to correlate with measures of both negative and positive symptom severity.
Methods: We administered probabilistic RL paradigms, in conjunction with fMRI scanning, to two cohorts of patients with schizophrenia spectrum disorders (SZ) and controls. In order to examine relationships between positive symptom severity and switching behavior, we used a three-card probabilistic RL task (after Hernaus et al.2), where reward contingencies abruptly shifted after participants reached a performance threshold. In this task, subjects selected one of three card decks, identified by color. A choice of the deck with the highest expected value led to a 100-point gain on 70% of trials and a 50-point loss on 30% of trials, while choices of two non-optimal decks led to 100-point gains on 50% and 30% of trials (and 50-point losses on

50% and 70% of trials), respectively). Subjects were instructed to try to identify the optimal deck as quickly as possible. In order to examine relationships between positive symptom severity and the strength of unsigned PE signals, we used a probabilistic RL task adapted from Pessiglione et al.1. In the task, subjects simultaneously learned 3 discriminations: i) a "Gain-Miss" pair, where possible outcomes were a 25-cent gain or no gain; ii) a "Loss-Avoid" pair, where outcomes were either a 25-cent loss or no loss; and iii) a non-monetary pair, with pictorial feedback. In all three pairs, a choice of the "correct" stimulus led to the better outcome 70% of the time, while a choice of the "incorrect" stimulus led to the better outcome 30% of the time. We estimated neural responses using a priori regions-of-interest (ROIs) in amygdala, anterior insula, and three striatal subregions. We computed psychotic symptom scores using the four reality distortion items from the Brief Psychiatric Rating Scale (BPRS; Suspiciousness, Grandiosity, Unusual Thought Content, and Hallucinations).

Results: In the context of the three-card probabilistic RL task with dynamic contingencies, we observed that "readiness to switch", as captured by the proportion of post-reversal losses leading to switches to alternative decks, related to positive symptom severity. Modeling analyses revealed that SZ patients with more severe negative symptoms showed less dynamic range, surrounding contingencies shifts, in modulating learning rates. We found that psychotic symptom scores from the BPRS were positively correlated with unvalenced PE signals evoked by the Pessiglione task in the limbic (ventromedial), associative (dorsolateral), and motor (dorsomedial) striatum, bilaterally.

Conclusions: These results provide further evidence that measures pertaining to the representation and use of uncertainty in learning and decision-making (such as the signaling of unsigned PEs, e.g.) relate systematically to the severity of positive symptoms and may have potential as sensitive, non-invasive markers of antipsychotic treatment efficacy.

11.2 RE-ORIENTATION OF NEUROLOGICAL SOFT SIGNS: IMPLICATIONS FOR PRECISION PSYCHIATRY FOR PSYCHOSIS

Raymond Chan*[1], Xin-lu Cai[1]

[1]*Institute of Psychology, Chinese Academy of Sciences*

Background: Increasing efforts to identify alternate expressions of mental disorders that are broader than the DSM or ICD diagnostic criteria reflects a growing consensus that multidimensional expressions of psychiatric disorders may advance the search for underlying etiological or modulatory factors. These alternate phenotypes or 'endophenotypes' of disorders may be more specific and amenable to objective measurement than clinical symptoms, which presumably reflects variation among smaller numbers of genes than more distal clinical symptoms. This presentation aims to address three unresolved issues of a promising endophenotype, neurological soft signs (NSS), including the debate of specificity of NSS across the different diagnostic groups of neuropsychiatric disorders, the predictive value of NSS on prognosis and outcome of schizophrenia, and the heritability of NSS.

Methods: The abridged version of Cambridge Neurological Inventory was administered to schizophrenia patients in three independent studies. The lifespan study recruited 738 schizophrenia patients, 155 unaffected first-degree relatives of schizophrenia patients, 256 individuals with schizotypy, 379 other psychiatric patients, and 1577 healthy controls. The predictive study of NSS recruited 39 patients with first-episode schizophrenia, 39 individuals with ultra-high risk (UHR), 39 individuals with schizotypy and 39 healthy controls. The heritability study recruited 267 pairs of monozygotic twins, 124 pairs of dizygotic twins, and 75 pairs of patients with schizophrenia and their non-psychotic first-degree relatives.

Results: Findings from lifespan study showed that individuals along the schizophrenia continuum exhibited elevated levels of NSS, with moderate effect sizes, in contrast to other psychiatric patients who had minimal NSS, as well as healthy controls. Schizophrenia patients exhibited a flat but overall elevated pattern, in contrast to a U-shaped pattern in healthy controls. Findings from the predictive study showed that individuals with UHR exhibited a higher prevalence of sensory integration items than individuals with schizotypy and healthy controls. Discriminant analysis also yielded an accuracy of 85.9% to classify individuals with UHR from healthy controls. Findings from heritability study demonstrated moderate but significant heritability in the healthy twins. Patients with schizophrenia also correlated significantly with their first-degree relatives on NSS.
Conclusions: Taken together, these findings support the endophenotype hypothesis of NSS by associating it with the neurodevelopmental model of schizophrenia. These findings also highlight the reo-orientated important roles of NSS in schizophrenia research and implicate for precision psychiatry for psychosis.

11.3 TRANSLATIONAL APPLICATIONS OF BIOMARKER RESEARCH FOR CLINICAL HIGH-RISK YOUTH

Vijay Mittal*[1], Tina Gupta[1], Derek Dean[2], Matt Goldrick[1], Laura Sichlinger[1], Emily Cibelli[1]

[1]*Northwestern University,* [2]*University of Colorado Boulder*

Background: Psychotic disorders include characteristic patterns of emotive and motor dysfunction. Prospective high-risk research has routinely reported similar deficits in the prodromal syndrome, but to date, there have been limited efforts to translate such biomarker research into clinically relevant applications. This study evaluates three novel types of biomarker assessment (language features, automated facial emotion analysis and instrumental motor function) that lend well to widespread clinical use (e.g., they use widely available information as a primary data source, are easily standardized, not expensive, and do not require specialized training to administer) and are also sensitive to specific disease mechanisms in clinical high-risk (CHR) youth.
Methods: Samples for the three studies ranged between 34-45 CHR and 36-46 HC participants. Language features (turn pauses between the interviewer and participant) as well as facial emotions (blunted or exaggerated expression of joy, sadness, surprise, fear, anger, and contempt from the participant) were taken from structured clinical interviews of groups of CHR and matched control individuals. Motor function (focusing on average normalized jerk, a proxy for motor stability characteristic of dyskinesia) was assessed with a sample of digital handwriting. Language variables were calculated by a reliable team of raters and both emotion and motor tasks were scored with automated analysis software.
Results: While there was not significant group effect for between-turn pauses, duration was closely tied to positive symptom severity in the CHR group ((β=0.047, χ2(1)=4.13 p =0.04)). Computerized analysis of facial emotions revealed blunted expressions of joy [F(1, 74)=9.72, p=.003] but increased anger expressions [F(1, 74)=7.50, p=.008] in the CHR group and notably, emotive abnormalities were correlated with poor social functioning r =.40, p=.02. and elevated risk calculator scores r=-37, p =.02. Finally, with respect to motor dysfunction, a group of CHR youth who showed worsening symptoms over one year exhibited an elevated average normalized jerk compared to CHR participants evidencing a steady or improving course [t=2.79, p=0.01, d=0.85] and healthy controls [t=2.87, p=0.01, d=0.87].
Conclusions: Taken together, the findings suggest that biomarker analyses that utilize widely available data sources including video, audio, and handwriting can tap into core mechanistic features that distinguish CHR individuals or further, tap into disease driving mechanisms. Use

of automated analyses and standardized assessments also lend well to widespread clinical application. This presentation will discuss these findings and also highlight opinions about where the future of a digital phenotyping approach may take us.

11.4 CHARACTERIZING HETEROGENEITY IN MOTIVATIONAL IMPAIRMENTS IN PSYCHOSIS

Kathryn Lewandowski*[1], Alexis Whitton[2]

[1]*Harvard Medical School/McLean Hospital,* [2]*Black Dog Institute, University of New South Wales, Sydney*

Background: Motivational deficits are a hallmark feature of psychosis that cut across diagnostic boundaries. They are important prognostic markers as they are strongly associated with poorer community functioning and predict diminished quality of life. However, motivation is a multidimensional construct, and there likely exists considerable heterogeneity in the nature and severity of motivational impairments both within and across diagnostic boundaries.

Different patterns of motivational impairment may be associated with different patterns of clinical and functional characteristics, as well as different neurobiological markers. We aimed to identify subgroups of patients who share similar motivational profiles using a data-driven approach, and to compare emergent groups on clinical symptoms, hedonic experience, and performance-based motivated behavior.

Methods: 196 people with psychosis, including schizophrenia spectrum disorders (n=96) and mood disorders with psychosis (n=100), and 53 healthy controls, were administered measures of motivation and hedonic experience (BIS/BAS scales, Effort Expenditure for Reward Task (EEfRT), Temporal Experience of Pleasure Scale (TEPS)) as well as measures of state and trait clinical symptoms and community functioning. BAS subscales (Drive, Fun Seeking, and Reward Responsiveness) and BIS were standardized to the control sample and entered into a hierarchical cluster analysis followed by a K-means cluster analysis. Groups were compared on demographic, clinical and functional measures, and on a performance-based measure of effort cost decision making.

Results: Comparisons of patients and controls showed significant differences on BAS Reward Responsiveness ($F(2, 237)=3.80$, $p<.05$) and BIS ($F(2, 237)=8.77$, $p<.001$), but no group differences on BAS Drive or Fun Seeking. However, cluster analysis revealed a four-cluster solution, with adequate differentiation at each level ($p<.01$ – $p<.0001$). Clusters were characterized as: 1) low approach and high avoidance, 2) very low approach and intact avoidance, 3) high approach and high avoidance, and 4) selectively elevated approach and low avoidance. Clusters differed significantly on measures of depression ($F=14.27$, $p<.0001$) and state and trait anxiety ($F=20.12$, $p<.0001$ and $F=48.90$, $p<.0001$, respectively), with the low approach/high avoidance cluster showing the highest symptom levels, and the selectively elevated approach/low avoidance group showing the lowest levels, particularly in trait anxiety. Clusters did not differ on symptoms of mania or positive or negative symptoms of psychosis. Clusters differed on effort cost decision making ($F(2, 237)=4.65$, $p<.01$) and anticipatory (but not consummatory) pleasure ($F(2, 237)=7.76$, $p<.001$). There were no diagnostic differences by cluster ($\chi2(3)=3.58$, $p>.05$).

Conclusions: Across the psychosis spectrum, motivation is impaired compared at the group level; however, considerable heterogeneity is evident. Cluster analysis revealed four groups with distinct patterns of motivational impairments, which did not differ across diagnostic

boundaries but were differentially associated with depression and anxiety symptoms and in vivo measures of motivated behavior. Identification of patterns of motivational impairment may hasten understanding of the neurobiological underpinnings of this heterogeneous symptom dimension and have clinical implications for treatment.

Plenary Session

12. ASSEMBLING THREE-DIMENSIONAL MODELS OF THE HUMAN BRAIN TO STUDY DEVELOPMENT AND DISEASE

Paola Dazzan

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

Overall Abstract: This Plenary Talk will be offered by Doctor Sergiu Pasca, Associate Professor at the Psychiatry and Behavioral Sciences - Stanford Center for Sleep Sciences and Medicine and head of a laboratory that explores the biological mechanisms of brain disorders using cellular models of the human brain. In this talk, he will present his innovative work on the creation of new cellular models that can advance our understanding of human brain development and dysfunction, and their potential for the study of neuropsychiatric disorders. He will specifically discuss how, starting from pluripotent cells, models of the nervous system can be generated in the form of brain organoids, and how these can be further developed and put together to create assembloids that can be further used to investigate cell migration and formation of neural circuits. He will additionally focus on the advantages offered by these models, which can be maintained in vitro for many years and can be used reliably in multiple experiments.

12.1 ASSEMBLING THREE-DIMENSIONAL MODELS OF THE HUMAN BRAIN TO STUDY DEVELOPMENT AND DISEASE

Sergiu Pasca

Stanford University

Individual Abstract: A critical challenge in understanding the programs underlying the development, assembly and dysfunction of the human brain is the lack of direct access to intact, functioning human brain tissue for direct investigation and manipulation. In this talk, I will describe efforts in my laboratory to build functional cellular models and to capture previously inaccessible aspects of human brain development and dysfunction. To achieve this, we have been using instructive signals to derive, from pluripotent stem cells, self-organizing 3D tissue structures called regionalized brain organoids or neural spheroids that resembles domains of the developing central nervous system. We have shown that these cultures, such as the ones resembling the cerebral cortex, recapitulate many features of neural development, can be derived with high reliability across dozens of cell lines and experiments, and can be maintained for years in vitro to capture advanced stages of neural and glial maturation and function. Moreover, we demonstrated that regionalized brain organoids can be put together to form integrated structures we named brain assembloids, which can be subsequently applied to investigate cell migration and formation of neural circuits. Lastly, I will illustrate how our modular, stem-cell derived 3D system can be used to study the cellular and molecular

consequences of mutations or copy number variants associated with neuropsychiatric disorders.

Concurrent Symposia

13. CAN TRANSDIAGNOSTIC MULTIMODAL APPROACHES HELP IDENTIFYING DISTINGUISHABLE BIOTYPES OF PSYCHOSIS?

Dominic Dwyer
Ludwig Maximilian University

Overall Symposia Abstract: Our ability to provide individualised treatment and make precise outcome predictions following a first psychotic episode is practically non-existent. Decades of research have shown that while factors such as earlier age of onset, male gender, longer duration of untreated illness, and insidious onset are each grossly associated with worse outcomes, none is sensitive or specific enough to be clinically useful. More recently, research has attempted to identify distinct neurobiological illness subtypes that could provide the basis for individualised treatment approaches.
Still, progress has been limited for a variety of issues. First, cohort studies of first-episode psychosis have mostly evaluated samples with schizophrenia rather than all psychoses, although diagnosis alone is not a sufficient predictor of outcome, and schizophrenia itself shows ample heterogeneity in illness course. Second, there has been variability in the approaches used to identify clinical and neurobiological predictors and correlates of outcome, with multiple methodologies being rarely integrated in a coherent mechanistic framework. Third, there has been great variability in the measures used to assess outcome.

This symposium will provide an opportunity to discuss alternative statistical, nosological and methodological approaches that could significantly advance our ability to define more precise clinical and neurobiological subtypes.

Dr. Dominic Dwyer (PostDoctoral Researcher; Male) will present new data on the clinical subtyping of psychosis. Using a novel clustering approach from cancer genetics with multidimensional clinical, demographic, functional and cognitive data, he has identified novel subgroup solutions that cross diagnostic boundaries, reveal differential longitudinal trajectories, and have novel genetic underpinnings.

Tao Li (Full Professor, China; Female) has used a top-down, cross-disorder (schizophrenia, major depression, bipolar disorder) approach, integrating genetics and neuroimaging. She will present her findings on three new biotypes in which patients clustered, according to expression levels of ZNF391 gene in the brain, performance in working memory and gray matter volume in the right inferior frontal orbital gyrus.

Lena Palaniyappan (Associate Professor, Canada; Male) will present data on the application of two different neuroimaging modalities across two distinct clinical samples. He will discuss his novel findings on the identification of a highly individualized pattern of structural dysconnectivity among patients with schizophrenia, showing that clustering patients into morphologically separable subgroups with distinct clinical characteristics is feasible.

Finally, Paola Dazzan (Full Professor, UK; Female), will discuss evidence from epidemiological, neuroimaging and integrated clinical trial studies that while supporting the

presence of individual clinical and neurobiological subtypes, also highlight the challenges to overcome to make such subtypes meaningful and useful at clinical level.

The discussion will be led by Robin M. Murray (Full Professor, UK; Male), internationally known for his contribution to schizophrenia research. We believe the compelling scientific arguments of our symposium are made even stronger by its diversity, with balance in gender, academic seniority (three senior academics, one mid-career and one junior academic) and geographical representation (from China, Canada, UK, and Germany). We believe this diversity is crucial for a thought-provoking and stimulating discussion on the current and future of research on the heterogeneity of psychosis.

13.1 RECONSIDERING CLINICAL SUBTYPING FOR PSYCHOSIS USING NEW TECHNIQUES IN THE CONTEXT OF ILLNESS COURSE AND BIOLOGICAL READOUTS

Dominic Dwyer*[1], Janos Kalman[2], Monika Budde[2], Joseph Kambeitz[3], Anne Ruef[4], Rachele Sanfelici[1], Lana Kambeitz-Ilankovic[3], Urs Heilbronner[2], Sergi Papiol[1], Peter Falkai[5], Thomas G. Schulze[2], Nikolaos Koutsouleris[1], & the PsyCourse Consortium[1], & the PRONIA Consortium[1]

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Background: Statistical subtyping of individuals with psychosis has been conducted for over 40 years using clinical data, yet biological subtype research is currently a translational focus. In this talk, I will question whether a movement away from clinical subtyping is premature and whether new methods can be applied in clinical domains to reveal new insights about course and aetiology. I will introduce a novel clustering approach from cancer genetics that can be used with high dimensional clinical data consisting of demographics, medical history, symptoms, quality of life, general functioning, and cognition. I will then outline how the application of this method in large European studies (PsyCourse/PRONIA) has revealed novel subgroup solutions that cross diagnostic boundaries, reveal differential longitudinal trajectories, have novel genetic underpinnings, and can be superior to brain decompositions in defining clinically meaningful groups.

Methods: PsyCourse is an ongoing multi-site, naturalistic, longitudinal study with three follow-up timepoints collected at 6-month intervals across 18 sites. Discovery data contained 765 cases and replication data contained 458 cases of individuals with mostly chronic bipolar (I/II) and schizophrenia diagnoses. Sparse non-negative matrix factorisation decomposed 188 clinical variables. Mixed models were used to characterize illness courses and ANOVA was used to determine differences in polygenic risk scores for schizophrenia, bipolar disorder, depression, and education controlling for ancestry effects. A similar pipeline was applied to the PRONIA discovery cohort (n=750) of individuals at risk of psychosis, in their first episode, or with major depressive disorder with results forthcoming.

Results: In the PsyCourse cohort, five subgroups were found and labelled as affective psychosis (n=252), suicidal psychosis (n=44), depressive psychosis (n=131), high-functioning psychosis (n=252), and severe psychosis (n=86). Quadratic illness course differences were found for psychosis symptoms ($F(4,1301.21)=7.7$, $p<0.001$), depression symptoms ($F(4,1283.02)=4.6$, $p=0.001$), global functioning ($F(4,1377.08)=5.7$, $p<0.001$), and quality of

life (F(4,1319.94)=3.8, p=0.005). The depressive and severe psychosis subgroups exhibited the lowest functioning and quadratic illness courses with partial recovery followed by reoccurrence of severe illness. Differences were found for educational attainment polygenic scores, but not for diagnostic polygenic risk. Results were largely replicated in the PsyCourse validation cohort. In the PRONIA cohort, we found that biological subgroups did not exhibit the same specificity in defining clinical phenotypes or outcomes when compared to the clinical subgroups.
Conclusions: Subgroups with distinctive illness courses and specificity for a non-diagnostic genetic marker were detected that were largely superior to brain subgroups alone. New data-driven clinical approaches are important for future psychosis taxonomies that are potentially combined with biological data. Clinically, the findings suggest a practical need to consider transdiagnostic, long-term service provision focusing on a restoration of functioning in patients stratified into depressive and severe psychosis subgroups. Overall, the results highlight the potential of clinical subtyping using novel methods that may enhance research and clinical precision.

13.2 ABERRANT TRIPLE-NETWORK CONNECTIVITY PATTERNS DISCRIMINATE BIOTYPES OF FIRST-EPISODE MEDICATION-NAïVE SCHIZOPHRENIA IN TWO LARGE INDEPENDENT COHORTS

Tao Li*[1], Liang Sugai[1]

[1]*West China Hospital, Sichuan University*

Background: Schizophrenia is a complex disorder associated with aberrant functional connectivity within a triple network model comprising the default-mode, central executive and salience (SN) networks. This study investigated subtypes of brain network-level dysconnectivity associated with phenomenology of schizophrenia attempting to parse the heterogeneity of this disorder.
Methods: The study sample comprised 300 first-episode antipsychotic-naïve patients with schizophrenia (FES) and 301 healthy controls (HC). At baseline assessment, resting-state functional magnetic resonance imaging data were captured for each participant, and concomitant neurocognitive functions were evaluated outside the scanner. Clinical information of forty-nine FES in the discovery dataset were reevaluated at a 6-week follow-up. Differential features were selected from triple-network connectivity profiles between FES and HC. The cutting-edge unsupervised machine learning algorithms were used to define patient subtypes. Clinical and cognitive variables were compared between patient subgroups.
Results: Two FES subgroups with differing triple-network connectivity profiles were identified in the discovery dataset and confirmed in an independent hold-out cohort. One patient subgroup appeared to have more severe clinical symptoms was distinguished by salience network (SN)-centered hypoconnectivity, associated with greater impairment in sustained attention. The other subgroup exhibited with hyperconnectivity and manifested greater deficits in cognitive flexibility. Compared to the hyperconnectivity subgroup, the SN-centered hypoconnectivity subgroup had more persistent negative symptoms at a 6-week follow-up.
Conclusions: The present study illustrates that clinically relevant cognitive subtypes of schizophrenia may be associated with distinct differences in connectivity in the triple-network model. This categorization may foster further analysis of effects of therapy on these network connectivity patterns, which may help to guide therapeutic choices to the goals of effective personalized treatment.

13.3 SIMILARITY VS. DIVERSITY IN THE NEUROANATOMY OF SCHIZOPHRENIA: A GARDEN-PATH PROBLEM

Lena Palaniyappan*[1], Yunzhi Pan[2], Liu Zhening[3], Hongtao Ruan[4], Qiang Luo[5]

[1]*University of Western Ontario,* [2]*Institute of Mental Health of Second Xiangya Hospital, Central South University,* [3]*The Second Xiangya Hospital of Central South University,* [4]*School of Mathematical Sciences, Fudan University, Shanghai,* [5]*Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, and Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education*

Background: The neurobiological heterogeneity of schizophrenia is widely accepted, but it is unclear how mechanistic differences converge to produce the observed phenotype. The unique phenotype of schizophrenia emerges when the subtle Bleulerian dimension of negative and disorganisation symptoms blends with the more readily apparent dimension of reality distortion. For a long time, a hitherto unknown single final common mechanistic pathway has been suspected to underlie the emergence of this blend. Given the emerging evidence of heterogeneity in the neurobiology of schizophrenia, the idea of such a singular mechanistic link suddenly appears untenable. We examine this issue using evidence from 2 different cohorts and 2 different modalities of neuroimaging.

Methods: COHORT 1 (Changsha): K-means algorithm clustering was applied to regional cortical thickness values obtained from 256 structural MRI-scans (179 patients with schizophrenia and 77 healthy controls (HCs) without diagnostic separation). GAP-statistics revealed 3 clusters with distinct regional thickness patterns. The specific patterns of cortical thinning, clinical characteristics and cognitive function of each clustered subgroup were assessed. COHORT 2 (Taiwan): K-means algorithm clustering was applied to diffusion tensor imaging data from 77 HCs, and 70 patients with schizophrenia. Furthermore, we tested whether topographic diversity in patients deviates sufficiently contributing to discrimination of schizophrenia phenotype from healthy controls

Results: COHORT 1: We observed 3 clusters of patients based on thickness patterns comprised of a morphologically impoverished-subgroup (25% patients, 1% HCs), an intermediate-subgroup (47% patients, 46% HCs) and an intact-subgroup (28% patients, 53% HCs). The 3 subgroups differed in terms of age-of-onset, N-back performance, duration exposure to treatment, total burden of positive symptoms and severity of delusions. Particularly, the morphologically impoverished-group had deficits in N-back performance and less severe positive symptom burden. COHORT 2: We noted a significantly reduced between-individual similarity of the structural connectivity in patients compared to healthy controls. At a system level, we found the diversity of the topographic distribution of the strength of structural connectivity was significantly reduced in patients ($P=7.21\times10\text{-}7$, $T142=5.19$ [95% CI: 3.37−7.52], Cohen's $d=0.91$). Interestingly, when this emergent systemic property (topographic diversity) was used as a discriminant feature to train a model for classifying patients from controls, it significantly improved the accuracy on an independent sample ($T99 = 5.54$; $P<0.001$).

Conclusions: These findings suggest that a highly individualized pattern of structural dysconnectivity is to be expected among patients with schizophrenia. Nevertheless, clustering patients into morphologically separable subgroups with distinct clinical characteristics is feasible when healthy variations are taken into account. Even the highly variable features that contribute to notable heterogeneity do appear to converge on an emergent common pathway to generate the clinical phenotype of the disorder. Establishing a pathophysiological model that

accounts for both neurobiological heterogeneity and phenotypic similarity is essential to inform stratified treatment approaches.

13.4 USING MULTIPLE APPROACHES TO DISSECT THE HETEROGENEITY OF PSYCHOSIS: THEIR PROMISE AND CHALLENGES

Paola Dazzan*[1]

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Background: Difficulties in the prediction of outcome after the onset of psychosis are linked to the high clinical and biological heterogeneity of this disorder. Epidemiological cohort studies of first episode psychosis have mostly been limited to prevalence samples with schizophrenia only, which tend to have an over-representation of patients with poorer outcomes and an under-representation of those who do not remain in treatment. Also, attempts to characterise neurobiological predictors of outcome have been confounded by the lack of standardised treatment protocols in the samples investigated, and by the paucity of strong biological markers.

What these studies have shown however is that there are brain structural alterations in psychosis, subtle and diffuse, and evident in both affective and non-affective psychoses, and possibly more so in a subgroup of patients with particularly poor outcome. To achieve a more detailed definition of the neurobiological subtypes associated with poorer (or better) clinical outcomes, data from large epidemiological, multi-centre MRI studies, using integrated clinical trial approaches should be used.

Methods: This presentation will discuss evidence from large multicentre epidemiological and neuroimaging studies, conducted in multiple datasets of patients evaluated at their first episode of psychosis, and followed up clinically from 1 month to 10 years. We used estimates of incidence and longitudinal evaluation of illness course (in n=340), and neuromorphological evaluation of brain structure in these patients (n=410).

Results: In the individual datasets, we found that lack of early response to treatment (with early remission) is a strong marker of later poorer illness course, and that smaller volumes and altered brain gyrification and structural connectivity are also associated with worse short and long term outcomes. We additionally show that these morphological alterations become particularly well defined once the trajectory of illness becomes more established after the first year of treatment. Crucially, by reducing the biological (rather than clinical) heterogeneity of the samples, for example by restricting the analyses to male patients only, the significance of the brain neuromorphological predictors increases, as it does when there is good balance in the number of subjects in each outcome class.

Conclusions: This evidence suggests that while multiple, integrated approaches can help define subtypes of psychosis, there are a number of challenges, of which biological heterogeneity is one, that should be addressed to improve our ability to identify clinically meaningful and useful neurobiological subtypes of psychosis.

14. LIFESTYLE INTERVENTIONS TO REDUCE HEALTH DISPARITIES IN SCHIZOPHRENIA

Susan Azrin

National Institute of Mental Health

Overall Symposia Abstract: People with schizophrenia experience substantial health disparities, dying an average 28.5 years earlier than do adults without a psychiatric disorder. Cardiovascular disease (CVD) is the leading cause of death for people with schizophrenia, and the health risks associated with this premature mortality—which include smoking, obesity, hypertension, dyslipidemia, sedentary lifestyle, poor fitness and diet—are more common and have earlier onset in people with schizophrenia and other serious mental illnesses. While these health risks are preventable, they typically go undetected and untreated in this population. Effective lifestyle interventions to prevent and/or reduce these modifiable health risks are often unavailable to people with schizophrenia, exacerbating the heath disparities.

This symposium features research from four studies that are addressing this knowledge gap by developing and testing practical lifestyle interventions to prevent or reduce CVD health risks associated with premature mortality in people with schizophrenia and other serious mental illnesses. These studies emphasize adapting evidence-based lifestyle interventions for effectiveness with this population and for broad implementation in real-world community settings, including primary care, residential facilities and community mental health centers.

Dr. Rebecca Rossom will present final results from the SMI Wizard study. This cluster RCT involving 78 primary care clinics and 1,289 patients with schizophrenia tested a clinician-facing, electronic health record-based clinical decision support tool for improving total modifiable CVD risk.

Dr. Dilip Jeste will present preliminary data from the MIDAS trial, which targets diabetes, physical inactivity and smoking through education, dietary intervention, increasing physical activity and smoking cessation/reduction in individuals with schizophrenia and other serious mental illnesses living in Board-and-Care Homes.

Dr. Ginger Nicol will describe employing user-centered design principles to develop a prevention-focused, interactive obesity treatment approach for individuals with early-phase serious mental illness in community mental health centers and present preliminary data from the pilot RCT.

Dr. Gail Daumit will report findings on adapting the ACHIEVE evidenced-based weight loss intervention for community mental health staff delivery to individuals with serious mental illness in order to promote ease of community adoption and sustained implementation.

Dr. David Shiers of the Greater Manchester Mental Health NHS Trust is a former general practitioner who is internationally recognized for his leadership in improving the physical health of young people with psychosis and preventing their premature mortality. His comments will reflect his lived experience as a longtime family caregiver to a daughter with schizophrenia.

14.1 ADAPTING AN EVIDENCED-BASED BEHAVIORAL WEIGHT LOSS INTERVENTION FOR PERSONS WITH SERIOUS MENTAL ILLNESS FOR DELIVERY BY COMMUNITY MENTAL HEALTH PROGRAM STAFF

Gail Daumit*[1], Kimberly Gudzune[1], Arlene Dalcin[1], Stacy Goldsholl[1], Joseph Gennusa[1], Gerald Jerome[2]

[1]*Johns Hopkins Medical Institutions,* [2]*Towson University*

Background: Obesity is epidemic among persons with serious mental illness and is a leading cause of preventable mortality through its effects on other cardiovascular risk factors. The Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) trial results showed that a behavioral weight loss intervention with healthy diet and exercise tailored to needs of persons with serious mental illness can lead to significant weight loss. However, the study team delivered the weight management counseling in ACHIEVE. In order to increase ease of adoption and sustained implementation of weight loss interventions, we needed to adapt the intervention for delivery by community mental health program staff. We used the Enhanced Replicating Effective Programs Frameworkto guide adaptation of this evidenced-based practice. We report results of this pre-implementation phase adaptation process.
Methods: To adapt the ACHIEVE intervention, we retained core components of the group weight management and exercise intervention, combined both elements into one group session, incorporated video-assisted content to facilitate delivery by mental health program staff, and modified the session schedule for delivery multiple times/week to embed messaging repetition. An interventionist delivered a two-month pilot of this modified curriculum at one community mental health program. Post intervention delivery, we conducted a focus group with participants with serious mental illness and another with staff/peers observing sessions. Two investigators coded transcripts for content, organized into themes to inform further intervention adaptations. We also measured pre/post eating behaviors in mental health consumer participants.
Results: Fourteen participants with serious mental illness attended the pilot intervention program, along with 3 staff members and one peer leader. Mental health consumers attended 71% of sessions, and reported improvement in sugar sweetened beverage consumption, reward-based eating and food cravings after the program. The focus groups' findings and suggested adaptations to ACHIEVE are here: For individuals with serious mental illness (N=14) key findings and suggested adaptations included: 1. ACHIEVE is best suited for clients ready to make lifestyle changes --> Incorporate ‘readiness to change’ assessment
2. Clients should be aware that they have to make lifestyle changes --> Modify promotional/informational strategies

3. Weigh-ins occurred several times a week, weight fluctuations common --> Modify frequency of weigh-ins to 1/week

For the staff/peer leader (N=4)) key findings and suggested adaptations included: 1. Staff appreciated the structured curriculum, but not all may be interested in leading these groups --> Work with program leadership to identify interested staff

2. Support from several staff needed to implement --> Work with leadership to identify two staff members and a peer leader

3. Group weigh-ins several times a week triggered stress when weight loss was not achieved --> Modify frequency of weigh-ins to 1/week

Conclusions: Through this Replicating Effective Programs pre-implementation phase process, we adapted the ACHIEVE evidenced-based weight loss intervention for community mental health staff delivery. Insight and feedback from participating individuals with serious mental illness and program staff was key to further refining the weight loss intervention. For next steps, we are training community mental health program staff to implement the adapted intervention across the State.

We appreciate funding from the NIMH P5011582 for this work as part of the NIMH ALACRITY Centers.

14.2 LIFESTYLE INTERVENTION FOR ADULTS WITH SCHIZOPHRENIA TARGETING THE RISK OF DIABETES: A RANDOMIZED CONTROLLED TRIAL

Dilip Jeste*[1]

[1]*University of California San Diego*

Background: Schizophrenia is associated with increased medical comorbidity and mortality from diabetes and cardiovascular disease. Unhealthy lifestyles, including high-calorie diet, sedentary behavior, and smoking are major risk factors for diabetes. There are evidence-based strategies to prevent and manage diabetes in the general population; yet, they are rarely offered to people with schizophrenia. The present study addresses that need. Board-and-Care Homes (BCHs), residential care facilities for patients with mental illnesses, provide a venue that can maximize sustainability of a lifestyle intervention.

Methods: This NIMH-funded four-year study is a pragmatic effectiveness-implementation trial of a Multi-component Intervention for Diabetes risk reduction in Adults with SMI (MIDAS) in BCHs in San Diego. Main components of MIDAS are: (1) Education about diabetes and lifestyle, (2) Dietary intervention at facility and resident level, (3) Increased physical activity, and (4) Smoking cessation/reduction. We use a cluster-randomized stepped wedge design involving 210 residents with schizophrenia from 12 BCHs. The 15-month trial period includes a 3-month initial control phase (no intervention), a 6-month MIDAS intervention phase, and a 6-month follow-up phase. All study participants are assessed by "blind" raters every 3 months. We train BCH staff to implement healthful dietary modifications, increased physical activity, and reduction in smoking in the residents. During the intervention, the Activity Director conducts twice-weekly manualized group sessions on education about diabetes and healthy lifestyle. We also measure blood-based inflammatory and metabolic biomarkers of accelerated aging and gut microbiome.

Results: In the early stages of the study, we focused on two key questions: (1) Is MIDAS feasible, acceptable, and/or appropriate (FAA)? and (2) What are the factors that affect MIDAS FAA? The initial results strongly supported the FAA model. We have been successful in recruiting the sample, delivering the intervention with fidelity, and retaining a majority of the subjects. The facility staff has participated actively. Several changes in the dietary patterns were implemented along with increase in physical activity. The most difficult aim to implement has been a reduction in smoking. We were in the mid-phase our study when the Covid-19 pandemic became a serious threat, resulting in closure of most of the B&CHs to non-essential outside visitors including research staff. This has significantly impacted assessments and intervention in some sites. We have switched to conducting as many assessments as possible remotely, and are also offering support to the residents and the staff of the facilities to maintain healthier lifestyle, using regular phone calls and Zoom meetings.

Conclusions: When the Covid-19 pandemic is controlled, the project will return to pre-Covid level. If successful, MIDAS can be sustained and disseminated, and would lead to reduction in medical comorbidity and mortality associated with schizophrenia.

14.3 ADAPTATION BEFORE IMPLEMENTATION: TAILORING A MOBILE HEALTH INTERVENTION FOR OBESITY PREVENTION IN EARLY EPISODE SEVERE MENTAL ILLNESS

Ginger Nicol*[1], Bradley Evanoff[1], Bridget Kirk[1], Carol Caraballo[2], Steven Proctor[2], Amy Miller[3], John Newcomer[2]

[1]*Washington University,* [2]*Thriving Mind South Florida,* [3]*Fellowship House*

Background: This presentation will describe a series of four studies employing user-centered design principles and a design-for-dissemination approach to adaptation and pilot testing of a prevention-focused, mobile interactive obesity treatment approach (iOTA) for individuals with early-phase severe mental illness (eSMI).
Methods: Study 1 was conducted to detect micro-processes influencing user engagement in a basic iOTA framework, young adults with early-stage psychiatric conditions were recruited to download an ecological daily needs assessment (EDNA) mobile application including daily health goal setting and self-monitoring. In Study 2, a modified 12-week iOTA derived from the Diabetes Prevention Program and evaluated in hospital workers was tested in 28 adults receiving services in clubhouse or community mental health clinic (CMHC) settings. In Study 3, following two weeks of iOTA text messages, focus groups were conducted with administrators (4), prescribers (4), nurses (4), case managers/peer support specialists (4), and members/patients (4). Employing Innovation Corps methodology, stakeholder "jobs to be done" and relevant "pains" and "gains" were identified. In Study 4, we created a digital research-facing dashboard for remote management of external study sites. This allowed us to quickly pivot to fully-remote study conduct at the beginning of the COVID-19 pandemic by incorporating e-consent, digital assessments, and phone or virtual health coaching sessions.
Results: In Study 1, individually dynamic needs and preferences were observed, illustrating daily variability within and between individuals. Users identified preferences for self-adapting features, simplified self-monitoring, and the ability to personalize message timing and content. In Study 2, short message service (SMS) texts supplemented monthly in-person sessions. Participants reported weekly weight and progress on health goals via SMS. Psychiatric symptom instability (Clinical Global Impression Severity score >5) and low treatment engagement during the first month of treatment (<80% SMS response rate) were associated with weight gain (14.3+/-19.4 lbs). Meeting threshold criteria was associated with weight loss (7.6+/-1.6 lbs). Study 3 revealed context- and population-specific themes to guide adaptation. Organizational setting and culture: interventions that enhance (not replace) client engagement were preferred; concern for lack of (pre-pandemic) reimbursement for digital client engagement. Population-specific treatment adaptations: simplify text messaging responses; include emotion regulation, interpersonal skills and mind-body awareness in treatment content. Training and evaluation: simplify training with recorded educational modules and quizzes; virtual supervision using recorded virtual visits.
In Study 4, an ongoing randomized clinical trial has to date screened 26 participants and 13 enrolled at sites in St. Louis (n=6) and Miami (n=7). The mean age of enrolled participants is 29.5 (SD 11.1) yrs; 49% (n=6) female; 51% black (n=7); 31% Hispanic (n=4). Pandemic-inspired adaptations included modifications of inclusion criteria to allow individuals with Class II obesity (BMI up to 39.9) and mild to moderate active symptoms to participate.

Conclusions: The results of these four studies outline a process for adapting mobile health interventions for use in patients with eSMI, including contextually relevant treatment adaptations to optimize uptake within real-world clinical settings, and recognizing this population's need for autonomy and independence, while making use of their comfort with electronic mobile technology to enhance treatment engagement.

14.4 PRIMARY CARE CLINICAL DECISION SUPPORT TOOL INTERVENTION TO REDUCE CARDIOVASCULAR RISK IN PEOPLE WITH SCHIZOPHRENIA

Rebecca Rossom*[1], A. Lauren Crain[1], Steve Waring[2], Patrick O'Connor[1], Kris Ohnsorg[1], Allise Taran[2], JoAnn Sperl-Hillen[1]

[1]*HealthPartners Institute,* [2]*Essentia Health*

Background: Cardiovascular (CV) disease is the leading cause of death for people with schizophrenia, but primary care clinicians are often slow to recognize and reduce this risk. To address this, we conducted a pragmatic cluster-randomized trial.
Methods: Across three Midwestern healthcare systems, 78 primary care clinics were randomized to receive or not receive access to a clinical decision support (CDS) tool aimed at improving CV care for adults with serious mental illness (SMI). Between March 2016 and September 2018, primary care clinicians received CDS alerts during visits with adults with SMI who met minimal inclusion criteria and had at least one CV risk factor not at goal. The PCP CDS included a summary of modifiable CV risk factors and patient-specific treatment recommendations. The primary outcome was change in total modifiable CV risk.
Results: Of 8,937 patients with SMI, 1,289 patients with schizophrenia had an index primary care visit in a randomized clinic and at least one follow-up visit, and they are the focus of these findings. For patients with schizophrenia, the mean age was 51.5 years, 33% were female, and 16% were Black. At baseline, 619 patients (48%) were smokers. The median estimated 10-year CV risk was 10.3, while their estimated median reversible CV risk was 4.7.
Compared to control patients at 12 months, intervention patients tended to be more likely to quit smoking and have lower systolic blood pressure and low density lipoprotein (LDL) levels, but these differences did not achieve statistical significance. However, the combined incremental effects of these changes resulted in significant differences in total modifiable CV risk that favored the intervention. Model-estimated total modifiable CV risk increased more slowly in intervention patients than in control patients, with a relative difference in the annual rate of relative risk of -10.0% (95% CI: -16.7%, -2.8%; $p<0.01$). The positive effects of the intervention were even more pronounced for Black, Indigenous and people of color (relative rate ratio 0.83, 95% CI: 0.77, 0.90; $p<0.01$).

Conclusions: In conclusion, the CDS tool was effective in impacting total modifiable CV risk for people with schizophrenia, with a more pronounced effect for Black, Indigenous and people of color.

15. REPLICATED EEG FINDINGS IN THE PSYCHOSIS RISK SYNDROME

Cheryl Corcoran
Icahn School of Medicine At Mount Sinai

Overall Symposia Abstract: Electrophysiology provides excellent temporal resolution for understanding circuit-based sensory and cognitive processes, and also patterns of activity when the mind is at rest. The data it hielos can be analyzed within the time-doman as grand averages in response to pateras of sensory stimuli, as well as within the frequency-domain, such that underlying oscillations can be identified.
In psychosis risk research, the focus has primarily been on abnormal auditory processing in response to standard and deviant tones in oddball paradigms. More recently, there has also been a focus on visual processing in psychosis risk states, including motion perception, as well as pateras of EEG microstates, that may represent neuronal network activity across the brain. For each of these - motion processing, EEG microstates, auditory processing - abnormal patterns have been identified in cohorts with the psychosis risk syndrome, either as features that discriminate from the normal, or which predict outcome. Remarkably, many of these have been replicated in independent psychosis risk cohorts, all ascertained using similar semi-structured interviews, from around the globe. The NIH has focused on rigor and reproducibility in clinical

research, citing these as the cornerstones of advancement in science. Replication is essential for identifying putative biomarkers of psychosis risk that can inform mechanisms and provide targets for preventive interventions.

In this symposium, each of the speakers will present data on EEG abnormalities that are mechanistic, robust and replicated.

First, Dr. Antigona Martinez will present data that show that a relative deficit in visual motion processing specifically characterizes psychosis risk, but not visual sensory-evoked stimulus-onset responses, in CHR cohorts in both the United States and in Chile. In the larger US CHR cohort, this motion processing deficit was associated with deficits in higher-order cognition and face emotion processing, and the relative deficit predicted transition to psychosis.

Second, Dr. Rolando Castillo will present new data showing abnormalities in EEG microstates in this same Chilean CHR cohort that are similar to those found in schizophrenia and associated with negative symptoms and cognitive deficits.

Third, Dr. Margaret Niznikiewicz will also present data from the Shanghai At Risk for Psychosis (SHARP) cohort on auditory P300's and mismatch negativity (MMN) elicited in response to infrequent stimuli during an oddball task, and on EEG microstates. At SHARP, auditory ERP's (duration MMN and "novel" P300's) were able to discriminate at-risk from the normal and predict remission and transition to psychosis.

Fourth, Dr. Holly Hamilton will present data from the North American Prodrome Longitudinal Study (NAPLS-2), also on auditory P300's and mismatch negativity elicited during an oddball task. For NAPLS-2, auditory ERP's also predicted transition to psychosis.

Finally, the discussant, Dr. Daniel Mathalon, will lead a discussion on how to integrate these replicated EEG findings, in particular in respect to auditory processing, into a mechanistic model that may inform the development of preventive interventions.

15.1 IMPAIRED MOTION PROCESSING IN THE ATTENUATED PSYCHOSIS SYNDROME: FINDINGS AND REPLICATION

Antigona Martinez*[1], Pablo Gaspar[2], Cheryl Corcoran[3], Daniel Javitt[4]

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Background: The ability to perceive the motion of biological objects, such as faces, is a critical component of daily function and correlates with impaired ability to successfully navigat social situations ("social cognition"). Deficits in motion-detection ability in schizophrenia were first demonstrated ~ 20 years ago but remain understudied, especially within the early, potentially prodromal, stages of the illness. We used electrophysiological (EEG) recordings to examine the neural bases of visual sensory-processing impairments, including motion, in patients with established schizophrenia and individuals with attenuated psychosis (clinical high risk) from two different sites - one in the United States and the other in Chile.

Methods: Data was acquired using a highly efficient visual stimulation paradigm that can assess three different components of visual processing in parallel: 1) sensory-evoked activity following the onset of a grating-pattern stimulus 2) motion-induces activity elicited by the onset of the grating drifting rightwards for 200 ms and 3) the steady state visual evoked response (ssVEP) elicited by counterphase reversals of the grating at 10 Hz. Electrophysiological

recordings were analyzed using oscillatory ("time frequency") approaches that differentiated motion-onset evoked activity from stimulus-onset and ssVEP responses. Participants at the US site (Columbia University) were 63 DSM-5 schizophrenia patients, 32 attenuated psychosis patients, 44 healthy volunteers of similar age to the schizophrenia group, and 23 healthy volunteers of similar age to the attenuated psychosis group. Chilean (University of Chile) Participants were 13 attenuated psychosis and 6 first-episode schizophrenia patients and 14 matched controls.
Results: Significant deficits in motion processing were observed across both schizophrenia and attenuated psychosis populations. Moreover, these deficits in motion processing correlated significantly with impairments in behavioral measures of face emotion recognition a well as with multiple domains of cognition in schizophrenia and attenuated psychosis patients. In contrast to motion, sensory-evoked stimulus-onset responses were intact in attenuated psychosis individuals but significantly reduced in established schizophrenia patients, relative to control subjects. Further, the relative deficit in motion- versus intact stimulus-onset responses predicted transition to schizophrenia. Using the same stimulus/task parameters, a similar pattern of results was obtained in the University of Chile cohort, with attenuated psychosis patients showing impairments in the motion, but not sensory-evoked, responses.
Conclusions: Overall, these data highlight the importance of sensory-level visual dysfunction in the etiology and personal experience of individuals with schizophrenia and demonstrate that motion processing deficits may predate illness onset and contribute to impaired function even in individuals with attenuated psychosis, who are at high risk of transition to schizophrenia.

15.2 DEVIANT EEG MICROSTATE TEMPORAL AND SYNTAX DYNAMICS IN ULTRA HIGH-RISK ARE RELATED TO COGNITIVE/NEGATIVE SYMPTOMS AND DEMONSTRATES GOOD CLASSIFICATION PERFORMANCE

Rolando Castillo*[1], Rodrigo Vergara[2], Rocio Mayol[1], Belen Aburto[1], Alejandro Maturana[1], Hernan Silva[1], Pedro Maldonado[2], Pablo Gaspar[1]

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Background: Resting-state microstate analyses in Schizophrenia (SZ) and 22q11 syndrome have previously demonstrated aberrant temporal and syntax dynamics of attentional (microstate D) networks. However, little is known about this topic in the ultra high-risk (UHR) state. Their classificatory capacity has not been tested either.
Methods: A four-minute EEG recording microstate resting-state analysis was performed in 23 UHR and 29 age- and sex-matched controls (CNT). UHR group was also assessed using the Structured Interview for Prodromal Syndromes (SIPS) and the MATRICS Consensus Battery (MCCB) for clinical and cognitive symptoms, respectively. EEG recordings were pre-processed and analyzed in an open-source microstate EEGLab toolbox for MATLAB. Finally, an unpaired t-test was performed to evaluate differences of each microstate statistic (duration [ms], coverage [%], occurrence [1/s], and GEV) and syntax (transition probability and directionality) between groups. Pearson's correlation was used to detect interactions with SIPS/MCCB scores. Spearman's correlation analysis was performed to discard any antipsychotic influence (measured as chlorpromazine equivalents [mg]) in results. Later, a random forest algorithm was used to determine ROC curve considering sociodemographic and EEG data. Subjects signed an informed consent, and the research was approved by the local ethics committee.
Results: UHR subjects presented a decreased microstate D duration (ms) ($p < 0.001$), coverage (%) ($p = 0.005$) and GEV ($p = 0.001$). UHR had a higher transition probability from B to C, and a decreased transition probability from D to A ($p < 0.05$) and D to C $p < 0.01$). Moreover,

UHR tended to have an inverted directionality in the B-D pair ($p < 0.01$). Although 78.3% UHR subjects were on atypical antipsychotics, no correlations were shown between microstate statistics or syntax and this treatment. Additionally, microstate D coverage (%) was negatively correlated with total negative symptoms score in UHR subjects ($p = 0.03$; $r = -0.460$), and microstate D duration (ms) was negatively correlated with the Speed of Processing MCCB domain ($p = 0.03$; $r = -0.445$) and Total MCCB score ($p = 0.02$; $r = -0.522$). Random forest analysis showed that microstate D duration (cutoff value = 80ms) had the higher classifier value. Taken together, sociodemographic and EEG microstate variables classified subjects with an accuracy of 88.5%, sensitivity of 94.7%, specificity of 84.9% and a positive predictive value (PPV) of 78.3%.

Conclusions: We replicated in UHR subjects previously described microstate D and other syntax abnormalities for SZ and 22q11 syndrome, suggesting abnormal resting-state connectivity in core attentional areas in psychosis spectrum disorders. Correlations between resting-state abnormalities, negative symptoms, and cognition provide insights about possible pathophysiological mechanisms behind these symptoms. Considering that this clinical and EEG approach had a good classification performance, we consider that this finding could represent an early SZ trait marker of potential clinical utility. Prospective and cross-validation studies should confirm these statements.

15.3 REPLICATIONS OF ELECTROPHYSIOLOGICAL FINDINGS IN LARGE STUDIES OF CLINICAL HIGH RISK POPULATIONS

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Background: Abnormalities in electrophysiological function as measured by event related potentials (ERP) and, more recently, by EEG microstates, and indicative of neurocognitive impairments, were identified in a number of studies in schizophrenia population. It has also become apparent that many of these abnormalities exist in clinical high risk for developing psychosis (CHR) populations. However, underpowered studies often make it difficult to draw firm conclusions regarding the presence of such abnormalities at a pre-frank psychosis stage. Therefore, large, well powered studies in CHR which allow for the replication of exiting results offer unique opportunities to identify most robust findings on the nature of neurocognitive dysfunction in this subject group.

Methods: We will present findings from a large study of CHR from the Shanghai at Risk for Psychosis Program (SHARP). ERP mismatch negativity amplitude and duration data (aMMN and dMMN) were obtained in 104 CHR and 90 HC. P300 oddball data were obtained in 104 CHR and 69 HCs, while P300 novel data were obtained in 131 CHR and 69 HC using 64 channel EEG system. All CHR subjects were followed up for one year and divided into CHR converters (CHR-C) and non-converters (CHR-NC), with CHR-NC further stratified into remitted and non-remitted subgroups. P300 oddball and novel amplitude and latency were analyzed contrasting CHR-C, CHR-NC and HC, as well as into CHR-C, non-remitted CHR, remitted CHR and HC. EEG microstates results were analyzed from EEG resting state of 163

CHRs and 185 HCs. Group differences between the activation strength, the spatial configuration and the temporal attributes of microstates were calculated.
Results: dMMN showed significant reduction in CHR vs HC (p=0.01) as well as significant differences between CHR who remitted and HC (p=0.004), with remitted CHR not different from HC (p=0.88) and non-remitters having reduced dMMN amplitude relative to remitters (p=0.007). In the P300 paradigms, CHR converters had lower fronto-central P300 novel amplitude (p=05) as well as marginally lower P300 oddball amplitude relative to HC (p=06). When CHR non-converters were divided into remitted and non-remitted individuals, P300 novel amplitude in remitted CHR was comparable to HC (p=0.41), and it was higher than that in CHR subjects who converted to psychosis or who did not remit (0.001). Thus, reduced P300 novel amplitude indexing impaired salience processing marked both conversion to psychosis and remission from psychotic symptoms. In the analyses of EEG microstates, relative to HCs, the CHRs had increased contribution (global explained variance, GEV) and coverage of microstates A and B while decreased contribution in microstate C and D.
Conclusions: As discussed in the Introduction, large data sets allow for greater confidence in identifying valid electrophysiological biomarkers in prodromal individuals. Here, MMN was reduced in CHR relative to HC, and it further distinguished between remitters and non-remitters. Likewise, P300 novel distinguished both between CHR and HC, and between remitted and non-remitted groups. These results are similar to several earlier MMN and P300 studies in CHR, and they complement data presented in this symposium from the NAPLS sample. Furthermore, abnormalities in EEG microstates, especially in C and D microstate have been found in the SHARP data and again such results are being reported from other groups working with CHR, including the data presented in this symposium. Together, these results provide strong support for disturbed early neuro-physiological processes in CHR group and for the value of large data sets from diverse geographical regions.

15.4 AUDITORY PROCESSING AMONG INDIVIDUALS WITH THE PSYCHOSIS RISK SYNDROME: PREDICTING CLINICAL OUTCOMES WITH MISMATCH NEGATIVITY AND P300

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Background: The identification of neurophysiological abnormalities associated with schizophrenia that predate and predict the onset of psychosis may clarify the pathogenesis of the illness and improve clinical prediction for individuals at clinical high-risk for psychosis (CHR). Amplitude reduction of the mismatch negativity (MMN) and P300 event-related potential (ERP) components, which reflect pre-attentive and attention-mediated processing deficits, respectively, are among the most replicated neurobiological findings in schizophrenia and are major candidate biomarkers of psychosis risk. Indeed, several studies have reported

that reduced auditory MMN and P300 amplitudes predict conversion to psychosis among CHR individuals. Accordingly, we examined whether MMN and P300 amplitudes are associated with future clinical outcomes in CHR individuals within the large multisite North American Prodrome Longitudinal Study (NAPLS-2) sample.
Methods: 580 individuals meeting CHR criteria, as well as 241 healthy control (HC) participants, completed baseline electroencephalography recording during auditory MMN and P300 oddball tasks. MMN and P300 amplitudes of CHR participants who converted to psychosis (CHR-converter; n = 77) were compared with those of nonconverters who were followed for two years and either continued to meet CHR criteria (CHR-persistent; n = 144) or remitted from the CHR syndrome (CHR-remitter; n = 94). Specific measures included MMN to frequency, duration, and frequency+duration double deviant stimuli, as well as P3b elicited by infrequent target stimuli and P3a elicited by infrequent nontarget novel stimuli.
Results: Replicating prior research, baseline MMN and target P3b amplitudes were reduced among CHR-converters relative to nonconverters, and smaller MMN and target P3b amplitudes were associated with a shorter time to psychosis onset. There were no differences in P3a amplitudes between CHR-converters and nonconverters. Further classification of CHR nonconverters into CHR-remitter and CHR-persistent groups based on clinical status after two years of follow-up revealed that target P3b at baseline was intact in CHR-remitters, such that CHR-remitters had similar target P3b amplitudes to HCs and larger amplitudes than the CHR-converter and CHR-persistent groups. In contrast, baseline MMN did not differ between the CHR-remitter and the CHR-persistent groups.
Conclusions: ERP results from the NAPLS-2 sample provide further evidence that auditory MMN and P300 amplitudes are associated with future clinical outcomes among individuals meeting CHR criteria. In addition, results suggest that auditory target P3b, in particular, is sensitive to future CHR remission, possibly reflecting the integrity of specific neurocognitive processes that confer resilience against persistence of the CHR syndrome and its associated risk for future transition to psychosis. These results also highlight the importance of distinguishing CHR-converter from both CHR-persistent and CHR-remitter groups in future studies aiming to identify predictors of prognosis among at risk individuals.

16. DIMENSIONAL MODELS OF SCHIZOPHRENIA: FROM MOLECULES TO PHENOTYPES

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Overall Symposia Abstract: Dimensional models of schizophrenia have gained increasing recognition in research, with regards to both transnosological approaches and investigations of continuities from clinical phenotypes into the subclinical spectrum. This symposium brings together an interdisciplinary and group of junior and senior scientists who work on dimensional models of schizophrenia. A particular focus is on the concept of schizotypy, i.e. the subclinical personality constellation that confers risk for schizophrenia. According to this approach, individuals with high levels of schizotypal traits display both phenotypic and aetiological features of schizophrenia. Intense research efforts have recently been directed at identifying and characterising those overlaps at various levels of analysis, using deep phenotyping, neuroimaging and genetic approaches. Neus Barrantes-Vidal will open the symposium by introducing the construct of schizotypy and providing comprehensive recent validation data on current psychometric measures of schizotypy. Philip Sumner will present recent evidence from two large studies aimed at clarifying which aetiological contribute towards the risk of

developing schizophrenia amongst schizotypal individuals. Specifically, the studies were motivated by the hypothesis that exposure to risk factors for psychosis leads to experiences of social defeat or ostracism, which in turn sensitizes the dopaminergic nervous system and results in experiences of psychosis. The findings of the studies support a relationship between schizotypy and experiences of social defeat and suggest that social defeat mediates the relationship between loneliness and schizotypy. Raymond Chan will present recent evidence from magnetic resonance spectroscopy (MRS) studies. His findings show that increased GABA levels are correlated with better sensory integration ability in individuals with low level of schizotypy. However, unlike patients with established schizophrenia, individuals with high level of schizotypy do not exhibit abnormalities in their GABAergic system or sensory integration ability. Finally, Gemma Modinos will present recent evidence from the ENIGMA consortium. This collaborative, worldwide effort involving MRI (cortical and subcortical morphometry) and schizotypy data in N=2952 healthy individuals from 26 cohorts revealed a significant relationship between higher schizotypy and greater thickness of the medial orbitofrontal/ventromedial prefrontal cortex, in the absence of confounding effects of antipsychotic medication or disease chronicity. Furthermore, cortical pattern similarity analysis significantly linked schizotypy and schizophrenia, thereby supporting a dimensional neuroanatomical continuity across the extended psychosis phenotype. The symposium will conclude with a discussion led by discussant Igor Nenadic, with a particular focus on the continuities and discontinuities between the clinical disorder of schizophrenia and subclinical phenotypic expressions such as schizotypy. The discussion will also consider the dimensionality of schizophrenia in a broader context, by making links with related clinical disorders such as depression or autism.

16.1 PREDICTIVE VALIDITY OF PSYCHOMETRIC SCHIZOTYPY FOR PRODROMAL AND SCHIZOPHRENIA-SPECTRUM SYMPTOMS, PSYCHOLOGICAL MEASURES, AND FUNCTIONING IN AN 8-YEAR MULTI-WAVE STUDY

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Background: The underlying vulnerability for schizophrenia-spectrum disorders is expressed across a dynamic continuum of traits, symptoms and impairment referred to as schizotypy. Rather than viewing schizotypy and schizophrenia as qualitatively distinct, schizophrenia, related spectrum disorders, and the prodrome represent the most extreme manifestations of the schizotypy continuum. The reliable assessment of schizotypy should enhance identification of relevant etiological factors and endophenotypes, facilitate understanding of developmental trajectories (including risk and protective factors), and is essential for developing prophylactic interventions. Although the psychometric high-risk method based on schizotypy has proven to be a highly cost-effective strategy for unravelling etiological and developmental factors for schizophrenia-spectrum disorders, there is a paucity of longitudinal studies in nonclinical populations demonstrating the predictive validity of the schizotypy dimensions. The goal of this study was to examine the predictive validity of positive and negative schizotypy across various re-assessments spanning a total of 8 years.

Methods: Data comes from the Barcelona Longitudinal Investigation of Schizotypy (BLISS). At Time 1 (T1), 547 unselected college students completed interview and self-report measures (mean age 20.6 years, SD=4.1; 83.2% women). A representative subsample oversampled for high schizotypy of 214 participants was reassessed at Time 2 (T2). Due to funding limitations,

a subsample of T2 participants that retained a similar distribution of schizotypy scores was selected for Time 3 (T3, n=103). At Time 4 (T4), 89 participants were reassessed. At Time 5 (T5), we targeted the T2 subsample and were able to re-assess 168 of the 214 participants (78,5%; mean age=28, SD=5.19; 80,5% women). The mean interval between T1 and T5 was 7.8 years (SD=0.5). A wide range of sub-clinical, functional and psychological measures have been used across the T2-T5 reassessments (e.g.,Wisconsin Schizotypy Scales, CAPE, SPQ, CAARMS, SCID-II Cluster A, Cognitive Schemas). Interview measures were not available at T5. T1 positive and negative schizotypy were entered simultaneously as predictors in linear regression models.

Results: T1 positive schizotypy uniquely predicted CAARMS positive symptoms at T2 and T3, whereas at T4 both dimensions did (although the magnitude for positive was greater than that of negative schizotypy). In contrast, T1 negative schizotypy uniquely predicted CAARMS negative symptoms as well as schizoid personality ratings (with large effect sizes) at T2, T3 and T4. Of note, negative schizotypy did not predict avoidant personality ratings, which suggests that the predictive association with schizoid personality is not merely driven by the behavioural component that these two personality disorders share. Both T1 schizotypy dimensions assessed predicted T2, T3 and T4 schizotypal PD traits, consistent with the mixed nature of SPD comprising both positive and negative features, as well as paranoid PD traits and suspiciousness. T1 positive schizotypy predicted T5 positive schizotypy, and negative schizotypy uniquely predicted T5 negative schizotypy 8 years apart. Mirroring findings at the previous waves, T1 positive schizotypy predicted a negative self-schema at T5, whereas T1 negative schizotypy predicted a low positive self-schema, which is consistent with the differential pattern of associations of schizotypy dimensions with negative and positive affect, respectively. In terms of functioning, only T1 negative schizotypy predicted dysfunctional impairment in a stable way across datawaves.

Conclusions: Both schizotypy dimensions showed a consistent and meaningful pattern of differential and overlapping predictions across 4 datawaves spanning 8 years. These results support the predictive validity of psychometrically assessed positive and negative dimensions in nonclinical samples and add evidence to the validity of positive and negative schizotypy as distinct dimensions. Overall, these results support the conceptualization of schizotypy as a useful and unifying construct for understanding schizophrenia-spectrum psychopathology.

16.2 TESTING THE SOCIAL DEFEAT HYPOTHESIS IN SCHIZOTYPY

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Background: According to the continuum model of psychopathology, people with schizotypal personalities and people with schizophrenia share at least some of the same aetiological processes, and phenotypic disease expression varies continuously. Whether or not a person actually develops clinical schizophrenia depends on the interaction between these aetiological processes, and a number of risk and protective factors. One hypothesis states that exposure to the risk factors for psychosis leads to experiences of social defeat or ostracism, which in turn sensitizes the dopaminergic nervous system and results in experiences of psychosis. Although some supportive evidence has been found in samples of people with schizophrenia, whether or not these relationships extend into schizotypy has not been explored. Thus, the aim of the current work was to investigate whether experiences of social defeat are predictive of schizotypy in non-clinical samples, and whether social defeat mediates any relationship between social network size or loneliness and schizotypy. Experiences of disorganized or

impoverished thought and speech were of particular interest because of their presumed impact on social functioning, as well as their apparent neglect amongst current schizotypy research.
Methods: Self-report data was collected using a series of online surveys from student samples (sample 1: n = 690; sample 2: n ≈ 350 with data collection ongoing) and a sample of the general population (n = 244).
Results: Preliminary correlation analyses showed evidence of associations between schizotypy and social defeat in the expected direction, particularly for negative and disorganized schizotypy. Correlations with social network size were mostly limited to negative schizotypy, whereas loneliness showed correlations with schizotypy more broadly. Moreover, social defeat appeared to mediate the relationship between loneliness and schizotypy.
Conclusions: These findings are consistent with a role of social defeat in the expression of schizotypy. However, longitudinal research is needed to determine the direction of causality represented by these relationships, and whether these relationships actually correspond with an increased risk of developing schizophrenia. Moreover, objective measures of social defeat and schizotypy may be useful to extricate the influences of neuroticism from external social stressors. Nevertheless, testing the social defeat hypothesis could be a fruitful avenue for the illumination of key trait-environment interactions in the pathogenesis of schizophrenia.

16.3 STRIATAL GABAERGIC FUNCTION AND SENSORY INTEGRATION IN INDIVIDUALS WITH HIGH LEVEL OF SCHIZOTYPY

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Background: Empirical findings show that altered gamma-aminobutyric acidergic (GABAergic) function may result in multisensory integration deficits in schizophrenia spectrum disorders. However, most of the done has been limited to patients with established schizophrenia and with little is known about individuals with schizotypy. The present study examined whether GABA would also be altered in individuals with high level of schizotypy. Moreover, it also aimed to examine the relationship between GABA levels and sensory integration ability in individuals with high level of schizotypy.
Methods: We recruited 19 participants with high levels of schizotypy and 21 participants with low levels of schizotypy. All of them underwent a proton magnetic resonance imaging scanning for the In vivo GABA+ and N-acetylaspartate (NAA) levels in the striatum. in Moreover, the sensory integration subscale of the abridged version of the Cambridge Neurological Inventory was also administered to all the participants to examine their sensory integration ability. Group differences in GABA+/NAA levels were examined between both groups. We also examined the correlation between GABA+/NAA levels and sensory integration ability in each group.
Results: Participants with high level of schizotypy exhibited comparable levels of in-vivo GABA+/NAA with those with low level of schizotypy. However, correlation analysis showed

that In-vivo GABA+/NAA levels were negatively correlated with sensory integration score in participants with low level of schizotypy. No such significant correlation was observed in participants with high level of schizotypy.
Conclusions: These preliminary findings suggest that the increased GABA level is correlated with better sensory integration ability in individual with low level of schizotypy. These findings support that GABAergic function plays a critical role in multisensory integration and suggest that unlike patients with established schizophrenia, individuals with high level of schizotypy do not exhibit any abnormality in their GABAergic system and sensory integration ability.

16.4 ENIGMA SCHIZOTYPY: MAPPING THE NEUROANATOMICAL SIGNATURE OF SCHIZOTYPY IN 2,952 INDIVIDUALS WORLDWIDE

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Background: Abnormalities in cortical and subcortical neuroanatomy have been found along a continuum from at-risk states to early and chronic psychosis. Recently, the Schizophrenia Working Group within the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) consortium reported large-scale meta-analytic evidence for robust cortical and subcortical alterations in chronic schizophrenia, while also indicating strong effects of illness severity and antipsychotic treatment on these findings. In this context, schizotypy research allows mapping neuroanatomical features associated with the expression of subclinical psychotic-like experiences in healthy individuals, without potential influences of psychotic illness severity or antipsychotic use. We aimed to conduct the first comprehensive meta-analysis of cortical and subcortical morphometry in schizotypy. Our second aim was to examine the shared morphometric characteristics of schizotypy with previously reported neuroanatomical abnormalities in three major psychiatric disorders (schizophrenia, bipolar disorder and major depression).
Methods: A total of 2,952 healthy individuals (12 to 68 years, 46.5% male) from 26 cohorts of the worldwide ENIGMA Schizotypy working group contributed to the meta-analysis. Partial correlation effect size maps between schizotypy scores and cortical thickness, surface area and subcortical volumes were generated using standardized methods applied to T1-weighted magnetic resonance images. Random-effects meta-analyses of partial correlation effect sizes were performed using R's metafor package and false discovery rate ($pFDR<.05$) was used to control for multiple comparisons. Pattern similarities between schizotypy-related cortical and subcortical maps were assessed with effect size maps of schizophrenia, bipolar disorder or major depression patients compared with controls (Pearson correlations for cortical maps and Spearman's rank for subcortical maps). Statistical significance of all cortical pattern correlations was assessed using spin permutation tests correcting for spatial autocorrelation.
Results: Cortical thickness of the right medial orbitofrontal cortex/ventromedial prefrontal cortex (mOFC/vmPFC) was positively correlated with schizotypy ratings ($pFDR=.02$), while schizotypy-related cortical surface area and subcortical volume showed more subtle correlations ($punc<0.05$). The schizotypy-related cortical thickness map was positively correlated with cortical abnormalities in schizophrenia ($pspin=.008$), but not bipolar disorder ($pspin=.156$) or major depression ($pspin=.095$). Schizotypy-related subcortical volume effects were negatively correlated with subcortical volume abnormalities in schizophrenia ($pspin=.006$), bipolar disorder ($pspin=.009$), and major depression ($pspin=.004$).
Conclusions: This cooperative, worldwide meta-analysis comprehensively mapped the morphometric signatures of schizotypy in the general population, revealing a significant relationship between higher schizotypy and greater cortical thickness of the mOFC/vmPFC.

Furthermore, the cortical pattern similarity between schizotypy and schizophrenia provides new insights for a dimensional continuity across the extended psychosis phenotype.

17. CURRENT DIRECTIONS IN NEGATIVE SYMPTOMS RESEARCH: FROM THE EXPRESSION AND INNOVATIVE ASSESSMENT METHODS IN DAILY LIFE TO THE DEDUCTION OF EVIDENCE-BASED TREATMENTS

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Overall Symposia Abstract: Negative symptoms are the strongest predictor of psychosocial functioning and subjective quality of life in patients with psychosis. Accordingly, they are referred to as an important treatment target by both patients and mental health professionals. At the same time, negative symptoms have been found to barely respond to treatment. One reason for the unsatisfying effects of existing approaches could be the limited understanding of the mechanisms driving negative symptoms in daily life and a lack of interventions directly targeting these mechanisms. The aim of this symposium is to merge findings of recent studies on negative symptoms in light of their relevance for the development of future interventions.
Inez Myin-Germeys will reflect on how negative symptoms are expressed in daily life. Based on the findings of an experience sampling study, she will review the phenomenology of negative symptoms and discuss potential mechanisms. She will further evaluate whether a lack of opportunity to participate in certain daily life activities could also explain the characteristic inactivity of patients with negative symptoms.

Stefan Kaiser will discuss the therapeutic potential of pro- and anti-dopaminergic agents in the treatment of patients with negative symptoms. He will review data from neuroimaging studies investigating dysfunctions in the neural reward system of patients with negative symptoms to deduce a rationale for the use of pro- and anti-dopaminergic agents. He will then present and evaluate the findings of two meta-analyses on the efficacy and the dose-response effect of these drugs on negative symptoms.

Andre Aleman will focus on the functional neuroanatomy of goal-directed behavior and apathy in patients with negative symptoms. Based on the findings of a recent randomized-controlled trial, he will evaluate the therapeutic potentials of transcranial magnetic brain stimulation to alleviate negative symptoms and especially apathy. He will also discuss methodological aspects of the trial design and the implications for neuroanatomical hypotheses about goal-directed behavior and negative symptoms.

Gregory Strauss will evaluate the potential benefit of digital phenotyping methods in the assessment of negative symptoms. He will review a series of studies that examined the psychometric properties of digital phenotyping, such as phone accelerometry and ambient sound as parameters of negative symptoms. Based on the findings of a machine learning algorithm, he will discuss the potential benefits of their use as outcome measures in clinical trials and psychopathology research.

The symposium will advance our knowledge on how negative symptoms manifest in daily life from a patients' perspective, how they could be treated and how negative symptom outcomes in clinical trials could be best assessed. This knowledge will inform future clinical research and the development of evidence-based treatment options for patients with negative symptoms.

17.1 THE PHENOMENOLOGY OF NEGATIVE SYMPTOMS IN DAILY LIFE ACROSS THE PSYCHOSIS SPECTRUM

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Background: Negative symptoms are often characterized as resulting from a change in underlying capacity (e.g. anhedonia) or a lack of drive (e.g. avolition) or motivation (e.g. asociality). However, it has also been argued that negative symptoms may be driven by changes in context and by limited opportunities. In order to understand negative symptoms more fully, it is therefore important to investigate negative symptoms at the early stages of psychosis, in the normal day-to-day context, and in relation to the wider circumstances that people live in.
Methods: Two studies were conducted, both using Experience Sampling Methodology (ESM), a structured diary technique. The first study examined anhedonia, social anhedonia and asociality in 51 individuals with a first episode of psychosis, 46 individuals with an at risk mental state and 53 healthy volunteers. The second study compared 149 individuals with psychotic disorder and 143 health volunteers, dividing social interactions as measured with ESM into those occurring in the context of work and other structured activities that patients have limited access to, and those occurring in the context of unstructured activities such as visits and conversations that both groups can choose relatively more freely.
Results: The first study showed no overall evidence for a blunting of affective experience. There was some evidence for anhedonia in FEP but not in ARMS. In contrast to our expectation, no evidence was found for greater social anhedonia in any group. FEP were more often alone (57%) than ARMS (38%) and controls (35%) but appraisals of the social situation did not point to asociality. The second study found that patients spent significantly smaller proportion of their time in structured social context, but matched the controls in the time spent in unstructured social contexts, and similar to what was found in the first study, they endorsed intact hedonic experience of both social contexts.
Conclusions: Overall, altered affective experience, anhedonia, social anhedonia and asociality seem to play less of a role in the daily life of individuals in the early stages of psychosis than previously assumed. With the experience of affect and pleasure in daily life being largely intact, changing social situations and appraisals thereof should be further investigated to prevent development or deterioration of negative symptoms. This seems particularly important, since employment and living situation, in addition to the severity of symptoms of avolition, predicted the proportion of time patients spent in structured and unstructured social contexts in the second study, supporting the notion that both lifestyle as well as disease-specific factors contribute to real-life social behavior in psychosis.

17.2 NEGATIVE SYMPTOMS AND REWARD SYSTEM DYSFUNCTION – FROM NEURAL MECHANISMS TO TREATMENT?

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Background: There is increasing evidence that a dysfunction in the dopaminergic reward system may play a key role in the pathophysiology of negative symptoms. This concerns in particular the amotivation dimension of negative symptoms including the symptoms avolition,

asociality and anhedonia. Deficits in reward anticipation, valuation and learning have been observed on the behavioral and the neural level. However, until now the available evidence for the association of negative symptoms and reward system dysfunction has had limited impact on treatment development. The goal of the current presentation is to explore the potential impact of pro- and anti-dopaminergic agents on negative symptoms by using a meta-analytic approach.

Methods: Two meta-analyses of randomized controlled trials investigating medication that influences reward system function will be presented. The first meta-analysis includes trials that investigate the effects of pro-dopaminergic drugs (including modafinil, L-Dopa, dopamine agonists). The second meta-analysis uses a dose-response meta-analytic approach to investigate the impact of the dose of antipsychotics as dopamine blocking agents on negative symptoms.

Results: In the meta-analysis for pro-dopaminergic drugs 10 randomized controlled trials were included. No overall effect on negative symptoms was found. However, there was a small and significant benefit in studies on modafinil which required patients to have at least a minimum threshold of negative symptoms. Very few studies reported the specific effects for dimensions or symptoms and no specific effect was found in these studies. In the dose-response meta-analysis 45 articles reporting results from acute phase studies were included. The strong dopamine-blocking agents haloperidol and risperidone showed a bell-shaped curve suggesting that higher doses are less effective for the treatment of negative symptoms than smaller doses or even detrimental. For antipsychotics with less dopamine-blocking properties this effect was less pronounced. The available data were not sufficient to calculate dose-response associations for individual negative symptoms or dimensions.

Conclusions: There is now clear evidence that reward system dysfunction is associated with negative symptoms. However, it is currently premature to draw conclusions on the effect of pro-dopaminergic drugs. Concerning treatment with antipsychotics, the present data suggest caution with high doses of strong dopamine-blocking agents which is consistent with clinical recommendations. In order to clearly delineate the effects of pro- and anti-dopaminergic agents it is imperative to report individual negative symptoms and dimensions.

17.3 RESULTS OF AN RCT ON TMS BRAIN STIMULATION FOR NEGATIVE SYMPTOMS WITH SPECIAL FOCUS ON APATHY

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Background: The use of noninvasive brain stimulation using electromagnetic fields for the treatment of psychiatric disorders has been increasing steadily in recent years. More specifically, repetitive transcranial magnetic stimulation (rTMS) has been studied most in regards to improving positive and negative symptoms of schizophrenia. In this presentation, we take stock of recent findings regarding negative symptoms and report the results of our latest clinical trial.

Methods: For negative symptoms, studies with rTMS have focused on the lateral prefrontal cortex, at 10 Hz or higher. In our most recent trial, we tested iTBS (intermittent theta-burst TMS) at 30 Hz over the right DLPC for improving negative symptoms (especially apathy) in patients with schizophrenia. The study was a multi-center, randomized, placebo-controlled, and rater-blinded trial. In each participating center, either rTMS or TDCS treatment was offered.

Allocation of rTMS or TDCS treatment to a specific center was primarily based on practical and feasibility reasons, while making sure that similar centers were allocated to each treatment arm (i.e. concerning illness severity of patients under care). Patients were randomized into active rTMS, active tDCS treatment, sham rTMS or sham tDCS treatment. Measurements included a pretreatment measurement session, two weeks of neurostimulative treatment, a post-treatment measurement, and follow-up measurements four and ten weeks after neurostimulative treatment.
Results: No significant improvement of apathy or of negative symptoms in general was observed for real versus sham treatment (both groups improved to a small extent). Tolerability was good.
Conclusions: Two weeks of brain stimulation with either iTBS or tDCS is not effective for improving apathy or negative symptoms. Recent meta-analysis, however, show that the published evidence yields an advantage of active rTMS stimulation versus sham. The results have methodological and clinical implications that will be discussed in order to guide future research.

17.4 DIGITAL PHENOTYPING AS AN ASSESSMENT TOOL FOR MEASURING NEGATIVE SYMPTOMS IN SCHIZOPHRENIA AND YOUTH AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Negative symptoms have traditionally been assessed using clinical rating scales, which rely on retrospective self-reports and have several inherent limitations that impact validity. Rapid developments in mobile technology make it possible to measure negative symptoms in the context of every-day life in ways that account for many of these limitations. However, it is unclear whether "digital phenotyping" methods (i.e., smart phone or band technologies used to acquire data in the context of everyday life) have adequate reliability and validity to be considered appropriate for use in clinical trials and experimental psychopathology studies.
Methods: A series of studies will be reviewed that evaluated active (i.e., tasks intentionally performed by the participant in daily life, such as ecological momentary assessment surveys and ambulatory videos) and passive (i.e., data unobtrusively collected by the internal sensors of a device, such as geolocation, accelerometry, and ambient sound) digital phenotyping methods in relation to reliability, convergent validity, discriminant validity, and incremental validity. Participants in Study 1 included outpatients in the chronic phase of illness who were diagnosed with schizophrenia or schizoaffective disorder (SZ: n = 52) and demographically matched healthy controls (HC: n = 55). Participants in Study 2 included youth at clinical high-risk for psychosis (CHR: n = 52) who met criteria for the attenuated psychosis syndrome and demographically matched healthy controls (HC: n = 35). In both studies, participants completed the same protocol, which included 1 week of active (surveys, ambulatory videos) and passive (geolocation, accelerometry, ambient sound) digital phenotyping recorded from a smartphone and smartband and a battery of clinical rating scale measures.
Results: Across both studies, adherence was adequate for EMA surveys and some passive measures (phone accelerometry, geolocation), but lower for other measures (ambulatory videos, ambient sound, band accelerometry). Relative to HC, SZ and CHR groups demonstrated anhedonia, avolition, and asociality on EMA surveys, which displayed good

convergent and discriminant validity. Ambulatory videos that were analyzed using automated facial and vocal software indicated the presence of blunted facial affect, blunted vocal affect, and alogia in SZ and CHR compared to HC; however, these symptoms were context dependent and more prevalent during social interactions. Ambulatory videos demonstrated modest convergent validity with the Brief Negative Symptom Scale. Various geolocation measures differed between HC and SZ or CHR groups (e.g., home time, distance from home, number of flights), which showed differential associations with measures of avolition, anhedonia, and asociality. Ambient sound measures reflecting the presence of speech amidst background environment differed between HC and SZ/CHR groups and predicted asociality. Machine learning algorithms used to determine which active and passive digital phenotyping measures were most predictive of the 5 distinct domains (anhedonia, avolition, asociality, blunted affect, alogia) were able to identify some measures that predicted the presence of negative symptoms broadly (e.g., geolocation meters from home), as well as others that were predictive of some individual negative symptom domains but not others, suggesting domain specificity.
Conclusions: Active and passive digital phenotyping measures can now be collected to assess negative symptoms in the context of daily life. These measures demonstrate adequate psychometric properties. However, there are complexities regarding the appropriate level of resolution, context, and time scale to calculate these measures in a way that makes them most applicable for use in clinical trials. Discussion will focus on practical recommendations for using digital phenotyping in clinical trials for negative symptoms.

18. LONGITUDINAL ASSOCIATIONS BETWEEN PSYCHOTIC EXPERIENCES AND PSYCHOSIS WITH SUICIDALITY IN CHILDREN AND YOUTH

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Overall Symposia Abstract: Psychotic experiences (PEs), which include both clinical symptoms (e.g. hallucinations and delusions) and subclinical/subthreshold experiences are associated with self-injury and suicidality in adolescents and adults. This has led to recommendations for universal screening of PEs in people who seek mental health care to improve risk assessments and implement strategies to prevent suicide. However, the clinical importance of PEs in children is poorly understood with limited understanding of future suicide risk in children with psychotic experiences. Further reverse causality is under researched. Are young people who present with suicidality at increased risk of future psychosis? Using longitudinal datasets and national cohorts, these papers examine the association between psychotic experiences, psychosis and suicidality through a developmental lens, exploring the emergence of suicidality during adolescence in children with hallucinations or delusional ideas. They also examine if youth presenting with suicidality are at increased risk of later psychosis. DeVylder and Oh examine parental reported hallucinations at 9 years in an ethnically diverse cohort of socially disadvantaged children in the United States. Children who hear voices were significantly more likely to self-harm or attempt suicide. Further, these children at 15 years have almost seven times the odds of experiencing suicidality at 15 years compared to children who did not hear voices.

Yamasaki and Nishida examined the relationships between psychotic experiences, help seeking and suicidality at three time points (10, 12 and 14 years) in a longitudinal cohort of Japanese children. Psychotic experiences predicted future suicidality in young children but also a reduced likelihood of being willing to seek help. Thus children at greatest risk of suicide were

less likely to seek mental health support. This raises questions as whether it is the stigma about psychosis and suicide in Japan that is an obstacle for help seeking or alternatively whether an intrinsic quality of psychotic experiences such as paranoia prevents these young people seeking help.

Hielscher and colleagues studied psychotic experiences and incident self-harm/suicide attempts in a cohort of 1239 adolescents where data were collected at baseline, 12-month, and 24-months. Those experiencing psychotic experiences only at baseline did not have an increased risk of future suicidality, whereas those whose psychotic experiences persisted across the 24 months had the greatest risk of self-harm and suicide attempts. There was no evidence that baseline suicidality was associated with later PE.

Bolhuis and colleagues examined the association between self-harm, psychosis and bipolar disorder in young adults. Using the register-based Finnish 1987 birth cohort, they show a bidirectional relationship. The study confirmed the known relationship that those with psychosis are at increased risk of future suicidality. The research extends knowledge demonstrating young adults who present with self-harm have a 7 fold increased risk of developing an incident psychotic or bipolar disorder, with most presenting to care in the subsequent four years.

Together, these papers show that PE in young children and the persistence of these experiences confers an increased risk of suicide and self-injury which continues through adolescence. Screening of children for psychotic experiences provides an opportunity for mental health service delivery in order to reduce their risk of self-harm and suicide. Young people presenting with suicidality should be monitored for future psychosis to avoid unnecessary delays in treatment.

18.1 CHILDHOOD CO-OCCURRENCE OF HALLUCINATIONS AND SELF-HARM, AND ITS CONTINUED RELEVANCE INTO ADOLESCENCE

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Background: Psychotic experiences are hallucination- and delusion-like symptoms that have provided insight into the etiology of psychosis and may carry their own clinical and functional relevance despite being "sub-clinical" in concept. They have been linked to drastically elevated rates of suicidal thoughts and behavior in adolescence and adulthood, though the associations in childhood are less understood. Also, research on this association among racial/ethnic minorities in the U.S. is lacking, despite an increasing suicide rate among Black and Latino children. Further, there is limited evidence on the continued clinical relevance in terms of predicting subsequent risk for suicidal thoughts and behavior.

Methods: We used data from the Fragile Families & Child Wellbeing Study to examine the association between hearing voices (i.e., "child hears sounds or voices that are not there," based on mother's report) and self-harm (i.e., "child deliberately harms self or attempts suicide," based on mother's report) at age nine, among a sample of predominantly Black and Latino children (Black: 50.0%; Latino: 25.6%; White: 20.9%; Asian/other: 3.3%) of single parents residing in urban centers of the United States (N=3309). In addition, we tested whether hearing voices, self-harm, or both, were associated with subsequent suicidal ideation at age 15 (i.e., "I

feel like is not worth living," self-reported by the child). Logistic regression was used for all analyses, adjusted for sex, income, race, and foreign birth.
Results: Three percent (n=99) of the children heard voices, and 2.3% (n=75) of the children exhibited self-harm or suicidal behavior at age nine according to parent report. Of these children, 29 exhibited both self-harm and heard voices, which were significantly associated with each other in adjusted analyses (OR=27.0; 95% CI: 15.7-46.4). This association was consistent across all racial/ethnic groups, but the point estimates were non-significantly greater among children of color (OR=33.1; 95% CI:18.3-59.8) compared to White children (OR=17.2;95%CI:2.8-107.3). Among all children with self-harm at age 9, psychotic experiences were associated with greater risk of continued suicidal ideation six years later at age 15 (OR=6.7; 95% CI: 1.2-36.7). Notably, only youths who experienced the co-occurrence of self-harm and hearing voices continued to report suicidal ideation at age 15, (OR=3.6; 95% CI: 1.4-9.5), as opposed to those who only heard voices (OR=1.2; 95%CI: 0.5-2.8), or only engaged in self-harm (OR=0.7; 95%CI: 0.2-2.8). When split by race, this association was only significant among children of color (OR=3.8; 95% CI: 1.5-10.1).
Conclusions: Findings provide two novel and clinically important insights regarding the association between psychotic experiences and suicide. First, this is the first study to show that parent-reported hallucinations are associated with self-harm, similar to self-reported psychotic experiences in childhood. This is relevant because nine year old children are unlikely to independently recognize the need for care and seek it out on their own. Second, the specific association between the co-occurrence of hearing voices and self-harm, and subsequent suicidal ideation, suggests that psychotic experiences at age 9 may predict clinical course among children with concurrent suicidal behavior. Finally, the association between psychosis and suicide may be particularly clinically impactful among children of color in the United States who are becoming increasingly vulnerable to suicide yet remain under-studied.

18.2 RECIPROCAL RELATIONSHIPS AMONG PSYCHOTIC EXPERIENCES, SUICIDAL BEHAVIOUR AND HELP-SEEKING IN ADOLESCENCE: EVIDENCE FROM TOKYO TEEN COHORT STUDY

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Background: Psychotic experiences are common in general population, especially in adolescents, and are increased the risk of mental health problems and suicidal problems. Recently our studies demonstrated that psychotic experiences are associated with reduced help-seeking for mental health problems among adolescents, and a combination of psychotic experiences and the absence of help-seeking intention was associated with a 16-fold risk of self-harm in large cross-sectional studies. However, the longitudinal relationship between them still remains unclear. We have commenced an adolescent longitudinal cohort study in Tokyo (Tokyo TEEN Cohort: TTC), and investigated the longitudinal relationship between psychotic experiences, help-seeking intention and self-harm from childhood (10 y.o.) to adolescence (14 y.o.).
Methods: We used 3-point longitudinal data from Tokyo TEEN Cohort Study (N=3,171) to disentangle the relationships between psychotic experiences, help-seeking intention and self-harm at age 10, 12 and 14 years old. Two-year (from 10 to 12 y.o.) and four-year (from 10 to 14 y.o.) follow-up rate of TTC were 94.8% and 84.0%, respectively. Psychotic experiences and self-harm were rated by self-report questionnaire. Help-seeking intention for mental health problems was evaluated by a case vignette. Cross-lagged model analysis was used to evaluate the longitudinal relationship among these three factors.

Results: Psychotic experiences were experienced by 28.3% of adolescents at age 10, 18.4% at age 12 and 15.1% at age 14. Self-harm was reported by 11.2% at age 12 and 5.9% at age 14. Cross-lagged model analysis revealed that reported psychotic experiences at age 10 significantly predicted reduced help-seeking at age 12 (β = -.06, p = .003) but the reverse direction was not significant. This was replicated between psychotic experiences at age 12 and reduced help-seeking at age 14 (β = -.05, p = .02). Psychotic experiences were also associated with an increased risk of self-harm both from age 10 to age 12 (β = .14, p<.001) and from age 12 to age 14 (β = .15, p<.001). Self-harm at age 12 significantly predicted decreased help-seeking at age 14 (β = -.07, p<.001), while the reverse direction was a trend-level significance (β = -.04, p=.056).
Conclusions: These results revealed that self-harm may mediate the longitudinal relationship from psychotic experiences to reduced help-seeking for mental health problems. Adolescent self-harm is highly stigmatised and psychotic experiences may be associated with a maladaptive coping strategy symptoms among adolescents, which leads to reduced help-seeking. Promoting adolescent help-seeking requires addressing the stigma of psychotic experiences as well as the stigma of self-harm in late childhood and early adolescence.

18.3 CAN'T GET YOU OUT OF MY HEAD: PERSISTENCE AND TRANSIENCE OF PSYCHOTIC EXPERIENCES IN ADOLESCENTS AND ITS ASSOCIATION WITH SELF-INJURIOUS BEHAVIOUR

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Background: Psychotic experiences (PEs) are associated with a broad range of adverse health and social outcomes in adolescence including self-injurious and suicidal behaviour. There is growing evidence that frequent PEs which persist over time (as opposed to single, fleeting episodes) are more specific predictors for psychotic disorders and other clinical and functional impairments. To date, no study has investigated persistence and remission of PEs, and its association with self-harm and suicide attempts, across three waves of prospective data. Also, no study has investigated whether persistence of different PE subtypes has differential associations with self-injurious behaviour.
Methods: Participants were from an Australian longitudinal cohort of 1239 adolescents (12–17 years) where data were collected at three waves: baseline, 12-month, and 24-month follow-up. Self-injurious behaviours (including self-harm and suicide attempts) were measured using the Self-Harm Behaviour Questionnaire. The Diagnostic Interview Schedule for Children was used to assess four different PE subtypes: auditory hallucinatory experiences (HEs) and three delusional experiences (thoughts being read, feeling spied upon, receiving special messages). Using logistic regression, we examined associations between baseline PEs and incident self-harm and suicide attempts during the 12-month and 24-month follow-up. PEresults: were grouped by subtype, as well as by their persistence across the three waves of data. We also explored whether there was any evidence of reverse temporality, where baseline self-harm/suicide attempts instead predicted occurrence of PEs at 12- and 24-month follow-up. All analyses were adjusted for age and sex.
Results: Any PE was associated with self-harm (OR range=1.73–2.09) and suicide attempts (OR range=1.89–4.33) in the following 12 and 24 months. However, when broken down by subtype, auditory HEs was the only subtype that was associated with both incident self-harm

and suicide attempts. Overall, persistence of PEs (with endorsement of PE across all three waves) was associated with the highest risk of self-harm and suicide attempts, whereas remission of PEs (with endorsement of PE at baseline only) was not associated with an increased risk of self-injurious behaviour. This pattern of association was evident for persistence of auditory HEs but not for most other PE subtypes. There was little evidence of reverse temporality, where baseline self-injurious behaviour was not associated with incident PEs (except for baseline self-harm and 12-month auditory HEs) and increasing persistence of self-injurious behaviour was not associated with an increased risk of PE occurrence.
Conclusions: Our results show that persistence of PEs is important to consider when predicting risk of self-injurious behaviour. Findings were variable across different PE subtypes, where screening adolescents for persistence of hallucinatory experiences may assist with predicting those at greatest risk of future self-harm and suicide attempts.

18.4 HOSPITAL PRESENTATION FOR SELF-HARM IN YOUTH AS A RISK MARKER FOR LATER PSYCHOTIC AND BIPOLAR DISORDERS: A COHORT STUDY OF 59,476 FINNS

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Background: Identification of individuals at risk of serious mental disorders, including psychosis and bipolar disorder, is a major focus of psychiatric research. Expanding our clinical strategies to identify high risk groups is a research priority. Given that individuals diagnosed with psychosis and bipolar disorder are at high risk of going on to self-harm, we wished to investigate the reverse order relationship (i.e., self-harm predicting psychosis/bipolar disorder). Specifically, we hypothesised that hospital presentation for self-harm would be a marker of high risk for subsequent development of psychosis/bipolar disorder and sought to test this hypothesis in a large population sample.
Methods: The register-based Finnish 1987 birth cohort included all individuals born in Finland in 1987 (N=59,476), with follow-up to age 28 years. We used healthcare registers to identify all presentations with self-harm as well as all inpatient and outpatient healthcare registrations of first diagnoses of psychotic and bipolar disorders, using 10th version of the International Statistical Classification of Diseases and Related Health Problems. Cox proportional hazards models were used to assess the prospective, potentially bi-directional, associations of self-harm hospital presentations with psychosis or bipolar disorder.
Results: In total, 481 individuals were recorded to have self-harmed throughout the follow-up. Self-harm presentations were associated with a markedly increased incidence of psychosis (hazard ratio [HR]=6.03, 95% confidence interval [CI] 4.56-7.98) and bipolar disorder (HR=7.85, 95% CI 5.73-10.76). Of all young people who had presented to hospital with self-harm, 10.6% went on to receive a diagnosis of psychosis and 8.5% a diagnosis of bipolar disorder. Risk for psychotic and bipolar disorders was higher in individuals whose index self-harm presentation had been at a younger age: for those who presented with self-harm before age 16 years, 27.3% developed psychotic or bipolar disorder by age 28 years. Median time to diagnosis with a psychotic disorder was 0.75 years (interquartile range [IQR] 0.13-3.62 years) and median time to diagnosis with bipolar disorder was 1.79 years (IQR 0.60-4.13 years).

Conclusions: Young people with psychosis or bipolar disorder were at elevated risk of self-harm presentations to hospital, in keeping with previous research. Importantly, we also found that young people who present to hospital with self-harm are at high risk of future psychotic and bipolar disorders, and they represent an important cohort for early detection and prevention of serious mental illness.

19. DISCONTINUATION OF ANTIPSYCHOTIC MEDICATION - THE STORY CONTINUES

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Overall Symposia Abstract: How long patients with a psychotic disorder should continue use of antipsychotic medication remains a controversial issue. Risk of psychotic relapse is higher in the year(s) after discontinuation, in particular if there has been more than one previous psychotic episode. Based on this knowledge, treatment guidelines recommend continuation of at least one year after remission of first episode psychosis and maintenance treatment after multiple episodes. Prolonged use, however, is a burden for many patients, due to potentially severe and lasting side-effects. Antipsychotic medication is associated with a range of adverse mental and physical effects that negatively influence health, level of functioning and quality of life.

Over the past decade, some studies showed a favorable course of illness and functioning after early dose reduction and discontinuation of antipsychotic medication, other research reported poorer outcomes in this group. Differences may depend on design and quality of studies, definitions of core concepts, patient- and illness-related characteristics, methods of dose reduction, available mental health services and duration of follow-up.

Recently, four randomized controlled trials (RCTs) were initiated to compare maintenance treatment with (early) discontinuation, in the United Kingdom, Denmark, Australia and the Netherlands. Primary aim of these studies was to investigate the effect of dose reduction / discontinuation on functioning, clinical outcomes and quality of life. In this symposium, preliminary results, insights and challenges of these RCTs are shared, in relation to clinical and scientific implications. Discontinuation studies – the story continues.

19.1 REDUCE: PROGRESS, PROBLEMS AND POTENTIAL SOLUTIONS IN AN AUSTRALIAN RCT OF ANTI-PSYCHOTIC DOSE REDUCTION IN FIRST EPISODE PSYCHOSIS

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Background: Anti-psychotic medication is the recommended front line treatment for first episode psychosis. However, there are a number of questions that remain unresolved. These include the usefulness of medication beyond the acute phase for promoting functional recovery, the impact on brain structure of prolonged exposure to medication, and the impact of taking medication on physical health. The Reduce study was established to address these questions.

Methods: Reduce is a 2 group RCT in which participants with first episode psychosis and who have achieved 3 months of remission from positive symptoms are randomised to either receive ongoing maintenance medication, or to participate in a dose reduction condition in which their dose of anti-psychotic medication is reduced 25% of their starting dose at each step. Participants can choose to stay on a step or continue on to the next reduction step. Each step is at least 1 month apart. Discontinuation is not the aim but may be an outcome for some participants. Participants in both groups receive a 9-month intensive psychosocial intervention consisting of manualised CBT and individual placement and support for vocational recovery. They then receive a less intensive 15 months of ongoing psychosocial support. Assessments occur at baseline, 9 months, 15 months and 24 months. Assessments include psychopathology, service usage, neurocognition, structural MRI with functional resting state, and measures of physical health. The recruitment target was 180. In order to maintain them in the service for the duration of the study – an ethical requirement – participants must be recruited before they have been in the service for 12 months.
Results: The study started recruiting in 2017 with a 3-year recruitment window and an aim of recruiting 60 participants per year in a service that sees 250-300 new first episode psychosis cases annually. However, recruitment has been very difficult with only 44 people being randomised as at end August 2020. In seeking to understand this low level of recruitment we have identified a number of issues that may be of interest to future studies seeking to examine the important questions that prompted Reduce. The two main reasons identified are having been in the clinical service for too long before reaching remission, and not taking or being compliant with medication as prescribed. Despite recruitment difficulties, those who have been recruited have tended to stay in the study irrespective of condition they were randomised to.
Conclusions: Given the lack of evidence to guide anti-psychotic prescribing beyond the short term, and the open questions that exist in the literature, there is an urgent need to conduct randomised studies to address these issues. Further, other literature suggests that there is a desire for guidance on dose reduction among clinicians and an assumption on their part, that young people with first episode psychosis would make better long-term functional recoveries with less ongoing anti-psychotic medication. However, trials addressing dose reduction, face significant obstacles. For Reduce, the key issue appears to be that young people are choosing to discontinue their medication anyway. Ways forward in this area are likely to include large-multisite studies in order to recruit sufficient numbers to a trial, or indeed carefully constructed naturalistic trials that follow the outcomes of people who choose to make their own decisions around their medication.

19.2 TO CONTINUE OR NOT TO CONTINUE? THE HAMLETT STUDY INVESTIGATING (DIS)CONTINUATION OF ANTIPSYCHOTIC MEDICATION IN FIRST-EPISODE PSYCHOSIS

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Background: When achieving remission after a first psychotic episode using antipsychotic medication, international guidelines generally recommend continuation of use for >1 year. However, patients often have a strong wish to stop earlier due to side-effects, affecting everyday functioning. Guidelines have been questioned as one Dutch study found that more patients achieved long-term functional remission in an early discontinuation condition. Yet, sample size was relatively small and their finding was not replicated in another recently

published study from Hong Kong. Psychiatrists, patients and family are unsure which regime to follow: to continue or not to continue?
Methods: The HAMLETT study is a multicenter pragmatic single-blind randomized controlled trial in two parallel conditions (1:1), investigating maintenance treatment versus discontinuation/dose reduction of antipsychotic medication after remission of first-episode psychosis on personal and social functioning, psychotic symptom severity and health-related quality of life. 512 participants will be included, recruitment takes place at 24 Dutch sites.
Main research question: Is long-term general functioning better if patients reduce/discontinue antipsychotic medication at an early stage (3-6 months after remission of their first psychotic episode), than when they continue medication >1 year?

Results: Inclusion has proven difficult after two years, so far we have included 260 patients of 512 needed which is only a limited percentage of first episode patients seen in participating centers. Adherence to the randomized condition also proves to be an important issue, about one third of the participants in both the continue and the discontinue group is a crossover to the other condition. Our interim analyses showed that serious adverse events (SAEs) were observed in 13 patients (18.6%) that had been randomized to the continuation group, compared to 7 patients (9.1%) in the discontinuation group. Hospitalization due to psychotic symptom exacerbation was the most common SAE (8 patients [11.4%] in the continuation group versus 5 patients [9.1%] in the discontinuation group). One patient was admitted for suicidal ideation and attempt (continuation group) and one death by suicide was reported which was not related to study treatment (discontinuation condition). 2 SAEs concerning voluntary hospital admissions for other psychiatric treatment-emergent symptoms were observed, both in the continue group. Three patients were admitted to the hospital due to a physical condition (two patients in the continue group and one in the discontinue condition).
Conclusions: Together with the three other (dis)continuation studies that are currently being underway, namely TAILOR (Denmark), RADAR (United Kingdom) and REDUCE (Australia), the HAMLETT study will offer evidence to guide patients and clinicians when evaluating optimal treatment duration for psychotic disorders. Yet, there are challenges to be addressed in this field of research, including low recruitment rates and generalizability of the study results

19.3 ENHANCING PATIENT CHOICE ABOUT LONG-TERM ANTIPSYCHOTIC TREATMENT: DESIGN AND IMPLEMENTATION OF THE RADAR TRIAL (RESEARCH INTO ANTIPSYCHOTIC DISCONTINUATION AND REDUCTION)

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Background: Antipsychotic medication is effective in reducing acute symptoms of psychosis and trials conducted with people with schizophrenia indicate an increased risk of relapse in the short-term following abrupt antipsychotic discontinuation. However, antipsychotics have a range of potentially serious and debilitating adverse effects and are often disliked by patients. Moreover, there is little evidence about the long-term outcome of a gradual process of reduction and discontinuation on social functioning, relapse and other outcomes. Guidelines stress that patients should have choice and be involved in decisions about their treatment, but although people who have had one episode of psychosis may be offered support to try to reduce and discontinue medication, most people with more than one episode are given lifelong antipsychotic treatment with no other options.
Methods: A new randomised trial has been set up in the United Kingdom to provide more information on the long-term outcome of a gradual process of antipsychotic reduction and

discontinuation. This is a multi-centre trial involving people with schizophrenia and related disorders who have had more than one episode. Participants are randomised to have a clinically-supervised, gradual reduction of antipsychotic medication, leading to discontinuation when possible, or to continue with maintenance treatment. Blinded follow-up assessments are conducted at 6, 12 and 24 months and the primary outcome is social functioning, measured by the Social Functioning Scale at 24 months. Secondary outcomes include severe relapse (admission to hospital), all relapses (as identified by an independent and blinded endpoint committee), symptoms measured by the Positive and Negative Syndrome Scale (PANSS), quality of life, adverse effects, self-rated recovery and neuropsychological measures.
Results: The trial started in 2016 and 253 participants have been enrolled and randomised. The trial is scheduled to finish in June 2022.
Conclusions: The trial will provide information on the short-term and long-term outcomes of a supported process of antipsychotic reduction that can help to improve patient choice over their long-term treatment.

19.4 DISCONTINUATION OF ANTIPSYCHOTIC MEDICATION IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA – REPORT OF THE FAILED RANDOMIZED CLINICAL TRIAL TAILOR

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Background: Discontinuation of antipsychotic medication in patients with first-episode schizophrenia are often attempted and heavily debated. Discontinuation increase the relapse risk but the effect on cognition and function remains unclear. The adverse effects of antipsychotic medication, such as obesity, cardiovascular disease and movement disorders and the risk of discontinuation should be balanced with the potential benefits of discontinuation when deciding on duration of treatment. The aim of the TAILOR trial was to examine early tapered discontinuation versus maintenance treatment regarding remission of psychotic symptoms and impact on other areas of life.
Methods: Patients with first-episode schizophrenia were included if they took antipsychotic medication and were in remission of psychotic symptoms. They were randomized to tapered discontinuation or maintenance treatment with antipsychotic medication during a one-year intervention in the early intervention unit OPUS. Assessments were made at baseline and one-year follow-up. The primary outcome was remission of psychotic symptoms and no antipsychotic medication. Other outcomes were cognitive function, social functioning, side effects, dose of antipsychotic medication, negative symptoms, substance and alcohol use, sexual function, quality of life, self-efficacy and experience of support.

Results: The trial was terminated due to insufficient recruitment and failed to report on outcomes. No statistical analyses were made, and results are reported as descriptive. In total 29 patients were included – 14 in the discontinuation group and 15 in the maintenance group. Adherence was poor in the maintenance group. All patients in the discontinuation group were tapered and 11 discontinued their antipsychotic medication. In the maintenance group six patients were tapered and five patients discontinued their antipsychotic medication. During the intervention-year two patients in the discontinuation group and three patients in the maintenance group relapsed. At follow-up simultaneous remission of psychotic symptoms and no antipsychotic medication for three months occurred in five patients in the discontinuation group and two patients in the maintenance group.
Conclusions: This study indicates no clear conclusion whether tapering of antipsychotic medication is followed by advantages or unfavorable outcomes compared to maintenance treatment. Recruitment and adherence to maintenance treatment encountered obstacles. Thus, evidence is still needed whether and when to maintain or discontinue antipsychotic medication in patients with first-episode schizophrenia and future studies should consider study design and feasibility.

Plenary Session

20. THE IDENTIFICATION OF CROSS-CULTURAL CAUSES OF MENTAL ILLNESS AND HOW TO ADDRESS THIS IN MENTAL HEALTH CARE WITH FOCUS ON PSYCHOSIS

Aristotle Voineskos
Centre for Addiction and Mental Health

Overall Abstract: The present proposal aims to consider what can be done for people with psychosis in relation to disparities among different cultures. It takes an innovative view via the COVID-19 pandemic, specifically in Toronto, Canada, summarizing risks to different cultural or ethnic populations due to COVID. Targeted approaches to support those populations in relation to COVID-19 serve as the lens through which similarly potentially targeted approaches might be useful for groups at higher risk of psychosis.

20.1 WHAT COVID-19 CAN TELL US ABOUT THE CROSS CULTURAL CAUSES OF PSYCHOSIS AND WHAT WE CAN DO ABOUT IT

Kwame McKenzie
Wellesley Institute

Individual Abstract: The literature has detailed differences in the rate of psychosis for racial and cultural groups in high income countries. For instance; in the UK, some racialized groups including people of African and Caribbean heritage and those with South Asian origins have been shown to be at higher risk of psychosis than the White British population.
There has been significant investigation of the possible causes for these increased incidence rates. This work has contributed to the renaissance in research into how social factors may influence psychosis risk. Complex and intriguing multi-level and life course perspectives on causation have led to integrative theories. These have included, but are not limited to concepts

such as gene environment interaction, neurogenesis and inflammation as pathways through which social inequities, adverse childhood experiences, stress and perceived racism get under the skin. There has also been consideration of the role of possible psychosis risk indicators such as stress reactivity among other concepts.

There has, however, been less consideration about what can be done to decrease disparities in incidence of psychosis.

In both wave 1 and wave 2 of the covid-19 pandemic, high income countries have reported higher rates of infection, hospitalizations and death for racialized groups. Black populations and those of South Asian origin have again been among the groups reported at higher risk. Similar to the psychosis literature, there has been significant discussion and investigation of possible causes of the disparities. Again, the role of social factors has been considered. The literature suggests that increased covid-19 risks for certain racialised populations may be because of at least four reasons:

1) increased risk of exposure to covid-19 because they are more likely to be essential workers and are more likely to be mobile;

2) decreased ability to protect themselves from covid-19 because they are less able to follow public health guidelines; for instance people who are lower income and live in over crowded homes are less able to physically distance;

3) increased risk of serious impacts of infection because of existing higher rates of chronic illnesses such as diabetes (which are in part linked to social factors) and poorer access to healthcare during a pandemic; and,

4) risks linked to the disproportionate impacts of the pandemic-related economic downturn.

But one difference in the covid-19 pandemic has been the number of places where the evidence of disparities has been used to develop multi-level interventions to both decrease disparities in illness rates and improve outcomes.

This presentation will explore how the identification of racial disparities in covid-19 infection in Toronto, Ontario led to a complex policy and practice intervention to promote equity and will discuss what we can learn from this about how to address the cross cultural causes of psychosis.

Concurrent Symposia

21. ANNUAL SIRS ETHICS SYMPOSIUM: GRAPPLING WITH THE ETHICS AND EVIDENCE OF PLACEBOS IN LONG-TERM SCHIZOPHRENIA CLINICAL TRIALS

Stephen Marder

University of California, Los Angeles, Semel Institute for Neuroscience

Overall Symposia Abstract: Sometimes called “medical mysteries,” placebos prompt a cessation of symptoms but lack the properties by which drugs or other interventions cause physiological changes. And while their use has been documented over centuries, it is only in the post-war period that placebos have become an indispensable part of clinical trial protocols, considered essential for separating medication effect from chance and bias. But their use in drug development and testing is not without controversy, especially in the case of

schizophrenia research. Here, enabling the persistence of untreated, severe mental illness has been argued to contravene ethics and human rights standards. As antipsychotic drug development has dwindled and long-term outcomes in schizophrenia continue to see limited gains, the question arises: what if clinical decision-making needs the evidence that placebo-controlled trials provides? This SIRS Ethics Symposium proposes to grapple with the challenges, controversies, and evidence-related quandaries of using placebos within schizophrenia research. The symposium brings together an international panel of leading as well as early career researchers working at the intersections of ethics, clinical trial methodologies, and placebo research. Symposium attendees will gain further insights into issues such as clinical equipoise, informed consent, antipsychotic dose reduction, and treatment outcomes—and the place of placebos in these. Dr. Suze Berkhout (Toronto) will provide the perspective of a psychiatrist-ethicist, addressing an overview of ethical considerations surrounding the use of placebos and placebo effects in this population. Dr. Ryan Lawrence (Columbia) will discuss ethical issues related to relapse prevention studies. Dr. Christoph Correll (Charité - Universitätsmedizin Berlin) will examine recent data concerning patient and illness characteristics that are associated with relapse or lack thereof among individuals with schizophrenia whose antipsychotic is continued and replaced by placebo. Dr. Donald Goff (NYU) will discuss the extent to which important issues in long-treatment might only be answered with placebo-controlled studies. Dr. Will Carpenter will serve as the discussant for the symposium.

21.1 INTERSECTIONS OF ETHICS, HISTORY, AND SCIENCE IN THE USE OF PLACEBOS IN SCHIZOPHRENIA RESEARCH: AN OVERVIEW

Susan Berkhout*[1]

[1]*University of Toronto*

Background: Throughout the history of medicine, placebos have simultaneously been hailed as medical mysteries and shunned as a sham. “Inert” substances and procedures that have the capacity to solicit well-being, seemingly unbidden, they have increasingly become objects of scientific study in their own right. This is particularly true in the post-war period, as placebos have solidified their place within the structure of clinical trials (Berkhout and Jaarsma 2018).

Methods: In this contribution to the SIRS Ethics Symposium, I offer a social, historical, and ethical analysis of the use of placebos within the apparatus of clinical trials, with a focus on these issues in schizophrenia research.

Results: First, I provide a brief historical overview of the use of placebo controls in clinical trials, linking their use to the rise of the standards and practices of evidence-based medicine (EBM) and sketching some of the challenges that have arisen in relation to pharmaceutical testing in recent years, such as the rising rates of placebo response in schizophrenia trials. I move on to explore the ethical considerations at stake in clinical trial research involving placebos—clinical equipoise, consent and capacity, and the obligations researchers have to vulnerable populations being chief amongst these. I highlight the ethical concerns regarding placebo controls as they are laid out within contemporary debates within the bioethics literature, and then provide a brief overview of the connection with respect to long-term trials of antipsychotic medication use in schizophrenia.

Conclusions: This paper will provide an overview and discussion of both theoretical and practical ethical issues in relation to placebos, placing these within a historical and scientific context. In doing so, I provide a foundation for the presentations that follow.

21.2 AN HISTORICAL REVIEW OF PLACEBO-CONTROLLED, RELAPSE PREVENTION TRIALS IN SCHIZOPHRENIA: THE LOSS OF CLINICAL EQUIPOISE

Ryan Lawrence*[1], Paul Appelbaum[2], Jeffrey Lieberman[1]

[1]*Columbia University Medical Center,* [2]*Columbia University*

Background: Recent ethical critiques have proposed that placebo-controlled, relapse prevention trials in schizophrenia are no longer justifiable and are therefore unethical. This review provides an historical perspective on the justifications for these trials and how arguments evolved over several decades.
Methods: We identified 87 placebo-controlled, relapse prevention trials published over the last seventy years and examined the purpose for each trial.
Results: We found that first-generation trials had compelling justifications, yet these arguments changed considerably over time. Second-generation trials offered comparatively weaker—and sometimes no—justifications for their conduct.
Conclusions: Without clear and compelling justifications for a given trial, it is not ethical to continue using this study design.

21.3 USE OF PLACEBO IN RANDOMIZED WITHDRAWAL STUDIES OF STABILIZED PATIENTS: WHAT ARE THE OUTCOMES AND THEIR PREDICTORS?

Christoph Correll*[1], Georgios Schoretsanitis[1], Jose Rubio[1]

[1]*The Zucker Hillside Hospital*

Background: Placebo-controlled withdrawal studies in stabilized patients are standard for seeking a maintenance or relapse prevention claim for medications used for patients diagnosed with severe mental disorders. In the US, the FDA still separates the regulatory process for an acute and maintenance/relapse prevention claim. In Europe, however, the EMA grants regulatory approval of a medication for an acute indication only if a positive, placebo-controlled relapse prevention study exists. This requirement in Europe is at odds with the ethics committees in many Western European countries who do not give permission for placebo-controlled trials in stabilized patients who have shown to benefit on the medication that is to be replaced with placebo.
Arguments for placebo-controlled withdrawal studies is that patients often decide by themselves to discontinue psychotropic maintenance treatment, give informed consent, that patients are withdrawn from the study upon impending relapse, so that the potential biopsychosocial consequences of a relapse are mitigated, and that the duration of untreated psychosis after worsening would be relatively short in a controlled study design and framework. Moreover, not all psychiatric disorders may require lifelong preventive medication treatment. However, in schizophrenia, data seem to suggest that extended, if not lifelong, maintenance treatment is needed, calling placebo-controlled withdrawal studies of antipsychotics in stabilized patients with schizophrenia more into question. This situation of antipsychotic withdrawal is accentuated by two recent trial programs of non-dopaminergic medications, roluperidone, a 5HT2A-Sigma-2 antagonist, and LuAF11167, a PDE 10A inhibitor, that target negative symptoms in the absence of potentially interfering dopamine blockade, although their own antipsychotic efficacy is still unclear.

Nevertheless, as antipsychotic response and remission are heterogeneous, so is the risk for relapse during assured antipsychotic treatment as well as after antipsychotic discontinuation. In this context, it is important to identify patient, illness and treatment characteristics that are associated with delayed or, even, absent relapse in in stabilized patients who have benefited from antipsychotic treatment.

Methods: We identified double-blind, placebo-controlled trials of antipsychotics for relapse prevention in schizophrenia or schizoaffective disorder in the YODA data repository. From these trials, we selected individuals who had been prospectively stabilized on an antipsychotic for ≥3 months and were then randomized to placebo. On these cohorts of individuals, we conducted a survival analysis and Cox proportional hazards regression, which yielded adjusted hazard ratios (aHR) and 95% confidence intervals (95%CIs) of the association between clinical covariates and relapse after antipsychotic withdrawal. Furthermore, we studied whether the method of stabilization (oral antipsychotic [OAP] vs long- acting injectable antipsychotic [LAI] antipsychotic) had an effect on risk of relapse after the antipsychotic had been cleared from plasma, by examining the survival curves and 95%CIs for individuals surviving in the model after 5 half-lives of the stabilizing antipsychotic. Finally, we measured the interaction terms between covariates and risk of relapse during the initial 30 days after discontinuation (vs after) of oral antipsychotic to measure investigate specific potential predictors of rebound psychosis.

Results: Across 5 randomized, placebo-controlled discontinuation clinical trials meeting eligibility criteria, 692 individuals were followed for up to 506 days (median follow up=118 days (IQR=52.75-209.25) after antipsychotic withdrawal. Individual patient data meta-analysis on the incidence and predictors of placebo relapses and non-relapse are currently ongoing and full results will be available at the time of the congress.

Conclusions: We expect results to contribute to the effects of placebo in relapse prevention studies, at least during the observation period. Regulators and ethics committees should consider requiring the collection and publication of extended post-study follow-up safety data during standard of care post study end due to non-relapse or relapse.

21.4 IMPORTANT ISSUES IN THE LONG-TERM TREATMENT OF SCHIZOPHRENIA CAN ONLY BE ANSWERED WITH PLACEBO-CONTROLLED STUDIES

Donald Goff*[1]

[1]*NYU School of Medicine*

Background: The current literature on maintenance treatment of schizophrenia is subject to a surprising degree of uncertainty and debate about key theoretical and clinical issues. This lack of consensus can only be resolved with placebo-controlled drug discontinuation trials. Many patients wish to participate in drug discontinuation studies despite the potential risk, and recent studies have demonstrated that close monitoring and the re-institution of medication prior to full relapse may be safe and feasible.

Methods: Literature review.

Results: As an example of fundamental questions that require study in placebo-controlled trials, it remains unclear whether observed reductions in brain volume and associated deterioration in functioning result from "neurotoxic" exposure to antipsychotic medication versus progression of illness. In addition, while the field has popularized the idea that brief episodes of nonadherence can produce clinical deterioration and relapse, that adherence with oral medication is often quite poor, and that constant D2 receptor occupancy by antipsychotics

is necessary, recent randomized controlled trials have largely failed to find benefit for long acting injectables compared to oral antipsychotics, thus raising questions about mechanistic models for the prevention of relapse. In fact, discontinuation studies have found that most patients do not experience relapse for weeks or months after drug discontinuation-- the biological mechanism underlying relapse remains a mystery that can only be addressed by placebo-controlled trials. Similarly, evidence from Wunderink and colleagues (2013) of better long-term outcomes in approximately 20% of patients who successfully discontinued medication requires replication in large placebo-controlled trials employing appropriate biomarkers.

Conclusions: Identification of biological mechanisms underlying illness progression, drug toxicity and relapse in placebo-controlled trials could lead to a precision medicine approach employing improved methods for the prevention of relapse and the selective discontinuation of medication in patients who might not require maintenance treatment.

22. INTEGRATION OF NEUROPSYCHOLOGICAL ASSESSMENT FOR THE TREATMENT OF PEOPLE WITH PSYCHOTIC DISORDERS - INSIGHTS AND TECHNOLOGICAL ADVANCEMENTS

Lisette Van der Meer

University of Groningen

Overall Symposia Abstract: Cognitive impairments in people with psychotic disorders are widely recognized in research and clinical practice. Significant effects of cognitive impairments on daily functioning have been demonstrated repeatedly. Commonly, neuropsychological impairments in people with psychiatric disorders are assessed with lengthy and expensive test batteries administered in-person by highly trained clinical staff. However, the ecological validity of many assessment batteries can be questioned. Most neuropsychological tests were not originally designed to predict daily functioning, but rather to draw diagnostic conclusions about the presence of deficits. That implies that in current psychiatric practice, neuropsychological tests are often used to answer different questions than for the purpose for which they were designed. Additionally, most neuropsychological tests do not account for the impact of contextual factors on cognitive performance in daily life. This may lead to incorrect assumptions regarding cognitive performance in real life, and thereby limiting integration of measured cognitive impairments into treatment.

These important drawbacks warrant adaptation of both neuropsychological assessment as well as integrating neuropsychological findings into treatment strategies. In this symposium, dr Sean Kidd will first summarize the literature that has sought to develop more comprehensive models of the cognition-functioning connection. He will do so by addressing various aspects of cognition that are usually assessed, possible mediators between cognition and functioning, and key considerations at the individual level. Subsequently, Dr. Kidd will discuss how and to what extent individual-level and contextual factors may influence the impact of cognitive impairments in real-world settings. Such individual-level and contextual factors additionally affect the integration into routine practice of established compensatory and restorative treatment strategies aimed at minimizing the impacts of cognitive disabilities on quality of life and community functioning. Dr. L. van der Meer will discuss factors that may impact the implementation of such interventions, in particular, factors associated with the attitude of mental health workers towards working with evidence based interventions. She will also

introduce an innovative implementation program aimed at optimizing the implementation process of cognitive rehabilitation interventions.

In the second part of this symposium we will discuss the rapidly advancing opportunities presented by technological developments that have the potential to improve the ecological validity of neuropsychological testing as well as provide cognitive rehabilitation programs in a real world environment. Dr. John Torous will discuss preliminary data on the use of smartphone digital phenotyping methods, including measures of geolocation, physical activity, screen use, cognition, and self reported surveys, to better understand the lived experiences of patients with serious mental illnesses like schizophrenia. Finally, Dr. George Foussias will discuss the use of Virtual Reality in cognitive and behavioural processes involved in goal-directed behaviour as well as the usability of VR-based neurocognitive assessments. Prof. Joseph Ventura will be the discussant of the symposium. He is an expert in the field of neuropsychological assessment and has also been involved in, amongst others, the development of a neurocognitive assessment battery.

22.1 COGNITION IN ASSESSMENT ENVIRONMENTS AND COGNITION IN THE OUTSIDE WORLD: THE MISSING VARIANCE CONUNDRUM

Sean Kidd*[1]

[1]*University of Toronto*

Background: An extensive body of literature has established the relationship between neurocognition and community functioning in schizophrenia populations. However, we remain much less informed about how neurocognition affects community functioning. There also remains the conundrum of why such foundational abilities in cognitive domains account for a relatively modest share of the variance in studies of community functioning. Unpacking these questions is essential to optimizing interventions designed to improve cognitive functioning and compensate for the impacts of cognitive impairments.

Methods: This presentation will review the current state of the literature that has sought to develop more comprehensive models of the cognition-functioning connection. Domains will include: (i) what aspects of cognition are assessed, (ii) emerging data on key mediators of the relationship between cognition and functioning, and (iii) key considerations at the individual level – including age and illness stage, access to resources and opportunities, and sociocultural factors such as discrimination.

Results: With respect to what cognitive domains are assessed, the predominant emphasis has been the major domains of neurocognitive functioning broadly categorized as attention, memory, and executive functioning and their subcomponents. More recently, metacognition and social cognition have been examined in relation to functioning. Metacognition broadly refers to the cognitive processes involved in thinking about thinking or how individuals otherwise monitor and control more fundamental cognitive processes. Social cognition refers to the processing and applying information specific to social interactions. These more specific cognitive domains play an important role in how cognition relates to functioning with, for example, substantial evidence suggesting that social cognition mediates the relationship between neurocognition and functioning. Other variables that are increasingly examined in efforts to unpack how cognition affects functioning include motivation, defeatist beliefs and, relatedly, internalized stigma. How these variables interact with cognition be it as mediators,

covariates, and in what functional domains influence is exerted, introduce complexity and also hold the promise of beginning to build models that better explain functional outcomes.
Finally, this presentation will summarize the preliminary evidence on individual-level and contextual factors that likely enhance or constrain how cognition is expressed in community functioning. Key considerations include the role of social support, educational and vocational opportunities and, by proxy, poverty and discrimination. Additionally, the evidence on how stage of life and illness in the relationship between cognition, functioning, and pertinent mediators will be addressed.

Conclusions: This summary of the emerging evidence that is beginning to better elucidate the role of cognition in the pathways to daily functioning provides a backdrop for considering (i) how we need to think about assessing cognition and critical mediators differently, (ii) how we need to refine and better target cognitive interventions, and (iii) how we need to tailor real-world implementation to the individual such that contextual challenges do not undo the potential for substantial gains in functioning.

22.2 IMPLEMENTATION OF A COGNITIVE REHABILITATION INTERVENTION: ASSOCIATIONS BETWEEN ATTITUDE OF MENTAL HEALTH PROVIDERS TOWARDS EVIDENCE BASED PRACTICE AND FACTORS AT INDIVIDUAL-TEAM- AND ORGANIZATIONAL LEVEL

Michelle van Dam[1], Jaap van Weeghel[2], Stynke Castelein[3], Marieke Pijnenborg[4], Lisette Van der Meer*[5]

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Background: Cognitive Adaptation Training (CAT) is a psychosocial intervention focusing on reducing the impact of cognitive disorders on daily functioning in people with severe mental illness (SMI), like schizophrenia. Despite the established effectiveness of CAT in diminishing the impact of cognitive impairments on functioning in people with SMI, multiple factors at the individual-, team-, and organizational-level hamper the implementation of CAT into routine care. This so called 'science-to-service gap' is a widespread problem in mental health care. Research on the implementation of guideline recommendations in schizophrenia treatment showed that only 0-7% of mental health care teams provide psychological or psychosocial evidence based practices (EBPs) to more than 70% of the people in their caseload, even though these interventions were available in the teams. Research also shows that attitude of the providers towards adoption of EBP is an important contributor to the use of and openness to EBP. The aim of the current study is to investigate which factors influence providers' attitudes towards using EBP. Understanding these factors will enable us to increase usage of EBP that incorporate knowledge regarding cognitive factors in the treatment of people with SMI.
Methods: The data used in this study was part of a larger research evaluating an innovative implementation program of CAT. Self-report data of 159 mental health professionals and observational questionnaires of 203 service users was collected between October and December 2018. All mental health professionals provide long-term daily clinical care in an inpatient setting to adult people diagnosed with a SMI according to DSM-IV or DSM-V criteria. The mental health professionals are nurses, social workers, peer support workers and other professionals who provide day-to-day care to the service users. Service users who receive outpatient treatment or those who are under the age of 18 were excluded from participation.

Assessments include measures on organizational climate, team climate, provider characteristics (age, gender, educational level, years working experience, years working in team, years working with this population and attitude towards EBP) and service-user variables (everyday functioning and cognitive functioning). Data was analyzed using regression analysis in SPSS with 'attitude towards EBP' as a dependent variable and the other variables as separate independent variables.
Results: Preliminary analyses show that team climate ($p<.008$) and organizational climate ($p<.043$) significantly predict the attitudes of mental health providers toward EBP. Age, gender, educational level, years working experience, years working with population and years working within team proved not to be significant. Analyses on the service-user variables as well as analyses on subscales of questionnaires are ongoing.
Conclusions: This study may provide valuable insights in the preconditions that need to be taken into account before implementing an EBP in routine practice to avoid failure, as this failure may negatively impact the providers' attitude toward EBP. This includes more thorough insights in how to target mental health workers and contextual variables to better integrate effective interventions in the daily routine of mental health professionals so that service users can benefit from effective interventions. We will discuss an innovative implementation program that incorporates these factors in order to improve implementation success and present preliminary data on the effectiveness of this implementation program.

22.3 CHARACTERIZING THE CLINICAL COURSE IN SCHIZOPHRENIA WITH DIGITAL PHENOTYPING

John Torous*[1], Matcheri Keshavan[2]

[1]*BIDMC / Harvard Medical School,* [2]*Harvard University*

Background: Digital phenotyping methods offer the potential to better understand the lived experiences of patients with serious mental illnesses like schizophrenia. Yet to date it is unclear if the digital biomarkers offered from this method are unique to certain conditions like schizophrenia, or rather are shared by diverse populations, and to what degree digital phenotyping data are correlated with patient and clinician assessments.
Methods: 60 patients with schizophrenia and 45 healthy controls collected smartphone digital phenotyping data for a three month duration including measures of geolocation, physical activity, screen use, cognition, and self reported surveys. In-clinic assessments at study start and at three months assessed cognition (Brief Assessment of Cognition in Schizophrenia), psychosis symptoms (Positive and Negative Symptom Scale; PANSS) and other measures. Clustering and correlational methods were utilized to compare active and passive data streams both within and across groups.
Results: Adherence to active data (surveys and cognitive assessments) on the phone was roughly 50%, both for those with schizophrenia as well as for the healthy controls. Four unique clusters that included both active and passive data emerged for each group and the clusters were distinct with unique symptoms, cognition, and passive data metrics. Each group also possessed distinct correlations between active and passive data, with the schizophrenia group having more statistically significant findings especially around sleep.
Conclusions: Digital phenotyping methods offer the potential to identify unique clusters of patients based on both their self reported as well as passive data. Future research will explore the utility of these clusters in predicting functional outcomes and offering personalized treatment.

22.4 VIRTUAL REALITY-BASED ASSESSMENTS OF NEUROCOGNITION IN SCHIZOPHRENIA

George Foussias*[1], Ishraq Siddiqui[2], Sarah Saperia[2], Susana Da Silva[4], Eliyas Jeffay[5], Konstantine Zakzanis[5], John Zawadzki[2], Albert Wong[2], Ofer Agid[2], Gary Remington[2]

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Background: Neurocognitive deficits are a prominent feature of schizophrenia psychopathology that has been consistently linked to functional impairment experienced by affected individuals. These deficits have direct impacts on community functioning and also influence the translation of motivation into goal-directed behaviours. Assessments of these neurocognitive deficits, however, have typically relied on abstract paradigms with limited direct relevance to everyday life. To address this, we evaluated two virtual reality-based (VR) paradigms employing real-world scenarios resembling a factory setting and a city to permit an ecologically-valid examination of discrete aspects of attention and goal-directed planning and action, respectively, for individuals with schizophrenia.

Methods: Stable outpatients between 18 and 55 years old with schizophrenia (SZ) and matched healthy controls (HC) were recruited for these studies. All participants underwent clinical, functioning, and neurocognitive assessments, followed by evaluations of real-world attention using the VR Conveyor Belt Task (VR-CT; Study 1), and goal-directed planning and action using the Multitasking in the City Task (MCT; Study 2) in a virtual environment.

Results: In Study 1, 66 participants (36 SZ and 30 HC) were assessed using the VR-CT for selective attention (SA), divided attention (DA) and alternating attention (AA). VR-CT performance was significantly decreased in SZ participants specifically in DA and AA tasks compared to HC participants ($z = -4.28$, $p<.001$, and $z = -4.82$, $p<.001$, respectively). Moreover, DA and AA task performance was significantly correlated with global cognitive performance (Brief Assessment of Cognition in Schizophrenia (BACS): rho = .583, $p<.001$; and rho = .635, $p<.001$, respectively), trail making test (TMT) performance (TMT A: rho = -.521, $p<.001$, and rho = -.482, $p<.001$, respectively; TMT B: rho = -.486, $p<.001$, and rho = -.523, $p<.001$, respectively), as well as with community functioning (rho = .386, $p=.001$, and rho = .505, $p<.001$, respectively). In Study 2, 104 participants (49 SZ and 55 HC) were assessed with the MCT where they completed a series of errands in a virtual city. Here, SZ participants demonstrated a lower overall performance score ($t(64.74) = -3.2$, $p = .002$, $d = -0.64$), and lower path efficiency in completing tasks ($t(93.47) = -2.83$, $p = .006$, $d = -0.56$) compared to HC participants. Notably, in SZ participants, path efficiency was significantly correlated with global neurocognitive functioning (BACS: $r = 0.34$, $p <.05$), including performance on the Tower of London task ($r = 0.30$, $p <.01$), amotivation ($r = -0.42$, $p < .01$), and community functioning ($r = 0.31$, $p<.01$).

Conclusions: Across this series of experiments, VR-based assessments provided objective and valid means of evaluating attention and goal-directed behaviour deficits experienced by individuals with schizophrenia in a naturalistic and functionally relevant manner not possible with traditional paper and pencil tasks. Moreover, substantial unaccounted variance in VR task performance potentially reflects the ability of these tasks to assess aspects of real-world cognitive functions that are beyond the scope of traditional assessment tools. Continued development and potential implementation in clinical practice of such VR-based assessments may enable earlier and more precise identification and treatment planning for functionally relevant cognitive deficits that contribute to ongoing disability for individuals with schizophrenia.

23. CARDIOMETABOLIC RISK IN PSYCHOSIS: DEVELOPMENT, AETIOLOGY AND CARVING A WAY FORWARD

Golam Khandaker
University of Bristol

Overall Symposia Abstract: Cardiometabolic disorders are commonly comorbid in psychosis and are a leading contributor to premature death. Their increased prevalence may be at least in-part related to the adverse-effects of antipsychotic medications and lifestyle factors such as reduced physical exercise, poor diet and smoking, all of which confer cumulative risk over time. However, confounding by iatrogenic or lifestyle factors may not be the whole story; recent evidence suggests that even after adjustments for socioeconomic and anthropometric factors, a cardiometabolic phenotype of raised fasting insulin and triglycerides, indicative of an insulin resistance (IR) phenotype, is associated with antipsychotic-naïve first-episode psychosis (FEP), and with psychotic symptoms in young adults. Additionally, recent evidence is emerging of early diffuse fibro-inflammatory myocardial processes in people with psychosis, which may occur independently of established cardiometabolic risk factors. Therefore, these disorders may share pathophysiologic mechanisms.

In this symposium, we will address potential shared inflammatory causes for psychosis and cardiometabolic disorders, presenting data obtained from rich and varied methods, from participants across the time-line of psychosis (pre-clinical and developmental, the first-episode of psychosis, and established psychotic disorders such as schizophrenia). Additionally, we will discuss clinically-relevant avenues to reduce the seemingly inherent cardiometabolic risk associated with psychosis.

Benjamin Perry will present novel research from a U.K birth cohort which has plotted trajectories of cardiometabolic development from early childhood and tested whether, and how far back in the life-course any specific cardiometabolic developmental trajectory may be associated with psychosis in adulthood. Toby Pillinger will present data from the first cardiac MRI study performed in schizophrenia examining for evidence of inflammatory changes within the myocardium of patients, alongside complementary largescale UK Biobank data examining for evidence of a genetic predisposition to cardiac dysfunction in psychotic illness. Outi Linnaranta will present novel research examining the interplay between cardiometabolic and inflammatory markers at First-Episode Psychosis and how these may relate to the severity of cardiometabolic adverse effects of antipsychotic medications as well as a summary of research of the repurposing of common cardiometabolic medications for the treatment of psychosis. Jackie Curtis will present an overview of exciting research showing how the right lifestyle interventions can truly have a positive impact on the lives of people with psychosis in the reduction of cardiometabolic morbidity.

Together, the symposium will show consistent evidence of an association with both soft- and hard-markers of cardiometabolic dysfunction in people throughout the trajectory of psychotic illness, but that the increased rates of morbidity and mortality currently associated with chronic psychosis are not a foregone conclusion; careful decisions by clinicians and the promotion of lifestyle changes make a difference.

23.1 LONGITUDINAL TRENDS IN INSULIN LEVELS AND BMI FROM CHILDHOOD SHOW DIFFERENT ASSOCIATIONS WITH RISKS OF PSYCHOSIS AND DEPRESSION IN YOUNG ADULTS

Benjamin Perry*[1], Jan Stochl[1], Rachel Upthegrove[2], Stan Zammit[3], Nicholas Wareham[1], Claudia Langenberg[1], David Dunger[1], Peter Jones[1], Golam Khandaker[1]

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Background: Cardiometabolic disorders are commonly comorbid with psychosis and depression, but the direction and mechanism of association are not fully understood.
Methods: We used growth mixture modelling to delineate developmental trajectories of body mass index (BMI) (n=10,473; ages 1-24y) and fasting insulin (FI) (n=5,790; ages 9-24y) in the ALSPAC birth cohort. We used regression analyses to examine characteristics of these trajectories, and their associations with risks for psychosis and depression at 24y, adjusting for sex, ethnicity, social class, and cumulative smoking and physical activity. Sensitivity analyses explored sex-specific associations.
Results: We identified three trajectories for FI and five for BMI. The persistently high FI trajectory was associated with psychosis at-risk mental state (adjusted OR=4·14; 95% C.I., 1·31-13·19) and psychotic disorder (adjusted OR=2·96; 95% C.I., 1·18-9·44), but not depression. Puberty-onset major BMI increase, but not persistently high BMI, was associated with depression (adjusted OR=3·46; 95% C.I., 1·33-10·53). This association was stronger in females. There was no consistent evidence for an association of BMI trajectories with psychosis.
Conclusions: The cardiometabolic comorbidity of psychosis and depression may have distinct, disorder-specific origins in early life. Disrupted insulin sensitivity could be a shared risk factor for cardiometabolic disorders and psychosis. Puberty-onset major BMI increase may be risk factor/risk indicator for depression. These cardiometabolic markers may represent important targets for treatment/prevention of cardiometabolic disorders in people with psychosis and depression. Further work is needed to understand antecedents of substantial BMI increase around puberty.

23.2 KEEPING THE BODY IN MIND: INTEGRATING EVIDENCE INTO ROUTINE CARE IN PSYCHOSIS

Jackie Curtis*[1], Hamish Fibbins[2], Oscar Lederman[2], Rachel Morell[2], Scott Teasdale[2], Andrew Watkins[3], Philip Ward[1]

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Background: Higher rates of obesity, tobacco use, cardiovascular disease and diabetes contribute to the 20-year reduced life expectancy of people living with psychosis, compared to the general population.
The seeds of this health inequality are evident early, and, in youth with first episode psychosis (FEP), antipsychotic medication initiation induces rapid deterioration in metabolic health.

Methods: The "Keeping the Body in Mind" (KBIM) program, Sydney, Australia has developed a multi-disciplinary integrated program for screening, prevention and intervention to address cardiometabolic health in psychosis.
Results: Evaluation of the 12-week intervention program, 2-year follow-up and replication data have demonstrated the effectiveness of a lifestyle and life skills intervention, in attenuating weight gain in youth aged 14–25 years with FEP. The addition of a pilot smoking cessation program "y-QUIT", was feasible and acceptable in this population and reduced tobacco-related

harm outcomes. The KBIM program commenced in youth and has been extended to adult mental health populations and now embedded in routine care.
Conclusions: Bringing evidence-based multi-disciplinary, early lifestyle interventions into routine care for the protection of cardiometabolic health in people living with psychosis may be an important means of achieving the key international Healthy Active Lives (HeAL) targets (www.iphys.org.au). Future research should focus on implementation strategies to achieve this at scale as a means to close the gap for people living with psychosis.

23.3 CARDIAC ALTERATIONS IN SCHIZOPHRENIA: A CONSEQUENCE OF DISEASE, LIFESTYLE, OR TREATMENT?

Toby Pillinger*[1], Emanuele Osimo[2], Rob McCutcheon[1], Enrico D'Ambrosio[1], Stefan Brugger[1], Antonio de Marvao[3], Ali Vazir[3], Stuart Cook[3], Declan O'Regan[3], Oliver Howes[4]

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Background: Schizophrenia is a developmental disorder with many genetic variants of individually small effect contributing to phenotypic variation. Brain structural alterations are well-established in people with schizophrenia, including reduced cortical thickness. These changes are observed at the onset of illness and prior to use of antipsychotic medication. Furthermore, increased polygenic risk for schizophrenia in the general population is associated with reduced cortical thickness. At the onset of psychosis there is evidence of alterations in multiple organ-systems, including immune, metabolic, and stress-axis dysfunction. These non-CNS alterations occur at effect size magnitudes comparable to those observed within the CNS, suggestive of schizophrenia representing a multi-system disorder. Schizophrenia is associated with premature cardiovascular mortality, traditionally blamed on lifestyle factors and antipsychotic treatment. However, the metabolic, inflammatory, and stress-axis alterations observed at the onset of disease are risk factors for cardiovascular disease (CVD). Thus, multi-system organ dysfunction that may be intrinsic to schizophrenia may also contribute to CVD.
Methods: First, we will describe the first cardiac MRI study performed in schizophrenia to characterise cardiac structure and function in patients compared with controls. 31 participants underwent cardiac MRI assessing myocardial markers of fibrosis/inflammation, indexed by native myocardial T1 time, and cardiac structure (left ventricular (LV) mass) and function (left/right ventricular end-diastolic and end-systolic volumes, stroke volumes, and ejection fractions). To reduce lifestyle/physiological confounds, all participants were physically fit without any cardiac/metabolic co-morbidities, and matched for age, gender, smoking, blood pressure, BMI, HbA1c, ethnicity, and physical activity.
Second, to characterise if cardiac alterations in schizophrenia have a genetic component, we will describe the first study to examine if polygenic risk for schizophrenia (PGRS-SCZ) in the general population is associated with myocardial dysfunction. Genetic and cardiac MRI data from 19,000 UK Biobank participants will used, and linear mixed models employed to test for associations between PGRS-SCZ and cardiac structural/functional parameters (left/right ventricular mass, end-diastolic volumes, stroke volumes, and ejection fractions).

Results: For the cardiac MRI study, compared with controls, native myocardial T1 was significantly longer in patients with schizophrenia (effect size, $d = 0.89$; $p = 0.02$). Patients had significantly lower LV mass, and lower left/right ventricular end-diastolic and stroke volumes (effect sizes, $d = 0.86\text{-}1.08$; all $p < 0.05$). Analyses for the PGRS-SCZ/cardiac study are ongoing and will be presented at the meeting.

Conclusions: The results of the cardiac MRI study suggest a diffuse fibro-inflammatory myocardial process in patients that is independent of established CVD-risk factors and could contribute to excess cardiovascular mortality associated with schizophrenia. It is unclear if these findings are secondary to antipsychotic treatment or are intrinsic to schizophrenia. An association between PGRS-SCZ and cardiac structural/functional alterations in the general population (as is seen for brain structural alterations) would point towards an intrinsic component to cardiac disease in schizophrenia, and will be discussed further at the meeting.

23.4 DETERMINANTS OF CARDIOMETABOLIC RISK DURING THE FIRST EPISODE OF PSYCHOSIS

Outi Linnaranta*[1], Jaakko Keinänen[2], Jarno Honkanen[2], Kalevi Trontti[3], Iiris Hovatta[3], Jaana Suvisaari[1]

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Background: Markers of cardiovascular risk are elevated in the early phases of psychosis. In this presentation, the results from the Helsinki First Episode Psychosis Study will be summarized to describe early phases of developing cardiovascular risk.
Methods: The cohort was collected in Helsinki, Finland, and included 129 first episode psychosis (FEP) patients and 130 matched controls; for analysis of gene expression, n=67 and 38, respectively . The baseline evaluation was done during the first weeks of antipsychotic medication. Follow-up data were collected at 2 months and at 1 year. At each evaluation, we measured fasting blood glucose, HOMA-index, lipids, body mass index (BMI), waist circumference, and high sensitivity C-reactive protein. We applied the NanoString nCounter in-solution hybridization technology to determine gene expression levels of 178 candidate genes reflecting activation of the immune system. We investigated Ingenuity Pathway Analysis (IPA) to visualize enrichment of genes to functional classes. Strength of positive or negative regulation of the disease and functional pathways was deduced from IPA activation Z-score at the three evaluation points. We correlated gene expression with plasma glucose, triglycerids and HDL and LDL, and used hierarchical cluster analysis to identify groups of genes with similar correlation patterns.
Results: At baseline, the patients showed abnormal glucose tolerance and increased triglycerides, both markers of developing insulin resistance. While the BMI was normal at baseline, insulin resistance (HOMA index) at baseline predicted increase in weight during the first months following antipsychotic treatment. Dysregulated lipid metabolism was seen after days on antipsychotic treatment. C-reactive protein (CRP), a robust marker of cardiovascular risk, was comparable to healthy controls at baseline. An increase in CRP during the first year followed an increase in waist circumference, accompanied by increase in low density lipoprotein. In patients, initially, genes associated with the innate immune system response pathways were upregulated, which decreased by 12 months. Furthermore, genes associated with apoptosis and T cell death were downregulated, and genes associated with lipid metabolism were increasingly downregulated by 12 months. At baseline, after controlling for multiple testing, 32/178 genes correlated with fasting glucose levels, and 55/178 genes with triglycerides in patients, and the genes clustered showing correlations only with triglycerides or in opposite directions for triglycerides vs glucose and HDL. By 12 months, downregulated genes correlated negatively with triglycerides and some showed a similar correlation with glucose.
Conclusions: The results suggest a functional link between peripheral immune system and metabolic state in FEP. The first months of psychosis present an important time window to

target dysregulated immunometabolic processes. For the long-term outcome, interventions targeting smoking and sedentary lifestyle as well as selection of a weight neutral antipsychotic medication are both essential in the early phases of psychosis. Promising approaches include medical interventions such as anti-inflammatory agents, statins or metformin to prevent initial metabolic changes.

24. GXE INTERACTIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDERS-AN UPDATE FROM EPIDEMIOLOGICAL STUDIES

Robin Murray

Institute of Psychiatry, King's College, London

Overall Symposia Abstract: A history of childhood adversity is associated with psychotic disorder, with an increase in risk according to the number or severity of exposures. However, childhood adverse events are also relative common in the general population, and it is unknown why only some exposed individuals go on to develop psychosis. One possibility is pre-existing polygenic vulnerability in addition to epigenetic modifications that may alter gene expression and affect trajectories to disease. Schizophrenia is highly polygenic, but it is yet to be determined if including both polygenic risk and childhood adverse events increases the relative risk above that of its individual components. Although twin studies show that schizophrenia has a heritability of 60-80% the proportion of the genetic liability accounted for by the recent large genome-wide association (GWAS) studies represents only a fraction of the effect that has been suggested by twin studies. Thus, there is a "heritability gap" between twin and molecular studies. In the proposed symposium novel approaches will be presented focusing on possibly synergistic effects of polygenic risk and childhood adversity as well as exposomic liability on the relative risk of schizophrenia. In addition, new biological targets examining whether epigenetic changes mediate the link between adversity and psychosis will be shown, closing the gap between the environment and the phenotype.

The first speaker will present novel data on interaction between polygenic risk score of schizophrenia and exposome score in schizophrenia from a dataset of 1699 patients, 1753 unaffected siblings, and 1542 healthy individuals. Multilevel regression models will be applied to investigate the independent and joint effects of polygenic risk and exposome score.

The second speaker will present epigenetic changes across the genome following polyvictimization in childhood exploring whether such changes mediate the association between adversity and psychosis. Data from the large genome-wide DNA methylomic (EWAS) profiling was collected from 366 patients with a first episode psychosis and 519 healthy individuals as part of the European network of national schizophrenia networks studying Gene-Environment Interactions (EUGEI).

The third speaker will demonstrate potential synergistic effects of childhood adversity and polygenic risk on the prevalence of psychosis from the EUGEI study consisting of 397 patients with a first episode psychosis and 702 healthy individuals.

24.1 EXAMINING THE INDEPENDENT AND JOINT EFFECTS OF GENOMIC AND EXPOSOMIC LIABILITIES FOR SCHIZOPHRENIA ACROSS THE PSYCHOSIS SPECTRUM

Lotta-Katrin Pries[1], Giovanna Dal Ferro[2], Jim van Os[3], EUGEI WP6 Investigators EUGEI WP6 Investigators[4], GROUP Investigators GROUP Investigators[5], Sarah Tosato[2], Bart Rutten[6], Sinan Guloksuz*[7]

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Background: Psychosis spectrum disorder has a complex pathoetiology characterized by a network of environmental and genetic vulnerabilities. Hereby, we aimed to investigate gene-environment interaction using aggregate scores of genomic (polygenic risk score: PRS-SCZ) and exposomic liability for schizophrenia (exposome score: ES-SCZ) across the psychosis continuum.
Methods: The sample consisted of 1699 patients, 1753 unaffected siblings, and 1542 healthy comparison participants collected in the Netherlands, Turkey, Spain, and Serbia. Total, positive, and negative schizotypy were measured using the Structured Interview for Schizotypy-Revised (SIS-R) in siblings and healthy comparison participants. The PRS-SCZ was trained using the Psychiatric Genomics Consortiums results. The ES-SCZ was estimated guided by the approach validated in a previous research in the current dataset. Multilevel regression models were applied to investigate the independent and joint effects of PRS-SCZ and ES-SCZ (adjusted for age, sex, and ancestry using 10 principal components).
Results: Both genomic and exposomic vulnerability were associated with case-control status. Furthermore, there was evidence for additive interaction between binary modes of PRS-SCZ and ES-SCZ (above 75% of the control distribution) increasing the odds for schizophrenia spectrum diagnosis (relative excess risk due to interaction [RERI] = 6.79, [95% CI: 3.32, 10.26], P<0.001). Sensitivity analyses using continuous PRS-SCZ and ES-SCZ confirmed gene-environment interaction (RERI = 1.80 [95% CI: 1.01, 3.32], P =0.004). In siblings and healthy comparison participants, PRS-SCZ and ES-SCZ were associated with each SIS-R dimension and evidence was found for an interaction between PRS-SCZ and ES-SCZ on the total (B = 0.006 [95%CI: 0.003, 0.009], P<0.001), positive (B = 0.006 [95%CI: 0.002, 0.009], P=0.002), and negative (B = 0.006, [95%CI: 0.004, 0.009], P<0.001) schizotypy dimensions.
Conclusions: The interplay between exposome load and schizophrenia genomic liability contributing to psychosis across the spectrum of expression provides further empirical support to the notion of etiological continuity underlying an extended psychosis phenotype.

24.2 EXPLORING EPIGENETIC MEDIATING MECHANISMS LINKING ADVERSITY AND PSYCHOSIS IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS – DATA FROM THE EUGEI STUDY

Luis Alameda*[1], Liu Zhonghua[2], Monica Aas[3], Victoria Rodriguez[3], Marta Di Forti[3], Giulia Trotta[3], Chloe Wong[3], Craig Morgan[3], John Mill[4], Murray Robin[3]

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Background: Epigenetics is emerging as an important player underlying the interactions between genetic and environmental risk factors in the aetiology of psychiatric disorders, including psychosis. DNA methylation has shown to be sensible to the impact of environmental exposure such as adversity in different mental disorders. We could hypothesize that epigenetics

changes related to adversity contribute to the underlying mechanism linking adversity and psychosis. We aim to explore, in a large sample of First episode of psychosis (FEP), whether changes in DNA methylation associated to polyvictimization scores, mediate the link between adversity and psychosis.

Methods: Genome-wide DNA methylomic (EWAS) profiling using the Illumina Infinium Methylation EPIC array in human peripheral blood tissue from 366 First episode Psychosis and 519 healthy population controls part of the EUGEI (European network of national schizophrenia networks studying Gene-Environment Interactions) study. Polyvictimization score was created with the Childhood Trauma Questionnaire (CTQ) ranging from 0-5. First, linear regression models testing the associations between CTQ scores and psychosis was first tested; second, we regressed each probe EWAS on polyvictimization scores and alternatively regressed case control status on each of the probes EWAS, adjusting by age sex, country, batch effects, cell type, smoking core and 10 principal components. Lastly, Divide-Aggregate Composite-null Test (DACT) for the composite null hypothesis of no mediation effect was conducted. We adopted Efron's empirical null framework for assessing statistical significance. Enrichment analyses will be conducted to explore potential biological pathways involved in the mediation between adversity and psychosis.

Results: Polyvictimization scores were significantly associated with psychosis (OR = 1.054, p value <0.001). EWAS mediation analyses showed acceptable inflation (Lambda inflation = 1.038). None of the probes appeared to significantly mediate the adversity-psychosis association according to Bonferroni correction ($p<5.8x10-8$), however 47 probes, located in 30 genes, survived to a more relaxed discovery threshold ($p<5x10-5$). These included genes involved with aetiopathogenesis of schizophrenia and previously associated with the disease, such as the Serotonine receptor gene (HTR7), a gene coding for Pannexins (PANX1), involved in glutamatergic function, and a gene coding for the Cadherins (CDH10), important for neural development.

Conclusions: Our preliminary resultsResults: show that polyvictimization before age 18 is associated with psychosis and with DNA changes that may be involved in mediating pathways previously related to Schizophrenia aetiopathogenesis. Full details on each of the relevant genes will be presented, and enrichment analyses will be carried out allowing to a better understanding of potential new biological pathways involved in the adversity-psychosis association.

24.3 CHILDHOOD ADVERSITY AND POLYGENIC RISK IN FIRST-EPISODE PSYCHOSIS: THE EU-GEI STUDY

Monica Aas*[1], Luis Alameda[2], Marta Di Forti[2], Diego Quattrone[3], Paola Dazzan[4], Evangelos Vassos[2], Charlotte Gayer-Anderson[2], Robin M. Murray[2], Craig Morgan[5]

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Background: A history of childhood adversity is associated with psychotic disorder, with an increase in risk according to the number of exposures. However, it is not known why only some exposed individuals go on to develop psychosis. One possibility is pre-existing polygenic vulnerability. Here we investigated, in the largest sample of first-episode psychosis (FEP) cases

to date, whether childhood adversity and high polygenic risk score for schizophrenia combine synergistically to increase the risk of psychosis, over and above the effect of each alone.
Methods: We assigned a schizophrenia-polygenic risk score (SZ-PRS), calculated from the Psychiatric Genomics Consortium (PGC2), to all participants in a sample of 397 FEP patients and 702 controls from the case-control component of EU-GEI study. Only participants of European ancestry were included in the study. A history of childhood adversity was collected using the Childhood Trauma Questionnaire (CTQ). Synergistic effects were estimated using the interaction contrast ratio (ICR) (OR exposure &PRS− ORexposure− ORPRS+ 1) with adjustment for potential confounders.
Results: Cases were four times more likely to report two or more childhood adversities than controls and the OR was higher for multiple (Odds ratio, OR: 4.56; 95% CI: 2.98-6.99; p<0.001) than for single adverse childhood experiences (Odds ratio, OR: 1.93; 95% CI: 1.33-2.82; p=0.001). There was some evidence that the combined effect of childhood adversities and polygenic risk was greater than the sum of each alone, as indicated by an ICR greater than zero (i.e., ICR 1.30, 95% CI:-1.27 to 3.87). Examining subtypes of childhood adversities, the strongest synergetic effect was observed for physical abuse (ICR 7.76).
Conclusions: Our findings suggest possible synergistic effects of genetic liability and childhood adversity experiences in the onset of first-episode psychosis, but larger samples are needed to increase precision of estimates.

24.4 INTERACTIONS BETWEEN CHILDHOOD MALTREATMENT AND GENETIC VULNERABILITY IN BIPOLAR DISORDER: POLYGENIC RISK SCORE AND BEYOND

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Background: Childhood maltreatment has been repeatedly associated with an increased vulnerability to bipolar disorder (BD). Such an early life stressor, not only is considered as a major risk factor to BD, but is also associated with a more severe, complex and unstable clinical expression of the disorder (for example in terms of psychotic features). In this context, a better understanding on how childhood maltreatment interacts with the genetic vulnerability and/or modifies gene expression is worth investigating. We will present a series of experiments that aim at disentangling how childhood maltreatment interacts with polygenic risk scores to modulate the clinical expression of BD and how childhood maltreatment may affect the level of expression of genes belonging to certain biological pathways.
Methods: First, within a Norwegian-French collaboration, we assigned a BD-polygenic risk score (BD-PRS), calculated from the Psychiatric Genomics Consortium, to each individual in a sample of 402 cases who have been assessed for childhood maltreatment using the Childhood Trauma Questionnaire (CTQ). We modelled the interactions between CTQ and BD-PRS on the clinical expression of BD. Second, in a smaller sample of about 50 cases with BD, we used qPCR to study the gene co-expression of several biological pathways (HPA axis, BDNF, circadian genes) in association with childhood maltreatment.
Results: Cases who reported more severe childhood maltreatment had a lower BD-PRS. An interaction between BD-PRS and childhood maltreatment was observed for the risk of rapid cycling only, however with no further interactions between BD-PRS and childhood maltreatment for other clinical characteristics (age at onset, suicide attempts, number of mood episodes, substance use disorders and psychotic symptoms). Gene co-expression analyses

suggested that an history of childhood maltreatment was associated with several gene expression modifications in the HPA and in the circadian pathways, but not in the BDNF pathway.
Conclusions: when investigating interactions and associations between childhood maltreatment and the genetic background in BD, we suggest that BD-polygenic risk score may play a role in the clinical expression of the disorder and, beyond, that childhood maltreatment may alter gene expression in certain biological pathways.

25. IMAGING GLUTAMATE IN SCHIZOPHRENIA: NOVEL METHODS AND BIG DATA

Kate Merritt
UCL

Overall Symposia Abstract: Glutamate dysfunction is implicated in the pathophysiology of schizophrenia, but the nature of this dysfunction is unclear, as meta-analyses report both reduced and elevated levels of glutamate in patients compared to healthy volunteers. Furthermore, how glutamate measures relate to other neurobiological systems and clinical symptoms is not fully understood. Examining these interactions will both advance understanding of the clinical relevance of glutamatergic abnormalities, and also highlight areas where the greatest therapeutic potential exists. This symposium will bring together seasoned and early career researchers using novel 1H-MRS techniques and big data to better understand glutamate alterations in schizophrenia.
Dr. Kate Merritt's work examines the effect of age, symptom severity, and antipsychotic medication exposure on glutamate levels in the largest multicentre dataset to date, in 1221 healthy volunteers and 1251 patients with schizophrenia. Glutamate metabolites in the medial frontal cortex were negatively associated with age in both schizophrenia and healthy individuals, and with the dose of antipsychotic medication in patients. Lower glutamate levels were found in patients compared to healthy volunteers, which may result from antipsychotic exposure rather than greater age-related decline. Elevated glutamate in patients was associated with more severe symptoms, providing support for the use of glutamate measures as a potential biomarker of illness severity.

Professor Lena Palaniyappan's work uses high field 7T 1H-MRS to examine whether a progressive reduction in glutamatergic transmission occurs in schizophrenia. A longitudinal cohort of minimally medicated first episode psychosis patients were scanned before and after 6 months of treatment. Consistent with Dr Merritt's cross-sectional analyses, patients had significantly lower overall glutamate levels than healthy volunteers, and they did not display progressive changes in glutamate over time.

Valerie Sydnor examined whether low reward responsiveness, which is seen in schizophrenia and depression, is associated with glutamate levels. Using the latest GluCEST technology in a transdiagnostic sample, including patients with depression, on the psychosis spectrum, and healthy volunteers, low reward responsiveness was associated with lower brain glutamate specific to the subcortical component of the reward network. This may indicate that pharmacologically increasing glutamate may correct reward responsiveness in patients.

Dr. Robert McCutcheon integrated fMRI, 1H-MRS and PET to examine the relationship between functional connectivity, and glutamatergic and dopaminergic signalling in 216

participants. In patients and controls, glutamate levels were negatively associated with a functional network centred around the salience network. Pharmacological manipulation of glutamate levels was also associated with connectivity changes that were salience network centred, but in the opposite direction. In addition, a functional network associated with striatal dopamine function was also focused around the salience network. These results suggest that the salience network represents a nexus for interactions between inter-areal functional connectivity and the neurotransmitters glutamate and dopamine.

In conclusion these results suggest that glutamate levels are lower in patients with schizophrenia, and that this is associated with low reward responsiveness. Furthermore, measures of both glutamate and dopamine are linked to salience network connectivity, suggesting that this may be a key target for therapeutic intervention.

25.1 IS THERE A PROGRESSIVE GLUTAMATERGIC REDUCTION IN EARLY STAGES OF SCHIZOPHRENIA?

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Background: Progressive reduction in glutamatergic transmission has been proposed as an important component of the illness trajectory of schizophrenia. Despite its popularity, to date, this notion has not been convincingly tested in patients in early stages schizophrenia.
Methods: In a longitudinal 7T magnetic resonance spectroscopy (1H-MRS), we quantified glutamate at the dorsal anterior cingulate cortex in 21 participants with a median lifetime antipsychotic exposure of less than 3 days and followed them up after 6 months of treatment. Healthy controls were also scanned at two time points.
Results: Patients with first episode schizophrenia had significantly lower overall glutamate levels than healthy controls ($F(1,27) = 5.23$, $p = 0.03$). We did not observe a progressive change of glutamate concentration in patients ($F(1,18) = 0.47$, $p = 0.50$), and the group by time interaction was not significant ($F(1,27) = 0.86$, $p = 0.36$). On average, patients with early psychosis receiving treatment showed a 0.02 mM/year increase, while healthy controls showed a 0.06 mM/year reduction of MRS glutamate levels (Cohen's d =0.26). Bayesian analysis of our observations does not support early, post-onset glutamate loss in schizophrenia. With respect to glutamine, repeated measures ANOVA revealed no group effect ($F(1,27) = 0.21$, $p = 0.65$) between FES and HC, no effect of time ($F(1,27) = 3.86$, $p = 0.06$), and no group × time interaction ($F(1,27) = 0.81$, $p = 0.38$). Annualized glutamine concentration values were not significantly different between the two groups ($t(29) = -1.50$, $p = 0.15$) and indicated a 0.59 mM/year (SD = 1.34 mM) increase in patients and a 0.01 mM/year (SD = 0.84) reduction in healthy controls, with the difference amounting to a medium sized effect (Cohen's d = 0.52).
Conclusions: To our knowledge, this is the first longitudinal examination of glutamate in 7T-MRS from the untreated state of psychosis. We provide evidence in favour of a lack of progressive glutamatergic changes, indicating that the glutamatergic level at the onset of illness was the best predictor of the levels 6 months after treatment. A more nuanced view of glutamatergic physiology, linked to early cortical maturation, may be required to understand glutamatergic dynamics in schizophrenia.

25.2 GLUTAMATE AND DOPAMINE CONNECTIVITY ASSOCIATIONS CONVERGE UPON THE SALIENCE NETWORK IN SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Alterations in cortical inter-areal functional connectivity, and aberrant glutamatergic and dopaminergic signalling are all implicated in the pathophysiology of schizophrenia. The relationship between these, however, remains unclear. We used multimodal imaging to identify areas of convergence between the three systems.
Methods: Three separate cohorts were examined, consisting of 216 participants in total, and all received resting state functional MRI to characterise functional brain networks. Study A used proton magnetic resonance spectroscopy (1H-MRS) to investigate the relationship between frontal cortex glutamate concentrations and network connectivity in individuals with schizophrenia and healthy controls. Study B also used 1H-MRS, and scanned individuals with schizophrenia and healthy controls before and after a challenge with the glutamatergic modulator riluzole, to investigate the relationship between changes in glutamate concentrations and changes in network connectivity. Study C used 18F-DOPA PET to characterise the relationship between striatal dopamine function and network connectivity in healthy controls. In all studies the network-based statistic was used to probe associations between neurochemical measures and connectivity, and neurochemical associated networks were then characterised in terms of their spatial distribution.
Results: Study A involved 77 individuals with schizophrenia and 82 controls, and identified a functional network negatively associated with glutamate concentrations that was concentrated within the salience network ($p<0.05$), and did not differ significantly between patients and controls ($p>0.85$). Study B involved 19 individuals with schizophrenia and 17 controls and found that riluzole associated increases in glutamate concentrations were linked to increases in connectivity within the salience network ($p<0.05$). Study C involved 21 controls and found that a network positively associated with striatal dopamine function was also centered around the salience network ($p<0.05$).
Conclusions: The salience network represents a nexus for interactions between inter-areal functional connectivity and the neurotransmitters glutamate and dopamine. Changes in network connectivity in response to glutamate modulation show the reversed effect compared to the relationship observed at baseline, which may complicate pharmacological attempts to simultaneously correct glutamatergic and connectivity aberrations.

25.3 A MULTICENTRE ANALYSIS OF 1H-MRS BRAIN GLUTAMATE LEVELS IN SCHIZOPHRENIA; INVESTIGATING THE EFFECT OF AGE, ANTIPSYCHOTIC MEDICATION AND SYMPTOM SEVERITY

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Background: Proton Magnetic Resonance Spectroscopy (1H-MRS) studies indicate that altered brain glutamate function contributes to the pathophysiology of schizophrenia and the

response to antipsychotic treatment. However, its relationship to clinical and demographic factors is unclear.
Methods: To determine the effects of age, symptom severity, level of functioning and antipsychotic treatment on brain glutamatergic metabolites we used a large multicentre dataset comprising participant-level data from 45 1H-MRS studies in 1251 patients with schizophrenia and 1221 healthy volunteers.
Results: In both patients and volunteers, medial frontal cortex (MFC) glutamate was negatively associated with age (0.2 unit reduction per decade). In patients, antipsychotic dose (in chlorpromazine equivalents) was negatively associated with MFC glutamate (estimate=0.09 reduction per 100mg, SE=0.03) and MFC Glx (est=-0.11, SE=0.04). MFC Glu/Cr was positively associated with total symptom severity (est=0.01 per 10 points, SE=0.005), and positive symptom severity, and negatively associated with level of global functioning (est=0.04, SE=0.02, 0.01). In the medial temporal lobe, Glx/Cr was positively associated with total symptom severity (est=0.06, SE=0.03), negative symptoms (est=0.2, SE=0.07), and worse clinical global impression (est=0.2 per point, SE=0.06). MFC glutamate and Glx were lower in patients than volunteers (P=0.03), and there was a trend for lower creatine (P=0.08). MFC creatine increased with age (est=0.2, SE=0.06), but was not associated with either symptom severity or antipsychotic dose.
Conclusions: These data infer that lower glutamate levels in patients may result from antipsychotic exposure rather than greater age-related decline. The finding of elevated glutamate in patients with more severe symptoms provides further support for the use of glutamate measures as a potential biomarker of illness severity. Future studies should adjust for age and prioritise CSF-corrected measures over Cr-scaled metabolites.

25.4 DELINEATING TRANSDIAGNOSTIC ASSOCIATIONS BETWEEN REWARD-RELATED PSYCHOPATHOLOGY AND BRAIN GLUTAMATE

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Background: Low reward responsiveness (RR), defined as a reduced capacity to experience pleasure or positive affect from the anticipation or obtainment of rewards, is a transdiagnostic symptom present across mood and psychosis-spectrum disorders. Low RR is a significant predictor of psychotropic treatment resistance (Uher et al., 2012; Wolf, 2006), thus identifying druggable targets for the efficacious treatment of RR-related psychopathology is a vital area of mental health research (Krystal et al., 2020). Preclinical research has provided strong evidence that reduced glutamatergic neurotransmission within reward brain regions can lead to diminished RR (Bisaga et al., 2008; Yoo et al., 2017; Zell et al., 2020), yet prior efforts aimed at translating these preclinical findings to humans have been largely unsuccessful. However, nearly all prior efforts solely analyzed glutamate within the anterior cingulate cortex (ACC). As such, in this innovative work we harnessed both advanced 7T neurochemical imaging methods and a meta-analytically derived functional map of the reward system to more appositely assess the hypothesis that glutamatergic deficits within the reward network contribute to low RR.
Methods: Ultra-high field neurochemical imaging data, including Glutamate Chemical Exchange Saturation Transfer (GluCEST) imaging (Cai et al., 2012) and 1HMRS data, were acquired on a Siemens 7T Terra. GluCEST data were available from a transdiagnostic sample

of 45 individuals ages 15-29 (11 with depression, 19 with psychosis-spectrum symptoms, 15 with no Axis 1 diagnoses), all of whom completed the Behavioral Activation Scale (BAS) to assess RR. GluCEST images were acquired in a 5 mm sagittal slice positioned in the right hemisphere near the midline to cover cortical, subcortical, and brainstem reward regions. The GluCEST % contrast, a measure of local glutamate concentration, was quantified in a meta-analytic functional reward network map (Bartra et al., 2013). A subsample of individuals (N=20) additionally had single voxel 1HMRS data collected within the ACC. Associations between BAS RR scores and brain glutamate were investigated using multiple regressions, controlling for age and sex.

Results: In line with our hypothesis, lower reward network GluCEST contrast was transdiagnostically associated with lower RR, both in the full sample (partial $r = 0.36$, $p = 0.02$, N=45) and in individuals with depression and psychosis symptoms (partial $r = 0.49$, $p = 0.008$, N=30). Anatomical subdivision of the reward network into cortical and subcortical components revealed that this GluCEST-RR association was primarily driven by subcortical (partial $r = 0.37$, $p = 0.01$) rather than cortical ($p > 0.05$) reward regions. RR was not significantly associated with non-reward GluCEST contrast, suggesting functional specificity. Moreover, RR was not associated with either the GluCEST contrast or 1HMRS-derived glutamate concentration within the ACC, corroborating prior findings and underscoring the importance of function-based parcellation for neurochemical investigations.

Conclusions: This work provides translational and transdiagnostic evidence implicating lower reward network glutamate concentration in diminished reward sensitivity; lower glutamate could index reduced reward network excitatory neurotransmission or altered network metabolism. The present findings offer new insight as to why psychiatric patients with RR-related psychopathology may exhibit treatment resistance to conventional monoamine- and dopamine-targeting (i.e. non-glutamatergic) psychotropics, and highlight the potential of neurochemical imaging-informed treatment stratification in mental health services.

26. BRINGING GENETICS INTO THE CLINIC FOR PATIENTS AND THEIR FAMILIES

Lynn DeLisi

Cambridge Health Alliance

Overall Symposia Abstract: In the last decade, the field of psychiatric genetics has accelerated at an extraordinarily rapid pace, taking advantage of new developments in the overall field of genetics to be able to advance our knowledge about the genetic architecture of schizophrenia and other major psychiatric disorders, as well as develop tools that might ultimately be available to clinicians to counsel families about risk of disease and patients about the best treatment based on their genetic makeup. It is now well established that there are many gene variants that confer small risk for schizophrenia when weighted together by a Polygenic Risk Score (PRS), while some people may also inherit rare variants of larger effect in crucial genes or may have these changes having developed de novo. In some cases, the inheritance of rare variants in genes may be linked to other medical conditions and can thus inform individuals early on about the steps they can take to mitigate these co-morbidities. It is thus imperative that researchers and academic scientists know where the research has taken us thus far in 2020, where the gaps still are in knowledge, and what they need to communicate to their colleagues practicing psychiatry and primary care. Recently the International Society of Psychiatry Genetics held their annual congress where the latest findings in the field and the views on how to translate them to clinical practice were aired and discussed. This symposium gathers together

prominent speakers from that congress to relay their latest information and guidance to colleagues focused on schizophrenia risk and outcome. The session will begin with Naomi Wray from Brisbane, Australia who has been a pioneer in psychiatric genetics establishing the value of Polygenic Risk Scores, describing the next steps in understanding their value and ultimately their clinical use, both in prediction and pharmacologic response studies. She will be followed by Anil Malhotra who is the Director of Psychiatric Research at Zucker-Hillside Hospital in New York. He will speak on using genetics, including the PRS to predict treatment response, as well as using genetics to define targets for new drug development. He also has some exciting new findings using genetic data, as well as brain imaging of striatal to cortex resting state MRI connectivity, to personalize patient care. The next speaker will be Jonathan Sebat, a geneticist and professor at UC-San Diego who will discuss the implications of inherited and de novo rare variants in people with schizophrenia, and that it is now clear that they are pleiotropic in that the same rare variant may contribute to other disorders as well. He will discuss how they relate to common risk variants and the value of screening for them clinically in patients. Rare variants are also of interest to pharmaceutical companies as potential targets for new treatments. The last speaker will be Jehannine Austin from the University of British Columbia in Vancouver. She is a professor of psychiatric and genetics, but most importantly, a pioneer in the use of genetic counseling for families with histories of psychiatric disorders, particularly schizophrenia. She will talk about the importance of genetic counseling and what can be learned from this form of therapy. A formal discussion will be led by Jim Kennedy, well known for his work in schizophrenia genetics and pharmacogenetics. The co-chairs, Sibylle Schwab (Australia) and Lynn DeLisi (USA) are both senior researchers in the psychiatric genetics field and will lead an audience discussion to follow.

26.1 UTILIZATION OF GENOMIC STRATEGIES TO ENHANCE OUTCOMES IN SCHIZOPHRENIA

Anil Malhotra*[1], Jianping Zhang[2], Max Lam[3], Delbert Robinson[4], Todd Lencz[5]

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Background: Antipsychotic drug discovery has predominantly focused on dopamine D2 receptor antagonism, despite robust interest in non-dopaminergic contributions to psychotic illness and the mechanism of action of antipsychotic drugs. Genomic evidence in support of this strategy is derived from large scale GWAS results (Ripke et al. 2014) implicating the gene that codes for the dopamine D2 receptor (DRD2) in susceptibility for schizophrenia, as well as series of pharmacogenetic studies suggesting a relationship between DRD2 variation and clinical response to antipsychotic drug response (Zhang et al. 2010, 2015) . Of note, for the most part, side effects associated with treatment, including blood dyscrasias and metabolic disturbances (Malhotra et al 2012), have been less related to dopamine receptor variation and has suggested that drug discovery tailored to ameliorating effects at these non-dopaminergic systems (e.g. MC4R and weight gain) could enhance outcomes without influencing efficacy.
Methods: More recently, polygenic risk scores (PRS) have been utilized to predict antipsychotic drug response. In general, PRS associated with increased risk for psychotic illness have been linked with poorer efficacy of drug treatment (Zhang et al. 2019). Unfortunately, these data often implicate hundreds to thousands of genetic variants scattered

across the genome and therefore drug discovery predicated on these results is challenging. Nevertheless, personalization of treatment based upon PRS, such as early use of clozapine – a drug usually administered as an agent of last resort – in patients in the upper ranges of PRS is currently being considered.
Results: Finally, several groups have recommended repurposing currently available, often non-psychotropic, drugs based upon genomic results (Lencz and Malhotra 2015, Ruderfer et al. 2016). As GWAS results become more robust, prioritization of top candidates for repurposing may provide a fast-track method for drug discovery, as well as provide the necessary data for new drug development. Recent data from our group derived from a GWAS meta-analysis, and subsequent gene-set and transcriptomic data, of over 350,000 subjects characterized for general cognitive ability has identified sixteen gene products that represent targets for pro-cognitive drug development (Lam et al. 2020).
Conclusions: Taken together, these diverse strategies including personalization of existing treatments, repurposing non-psychotropic agents, and new drug development based upon large scale GWAS results, may offer the prospect of enhancing outcomes for the many patients who suffer from these devastating and disabling psychotic disorders.

26.2 REALISTIC EXPECTATIONS FOR THE ROLE OF POLYGENIC RISK SCORES

Naomi Wray*[1]

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Background: Technological advances of the last decade have provided overwhelming evidence that the genetic contributions to common psychiatric disorders have polygenic genetic architectures with thousands of DNA variants implicated in risk of each disorder. At an individual level, this means that each of us harbour risk loci and that each affected person likely carries both a higher burden, and a unique portfolio, of risk alleles. In addition, genome-wide genetic data have demonstrated important genetic sharing (pleiotropy) between the psychiatric disorders, providing etiological clues that were often previously undetectable from standard epidemiology. The observed polygenic and pleiotropic architectures are consistent with the difficulties associated with diagnostic classifications based on clinical phenotypes superimposed onto this genetic spectrum of disorders. Much research is now focused on understanding the functional roles of newly identified associated DNA variants, with the long-term goals of new treatments or prevention strategies. Treatments or interventions tailored to individuals in so-called Precision Medicine is viewed as the future of clinical practice. A key question is how will we stratify patients for these personalized approaches. I will discuss the possible utility of genetic risk prediction in the context of psychiatry. These predictive tools are likely to become a useful part of the clinical toolbox, but it is important that the expectations of what genetic and genomic technologies can deliver are realistic and not overstated.
Methods: as above.
Results: as above.
Conclusions: as above.

26.3 ANALYSIS OF GENOMIC COPY NUMBER VARIATION ACROSS PSYCHIATRIC DISORDERS INCLUDING SCHIZOPHRENIA

Jonathan Sebat*[1], Marieke Klein[1], Omar Shanta[1], Oanh Hong[1], Jeffrey R MacDonald[2], Bhooma Thiruvahindraouram[2], Agathe de Pins[3], Alexander Charney[3], Stan Letovsky[4], Jake

Humphrey[4], Elise Douard[5], Zohra Saci[5], Sebastian Jacquemont[5], Schizophrenia, Bipolar and Autism CNV Workshops[6], Stephen Scherer[2]

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Background: Copy number variants (CNVs) have been identified as a major risk factor in neuropsychiatric disorders and are implicated across many neurodevelopmental disorders, partially contributing to their shared genetic etiology. The pleiotropic effects of CNVs in which specific risk alleles may increase risk for multiple disorders have previously been demonstrated.

Methods: This study set out to determine associations of 93 known pathogenic CNVs across multiple psychiatric and developmental disorders, and to characterize the range of psychiatric risk associated with each CNV.
CNVs were called in the PGC-Autism, PGC-Bipolar, PGC-Schizophrenia and a large cohort of (mostly pediatric) subjects ascertained through clinical genetic testing (CLIN; mostly developmental delay). In total, we analyzed data from 307,236 individuals who passed CNV quality control, including 15,016 patients with autism spectrum disorder (ASD), 27,372 patients with bipolar disorder (BD), 35,609 patients with schizophrenia (SZ), 115,850 control samples, and 113,389 individuals from two clinical genetics datasets (referred to as CLIN). We analyzed 93 pathogenic CNVs, including both their reciprocal deletions and duplications, for association with the different psychiatric disorders. We compared effect sizes across diagnostic categories and performed cluster analyses to determine genetic relationships between disorders and to determine whether CNVs can be clustered into distinct groups based on their trait associations.

Results: Overall reciprocal deletions and duplications had divergent effects across diagnostic categories, as effect sizes for "developmental delay" (ASD and CLIN) were significantly positively correlated, whereas we observed significant "mirror" effects for SZ, i.e. higher effect sizes for deletions were correlated with lower effect sizes for duplications and vice versa. Clustering of diagnostic categories across CNVs revealed that disorders clustered according to period of onset with pediatric disorders (ASD and CLIN) being highly correlated and adolescent/adult-onset disorders (BP and SZ) being correlated. We identified groups of CNVs which tend to cluster into groups based on phenotype association, with one subgroup being predominantly "CLIN" and other groupings that differ from each other based on their combination of psychiatric associations; for example some with a predominant ASD, some with predominant SZ and others with differing combinations. Most distinct patterns were seen for loci where risk is primarily associated with adult psychiatric disorders and we identified one cluster to be significantly different from others ($p < 0.009$). The significant cluster included the 1q21.1, 2q11.2 and 2q13 loci and showed larger effects in BD and SZ.

Conclusions: These results suggest that specific CNV alleles have distinct psychiatric risk profiles, and further suggest that a psychiatric profile may be attributable to the functions or expression of the underlying genes in the brain. Most importantly, none are specific to schizophrenia uniquely, but rather each one can lead to different psychiatric phenotypes. Our ongoing studies will test for enrichment of biological processes or spatial and temporal brain expression of genes within each cluster to better understand the biological mechanisms within the CNV groups. In addition, we will determine how those that particularly occur in families

with schizophrenia also interact with the multiple common risk alleles. It will be important to determine how detecting these rare mutations can be used to predict illness or determine prognosis and ultimately lead to targets for new drugs.

26.4 IMPROVING PATIENT OUTCOMES THROUGH PSYCHIATRIC GENETIC COUNSELING

Jehannine Austin*[1]

[1]*The University of British Columbia*

Background: Though genetic counseling is often misconceptualized as being concerned exclusively with the provision of genetic test results, or with discussions about the chances for children to develop a condition in the family, it actually involves helping people to "understand and adapt to the medical, psychological and familial implications of genetic contributions to disease".
The world's first specialist psychiatric genetic counseling service opened in Vancouver in 2012, and data collected in this context are allowing for important questions to be addressed around how to optimize the intervention to produce the best patient outcomes.

Methods: In this presentation, we will review the data regarding the outcomes of psychiatric genetic counseling, and consider some case studies that illustrate the process of providing this intervention for people with psychiatric disorders and their families.
Results: The data show that psychiatric genetic counseling results in meaningful increases in empowerment and self efficacy for people who live with psychiatric disorders, and for their family members. Emerging data suggest that people may be more likely to engage in behaviour change to protect their mental health after psychiatric genetic counseling. It is important to note that these outcomes are produced even in the absence of genetic test results being provided.
Conclusions: The profession of genetic counseling is about 50 years old, and has grown from its original roots that focused on genetic syndromes and prenatal contexts, to embrace a wide range of areas of medicine including cardiovascular diseases, oncology, and psychiatry. Genetic counseling is burgeoning as an academic discipline in its own right, with a growing and vibrant body of research amassing that explores patient outcomes of the intervention in different contexts. In the context of psychiatric genetic counseling, research data show that meaningful positive outcomes for people with psychiatric disorders and their families (including increases in empowerment and self-efficacy) can be achieved even without the provision of genetic test results.

27. CAN COMPUTER ALGORITHMS DETECT EMERGENT PSYCHOSIS THROUGH ANALYZING LANGUAGE AND BEHAVIOR?

Cheryl Corcoran

Icahn School of Medicine At Mount Sinai

Overall Symposia Abstract: Subtle language impairment is a feature of schizophrenia and its risk states. It is characterized by reductions in coherence (tangentiality, derailment) and complexity (concreteness, poverty of content). Recently, artificial intelligence has been used to characterize this subtle language impairment, such that linguistic biomarkers of psychosis and its risk states have been identified and even replicated. They are now being evaluated at

the population level for variance with demographics, and studied in respect to neural correlates, such that these biomarkers may be informative in respect to theories of pathophysiology.
This symposium includes four presenters who together have done much of the pioneering work in the use of artificial intelligence, specifically natural language processing (NLP) and machine learning (ML), to understand language impairments in psychosis and its risk states. The field is now at a crossroads. The speakers will not only present data, but along with the discussant, Dr. Barnaby Nelson, also consider potential pitfalls, provide a roadmap to move these biomarkers along to clinical practice, and also review how artificial intelligence and human intelligence may be applied to the same data in parallel, potentially increasing synergy.

The first presentation will be by Dr. Brita Elvevåg, who first applied the NLP approach of latent semantic analysis (LSA) to speech and language in schizophrenia more than a decade ago. Dr. Elvevåg used LSA to operationalize decreases in coherence, finding correlates in clinical ratings, neural activity, genetics and function. She has used NLP to develop applications for cognitive assessment that are brief, acceptable and easy to use. In this presentation, Dr. Elvevåg will review potential pitfalls in NLP analyses in psychosis, including concerns re generalizability and specificity, and risk for bias. She argues for models that are explainable and transparent, rely on longitudinal data, and incorporate other modes of communication.

The second presentation is by Natália Mota, who has applied graph theory to the study of language in psychosis, finding expected differences between mania and nonaffective psychosis, identifying correlates with negative symptoms, cognitive deficits and brain activity and predictors of psychosis and schizophrenia diagnosis. Dr. Mota is dedicated to translating her work on language and psychosis risk to real-life screening and clinical practice in Brazil, and other low-income countries. Dr. Mota will describe work she has done in developing an app for language analysis that is inexpensive, friendly and easy to use, which has been piloted in children, and also in rural and urban areas of Brazil.

In the third presentation, Dr. Rezaii will describe her work on the use of NLP to predict psychosis among individuals at clinical high risk for psychosis, finding accuracy rates that exceed symptom ratings. She will present on the use of additional methods, beyond LSA and speech graph analysis, to examine the poverty of content in speech, specifically by measuring semantic density (the number of components of meaning in a sentence). She also introduces the idea of using the specific content or meaning of what is said to expand predictive power.

In the last presentation, Dr. Guillermo Cecchi will discuss novel applications of NLP in schizophrenia and to better understand through language proposed core deficits, such as in ipseity, or the concept of disturbance of perception of self. His approach is a model for combining human intelligence (clinical ratings, qualitative research) with artificial intelligence to better understand schizophrenia and other disturbances in thought, language and self-concept.

27.1 USING LANGUAGE TECHNOLOGIES IN PSYCHIATRIC RESEARCH: CHALLENGES AND OPPORTUNITIES OF TRANSLATING INTO PRACTICAL TOOLS

Brita Elvevåg*[1], Chelsea K. Chandler[2], Terje B. Holmlund[1], Alex S. Cohen[3], Catherine Diaz-Asper[5], Peter W. Foltz[2]

[1]*University of Tromsø - the Arctic University of Norway,* [2]*University of Colorado - Boulder,*[3]*Louisiana State University,* [4]*Marymount University*

Background: The excitement about potential psychiatric applications of machine learning (ML) and natural language processing (NLP) techniques is tempered by the risk that decisions will be made for spurious reasons, models may not generalize to unseen data, and biases inherent in datasets may propagate into predictions with harmful results. Indeed, the current state of this field is that the algorithms and models in psychiatric research are, in most cases, not ready to be translated into practice. However, the field is sufficiently ripe that the results from sophisticated measurement techniques can refine the tasks and (intermediate) phenotype or biomarker, but to do this requires a new psychometrics to incorporate the sheer volume and new types of data.

Methods: Our research has collected clinical data, developed methods to assess patient states based on language and other natural behavior, and validated performance while seeking to ensure that the resulting models are sufficiently (i) explainable, (ii) transparent and (iii) generalizable to be more broadly applied, and thus in the near future translate into real clinical programs of detecting risk of developing psychosis, and monitoring treatment responsiveness. It is further necessary to (i) operationalize language as dynamical behavior, (ii) conceptualize language as data with multiple components, and (iii) build models with the assumption that humans are multi-channel communicators.

Results: For models to be sufficiently trustworthy it is essential that they are explainable (i.e., the reason a prediction was generated is clear) and transparent (i.e., the implementation details and assumptions of a model are explicitly shared with users). Although these new measures demonstrate sensitivity for detecting various clinical phenomena, specificity to specific conditions has rarely been demonstrated yet this is essential if they are to have clinical translation value. Also, despite the latest-generation of NLP-based measures being frequently hailed as sensitive and objective, thus far they have been examined mostly in isolation and rarely combined with other measures. Yet when making inferences about patient state, multiple channels of behavioral features must be considered and longitudinal examination is necessary to more accurately capture subtle changes innate to human behavior. Indeed in the same way that expert clinicians make critical decisions based upon many observations and several types of data, so too is it necessary that machines leverage multiple channels and types of data while also considering the dynamic and temporal relationships between these channels. Such multimodal modeling is required to establish specificity such that measures concern not just language variables but also individual differences, cognitive ability and general health. Examination of the features of the discriminative signals from these ML results can be used to inform subsequent task design.

Conclusions: Modern ML and NLP techniques enable a variety of language aspects (e.g., semantic structures, discourse organization, acoustic and timing characteristics) to be measured, and powerfully so if modeled in a dynamic, longitudinal, and multi-dimensional manner. Indeed, leveraging language data and NLP methods provide unprecedented opportunities for understanding psychiatric conditions and for translating into precision medicine tools. However, clear guidelines are essential so as to avoid generating conclusions that may not generalize or may have adverse consequences when applied clinically. The next generation of psychiatric assessment tools will challenge the cross-sectional approach to assessment as they enable continuous monitoring via smart devices and associated sensors. Research on measurement approaches integrating language, temporal dynamics and multiple modalities will need to continue to adapt and evolve to allow for the detection of fine-grained changes in mental states over multiple measurements time points.

27.2 USING MACHINE LEARNING TO DISCOVER LINGUISTIC INDICATORS OF FUTURE PSYCHOSIS

Neguine Rezaii*[1], Phillip Wolff[2], Elaine Walker[2]

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Background: The onset of psychosis is usually preceded by a prodromal phase characterized by subclinical abnormalities in thought, perception, and communication. Clinical practice's challenge is to detect these potential markers of future mental illness while they are still subtle and indistinct. Recent advances in machine learning and natural language processing are making such detection possible. Here we capitalize on these advances to show how nonobvious features of people's natural language may be mined to predict the later emergence of psychosis.
Methods: We introduce automated methods for extracting two potential linguistic biomarkers of psychosis: poverty of content—or what we will refer to as low semantic density—and talk about voices and sounds. Speech samples were drawn from 40 participants of the North American Prodrome Longitudinal Study (NAPLS) at Emory University. Semantic density was measured using the technique of vector unpacking, a method that uses gradient descent to discover the number of components of meaning in a sentence by finding the linear combination of word vectors that best approximate a sentence vector. Semantic density is determined by dividing the number of components by the number of words in the sentence. When there is minimal semantic overlap among the words in a sentence, all the words in the sentence vector are usually recovered, reflecting high semantic density. However, when the semantics of the content words in a sentence overlap in meaning, the number of meaning vectors needed to create the sentence will be less than the number of content words, implying a reduction in semantic density.
To discover latent semantic content, we selected the 95% most common words in English and retained the words with high cosine similarities to vectorizations of the sentences. Probe words were included for further analysis when they were of higher similarity to sentences produced by the participants than to the sentences produced in ordinary conversations. Baseline similarities for each word were determined by probing the sentences generated by 30,000 individuals who engaged in online discussions on the social media platform Reddit. Distinctive content words were identified using the tf-idf weighting algorithm. The word embeddings of the most distinctive probe words were subjected to a dimensionality reduction using the t-SNE dimensionality reduction algorithm and clustered using k-means++, with the number of clusters determined by the k that maximized the Silhouette Coefficient.

Results: Conversion to psychosis was signaled by low semantic density and talk about voices and sounds. When combined, these two variables predicted conversion to psychosis with 93% accuracy in the training and 90% accuracy in the holdout datasets. Model prediction was improved by the inclusion of these two variables because each captured different kinds of information. As predicted, semantic density, but not talk about sounds, correlated negatively with the negative symptoms, and talk about sounds, but not semantic density, correlated positively with positive symptoms, both as measured by the SIPS.
Conclusions: Our findings add to the growing evidence showing that machine learning methods can be used to discover and measure linguistic abnormalities associated with conversion to psychosis in Clinical Risk for Psychosis (CHR) individuals. In the present study, we were able to predict the onset of psychosis two years in advance of conversion using just two variables -- both of which have a strong theoretical foundation – and replicate this finding in a holdout dataset with high accuracy. The results point to a larger project in which automated analyses of language are used to forecast a broad range of mental disorders well in advance of their emergence.

27.3 HAPPY THOUGHTS: ASSOCIATION BETWEEN STRUCTURAL AND EMOTIONAL ANALYSIS FROM A TIME-LIMITED POSITIVE IMAGE NARRATIVE

Natália Mota*[1], Mauro Copelli[1], Sidarta Ribeiro2

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Background: Speech and language analysis from free speech protocols has recently provided a discriminative signal, useful for early diagnosis of schizophrenia. Although different aspects of language (such as structural and semantic coherence) have been applied to different contexts using different data collection protocols, we need to standardize a safe and minimum-effort protocol that can reveal discriminative data, enabling large and remote data collection. Also, we need to understand the correlations between semantic, structural and emotional analysis from the same dataset. In the past decade, we have developed a non-semantic structural analysis based on graph theory that is able to automatically discriminate speech samples from patients with schizophrenia diagnosis with more than 90% accuracy in chronic and first-episode patients, and in different languages. Moreover, we could verify correlations with negative symptoms, as well as cognitive performance in patients and in typical school-aged children . But the most predictive contents come from dream reports (sometimes absent) or negative image reports (which could cause a psychological burden for some subjects). The current project aims to verify the accuracy in discrimination of schizophrenia reports from 3 different positive image prompts, using a minimum of 30 seconds reports. Moreover, we aimed to verify correlates between semantic, structural and emotional analysis.
Methods: We analyzed 3 positive image reports from 31 subjects (10 matched controls and 21 at the first episode of psychosis - 11 with schizophrenia and 10 with bipolar disorder as a final diagnosis after 6 months of follow-up). We performed speech graph analysis to extract speech connectedness attributes. In sequence, we combined connectedness measures from the 3 prompts (after extracting collinear measures) to create a disorganization index (performing multilinear correlation with the PANSS negative subscale). We used this index as an input to a machine learning classifier to verify the accuracy of discriminating reports from the schizophrenia group. To conclude, we studied the correlations between the disorganization index based on connectedness and minimum semantic coherence between consecutive sentences, and the emotional intensity measured by the proportion of emotional words.
Results: Speech connectedness of positive image reports was correlated with negative symptomatology severity measured by the PANSS negative subscale ($R2 = 0.73$, $p = 0.0160$), and the disorganization index was able to discriminate the subjects diagnosed with schizophrenia disorder six months later with AUC = 0.82. Moreover, disorganization index was negatively correlated with positive emotional intensity ($Rho = -0.48$, $p = 0.0061$), but not correlated with minimum semantic coherence ($Rho = -0.06$, $p = 0.7442$), and emotional intensity was not correlated with minimum semantic coherence ($Rho = 0.17$, $p = 0.3458$).
Conclusions: This safe, short and standardized data collection protocol is informative and reveals an interdependent relationship between computational language analyses. With fewer than two minutes of oral speech data, we can accurately discriminate reports from the schizophrenia group at the first interview, and verify that the less connected the report, the fewer positive emotional words are used. Future directions point to the feasibility of automatic and remote access to a large and diverse population.

27.4 DISTURBANCE OF SELF USING AUTOMATED LANGUAGE ANALYSIS

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Background: The concept of disturbance of perception of self, or ipseity, has been proposed as a key aspect of the schizophrenia experience. Different approaches for eliciting patients' responses and for quantifying them along qualitative metrics have yielded results that inevitably depend of both contexts. We will describe an approach to formalize specific interpretations of ipseity disturbance using computational linguistics in an attempt to identify possible quantitative and invariant metrics.
Methods: We studied transcribed speech from 350 open-ended interviews with clinical high risk of psychosis (CHR) and schizophrenic patients (SZ), as well as matching controls, using computational techniques to identify syntactic and semantic patterns associated with self-reference, including emotional and cognitive self-valuation, and in particular attempting to capture Sass's notion of hyperreflexivity. We also studied other psychiatric conditions to understand the specificity of ipseity disturbance for schizophrenia, using a similar speech-eliciting setting in individuals suffering chronic pain and depression.
Results: We obtained results indicating that structural features, e.g. the frequency of first-person pronouns (I, me), and semantic features, e.g. the use of modal verbs (can, may, should) are significantly different in the CHR, SZ and control cohorts. Moreover, these features seem to be specific to the schizophrenia spectrum, as distortions of ipseity in chronic pain and depression patients is characterized in contrast by significant negative emotional valuation of their self and their behavioral context.
Conclusions: The preliminary results suggest that a computational approach to ipseity is at least feasible. At the same time, they warrant a more systematic analysis and comparison with qualitative evaluation of interviews and clinical assessment, and eventually studies across different speech-eliciting settings.

Plenary Session

28. EARLY LIFE STRESS - IMPLICATIONS FOR RISK TRAJECTORIES IN PSYCHIATRY

Lynn DeLisi
Cambridge Health Alliance

Overall Abstract: Introduction: Genetics underlies a huge portion of the biology of variance in human behavior and the field of genetics has progressed substantially just during my professional lifetime. This year marks the 20th anniversary of the complete sequencing of the human genome. When I began in schizophrenia research in 1978, we knew nothing about individual genes, and the Rosenthal and Kety Denmark adoption studies were the sensation in psychiatry because they implicated the significance of inherited biology. Fast forward to 2021, and we now have through an unusually large world-wide genomics collaboration, at least 270 common genetic variants that combined form a genetic basis for some schizophrenia. these are clues that can lead to targets for future interventional clinical measures. In addition, the field of pharmacogenetics has developed rapidly and become reliable as it begins to provide ways in which to inform clinicians about individual patient's risks for medicine side-effects and treatment response, based on their inheritance of relevant drug metabolism genes. This

symposium will thus bring researchers on schizophrenia up-to-date on the all too rapidly growing progress in the field of genetics that clearly is relevant to their research.

28.1 EARLY LIFE STRESS - IMPLICATIONS FOR RISK TRAJECTORIES IN PSYCHIATRY

Elisabeth Binder

Max-Planck Institute of Psychiatry

Individual Abstract: Early adverse exposures, including maternal stress during pregnancy, have been shown to result in long-lasting consequences on neural circuit function and stress hormone regulation and ultimately in an increased risk for psychiatric, including schizophrenia, but also medical disorders later in life. This presentation will focus on increased exposure to stress hormones, i.e glucocorticoids (GCs) in utero as one mechanism mediating such increases in risk.

The presentation will first highlight data from a human hippocampal cell line that identify long lasting changes in DNA methylation in response to GCs that increased transcriptional sensitivity to future stress exposure, suggesting that prenatal GC exposure could prime the transcriptional response to subsequent stress exposure. Data from human brain organoids and single cell sequencing will then delineate that specific nervous system cell subtypes show differential sensitivity to early GC exposure during brain development. Specifically, GC-responsive transcripts in neurons are significantly enriched among genes with associations with behavioral traits and psychiatric diseases in large GWAS or carrying rare variants found in neurodevelopmental disorders. The GC-responsive transcription factor ZBTB16 will be presented as a downstream candidate potentially mediating GC-induced changes in neural differentiation. Overall, the presentation will outline how in utero stress-exposure can have lasting effects on cell and tissue function, potential genetic moderators and how this relates to risk or resilience psychiatric disorders in the context of common genetic variation.

Diversity Task Force Workshop

29. DIVERSITY AND SIRS: FUTURE DIRECTIONS AND THE HILLS TO CLIMB

Sohee Park

Vanderbilt University

Overall Abstract: The Diversity Task Force (DTF) aims to prioritize diversity and inclusivity as essential core values of SIRS and to support multicultural perspectives. In this second DTF workshop, we highlight diverse and innovative approaches to achieving progress in global mental health research and addressing ethnic and gender disparities on multiple levels.

1. Drs. Jun Miyata and Nicolas Crossley will describe their efforts to implement large international research networks and offer insight gained from multinational collaborations.

2. Drs. Eric Tan and Sara Ann Lee will depict the state of the psychosis research in Asia and draw attention to the challenges facing Asian scientists and clinicians.

3. Dr. Lebogang Phahladira will provide an overview of the current state of psychosis research in the sub-Saharan Africa, with a specific focus on South Africa.

4. Dr. Lynn DeLisi will highlight the prevalence of gender bias in science and barriers that prevent women from breaking the glass ceiling.

5. Drs. Kia Crittenden and Margaret Niznikiewicz will discuss the importance of engaging women and minorities in clinical trials and evaluate potential strategies to improve inclusivity.

After these presentations, we will invite the audience for discussions moderated by Drs Mary Cannon and Kim Do.

We have much to learn and benefit from the work conducted around the world by all stakeholders including researchers, clinicians, educators, as well as persons with lived experiences. Enhanced diversity of ideas, expertise and resources through open dialogues, exchanges and collaborations at SIRS will facilitate progress in the field.

29.1 REGIONAL DIVERSITY SURVEY: HOW WELL IS SIRS KNOWN TO OUTSIDE THE WESTERN DEVELOPED WORLD?

Jun Miyata

Kyoto University

Individual Abstract: SIRS is driving forward diversity and inclusion. Regional diversity is one of the important issues, especially considering that 617 of 804 SIRS 2020 members are from North America and Europe.
A critical question in promoting regional diversity / inclusion is whether SIRS is known by schizophrenia researchers across the world. Knowing this can improve efficacy of our efforts. Thus, we conducted a survey on regional schizophrenia research communities in Japan and South America.

In this presentation we will show the results and discuss what are the necessary and effective next steps to realize diversity and inclusion.

29.2 REGIONAL DIVERSITY SURVEY: HOW WELL IS SIRS KNOWN TO OUTSIDE THE WESTERN DEVELOPED WORLD?

Nicolas Crossley

Facultad de Medicina, P. Universidad Catolica de Chile

Individual Abstract: Please see Jun Miyata's abstract for more information.

29.3 AS SUBMITTED BY DR ERIC TAN

Sara-Ann Lee

Institute of Mental Health, Singapore

Individual Abstract: As submitted by Dr. Eric Tan.

29.4 BEHIND THE VEIL OF SCHIZOPHRENIA RESEARCH IN ASIA

Eric Tan

Swinburne University of Technology

Individual Abstract: Schizophrenia research and researchers in Asia have relatively reduced visibility compared to traditional powerhouses around the world. This presentation will provide an overview of the prevalence of schizophrenia research in Asia, as well as discuss the challenges faced by Asian researchers, with a particular focus on cultural norms, mental health literacy and stigma. The presentation will conclude with some suggestions to increase engagement with Asian research, diversity and inclusivity within SIRS.

29.5 AN UPDATE ON PROGRESS IN SCHIZOPHRENIA RESEARCH IN AFRICA

Lebogang Phahladira

Stellenbosch University

Individual Abstract: Many institutions in African have years of experience in collaborative research with institutions in developed countries. It was through some of the collaborations that scholars from the continent were able to contribute new scientific knowledge on first-episode psychosis and early intervention questions. However, the continent still faces challenges such as capacity development, lack of a cohesive research strategy for mental, ageing cadre of mentors, funding opportunities and limited influence on policy. Funding opportunities with increased emphasis on capacity building for research, advances in technology for communication, new breed of researchers and the unique socio-economic factors present opportunities that may help Africa enhance progress in schizophrenia research.

29.6 WOMEN IN ACADEMIC PSYCHIATRY: BREAKING THROUGH BARRIERS AND IMPLICIT SYSTEMIC BIAS

Lynn DeLisi

Cambridge Health Alliance

Individual Abstract: Women have long sought to break out of the traditional roles for themselves that they have inherited in society. Some cultures have welcomed equitable roles for women more than others, and thus there is world-wide variation in how women are perceived in societies. The focus here will be on the barriers for woman in professional life, particularly as scientists, in the USA, assuming that many of the experiences are those of women in other countries as well. Women were only able to obtain the right to vote in the USA in 1919, 143 years after the country gained independence from Great Britain. Even with that right, they were clearly discriminated against in many ways for years. In the 1970's, the "woman's liberation movement" began. At that time woman were not treated equal to men when it came to admissions to medical schools and later obtaining faculty appointments and leadership roles. The atmosphere has clearly changed over the past 50 years, but subtle systemic biases still exist. The first step may be to recognize their presence, the second to educate all people in leadership roles about them, and the third to continue ongoing discussions about how to implement change. The biases and treatment of women parallels the same systemic biases that place barriers in front of people of color and all minority groups. As leaders

in mental health fields we have a responsibility to actively pursue what it takes to successfully practice equity and inclusion in our professional roles.

29.7 RACIAL DISPARITIES IN CLINICAL TRIALS

Kia Crittenden-Ward

Signant Health

Individual Abstract: The presentation will touch upon someone of the racial disparities in clinical trial participation and why we should care. Some of the major barriers to clinical trial participation will be discussed. The presentation seeks to leave the audience interested in digging for their own deeper understanding of how to enact change.

29.8 RACIAL DISPARITIES IN CLINICAL TRIALS

Margaret Niznikiewicz

Harvard Medical School/BHCS

Individual Abstract: Please see Kia Crittenden-Ward's abstract for more information.

Plenary Session

30. REMOVING THE RELIABILITY BOTTLENECK IN FUNCTIONAL MAGNETIC RESONANCE IMAGING RESEARCH TO ACHIEVE CLINICAL UTILITY

Robert Buchanan

University of Maryland School of Medicine

Overall Abstract: The proposed plenary will identify and discuss four critical gaps in efforts to achieve clinical utility, which if not corrected, can jeopardize the progress of psychiatric fMRI research.

30.1 REMOVING THE RELIABILITY BOTTLENECK IN FUNCTIONAL MAGNETIC RESONANCE IMAGING RESEARCH TO ACHIEVE CLINICAL UTILITY

Michael Milham

Child Mind Institute

Individual Abstract: Functional MRI (fMRI) investigators have long sought to inform psychiatric research and practice. First, through developing a better scientific understanding of normative human brain development, the perturbations that lead to mental illness, and the impact of therapeutic interventions. Such knowledge can inform clinical nosology and decision making, as well as help identify critical periods for intervention and prevention. Secondly, by developing clinical applications of fMRI that can guide individual-specific decisions (e.g., diagnosis, prognosis, treatment selection) and interventions (e.g., imaging-guided brain

stimulation). While these goals once seemed unattainable, the maturation of fMRI techniques has brought the measurement of individual-level differences - a critical prerequisite - within reach. This plenary will identify and discuss four critical gaps in efforts to achieve clinical utility, which if not corrected, can jeopardize the progress of psychiatric fMRI research.

Concurrent Symposia

31. INVESTIGATING RESPONSE TO COGNITIVE REMEDIATION THERAPIES

Rafael Penadés
Hospital Clinic Barcelona, Universitat Barcelona, IDIBAPS, CIBERSAM

Overall Symposia Abstract: The main goal is to investigate the role of different aspects related with the response to cognitive remediation therapies. Moderators of response, long-term effects, role of negative symptoms and role of metacognition will be considered. Precision Medicine pursues the goal of offering the right medical treatments to the individual characteristics of each patient. But it does not necessarily mean the creation of different treatments for different particular patients. Alternatively, categorising patients into subpopulations that differ in their response to treatment, could also help to provide more precise clinical practice. Thus, providing evidence-based data about the different patterns of response to cognitive remediation might help to offer it in routine clinical settings with the precision perspective.
Isabelle Amado will take issue with the effects of cognitive remediation on functionality in everyday life. Depending on the remediation programs, transfer to everyday life might include different tools such as homework tasks, specific group sessions, or more ecological training. Unfortunately, few studies have looked at the long-term outcome in participants who benefited from cognitive rehabilitation programs. She will present data from a retrospective study examining the outcome of persons 2 to 9 years after personalised cognitive programs.

Antonio Vita will present new data form meta-analytic study testing not only evidence of cognitive remediation effectiveness but also testing the role of different moderators of response. Meta-regressions and subgroup analyses were performed in order to specifically analyse different moderators of response. A number of moderators emerged from the analyses, either related to patients' characteristics, intervention features, or to the context of which cognitive remediation intervention was applied.

Rafael Penadés will address the issue of negative symptoms. Cognitive impairment and negative symptoms seem to be correlated but their relationship is not completely understood. Moreover, cognitive remediation seems to have significant effects on negative symptoms. However, owing to the heterogeneity of negative symptoms, it is difficult to determine the specificity of those effects. Data from a randomised and controlled trial allowed to analyse the effect of cognitive remediation in different aspects of negative symptoms in different domains such as expressive and experiential negative symptoms subfactors.

Caroline Cellard will discuss about how metacognition is related to transfer in daily life of patients with psychotic disorders. Theoretical models of metacognition will be reviewed to pinpoint the role of metacognition and its neuropsychological underpinnings. The conceptual analysis suggests that monitoring is important to target in cognitive remediation. The use of strategies and the response to cognitive remediation will be discussed with the CIRCuiTS

program – a program focusing on metacognitive knowledge and regulation to improve cognition.

Til Wykes will discuss the data and topics presented and will highlight the taken-home messages.

31.1 MODERATORS OF RESPONSE TO COGNITIVE REMEDIATION THERAPY

Antonio Vita*[1], Stefano Barlati[2], Gabriele Nibbio[1], Anna Ceraso[1], Giacomo Deste[3]

[1]*University of Brescia (IT),* [2]*University of Brescia, Spedali Civili Hospital, Brescia, Italy,* [3]
[3]*Spedali Civili Hospital, Brescia, Italy*

Background: Cognitive impairment is a core feature of schizophrenia, with negative consequences on functional outcomes. Although cognitive remediation has been proven to be effective and mentioned in some treatment guidance for schizophrenia, its active ingredients and moderators of effect are still debated.
Methods: In this context, we aimed to identify and analyze the role of moderators of the effects of cognitive remediation on both cognitive performance and psychosocial functioning.
To do this, a systematic review of the literature, and a meta-analysis of the available evidence of cognitive remediation effects were performed. Then, meta-regressions and subgroup analyses were performed in order to specifically analyze the role of different moderators of response.

Results: We included 127 studies for a total of 8654 participants. A number of moderators emerged from the analyses, either related to patients' characteristics, intervention features, or to the context of which cognitive remediation intervention was applied.
Conclusions: We conclude that cognitive remediation is a most valuable treatment for people with schizophrenia, proven to be effective in ameliorating cognitive performance and psychosocial functioning. These effects could be maximized when taking into account specific patients' demographic and clinical characteristics, particular modalities of cognitive remediation delivery, and, possibly, the interaction between such variables. Finally, the role of the rehabilitative context in which cognitive remediation is implemented must be taken into account and further investigated.

31.2 PERSONALIZED PROGRAMS OF COGNITIVE REMEDIATION: LONG TERM OUTCOME

Isabelle Amado*[1]

[1]*GHU Paris Psychiatry and Neuroscience*

Background: Cognitive remediation (CR) with personalized programs and psychosocial rehabilitation (Rehab) provide good satisfaction and functional outcomes with easier transfer of cognitive benefits to everyday life. Rehab encompasses psychoeducation for users and care-givers, cognitive behavior therapy or psychosocial skills intervention. The French Center for Cognitive Remediation and Psychosocial Rehabilitation (C3RP) deliver personalized CR as well as Rehab programs for persons with schizophrenia, autism or complex neurodevelopmental disorders. These are delivered in a patient-centred approach to provide services responsive to patients' preferences and wishes, focusing on the cognitive profile, in coordination with the clinical teams referring to their home. CR is delivered when the

perspective of integration in the community is set up, 6 to 10 months before the realization of the project, to obtain a “stepping stone” effect. Depending on the CR method, transfer to everyday life include homework tasks, specific group sessions, or is ensured explicitly during an immersive experience in a virtual town. However, few studies looked at the long-term outcome in participants who benefited from these rehabilitation course. Hence, we carried out a retrospective survey to examine the outcome of persons 2 to 9 years after personalized CR programs.

Methods: The survey included questions relevant to work, studies, hobbies, housing before (T1) and after CR (T2). Feelings of the participants concerning CR were expressed in a narrative interview and a psychometric analysis has been done.

Results: Neurocognitive or social cognition CR were delivered to 65 persons, suffering from schizophrenia (80.3%), neurodevelopment disorder (15.2%) and bipolar disorder (4.5%). Significant difference between T1 and T2 were found for: job employment ($P<0.001$), even for competitive jobs ($p<0.007$), performing studies ($p=0.033$), practicing a physical activity (0.033) or reading (0.002).When referred to the delay from CR, splitting the sample in G1: CR delivered in 2009-2013 (n=37), G 2: CR 2014-2016 (n=29) groups’, we showed that more persons were working in G1 ($p=0.037$). G2 was younger ($p=0.04$) with more persons studying ($p=0.02$). At T2 the percentage of relapse was for G1: 56.8%, for G2: 79.1%. Lastly feelings concerning CR mentioned more clarity of thoughts, self-confidence, direct incidence on cognition, and efficient help for work and studies.

Conclusions: Although this survey was retrospective with no control group, personalized programs of CR combined with Rehab provide very good long-term outcomes in terms of employment, studies, or other determinants for recovery such as leisure or physical activity practice. A prospective study is necessary to confirm these results.

References:

Amado I, Moualla M, Jouve J, Brénugat-Herné L, Attali D, Willard D, Rigaut B, Malangin B, Kern L, Meyniel C, Gaillard R, Plaze M, Perquier F, Morvan Y . Employment, Studies and Feelings: Two to Nine Years After a Personalized Program of Cognitive Remediation in Psychiatric Patients Front Psychiatry 2020.

31.3 THE ROLE OF NEGATIVE SYMPTOMS

Rafael Penadés*[1], Clemente García-Rizo[1], Guillem Masana[2], Rosa Catalán[1]

[1]*Hospital Clinic Barcelona, Universitat Barcelona, IDIBAPS, CIBERSAM,* [2]*Hospital Clínic Barcelona*

Background: Cognitive remediation is a psychological therapy aiming to treat cognitive impairment in persons with schizophrenia. Beyond its effect on cognition, cognitive remediation may also have a positive effect on negative symptoms. Unfortunately, cognitive impairment and negative symptoms seem to be correlated but their relationship is not completely understood. Besides, owing to the heterogeneity of negative symptoms, it is difficult to determine the specificity of those effects.

Methods: Data from a randomised and controlled trial (RCT) with 60 patients are studied in a General Linear Model. Means of different experimental conditions, a computer-assisted cognitive remediation or treatment as usual without any sort of cognitive treatment, are compared. We aim to examine the effects of cognitive remediation not only in cognition but also in different domains of negative symptoms such as expressive and experiential negative symptoms subfactors. Different analyses of regression and covariation are performed.

Results: Cognitive remediation was associated with a reduction of negative symptoms at post-therapy compared with treatment as usual. Those findings suggest that cognitive remediation has benefits for negative symptoms ($F = 37,655$; $p < 0.0001$). Moreover, those effects are more significant in terms of effect sizes for the expressive dimension ($x2 = 0,41$) than the experiential dimension ($x2 = 0,29$). Thus, even though negative symptoms are not its primary target, cognitive remediation can usefully contribute to the treatment of those pervasive symptoms. Maybe, some domains of negative symptoms, such as the expressive domain, are more responsive to the cognitive treatment.
Conclusions: These results are promising and indicate that cognitive remediation could be a useful treatment for reducing the negative symptoms of schizophrenia. They are in line with previous research but open the question about the specificity of cognitive remediation on different subdomains of negative symptoms. Future research should explore in detail the relationship between cognitive remediation and specific domains of negative symptoms in schizophrenia.

31.4 THE ROLE OF METACOGNITION IN THE THERAPEUTIC RESPONSE TO COGNITIVE REMEDIATION THERAPY

Caroline Cellard*[1], Til Wykes[2]

[1]*Université Laval,* [2]*Institute of Psychiatry, Psychology & Neuroscience*

Background: CIRCuiTS is a computerized cognitive remediation therapy (CRT) program that targets cognitive domains such as attention, memory, and executive functions. Its focus is on the transfer and generalization to daily life of the skills learned through the program. This program presents an innovative approach based on the development of metacognitive knowledge (i.e. knowledge about one's own cognition) and regulation (i.e. using efficient strategies to overcome cognitive difficulties) to improve cognition. The program is built to promote the development of metacognition before and after the exercises are completed with the therapist. Many studies showed the acceptability and feasibility of CIRCuiTS, as well as improvements in different aspects of cognition (Reeder et al., 2017). The aim of this presentation is to highlight how metacognition is related to transfer in daily life of patients with psychotic disorders.
Methods: Theoretical models of metacognition will be reviewed to pinpoint the role of metacognition and its relevance to enhance cognitive and daily functioning.
Results: This conceptual analysis suggests similarities and differences between executive function and metacognition. One important difference between the two concepts is monitoring.
Conclusions: Metacognitive monitoring should be considered to predict when and why executive process are initiated, changed or interrupted. This monitoring may be crucial to help the patient to use strategies during CRT and to transfer the strategies in his daily life.

32. SCHIZOPHRENIA AND THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE: EPIPHENOMENA

Mary Cannon

Royal College of Surgeons in Ireland

Overall Symposia Abstract: Current research delving on the perinatal origins of schizophrenia can line up with the developmental origins of health and disease model, with interesting findings in metabolism, neuroimaging, cognition, clinical symptomatology and

functional outcome. While an indirect marker of the intrauterine environment, such as birth weight has been able to correlate with different metabolic parameters, cognitive function or cortical morphology, further traslational research is required to fully evaluate the impact of the intrauterine development and its difficulties-obstetric complications- on the outcome of psychosis.
The initial prenatal origins of disease model coined by David Barker has later been widened to include also the perinatal events and its first two years in order to fully understand how mammals are programmed due to the environment for a better chance of survival. Interestingly the epigenetic programming mechanisms work under the expected perinatal circumstances however if the environment modifies the mechanism become maladaptive, diseases arouse and mortality increases. So, previous mechanism might underlie the excess of medical morbidity and early mortality found in schizophrenia and other abnormalities at onset.

We aim to work out later research in the realm of obstetric complications and its outcome in different areas of schizophrenia.

Metabolic findings which might underlie the excess of morbidity and early mortality.

Neuroimaging aspects which might help decipher its presence at onset.

Cognitive outcomes which might be present at onset due to early life stressful events.

Clinical and epidemiological issues which might help understand the co-occurrence of psychosis and other findings.

Our approach would like to highlight the already proved effect of early life stressful events (obstetric complications) in the outcome of schizophrenia (metabolism) while suggesting its effect on other areas such as neuroimaging, cognition, clinical and describing specific pathways. Our approach suggest that some disturbances found in patients even at onset might be epiphenomena from previous perinatal conditions.

32.1 FETAL PROGRAMMING, SEVERE MENTAL ILLNESS AND METABOLIC RELATED DISTURBANCES

Marina Garriga*[1]

[1]*Bipolar and Depressives Disorder Unit. Institute Neuroscience. Hospital Clinic Barcelona*

Background: Metabolic disturbances are more prone on severe mental ill patients than in general population. Metabolic disarrangements related with increased weight gain and type 2 diabetes are found on mental ill patients, even before any psychopharmacological treatment is started. Thus, the presence of these metabolic related disturbances is a frequent reason for treatment discontinuation, subsequently increasing the risk of relapse and negatively affecting patient well-being. Despite its consequences, to date few risk factors have been identified (age, gender, body mass index at baseline) for this increased risk, with some authors suggesting the implication of fetal programming models related with early life stressful events and perinatal conditions. The objective of this proposal is to explore the potential role of fetal growth (clinically translated as birth weight) on the risk of metabolic disturbances on severe mental illness patients while increasing current knowledge on the field of fetal programming.
Methods: To achieve the proposed aims we firstly studied the prospective differential role on weight gain due to antipsychotics on two clinical cohorts: antipsychotic naïve patients at the onset of the psychotic disease starting olanzapine and another cohort of psychosis-resistant

patients switching to clozapine. Next, we decided to explore whether birth weight (and ponderal index) might account for or modify the prospective association between developing a severe mental illness and the later risk for developing type 2 diabetes on a birth cohort followed until age 65.Independent linear mixed model analyses on the first study and Cox proportional hazards regression models were used to estimate the associations were used on the second study.
Results: As summary of the results, weight gain due to antipsychotics was only predicted for birth weight on the naïve for treatment cohort, while male gender and body mass index at baseline were associated in both cohorts (naïve and chronic) of patients. On type 2 diabetes regards, those with a severe mental illness (especially schizophrenia spectrum disorders) and low birth weight were at higher risk of diabetes, followed by those without a severe mental illness but low birth weight and being the group of non severe mental ill patients and normal birth weight the ones at lower risk.
Conclusions: The current findings suggest that early environmental events related with impaired fetal growth, and clinically translated on extremes on birth weight might be playing a role on the already increased risk for metabolic disturbances such as weight gain and type 2 diabetes. The modifier effect of birth weight might be higher at the beginning of the severe mental illness and for those suffering from a schizophrenia spectrum disorder (in comparison with those with an affective spectrum disorder).

32.2 NEUROIMAGING PRENATAL ANTECEDENTS OF SCHIZOPHRENIA

Unn Kristin Haukvik*[1]

[1]*Institute of Clinical Medicine, University of Oslo*

Background: Following the neurodevelopmental hypothesis of schizophrenia, obstetric complications such prenatal hypoxia and low birthweight may affect both brain structure and increase the risk of developing schizophrenia. Specific brain structures have been reported to be vulnerable to detrimental prenatal development, in particular the hippocampus, amygdala, and cortical regions which are also regions that have been associated with schizophrenia. By mapping the prenatal antecedents of schizophrenia, neuroimaging studies may contribute to elucidating the pathophysiological mechanisms of the disorder.
Methods: Obstetric hospital records or medical birth registry data, in a Swedish and a Norwegian subject sample, each including schizophrenia patients and healthy controls, and in addition patients with disorders across the psychosis spectrum in the Norwegian sample, were screened thoroughly for prospective information on a wide range of prenatal and perinatal complications and adversities. All participants underwent clinical characterisation, including current symptom registration and neuropsychological testing. MRI scans were obtained on one scanner at each site, and the cohorts were analysed in separate studies. All MRI-scans were automatically segmented with FreeSurfer, and subcortical structure volumes or cortical surface area/thickness/folding pattern estimates were analysed in GLMs including age, sex, and ICV as covariates, and a mediator model was applied to test the influence clinical characteristics in one of the studies. Prenatal adversities were either scored according to the McNeil-Sjöström scale to create composite scores or analysed independently (e.g. birth weight). Within each study, appropriate adjustment for multiple comparisons was applied.
Results: In the Swedish subject sample (n=108), severe obstetric complications were significantly associated with hippocampal volume as well as cortical folding patterns in the pars triangular in both schizophrenia patients and healthy controls. In contrast, no associations were found between obstetric complications and cortical thickness or basal ganglia volumes, even after additionally controlling for medication use.

In the Norwegian sample (n=359), with data extracted from the medical birth registry, lower birth weight as a continuous variable was significantly associated with smaller total surface area across all groups, and within specific regions of the temporal, parietal, and frontal cortex bilaterally. There were no associations between birth weight and cortical thickness, and no diagnosis by birth weight interaction effects on cortical thickness or surface area. Smaller cortical area and lower birth weight were significantly related to poorer working memory performance in all diagnostic groups except schizophrenia.

Conclusions: The associations between prenatal adversities and specific regions susceptible to hypoxia (the hippocampus) or reflecting prenatal neuronal migration and cortical development (cortical area and folding patterns) point towards possible pathophysiological mechanisms. The associations were, however, not specific for schizophrenia patients. Taken together, this suggests that while prenatal adversities may render the brain susceptible for future development of schizophrenia, other factors including genetic risk and environmental hazards are also of importance. Future MRI-studies exploring the interaction between prenatal adversities and other biological and/or environmental risk factors may further help elucidate the mechanisms underpinning the prenatal antecedents of schizophrenia.

32.3 SCHIZOPHRENIA AND THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE: EPIPHENOMENA

Charlotte Teigset*[1], Christine Mohn[2], Bjørn Rishovd Rund[1]

[1]*University of Oslo,* [2]*Vestre Viken Hospital Trust*

Background: Cognitive deficits are a core feature of schizophrenia and appear with increased severity in early-onset schizophrenia (EOS). EOS is defined as onset of symptoms before 18 years of age. Affected youths often experience more symptoms compared to those with later onset, in addition to a worse clinical course and outcome. Evidence indicates that the disease reflects underlying deviations in early brain development, and that fetal exposure to obstetric complications (OC) is a risk factor for developing the illness and may also affect cognitive deficits. Our studies aimed to investigate the neuropsychological development in EOS, with a special focus on the impact of OC. Research questions examined were whether cognitive deficits in EOS may derive from exposure to OC, and if so, how the individual OC affect different areas of cognition. Moreover, research shows extensive brain maturation starting at birth, suggesting newborns to be particularly vulnerable for perinatal insults. Executive function is mainly mediated by the prefrontal cortex, an area that matures late during pregnancy. Thus, exposure to perinatal complications may particularly influence executive dysfunction.

Methods: Our research was based on neuropsychological data from a longitudinal study carried out at the University of Oslo between 2005 and 2009. The participants were 19 EOS patients and 53 healthy controls. All participants were tested with the MATRICS Consensus Cognitive Battery (MCCB), and executive functions were assessed with the D-KEFS Color Word Interference Test and the Wisconsin Card Sorting Test. Information on OC was obtained from the Norwegian Medical Birth Registry.

Results: Our results gave no indication of group differences in OC in EOS and healthy controls. When examining the relationship between OC and cognition (MCCB), a shorter gestational length in the EOS group led to significant decreases in the overall cognitive composite score, and in processing speed. Perinatal complications, and especially shorter gestational lengths, were significantly associated with significant executive dysfunctions in EOS. Perinatal complications did not affect executive function among healthy controls. A

significant relationship between lower Apgar 5-minutes scores and executive dysfunction was found among both EOS patients and healthy controls.
Conclusions: Our results suggest that the overall cognitive deficits in EOS may be partly attributable to the length of gestation. Cognitive dysfunctions did not appear among controls, so gestational length had a different impact on the two groups. We found no indication of group differences in OC in EOS and healthy controls. Hence, a shorter gestational length did not increase the risk for early psychoses but did significantly affect the cognitive difficulties in this group. When examining executive dysfunctions particularly, we found that exposure to perinatal complications was associated with such deficits in EOS. As with other cognitive functions, exposed healthy controls did not exhibit similar executive difficulties, suggesting that the EOS patients seem especially vulnerable for executive deficits due to perinatal insults. These findings indicate that EOS youths process information more slowly and experience more difficulty with problem-solving, which carry important implications for clinical practice. Lower Apgar 5-minutes scores were associated with executive dysfunction in both groups and may therefore be an important early indicator of executive difficulties among adolescents, independent of diagnosis.

32.4 MATERNAL INFLAMMATION DURING PREGNANCY: SYMPTOM PRESENTATIONS AND DIAGNOSTIC SPECIFICITY

Lauren Ellman*[1], Alan Brown[2], Emily Lipner[1], Naoise Mac Giollabhui[1], Lauren Alloy[1], Barbara Cohn[3], Nickilou Krigbaum[3], Piera Cirillo[3], Christian Perez[4], Catherine Schaefer[5], Michaeline Bresnahan[6], Ezra Susser[7], Elizabeth Breen[4]

[1]*Temple University,* [2]*Columbia University Medical Center,* [3]*Public Health Institute, Child Health and Development Studies,* [4]*University of California-Los Angeles,* [5] *Kaiser Permanente,* [6]*Columbia University Mailman School of Public Health; New York State Psychiatric Institute,* [7]*Columbia University, New York State Psychiatric Institute*

Background: Infection during pregnancy has been associated with increased risk of offspring psychopathology, such as schizophrenia and depression. However, most infections do not cross the placenta; therefore, maternal immune responses to infection (e.g., inflammation) have been proposed as a contributor to these findings.
Methods: In a series of studies, we have explored how maternal inflammation during pregnancy influences the course of schizophrenia and whether prenatal inflammation has diagnostic specificity for other non-psychotic symptom presentations. These studies used a well-characterized, prospective pregnancy cohort, which followed pregnant women from 1959-1967, including archiving maternal serum samples. Multiple follow-up studies of this cohort have been conducted, including ascertainment of schizophrenia spectrum disorder diagnoses, semi-structured symptom assessment, structural magnetic resonance imaging (sMRI), and continuous follow-up of a subsample of offspring during childhood and adolescence.
Results: This talk will present findings that maternal inflammation during pregnancy is associated with a worsened course of schizophrenia, characterized by more severe brain abnormalities and increases in negative symptoms. In addition, results will be presented indicating that prenatal inflammation also increases risk for depressive symptoms in adolescent offspring. Finally, findings will be presented suggesting that the timing of gestational exposure to inflammation and fetal sex matters for childhood symptom presentations, with these timing and sex effects disappearing by adolescence. Specifically, maternal inflammation during the first trimester was associated with increases in externalizing symptoms during childhood (primarily for boys), whereas maternal inflammation during the second trimester was

associated with internalizing symptoms during childhood (primarily for girls). Both of these pathways lead to adolescent depressive symptoms in a moderated mediation analysis.
Conclusions: Cumulatively, our findings suggest that maternal inflammation during pregnancy is associated with a more severe course of schizophrenia, with evidence of worsened structural brain abnormalities and increases in negative symptoms. Nevertheless, our results also indicate that maternal inflammation during pregnancy is associated with depressive symptoms in offspring, suggesting that maternal inflammation may be more related to a shared phenotype that occur in schizophrenia and depression, rather than the full diagnostic presentations. Finally, these studies implicate timing and sex-specific influences of fetal exposure to maternal inflammation that are apparent during childhood, but disappear during adolescence. Overall, these results have implications not only for early intervention and prevention strategies, but for future studies examining prenatal inflammation, which largely have not focused on intermediary outcomes during childhood.

33. PREDICTING CLINICALLY IMPORTANT OUTCOMES IN SCHIZOPHRENIA

Diana Perkins
University of North Carolina At Chapel Hill

Overall Symposia Abstract: There is a major drive to personalise diagnosis and treatment of psychotic disorders. However, there is considerable variability between patients in terms of clinically important outcomes such as who develops psychosis, whether it is an affective or schizophreniform psychotic disorder, whether their illness will respond to first-line antipsychotics or not and require clozapine treatment, and if they will develop metabolic syndrome as well. This variability is a major clinical problem as it leads to inappropriate and delayed treatment, which leads to health burden, side-effects and costs.
This symposium brings together complementary approaches to address this challenge. Dr Cannon will present the latest, unpublished data on clinical and neuroimaging predictors of psychosis from one of the largest and longest longitudinal studies of people at risk for psychosis in the world. He will focus on a frequent phenotyping approach that integrates imaging and clinical measures, showing that the trajectory of brain imaging changes distinguishes people who will go on to develop psychosis from those who remit. Dr. Tamminga will present novel EEG, neuroimaging and cognitive data from a large transdiagnostic multi-centre study of people with psychotic disorders that predicts response to treatment. Dr. Howes will present new data on the potential of dopaminergic and glutamatergic imaging to predict treatment resistance and pharmacoeconomic analysis on the cost-saving of fast-tracking treatment resistant patients to clozapine. Dr. Perry will present the development of a tool to predict the development of metabolic syndrome in patients with first-episode psychosis, and its evaluation in two different clinical cohorts and a birth cohort, and the potential of this to guide treatment choices. Finally, Dr Suvisaari will discuss the new understanding and lessons that can be drawn from the different approaches covered in the symposium. She is both a practising psychiatrist as well as a researcher with expertise in precision medicine, so will be able to provide both translational and research perspectives.

The symposium shows geographical, gender and career diversity, including contributors from six different institutions and three different countries, as well as leading female researchers and clinicians and early career researchers (Perry, Suvisaari, Tamminga). Moreover, the symposium covers a range of clinical and experimental techniques, including structural and

functional imaging, EEG, and metabolomics. In addition, a number of different linear and non-linear analytic and prediction models are considered. By drawing these different approaches together in one symposium, the session will enable comparisons to be made across techniques and approaches to consider the potential to develop personalised diagnosis and treatment for people with psychotic disorders.

33.1 TRAJECTORIES OF NEUROIMAGING BIOMARKERS IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

Tyrone Cannon*[1]

[1]*Yale University*

Background: Individuals who meet clinical high-risk for psychosis (CHR-P) criteria have been observed to show at least three distinct clinical outcome trajectories over a 1- to 2-year follow-up period: conversion to full psychosis, remission of CHR-P symptoms, and continuity/progression of CHR-P symptoms. Prior work has shown an association between conversion to psychosis and a steeper rate of cortical thinning over time, but how soon after ascertainment differential rates of change in cortical thickness and other imaging-based biomarkers are evident (and potentially predictive of clinical outcomes) is unknown.
Methods: Here I present findings from the recently-completed third phase of the North American Prodrome Longitudinal Study (NAPLS3), in which CHR-P individuals (N=568) were evaluated with structural and functional neuroimaging and other assessments at baseline, 2-, 4-, 6-, and 8-month follow-up.
Results: Using longitudinal mixed-effects growth curve modeling, the three outcome groups (conversion, remission, continuity/progression) were observed to show distinctly different trajectories of change over time in cortical thickness as well as in measures of resting-state functional connectivity, with particular changes evident as soon as 2-months following initial ascertainment. Analyses in progress are assessing the degree to which individual baseline values and slope estimates from the structural and functional neuroimaging measures are differentially predictive of conversion, remission, and continuity/progression outcomes at the individual case level, and whether such measures add to the prediction of these outcomes over and above the contributions of clinical and demographic measures.
Conclusions: CHR individuals who eventually convert to psychosis and remit from a CHR syndrome show differential trajectories of change over time in structural and functional brain imaging parameters that are detectable within a few months after initial ascertainment and may help in prediction of these outcomes.

33.2 PREDICTION OF TREATMENT RESPONSE IN PSYCHOSIS USING A NOVEL IMAGING APPROACH

Oliver Howes*[1], Sameer Jauhar[2], Arsime Demjaha[3], Hugh Salimbeni[4], Enrico D'Ambrosio[5], Federico Turkheimer[6], Paul McCrone[6], Jin Huajie[6], Mattia Veronese[7]

[1]*MRC LMS and KCL,* [2]*King's College London/ MRC Clinical Sciences Centre,* [3]*King's College London, Institute of Psychiatry, Psychology & Neuroscience,* [4]*Imperial College London,* [5]*University of Bari 'Aldo Moro', Italy,* [6]*King's College,* [7]*Center for Neuroimaging Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London*

Background: Treatment resistant schizophrenia (TRS) occurs in 35% of patients. Clozapine is the only drug licensed for TRS but identifying them requires empirical trials of different drugs, leading to long delays and side-effects. Patients with TRS show differences on imaging of the dopamine and glutamate systems relative to patients who respond to treatment but the potential of imaging to predict response and non-response and the pharmacoeconomics of this has not been evaluated.
Methods: We developed a novel 10 minute PET imaging protocol (SUVRc) and evaluated the reliability of this in a test-retest study. We then tested the clinical utility of this test using a simplified analysis approach and linear and non-linear machine-learning (i.e. Bernoulli, support vector, random forest and gaussian processes) in two independent studies. The first was a study comparing patients with established TRS and antipsychotic response using both dopamine PET and MRS glutamate imaging. The second was a prospective longitudinal study of first episode, antipsychotic naïve patients who received dopamine PET and MRS glutamate imaging and were then treated with antipsychotic drugs and followed-up for six months to establish response. Total patient sample n=136. Pharmacoeconomic modelling was conducted.
Results: SUVRc had excellent test-rest reproducibility (ICC:0.76-0.91, significantly better than chance: $p<0.001$). Both our linear and non-linear classification models showed good predictive power to distinguish responders from non-responders (receiver operating curve area under the curve for: SUVRc=0.8 ($p<0.001$); for voxel-wise approach using a linear support vector machine: 0.88), and similar sensitivity for identifying treatment non-responders with 100% specificity (Kicer: ~50%, SUVRc:40%-60%). Glutamate levels were higher in treatment resistant patients that treatment responsive patients (cohen's d=0.8, $p<0.05$) and the distribution of data was most consistent with a bimodal distribution, consistent with sub-types of disorder varying on glutamate levels. However, glutamate levels did not predict response to treatment in first episode patients. Economic analysis indicated a potential healthcare cost saving of ~£3,400 (equivalent to $4,232 USD) per patient.
Conclusions: These findings indicate [18F]FDOPA PET dopamine imaging has potential as biomarker to guide treatment choice early in the course of psychosis, and that a simplified imaging acquisition shows good reliability and significant potential cost savings for the early identification of patients who will benefit from clozapine treatment.

33.3 BIOLOGICALLY-BASED FINGERPRINTS FOR PSYCHOTIC DISORDERS FROM B-SNIP

Carol Tamminga*[1], Brett Clementz[2], Godfrey Pearlson[3], Matcheri Keshavan[4], Elliott Gershon[5]

[1]*University of Texas Southwestern Medical Center,* [2]*University of Georgia,* [3]*Yale University,* [4]*Harvard University,* [5]*University of Chicago*

Background: The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) is a 5-site consortium which has carried out deep phenotyping across a psychosis dimension in order to find biologically congruent clusters within psychosis. Across the 5 matched and trained sites we have Biotyped over 2000 psychosis cases; these have fallen into 3 different biologically characteristic groups, Biotype-1, -2 and -3. The consortium has carried out an initial defining study and then a replication study, 5 years later.
Methods: All B-SNIP sites are trained on evaluations, have matched test equipment and learn to collect biomarker data similarly; human as well as machine phantom data are collected. All data from a single biomarker set is analyzed in a single expert laboratory to decrease variability. Psychosis individual are recruited from the community, including schizophrenia (SZ), bipolar disorder with psychosis (BDP) and schizoaffective disorder (SAD), then participate in the

collection of clinical, diagnostic, cognitive, oculomotor, brain imaging and electrophysiological data over 4-5 days. Data have been analyzed using various forms of supervised and unsupervised machine learning.
Results: Analyses began by testing for biomarkers and biofactors as they characterized conventional diagnoses, but found none. So, the biomarkers themselves were used to cluster across the psychosis dimension generating psychosis Biotypes-1, -2 and -3., each with characteristic biomarker characteristics. B1 and B2 have similarly low cognition, with B1 having low EEG power and intrinsic activity, where as B2 has the opposite EEG profile. We have targeted biomarker characteristics for treatment, wanting to be able to treat by test rather than by symptoms. It is an experiment each time, to target a pathological biomarker to see what aspects of the psychosis will recover. Because we know that biomarker replication is strong, the methodology provides confidence.
Conclusions: Rational biomarkers for psychotic disorders tested comprehensively on a large number of psychotic individuals have produced seemingly generative clusters of biologically-defined psychosis disorders. Currently testing is underway to reveal whether there exist responsive elements to rational treatment directions, this being one element on the way to personalized medicine in psychosis therapeutics.

33.4 DEVELOPMENT AND EXTERNAL VALIDATION OF PSYMETRIC: A CARDIOMETABOLIC RISK PREDICTION CALCULATOR FOR YOUNG PEOPLE WITH PSYCHOSIS

Benjamin Perry*[1], Emanuele Osimo[1], Rachel Upthegrove[2], Pavan Mallikarjun[2], Jessica Yorke[3], Stanley Zammit[4], Oliver Howes[5], Peter Jones[1], Golam Khandaker[1]

[1]*University of Cambridge,* [2]*University of Birmingham,* [3]*Birmingham Womens and Childrens NHS Trust Early Intervention Service,* [4]*University of Bristol,* [5]*MRC LMS and KCL*

Background: Young people with psychosis are at substantially higher risk of cardiometabolic disorders than the general population, and signs of developing cardiometabolic comorbidity are detectable from the first-episode of psychosis. Cardiometabolic risk prediction algorithms are commonly used in the general population as tools to encourage informed, personalised treatment decisions with the aim of primary prevention of longer-term cardiometabolic outcomes. Yet, A recent systematic review of cardiometabolic risk prediction algorithms found that only one was developed in a sample of older adults with mental illness, and none were developed for young people with psychosis.
Methods: We developed and externally validated two Psychosis Metabolic Risk Calculator (PsyMetRiC) algorithms to predict risk of incident metabolic syndrome in young people with psychosis (16-35y). The partial-model included commonly recorded sociodemographic, lifestyle and clinical variables. The full-model also included commonly measured blood testresults. PsyMetRiC was developed using clinical data from two UK psychosis early-intervention services (EIS) (n=651); and was externally validated using data another UK EIS (n=510). A young-persons advisory group was consulted throughout the model development process. We conducted a sensitivity external validation analysis in 505 UK birth cohort participants (aged 18y) who were at risk of developing psychosis. Algorithm performance was primarily assessed using measures of discrimination (c-statistic), calibration plots and decision curve analysis. Additionally, we produced an online data-visualisation sandbox app.
Results: Both algorithms performed well at internal (full-model: C=0.80, 95% C.I., 0.76-0.84; partial-model: C=0.79, 95% C.I., 0.73-0.84) and external validation (full-model: C=0.75, 95% C.I., 0.69-0.80; partial-model: C=0.74, 95% C.I., 0.68-0.80); calibration plots were acceptable. The full-model had superior net-benefit across most risk thresholds (e.g. at a cut-off of 0.25,

PsyMetRiC improved net benefit by 4.8%; equivalent to about 5 additional detected patients with metabolic syndrome per 100 patients.
Conclusions: We have developed an age-appropriate cardiometabolic risk prediction algorithm for young people with psychosis. PsyMetRiC can predict risk of incident metabolic syndrome, which is a precursor to cardiovascular disease and early mortality. PsyMetRiC has the potential to become an invaluable resource for healthcare professionals working in EIS to assess and manage both physical and psychiatric health in tandem.

34. LET'S TALK ABOUT LOVE! STUDIES ON ROMANTIC RELATIONSHIPS AND SEXUALITY IN INDIVIDUALS WITH A PSYCHOTIC DISORDER

Tania Lecomte
University of Montreal

Overall Symposia Abstract: Loneliness is currently considered one of the biggest risk factors for mortality and morbidity. Individuals with a severe mental illness such as a psychotic disorder are at high risk of becoming socially isolated – in part because of the stigma linked with their condition, as well as their difficulties in engaging and maintaining romantic relationships. A healthy romantic relationship is considered a protective factor against the negative effects of stress on one's mental health and can help support the person' recovery, but unhealthy or tumultuous romantic relationships can also become stressors and risk factors for relapse. Love, sexuality, and the development of intimate bonds are basic human needs and are also considered an important part of one's personal recovery. Yet, a long history of taboo surrounding the existence of a sexual and romantic life of people with mental disorders have contributed to the paucity of information currently available in this domain.
The current symposium presents novel results stemming from three teams working on this topic (Montreal, Canada, Maastricht, Netherlands, and Manchester, England).

First, a systematic review on romantic relationships and sexuality will be presented by Briana Cloutier (team of T. Lecomte), covering 43 studies on sexuality. The review highlights the international interest for this topic, as well as the gaps in the literature.

The second presentation, by José de Jager (team of J. van Os), will describe subjective perceptions of problems participants encountered in establishing intimacy and maintaining intimate relationships. This qualitative study of 28 participants with psychotic disorders revealed five important themes related to various obstacles they encountered. This will be followed by Rebecca White (team of F. Varese) discussing the results of an online survey pertaining to romantic relationship satisfaction in link with other well-being and psychological variables in young individuals with a psychotic disorder.

Finally, Tania Lecomte will present results from a multiple single-case experimental design study assessing the impact of a novel group intervention to help young men with early psychosis develop healthy romantic relationships.

34.1 ROMANTIC RELATIONSHIPS, SEXUALITY, AND PSYCHOSIS: A SYSTEMATIC REVIEW OF RECENT FINDINGS

Briana Cloutier*[1], Audrey Francoeur[1], Crystal Samson[1], Alexandra Ghostine[1], Tania Lecomte[1]

[1]*Université de Montréal*

Background: For individuals with a psychotic disorder, dating can present several challenges and lead to exclusion from intimate relationships. These difficulties may stem from a number of factors, including impairments in social and sexual functioning. Although scientific interest in this topic is mounting, the last quantitative review of the literature dates back to 2003. The aim of this systematic review was to synthesize quantitative data from studies published in the last 15 years on romantic relationships and sexuality in the context of psychosis.
Methods: Articles were retrieved from PsycINFO, PubMed, Web of Science, and ProQuest databases. Inclusion criteria were: (1) original research, (2) complete or partial sample with a psychotic diagnosis, (3) provision of quantitative data specific to the population of interest, and (4) studies focusing on romantic relationship and/or sexuality variables as correlates, predictors, mediators, or outcomes. Study quality was evaluated using PRISMA criteria.
Results: 43 studies were identified, 24 of which were categorized as obstacle-related (e.g., sexual risk behavior, sexual offending, intimate partner violence) and 19 of which were deemed neutral or recovery-oriented (e.g., marital and sexual functioning, family planning and reproductive health, sexual fantasies).
Conclusions: Despite missing terms and age-group limitations, our results highlight a need for greater communication and assistance in the areas of intimacy and sexuality for persons with psychosis. Better access to resources (e.g., dating skills and couple therapy programs) and higher quality, consumer-oriented research is needed.

34.2 INTIMACY AND ITS BARRIERS: A QUALITATIVE EXPLORATION OF INTIMACY AND RELATED STRUGGLES AMONG PEOPLE DIAGNOSED WITH PSYCHOSIS

José deJager*[1], Bahar Cirakoglu[1], Annet Nugter[1], Jim van Os[2]

[1]*GGZ noord holland noord,* [2]*Utrecht University Medical Centre*

Background: Intimacy is a fundamental part of human life. Establishing and maintaining intimate relationships, however, is not always self-evident for people with psychosis. To facilitate the recovery process of people with psychosis and to maximize the quality of life, it is important to understand what barriers people with psychosis encounter when it comes to the formation of intimacy and intimate relationships. The presented study aimed to explore which problems participants encounter in establishing intimacy and maintaining intimate relationships. As a basis for this exploration, the interpersonal process model in volving the concepts of self-disclosure and responsiveness was used.
Methods: Twenty-eight participants with a psychotic disorder receiving flexible assertive community treatment were interviewed about their needs and experiences with intimate relationships, using semi-structured in-depth interviews. The interviews were transcribed and coded using Grounded Theory methodology.
Results: Five overarching categories in relation to problems in establishing and maintaining intimate relationships emerged: side effects of medication, mental symptoms, stigma and selfstigma, sexual abuse, and lack of social skills and experience. Loss of self-esteem was an overarching central theme common to all five categories.
Conclusions: This study enhances our understanding of the barriers toward intimacy experienced by people with psychosis. The identified barriers may guide (the development of)

interventions. Further research should explore the relationships between the five categories, self-esteem and intimacy in a quantitative matter. This research is currently ongoing.

34.3 IS SATISFACTION WITH ROMANTIC RELATIONSHIP STATUS ASSOCIATED WITH MENTAL HEALTH AND WELL-BEING FOR PEOPLE WITH EXPERIENCE OF PSYCHOSIS?

Rebecca White*[1], Filippo Varese[1], Maria Haarmans[1], Richard Bentall[2], Gillian Haddock[1]

[1]*University of Manchester,* [2]*University of Liverpool*

Background: Romantic relationships represent one of the most salient sources of social support in general population studies and are associated with both physical and psychological benefits. Research suggests that for people with psychosis romantic relationships may also have a positive impact on a range of outcomes, but the reasons for these associations are still unclear. This study aims to investigate whether satisfaction with romantic relationships status is associated with better wellbeing outcomes in people with experience of psychosis, and to explore the psychological mediators and moderators of this relationship.
Methods: Participants who had previously sought support for psychosis (n = 175) completed an online survey including measures of relationship status satisfaction (the Satisfaction with Relationship Scale) as well as measures of psychotic complaints (the CAPE-42), general well-being (Short Warwick-Edinburgh Mental Wellbeing Scale) and several psychological variables relevant to the pathway between romantic relationships and well-being outcomes, namely loneliness, internalised stigma, perceived social support, self-esteem, and attachment.
Results: The findings of mediation and moderation models pertaining to the role of self-esteem, loneliness, internalised stigma, attachment, and perceived social support will be presented.
Conclusions: The findings highlight areas of consideration for future research and service provision.

34.4 THE POWER OF TWO : BUILDING ROMANTIC RELATIONSHIPS IN YOUNG MEN WITH PSYCHOSIS

Tania Lecomte*[1], Briana Cloutier[1], Amal Abdel-Baki[2], Martin Lepage[3], Marie Villeneuve[541]*University of Montreal,* [2]*CHUM,* [3]*McGill University,* [4]*IUSMM*

Background: Young men with psychosis are often single for years following their first episode. Yet, a healthy romantic relationship is often desired, and a protective factor against relapse. Objectives : This study aimed to investigate the effects of a novel group therapy for single young men with psychosis called the Power of Two on relevant outcomes.
Methods: The study used a repeated single-case experimental design, whereby participants were assessed twice (at one month apart) prior to taking part in the group intervention, and twice (one month apart) after having finished the group intervention. Participants received 12 weekly sessions of The Power of Two, a CBT group intervention including skills training, metacognition, attachment and self-esteem/stigma and sexuality. Measures assessed : romantic functioning (RRFS), internalized stigma (ISMIS), social functioning (FESFS - subscales Intimacy and Friendships), self-esteem (SERS-SF), sexuality (MSQ) and psychiatric symptoms (BPRS).
Results: At the time of this submission, the results of 12 young men show that the scores for all the measures were stable prior to the group and that they greatly improved at post-therapy, with continued improvements at one-month follow-up for : RRFS (skills), RRFS (facing

stigma), self-esteem, internalized stigma, overall positive sexuality, and overall psychiatric symptoms (BPRS).
Conclusions: These initial results suggest that the Power of Two group has potential to improve romantic relationship skills and sexuality, and also impact other domains that are central to developing a healthy romantic relationship. This study is underway and results with a larger sample will be presented.

35. SYMPTOMATOLOGY, COGNITION, AND FUNCTIONING RESULTS OF UNTREATED CHRONIC PSYCHOSIS FROM THREE LOW AND MIDDLE INCOME COUNTRIES

Lawrence Yang
New York University

Overall Symposia Abstract: This symposium presents research findings from three geographically distinct, low and middle-income countries (LMIC) with samples ascertained primarily from rural locales. Many individuals with chronic psychotic disorders in under-resourced LMIC settings have a prolonged duration of untreated psychosis (DUP) prior to their first contact with treatment services, providing a unique opportunity to study how prolonged DUP is associated with clinical outcomes. The identification and treatment of these individuals is a high priority goal of several low- and middle-income countries. This provides a unique opportunity to characterize the untreated course of psychosis using modern diagnostic tools by comparing the characteristics of recent-onset cases to those of individuals with 10 to 50 years of untreated psychosis at the time of their initial contact with treatment services. Additionally, increasing efforts to identify and initiate treatment for individuals with psychosis (IWP) in rural regions of LMIC has led to new programs to treat these IWP at first contact. In this symposium, we present ongoing research from the some of the most prominent community-based and first contact studies of IWP from China, India, and Ethiopia. Symposium presenters will address how symptomatology, cognitive functioning, and functional outcomes manifest in untreated IWP, and how these may vary among IWP with short and long DUP. Assessing IWP from LMICs with much longer DUP (10-50 years) will enable delineation of the natural trajectory of long-term functional declines in IWP, providing crucial insights into the neurobiological course of chronic psychosis. Further, a new treatment program for first contact IWP will be described in India, as well as the challenges in establishing a first-contact treatment center within a low-resource setting. Lastly, we present new data concerning modifications to established cognitive functioning measures that are required to assess IWP from rural areas who often have very low education and are unfamiliar with Western testing procedures. Presenters will also compare the findings from these three countries with findings from first-contact studies in high income countries to illuminate the course of untreated psychosis as well as treatment targets for LMIC across different global settings.

35.1 SELECTIVE INCREASE OF COGNITIVE DEFICITS WITH LONGER DURATIONS OF UNTREATED PSYCHOSIS (<1.0 – 58.0 YEARS) IN A RURAL CHINESE SAMPLE

William Stone*[1], Cai Bing[2], Xinhua Liu[3], Grivel Margaux[4], Gary Yu[4], Xu Yangmu[5], Xinyi Ouyang[2], Hanhui Chen[2], Fei Deng[2], Fang Xue[2], Huijun Li[6], Jeffrey Lieberman[3], Matcheri Keshavan[7], Ezra Susser[8], Lawrence Yang[4], Michael Phillips[2]

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Background: Cognitive deficits are core features of schizophrenia. Most studies have focused on premorbid periods and the first episode of psychosis. Cognition in chronic psychosis has been studied less but viewed largely as stable, though performance is confounded with effects of antipsychotic medications. Thus far, relationships between duration of untreated psychosis (DUP) and cognition have been inconsistent in studies that assessed relatively short periods of DUP. The current study assessed cognition in a rural Chinese sample with durations of untreated psychosis that ranged from <1 to 58 years.

Methods: Untreated subjects (n=206) were recruited from the Ningxia Hui Autonomous Region in northeast China, with the assistance of a provincial-level registry that is part of the National Continuing Management and Intervention Program for Psychoses (the '686' program). Healthy controls were identified from lists of individuals registered in local health clinics. Potential subjects were assessed with the Chinese version of the Structured Clinical Interview for DSM-IV (SCID-IV). Drug-naïve subjects who met criteria for schizophrenia, schizoaffective disorder or delusional disorder, with no history of intellectual disability or other organic mental disorder, and who provided informed consent along with a relative, were recruited into the study. Healthy controls (n=220) were also interviewed with the SCID-IV and were matched to untreated psychotic subjects by age, type of residence (rural or urban), ethnic group and educational levels. All subjects received the Mini-Mental State Examination (MMSE) and an adapted version of the MATRICS Consensus Cognition Battery (MCCB). Due to low levels of education and lack of familiarity with psychological tests and instruments, rules were developed to identify 'valid' and 'invalid' test results.

Results: Untreated patients (not divided by DUP) did not differ significantly from healthy controls by age, gender or level of education. Comparisons between healthy controls and untreated patients showed that patients performed worse than controls on the MMSE, provided fewer valid tests and domains and performed worse on all MCCB individual tests using valid test results. They also performed worse on a social cognition test that was substituted for the MCCB social cognition test, and remained significant after accounting for multiple comparisons. When subjects who provided invalid data are included with those who provided valid data, the group differences were strengthened further. Using Spearman partial correlation coefficients to assess associations between DUP and cognitive performance, with gender, education and age of onset as covariates and using only valid data, 3 out of 9 cognitive measures showed lower scores with greater levels of DUP. All 3 emphasized aspects of executive function (learning, processing speed and problem solving). Another 4 tests also showed lower scores when the invalid data were included.

Conclusions: This is the first study, to our knowledge, to assess cognition and clinical symptoms in individuals who endured untreated psychosis for up to 58 years. As such, it offers a previously unseen picture of chronic psychotic illness that is unaltered by medications or long-term hospitalizations. Our study thus provides a fresh look at longstanding issues concerning the stability of cognitive functions in chronic psychosis. Our findings that long-term untreated psychosis was associated with selective declines in cognitive abilities, if

confirmed, challenge the view that cognition in psychosis is characterized mainly by stable deficits that develop early, and are explained fully by a neurodevelopmental etiology.

35.2 IS THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB) APPROPRIATE FOR ASSESSING COGNITIVE FUNCTIONING IN PERSONS WITH CHRONIC SCHIZOPHRENIA FROM RURAL PARTS OF LOW- AND MIDDLE-INCOME COUNTRIES?

Michael Phillips*[1], Cai Bing[1], Fang Xue[1], Xinyi Ouyang[1], Fei Deng[1], Hanhui Chen[1]

[1]*Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine*

Background: The MCCB is the most widely used method of assessing cognitive functioning in schizophrenia but the development and use of this battery has been largely based on relatively young (usually first-episode), high-school educated patients enrolled at psychiatric clinics in urban centers. The utility of this cognitive battery in chronically ill, community-dwelling patients with little education from low-resource settings such as the rural areas of low- and middle-income countries (the locations where most persons with chronic psychosis reside) has not been assessed.

Methods: The MCCB Letter-Number Span (LNS) test was dropped because Chinese respondents don't use the Latin alphabet and an adapted version of the Reading the Mind in the Eyes Test (RMET) replaced the MCCB Mayer-Salovery-Caruso Emotional Intelligence Test (MSCEIT) to assess social cognition. The method of administering the MCCB was adapted for use with a largely rural, under-educated sample and then the nine MCCB tests were administered by trained interviewers to three groups of community-dwelling residents in Ningxia Province in China: 85 never-treated individuals with chronic schizophrenia, 85 treated controls, and 85 healthy controls [matched for gender, age, ethnicity, duration of education, urban v. rural residence, and (for the patient groups) duration of illness]. Among these 255 respondents, 96.5% were rural residents, 61.2% were female, their mean age was 49.4 years, their mean years of education was 3.7 years (34% had never attended school), and 91.8% had never used a computer. Among the 170 individuals with chronic schizophrenia the mean duration of illness was 21.8 years. The validity of the result of each MCCB test was classified into 6 groups, three types of 'incomplete' results (refused to start or complete the trial; unable to complete the trial due to physical or educational limitations; and no active response without other evidence that respondent understood the task) and three types of 'successful completion' results (no active response during formal test but responded during training or provided other evidence of understanding what was expected; active response during formal test but '0' score; and active response during formal test resulting in a positive score).

Results: The proportion of incomplete results in the nine tests ranged from 15.3%-50.6% in the untreated group; 2.4%-34.1% in treated controls; and 0%-10.6% in healthy controls. The proportion of respondents who validly completed results assessing 5 or more of the 9 cognitive domains assessed by MCCB (the number of domains needed to generate an overall cognitive index) in the three groups were 71.8%, 94.1% and 98.8%, respectively. If 'successful complete' results are restricted to tests with positive scores, the proportion of invalid results increased to 25.9%-77.6% in untreated patients, 9.4%-63.5% in treated controls, and 0%-41.2% in healthy controls. Using this more rigorous measure of successful completion, only 44.7% of untreated patients, 61.2% of treated controls and 89.4% of healthy controls successfully completed results assessing 5 or more cognitive domains. The Continuous Performance Test (which required respondents to use a computer mouse) and the RMET (which included vocabulary terms describing emotions that many respondents did not know) had the lowest proportion of successful test completions.

Conclusions: The method of administering the MCCB to assess cognition in chronic psychosis needs to be revised when assessing community residents in low-resource settings, and some of the MCCB tests may need to be replaced with tests that are suitable for respondents with little education who are unfamiliar with computers. The common method of including 'incomplete' results in the analysis of MCCB data (by coding all such results as '0') needs to be reconsidered.

35.3 SYMPTOMATOLOGY, COGNITION, AND FUNCTIONING OF UNTREATED PSYCHOSIS IN INDIA: SCARF SNAPSHOTS

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Background: There is a huge mental health gap in India, especially in the rural areas. Our research has found that rural patients with psychotic disorders have an average DUP of around 10 years. This has enabled a detailed study of the various facets of their illness and treatment. We present the results of three studies conducted over the last decade at the Schizophrenia Research Foundation (SCARF) at Chennai, India. These have examined rural untreated cases of schizophrenia from the community and first episode from our urban clinic.

Methods: The SCARF Telepsychiatry in Pudukottai (STEP) program in a catchment area-based population of about 250,000 people identified through a door to door survey, persons with chronic untreated psychotic disorders. The psychopathology of the individuals as well as their functioning was studied. The second study is the INTREPID which is an international Collaborative study on psychoses held in India, Nigeria and Trinidad and co-ordinated by the Kings College London. The on-going INTREPID II is a catchment area based epidemiological study that look at identifying and recruiting cases using a variety of strategies including key informants in the community, survey and through service providers from both the formal and informal sectors. SCARF runs a first episode psychosis clinic and we have been following up such persons for over two years. The ongoing WIC study is also looking to protocolise the management of such cases in the Indian setting. Psychopathology, role of families in engaging with care and outcomes are studied. This is a predominantly urban population.

Results: STEP study: Of the identified cases of psychoses, only 42.4% were accessing clinical care, with 28.2% having discontinued all forms of treatment and 24.4% being never treated. For the never treated group the DUP ranged from 1 month to 34 years (Mean (SD) in years = 9.8 (8.3)). A comparison between long and short DUP cases will be presented and discussed . INTREPID: Of the identified and recruited cases the majority (65%) were female, , were above the age of 45 (47%) and the average DUP was 9 years with only 21% having a DUP less than 2 years. Only a little over 30% had accessed any type of assistance from both the formal health sector and from religious/traditional healers.

FEP clinic: We found that substantial improvement in the positive and negative symptoms in the FEP occurred in the first three months and the social functioning improved by the first six months. The one-year follow-up data has shown that the improvement achieved at the end of 12 months is not statistically different from the three-month scores. Nearly 50% of the subjects recruited for the follow-up are in contact only through the phones and nearly 40% of them are not on medications and yet in remission.

Conclusions: The challenges in identifying untreated persons with psychoses in remote and rural settings with very little accessible health care services will be discussed. Equally, if not more daunting is the assessment of cognitive functions in illiterate populations. The lack of availability of normative data for the local population adds to the complexity of this task. In the urban FEP clinic, the primary challenge has been the continued engagement of the young

people with the services since they seem to achieve remission fast. The strategies used to work around this will be discussed.

35.4 SYMPTOMATOLOGY, COURSE AND OUTCOME OF SCHIZOPHRENIA IN RURAL COMMUNITY IN ETHIOPIA

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[1]*Addis Ababa University*

Background: There is scarcity of data on symptom profile, course and outcome of untreated chronic psychosis in LMICs. A cohort of untreated people with schizophrenia, bipolar disorder and depressive disorder was recruited and followed for over ten years in Butajira, a rural district in Ethiopia. We report here on cases of schizophrenia

Methods: A House to house survey was conducted to recruit patients (aged 15 to 49) with schizophrenia in Butajira District using CIDI and key informants as a first stage screening. Those screened positive by the two methods were interviewed by clinicians who were trained how to administer SCAN, a diagnostic tool for a definitive diagnosis. Those who were diagnosed to have schizophrenia were enrolled for treatment with first generation antipsychotic medication and monthly follow-up. Clinical and functional statuses of the cases were assessed during follow-up visits.

Results: By the end of the survey 68,378 individuals were interviewed with the CIDI and key informants also identified potential cases. A total of 2,285 SCAN interviews were done on potential cases identified by the CIDI and/or key informants. The SCAN interview identified 321 (4.69/1,000) cases with schizophrenia. Of these, 267 (83.2%) were males and only 10% of the cases have had at least one encounter with modern treatment at the time of recruitment. According to ICD 10 criteria the leading category of symptoms identified was undifferentiated (30.0%) followed by paranoid (29.6%). When it comes to duration of illness 238 (74.1%) the cases had been ill for 2 years and above when recruited into the cohort. Only 18.0% of the cases had achieved complete symptomatic remission for 75% of the follow-up period. A total of 121 (13.0%) cases died during the ten year follow-up period. Social and physical functioning of the cohort was lower than the population norm over the follow-up period. Functional impairment was not associated with symptom profile, duration of illness or socio-demographic characteristics when controlled for baseline functionality.

Conclusions: The outcome of schizophrenia in this rural district of a low income country has not been as favourable as expected. Further studies are recommended to elucidate the claimed difference between low and high income countries with regards to outcome of schizophrenia.

36. DIGITAL HEALTH INTERVENTIONS FOR SEVERE MENTAL ILLNESS

Evelyne van Aubel

Center for Contextual Psychiatry, KU Leuven

Overall Symposia Abstract: Most mental health disorders already emerge at a young age and are preceded by an admixture of symptoms including anxiety, depression, and psychotic experiences, the latter of which may signal a heightened risk to develop a psychotic disorder later on. Although a large percentage of individuals fully recover from an initial mental disorder, relapse is common, the precedents of which are often noticeable early in advance. The current COVID-19 pandemic with its co-occurring challenges including social isolation and economic insecurity amongst many will most likely only increase adverse mental health

outcomes and further highlights the need for early interventions that are effective and sustainable while empowering patients to take their mental health into their own hands.
Digital health technologies provide new and innovative vistas to meet these needs. In this respect, Experience Sampling Method (ESM) applications are now gaining more popularity to help clinicians and patients get a more fine-grained insight into real-life patient-specific dynamics of symptoms, cognitions, mood, and stressors, insights that may ultimately facilitate the use of more adaptive coping strategies and improve illness self-management. What is more, these applications allow clinicians and patients to better understand the specific course of patients' mental states, identify early warning signs of relapse, identify triggers, and oversee the effects and side effects of psychotherapies and medication. In extension, Ecological Momentary Intervention (EMI) applications are often a combination of ESM as a clinical tool with personalized and targeted momentary psychotherapeutic messages and exercises to cope with stressors and symptoms. As such, EMIs allow patients to practice coping skills within the context of their daily lives, where it is needed the most, therefore bridging the therapy-real-world gap given that only ongoing practice in a real-world context will lead to sustainable and generalized results.

In this symposium, we will update the audience on four innovative applications of ESM and EMI as clinical tools in the prevention and treatment of severe mental illness including psychosis.

36.1 ECOLOGICAL MOMENTARY INTERVENTION (EMI) AUGMENTED TREATMENT FOR ULTRA HIGH RISK INDIVIDUALS

Matthias Schwannauer*[1]

[1]*University of Edinburgh*

Background: Ultra High Risk Mental States in relation to psychosis and common associated emotional distress, liked to depression and anxiety instability are a highly compromising condition characterised by significant social and developmental difficulties. Early identification of vulnerabilities is crucial, yet at risk mental states remain notoriously hard to identify and treat and long delays between onset and appropriate recognition and treatment are common.
Methods: We developed an interpersonally focused treatment (CIT) for individuals at risk of developing psychosis and following a first episode. In a case series design we randomised 40 individuals of both groups to CIT and CIT augmented with an app based momentary assessment and feedback tool. The paper will consider the feasibility of using an app based tool as an integral part of the intervention and its impact on efficacy and patient experience.
Results: Utilising longitudinal multi level models the results of this pragmatic RCT of CIT for adolescents at high risk of psychosis indicate that CIT augmented by EMI can be a highly effective treatment producing clear treatment effects on symptoms of mood related distress.
Conclusions: Augmentation of a structured psychological intervention with an EMI is a promising approach to enhance treatment effects and client engagement.

36.2 EFFICACY OF ACCEPTANCE AND COMMITMENT THERAPY IN DAILY LIFE (ACT-DL) IN EARLY PSYCHOSIS: FINDINGS FROM A MULTI-CENTRE RANDOMIZED CONTROLLED TRIAL

Inez Myin-Germeys[1], Evelyne van Aubel*[1], Thomas Vaessen[1], Henrietta Steinhart[2], Annelie Klippel[3], Tim Batink[3], Ruud van Winkel[4], Lieuwe De Haan[5], Mark Van der Gaag[6], Therese Van Amelsvoort[2], Machteld Marcelis[2], Frederike Schirmbeck[5], Ulrich Reininghaus[7]

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Background: Distress associated with psychotic experiences (PEs), global and social functioning, intensity of PEs, and intensity of psychopathology are important targets for early intervention in individuals with Ultra-High-Risk (UHR) for psychosis or First Episode Psychosis (FEP). Acceptance and Commitment Therapy (ACT) is a promising, next-generation Cognitive Behavioural Therapy (CBT) that aims to modify these targets, but evidence on sustainable change remains limited. The aim of the current study was to investigate the efficacy of a novel ecological momentary intervention, Acceptance and Commitment Therapy in Daily Life (ACT-DL) in a multi-center randomized controlled trial (RCT) of individuals with UHR or FEP.

Methods: In a multi-center RCT, individuals aged 16–65 years with UHR or FEP were randomly allocated to ACT-DL in addition to treatment as usual (TAU) as the experimental condition or a control condition of TAU only, which included – for the entire study period – access to routine mental health care. ACT-DL consisted of 8 face-to-face ACT sessions augmented with an ACT-based smartphone application that allowed participants to practice ACT skills in their daily lives by making use of questionnaires and ACT exercises, therefore bridging the therapy-real-world gap. Blinded assessors completed assessments at baseline, post-intervention, and at 6- and 12-month follow-up. The primary outcome was distress associated with psychotic experiences. Secondary outcomes were global (SOFAS) and social functioning (SFS), global intensity of psychopathology (BPRS total), and the intensity of positive (BPRS positive), negative (BPRS negative; BNSS total), affective (BPRS affective), and mania (BPRS mania) symptoms.

Results: We randomised n=148 participants from 11 sites to either the control (i.e. TAU; n=77) or the experimental condition (i.e. ACT-DL + TAU; n=71). There was no evidence of an effect of ACT-DL on the primary outcome. However, in comparison to TAU, individuals randomized to the experimental condition showed improved SFS scores at post-intervention (Δ=2.44; p=.045) and 6-month follow-up (Δ=3.67; p=.017), as well as improved SOFAS scores at post-intervention (Δ=4.68; p=.026), and at 6-month (Δ=6.26; p=.009) and 12-month (Δ=5.33; p=.031) follow-up. In addition, they showed improved BPRS total (Δ=-5.44; p=.001), BPRS affective symptom (Δ=-2.33; p=.005), BPRS negative symptom (Δ=-1.73; p=.003) and BNSS negative symptom (Δ=-7.96; p=.001) scores at 6-month follow-up as well as improved BPRS negative symptom scores at 12-month follow-up (Δ=-2.15; p=.002).

Conclusions: This is the first study to investigate the efficacy of an ACT-based EMI in early psychosis in a confirmatory multi-center RCT. Our findings suggest beneficial effects of ACT-DL on global psychopathology and functioning, and more specifically on affective and negative symptoms. Interestingly, these effects were evident at 6-month and, in part, 12-month follow-up, suggesting a gradual and (partially) sustained effect of ACT-DL in early psychosis.

36.3 THE EFFECTS OF A NOVEL TRANSDIAGNOSTIC ECOLOGICAL MOMENTARY INTERVENTION FOR ENHANCING RESILIENCE IN YOUTH AT-RISK FOR SEVERE MENTAL DISORDER

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[1]*Central Institute of Mental Health, University of Heidelberg*

Background: While most mental disorders emerge in youth, this is particularly evident for psychotic disorders, for which risk manifests already at a developmentally earlier stage in the form of subclinical psychotic experiences. These experiences often co-occur with anxiety, depression and mania, reflecting a transdiagnostic phenotype associated with a range of psychopathological outcomes. Elevated stress sensitivity is one of the most widely studied psychological mechanisms underlying psychotic and affective mental health problems. Thus, targeting this mechanism is a promising strategy for preventing future adverse outcomes. Compassion-focused interventions (CFIs) offer a wide range of innovative therapeutic techniques particularly amenable to being implemented as an Ecological Momentary Intervention (EMI) to enable youth to access interventions in a given moment and context in daily life. The current study aims to examine the clinical feasibility, candidate underlying mechanisms, and initial signals of efficacy of a novel ecological momentary intervention for improving emotional resilience to stress (EMIcompass) in help-seeking youth.
Methods: In an exploratory randomized controlled trial (RCT), youth aged 14-25 with current distress, a broad Clinical High At-Risk Mental State (CHARMS) or a first episode of a severe mental disorder will be randomly allocated to the EMIcompass intervention in addition to treatment as usual (TAU) or a control condition of TAU only. Primary (stress reactivity) and secondary candidate mechanisms (resilience, interpersonal sensitivity, threat anticipation, negative affective appraisals) as well as primary (psychological distress) and secondary outcomes (primary psychiatric symptoms, general psychopathology) will be assessed at baseline, post-intervention and 4-week follow-up.
Results: Overall, our findings indicate excellent feasibility based on successful recruitment (3:1 conversion rate from first contact to inclusion in the study), randomisation (all included participants randomized) and assessment of outcomes (completion rate, 100% at baseline, 95,5% at post-intervention, 97,5% at 4-week follow-up). Further, findings from our pilot study showed reduced stress reactivity, momentary negative affect, and psychotic experiences as well as increased positive affect at post-intervention and 4-week follow-up as well as reductions in psychotic, anxiety, and depressive symptoms of medium to large effect size.
Conclusions: The current study is the first to establish feasibility, evidence on underlying mechanisms, and preliminary signals of efficacy of a compassion-focused EMI in youth. If successful, a confirmatory RCT will be warranted. Overall, our approach has the potential to significantly advance preventive interventions in youth mental health provision.

36.4 EMPOWER: A FEASIBILITY CLUSTER RANDOMISED CONTROLLED TRIAL BLENDING SMARTPHONE TECHNOLOGY WITH PEER SUPPORT

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[11]*Monash University,* [12]*Australian Catholic University, School of Psychology, Melbourne,* [13]*La Trobe University*

Background: Relapse is a major factor determining outcomes for people with a diagnosis of schizophrenia. Early warning signs (EWS) frequently precede relapse and there is low-quality evidence to suggest an effect of EWS based interventions on hospitalisation and relapse. We therefore asked if it was feasible to deliver a study to investigate the effectiveness of a digital intervention to recognise and promptly manage EWS of relapse in schizophrenia with the aim of preventing relapse.
Methods: We conducted a multi-centre, two arm, parallel groups cluster Randomised Controlled Trial with 12 month follow-up in Glasgow, UK and Melbourne, Australia. Participants were service users over 16, had a diagnosis of schizophrenia spectrum disorder, and had a relapse within the previous two years. Carers were eligible for inclusion if nominated by an eligible service user. The EMPOWER Intervention enabled participants to daily monitor changes in their wellbeing using a smartphone, blended with peer support. Clinical triage of changes in wellbeing suggesting EWS was enabled through an algorithm. This algorithm triggered a check in prompt that the decision whether or not to trigger a relapse prevention pathway.
Results: The main outcomes were feasibility of the trial; feasibility, acceptability and usability of the intervention; and safety and performance. Our candidates for primary outcomes were relapse and fear of relapse. We recruited 86 service users, of whom 73 were randomised (42 to EMPOWER and 31 to Treatment as Usual (TAU)). Primary outcome data were collected for 84% of participants at 12 months. Feasibility data suggested that the app was easy to use and had a positive impact on motivations and intentions in relation to mental health. Actual app usage was high with 91% of users who completed the baseline period meeting our a priori criterion of acceptable engagement (>33%). We will also report outcome signals in terms of relapse, time to relapse and putative mechanisms of change.
Conclusions: A trial of digital technology to monitor EWS blended with peer support and clinical triage to detect and prevent relapse is feasible and safe.

37. CAN WE PREVENT PSYCHOSIS? EVIDENCE FOR RISK, PROTECTIVE AND MEDIATING FACTORS FOR PSYCHOTIC EXPERIENCES AND PSYCHOPATHOLOGY IN YOUTH

Mary Cannon

Royal College of Surgeons in Ireland

Overall Symposia Abstract: Prevention has been proposed as one of the “grand challenges” for global mental health and the dividends of prevention are potentially much greater for mental health than for physical health. The study of psychotic experiences in the general population has become a major paradigm in mental health research. Psychotic experiences are a relatively prevalent phenomenon, particularly in youth and are clustered with other psychopathology and poor functioning and are associated with a four-fold increased risk of later psychotic disorder and an increased risk of other mental disorders. Therefore they provide a promising target for preventive approaches. The ultimate aim of identification of young people at risk is to intervene to prevent mental disorder outcomes and we can do this by targeting known risk factors and by enhancing known protective factors.

The presenters in this symposium will take us through risk, protective and mediating factors influencing the association between psychotic experiences in youth and progression of psychopathology.

Johanna (Hanneke) Wigman (Groningen University, The Netherlands) will present results from the Mapping Individual Routes of Risk and Resilience (Mirorr) study which is an innovative design based on diaries kept over a period of 3 years by young people in in difference levels and stages of risk for psychosis. She found that the young people in more severe stages perceive the world around them in a more negative and stressful way and experienced greater need for support. This study points to building resilience and coping skills in young people as a potential protective mechanism in preventing progression to a higher level of risk for psychosis.

Colm Healy (RCSI University of Medicine and Health Sciences, Ireland) presents findings from the Growing Up in Ireland study showing that parent-child conflict and self esteem are key mediators of the bidirectional relationship between psychotic experiences and psychopathology in youth. Targeting the parent-child relationship and child self-esteem are likely to be fruitful avenues for preventing development of comorbid mental health disorders in young people who experience psychotic experiences.

Merete Nordentoft (Mental Health Centre Copenhagen, Denmark) will present results from The Danish High Risk and Resilience Study (VIA-7) – a study of 7 year old children with a family history of schizophrenia or bipolar disorder. She will show that children with a family history of psychosis report high rates of severe psychotic experiences, higher rates of other mental disorders and poorer functioning compared with control children and represent a group that would benefit from a targeted prevention approach.

Helen Fisher (Institute of Psychiatry, Psychology and Neuroscience, Kings College London) will focus on protective factors and will present results from the Environmental Risk Longitudinal Twin Study (E-Risk) showing that social support, a positive home atmosphere and higher levels of neighbourhood social cohesion were protective against childhood psychotic phenomena among polyvictimised youth. These findings could inform preventive interventions to reduce the emergence of psychotic symptoms in young people who have experienced adversity and trauma.

Finally, our discussant, Celso Arango (University of Madrid) will show how these findings give a blueprint to how to approach prevention in youth at-risk of psychopathology with a model of indicated and selective prevention in youth alongside general health promotion initiatives.

The symposium chairs (Mary Cannon, RCSI University of Medicine and Health Sciences) and Martin Rimvall (University of Copenhagen, Denmark) will then open up the discussion to the audience and the presenters to discuss how the field of psychosis can shift its focus to a public health approach and face up to the “grand challenge” of prevention for the sake of our youth and future generations

37.1 FACTORS OF RISK AND RESILIENCE IN INDIVIDUALS WITH DIFFERENT LEVELS OF RISK FOR PSYCHOSIS

Johanna Wigman*[1], Sara van der Tuin[1], Marijke Muller[1], Sanne Booij[1]

[1]*Groningen University*

Background: The clinical staging model states that psychosis develops gradually through subsequent stages of illness severity. However, questions remain regarding what drives progression to more severe stages. To investigate this, the Mapping Individual Routes of Risk and Resilience (Mirorr) study was designed.
Methods: Mirorr is an in-depth diary study that follows N=96 young adults aged 18-35 years for three years. Participants were divided across four subgroups that represent increasing levels of risk for psychosis. Subgroup 1 includes individuals from the general population and represents stage 0 (lowest risk). Subgroups 2, 3 and 4 are recruited in mental health care. Subgroups 2 and 3 both represent stage 1a (intermediate risk), and include respectively individuals receiving mental health care without (subgroup 2) and with (subgroup 3) psychotic symptoms. Subgroup 4 includes individuals who are at Ultra High Risk (UHR) for psychosis (highest risk). Cross-sectional data and 90-day daily diary data on psychopathology, well-being, psychosocial functioning, risk and protective factors were collected. Here, we describe how the subgroups (stages) differed regarding factors of risk and resilience at baseline.
Results: The four subgroups showed a nuanced profile of differences and similarities. Patterns of differences were not always linear or identical. Some differences were subgroups 1 and the other subgroups (suggesting differences between non-clinical and clinical populations), some between subgroups 1 and 2 on the one hand and subgroups 3 and 4 on the other hand (suggesting largest differences between those with and without substantial psychotic experiences) and some between subgroup 4 and the other subgroups (suggests specific patterns for those at UHR for psychosis).
With regard to factors of risk and resilience, no differences were found between the subgroups in the experience of social support, but rather in experienced need for support. In addition, the more severe subgroups experienced more negative and less positive daily events and rated positive events as less positive. This may suggest that the experience of daily hassles impacts more strongly on individuals in more severe stages. Resilience was also significantly lower in subgroup 2, 3 and 4, compared to subgroup 1. Finally, individuals in more severe subgroups reported more non-adaptive coping and individuals in less severe subgroups more adaptive coping. These results tentatively suggest that individuals in more severe clinical stages perceive the world around them in a more negative and stressful way and, additionally, feel less able to deal adequately with stressors.

Conclusions: As these results pertain to cross-sectional data, no conclusions regarding causality can be drawn. However, this study enables the characterization of clinical stages in terms of not only psychopathology and risk factors, but also in terms of well-being, protective factors and patterns of daily experiences. This is an important next step to understand the development of mental health problems in young people and could improve our identification of those at highest risk for developing (more severe) mental health problems.

37.2 WHAT MEDIATES THE LONGITUDINAL RELATIONSHIP BETWEEN PSYCHOTIC EXPERIENCES AND PSYCHOPATHOLOGY?

Colm Healy*[1], Mary Cannon[1]

[1]*Royal College of Surgeons in Ireland*

Background: Psychotic experiences (PEs) are common in early adolescence and are associated with both psychotic and non-psychotic psychopathology. However, not all adolescents with

PEs have subsequent psychopathology and vice-versa. To date, factors mediating the longitudinal relationship between PEs and psychopathology have been under-studied.
Aims: To investigate the bidirectional relationship between PEs and psychopathology in adolescence, 2) to investigate potentially malleable mediators of these relationships.

Methods: Data from two waves (age-13 and 17 years) of Cohort'98 of the Growing-Up in Ireland study were examined (n=6206). Using KHB-pathway decomposition, we investigated the following as potential mediators of the relationship between psychopathology and PEs: Parent-child relationship (conflict and positive), self-concept and child-peer relationship (alienation and trust). Supplementary counterfactual mediation and sensitivity analysis were conducted.
Results: Early adolescents with psychopathology had a two-fold increased odds of late adolescent PEs (Internalizing Problems: OR:2.03,95%CI:1.56-2.62; Externalizing problems: OR:1.99,95%CI:1.51-2.60). Parent-child conflict explained between 23-34% of the associations between internalizing and externalizing problems and subsequent PEs. Early adolescents with PEs had an increased odds of late adolescent psychopathology (Internalizing Problems: OR:2.01,95%CI:1.61-2.50; and Externalizing Problems: OR:1.70,95%CI:1.25-2.31). Self-concept alone accounted for 52% of the relationship between PEs and subsequent internalizing problems.
Conclusions: There is a bidirectional heterotypic relationship between psychopathology and PEs. Parent-child conflict and self-concept are important characteristics that account for a proportion of the relationship between PEs and psychopathology. Interventions targeting parent-child conflict in the context of psychopathology and self-concept in the context of PEs may assist in reducing the incidence of poorer outcomes.

37.3 PSYCHOTIC EXPERIENCES IN SEVEN-YEAR-OLD CHILDREN WITH FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER IN: THE DANISH HIGH RISK AND RESILIENCE STUDY – VIA 7; A POPULATION-BASED COHORT STUDY

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Background: We aimed, for the first time, to assess the occurrence of psychotic experiences (PEs) in a population of young children, all at the same age, with familial high risk of schizophrenia and bipolar disorder in comparison with controls. A priori, we hypothesized that children with children at familial high risk of schizophrenia (FHR-SZ) would report higher rates of PEs compared with controls and that children at familial high risk for bipolar disorder (FHR-BP) would report more PEs than controls, but lower than FHR-SZ. Furthermore, we

hypothesized that the occurrence of PEs would be associated with a higher prevalence of mental disorders and lower levels of functioning across the entire sample. In exploratory analyses, we aimed to investigate possible associations between PEs and mental disorders as well as level of functioning.
Methods: A cohort of seven-year-old children with FHR-SZ (N=199), FHR-BP (N=118) and controls (N=196) was recruited through Danish nationwide registers. Lifetime PEs were assessed through interviews using the psychosis section of the 'Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version' (K-SADS-PL). Lifetime DSM-IV diagnoses were ascertained through K-SADS-PL and the level of functioning of the children through 'Children's Global Assessment Scale'.
Results: Both children with FHR-SZ (OR=2.9, 95% CI=1.4-6.2, p=0.005) and FHR-BP (OR=2.9, 95% CI=1.3-6.7, p=0.011) had an increased risk of having experienced "severe" PEs compared with controls. In the overall cohort PEs were associated with any lifetime mental disorder, Attention-Deficit/Hyperactivity Disorder, anxiety disorders and a lower level of functioning.
Conclusions: The findings of a higher proportion of high risk children reporting PEs could represent an early manifestation of later more severe psychopathology or simply an unspecific transitory symptom. Future follow-up studies of this cohort will explore the predictive value of the occurrence of PEs at age seven.

37.4 PROTECTIVE FACTORS FOR PSYCHOTIC EXPERIENCES AMONG POLY-VICTIMISED CHILDREN AND ADOLESCENTS

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Background: Psychotic experiences, such as hearing voices, having visions and being extremely paranoid, are relatively common during late childhood and throughout adolescence and predict the development of schizophrenia and a wide range of other severe mental health issues and functional difficulties in adulthood. Therefore, it is important to prevent these early psychotic phenomena from emerging. Children and adolescents are significantly more likely to experience psychotic phenomena when they have been exposed to multiple forms of victimisation (poly-victimisation) but a substantial proportion of poly-victimised individuals do not develop such subclinical phenomena. This talk will explore the individual, family, and community-level factors that could explain why some of these high-risk youth appear to be protected from developing psychotic experiences.
Methods: Data are drawn from the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative cohort of 2232 twins born in 1994 and 1995 across England and Wales and followed to age 18 (with 93% retention). Exposure to different types of victimisation between 0-12 years was assessed during childhood using caregiver and child reports, researcher observations and social services' referrals, and at age 18 participants were interviewed using a modified version of the Juvenile Victimisation Questionnaire about victimisation experiences occurring between 12-18 years. Private interviews with participants were conducted at ages 12 and 18 regarding psychotic experiences. Multi-level putative protective factors were measured at ages 5, 7, 10, 12 and 18.
Results: Exposure to poly-victimisation during childhood (OR=4.61, 95% CI 2.82–7.52) and adolescence (OR=4.62, 95% CI 3.59-5.94) was associated with psychotic experiences, but a sizeable proportion of poly-victimised youth reported having no psychotic experiences (childhood: 80.7%, adolescence: 40.1%). Having a relatively high IQ, a more positive

atmosphere at home, and higher levels of neighbourhood social cohesion were found to be protective against childhood psychotic phenomena among poly-victimised children and also in the whole sample. Greater social support was found to be protective against adolescent psychotic experiences among those exposed to poly-victimisation. Notably, social support was also generally associated with a reduced likelihood of adolescent psychotic experiences in the whole sample (along with engaging in physical activity and greater neighbourhood social cohesion).
Conclusions: Protective factors for early psychotic experiences were identified across multiple levels among high-risk poly-victimised youth, though these also appeared to be protective among unexposed youth. If replicated, these findings could inform early intervention efforts to prevent the emergence of psychotic phenomena and subsequently prevent severe mental health issues and functional difficulties in adulthood.

Plenary Session

38. TYPICAL BRAIN DEVELOPMENT DURING PRENATAL AND EARLY LIFE AND PATHWAYS TO PSYCHOTIC DISORDERS: A POPULATION-BASED PERSPECTIVE

Merete Nordentoft
Mental Health Centre Copenhagen

Overall Abstract: Schizophrenia and bipolar disorder are among the most costly and debilitating disorders both in terms of personal suffering for those affected, for the relatives and the society. Identifying disease mechanisms and possibilities for prevention before onset of illness will therefore be extremely valuable. As schizophrenia and bipolar disorder are rare in the general population, very large sample sizes or studies of enriched populations such as clinical high risk groups or children with familial risk of these disorders can be fruitful and provide insight into the early disease processes. Structural and functional brain changes are present in drug naïve adult patients with schizophrenia, and some of the strongest risk factors exert their influence already in the pre- or perinatal period. It is hypothesized that brain changes start developing during fetal life, childhood and adolescence, but repeated structural and functional MR scans of a large groups have never been carried out before. MR scans before, during and for many individuals after puberty will permit us to study brain development during these crucial periods in a coherent approach, and in some cases even during early disease formation, and combine it with very good clinical data.

38.1 TYPICAL BRAIN DEVELOPMENT DURING PRENATAL AND EARLY LIFE AND PATHWAYS TO PSYCHOTIC DISORDERS: A POPULATION-BASED PERSPECTIVE

Tonya White
Erasmus University Medical Centre

Individual Abstract: The core symptoms of schizophrenia typically emerge during late adolescence and early adulthood and there is considerable evidence that the emerging symptoms are nested within neurodevelopment processes that take place earlier in

development. However, many questions remain regarding at what stage during typical brain development do the deviations take place in those who begin showing prodromal or more severe symptoms of schizophrenia. Large population-based studies provide the opportunity to study trajectories of brain development, including premorbid and early prodromal measures of brain structure and function. The goal of this presentation is to provide an overview of the neuroimaging and behavioral component of the Generation R Study, which is a large epidemiological study of child development. The role of population-based neuroimaging studies in better understanding emerging psychopathology will be discussed. In addition, there will be a focus on typical development during fetal and early life and one potential pathway to the development of psychotic disorders that could potentially be translated into primary prevention. Put on your seat belt for this talk, it'll be fun.

Plenary Session

39. BRIDGING IMPLEMENTATION SCIENCE AND LEARNING HEALTHCARE IN EARLY PSYCHOSIS TREATMENT SYSTEMS

Neeltje Van Haren

Erasmus Medical Centre, Rotterdam, Netherlands

Overall Abstract: This session truly aligns with the theme of this year's meeting "Bringing Precision Medicine to Mental Health Services". Both presentation focus on how evidence based research findings can find their way to outside of the academic research clinics, to reach surrounding communities. Dr. Dixon will discuss successful strategies and pitfalls of how implementation science can help a statewide adoption of an evidence based early psychosis program in New York State. Dr. Heinssen will introduce the concept of learning healthcare and the Early Psychosis Intervention Network (EPINET). These initiatives show the power of working together – researchers, clinicians, service users and their families – and standardization to improve health care and stimulate research.

39.1 MOVING EARLY PSYCHOSIS INTERVENTION FROM RESEARCH TO ON-THE-GROUND COMMUNITY PRACTICE

Lisa Dixon

NYSPI/Columbia University Medical Center

Individual Abstract: Evidence-based interventions for early psychosis are common in many countries, with several examples of long-standing and evolving programs. Until recently, such programs in the United States were limited mostly to academic research clinics, with limited reach into surrounding communities. Starting in 2014, increased federal funding promoted research-based interventions for early psychosis in public health settings. This presentation will describe the pathway from implementation research to statewide adoption of an early psychosis program in New York State. It will describe how an intermediary organization can utilize the principles of implementation science to inform efforts to scale a complex evidenced based practice. It will also discuss successful strategies and barriers to building partnerships with service users, clinicians, and administrators to establish a new culture of care. Successful

strategies and barriers to the collection of data and its use in routine care and quality improvement to evaluate program effectiveness and drive quality improvement across sites will be described. Finally, it will present some examples of how this approach contributes to research in the care of individuals with early psychosis.

39.2 CULTIVATING A NATIONAL LEARNING HEALTHCARE NETWORK IN EARLY PSYCHOSIS INTERVENTION

Robert Heinssen

National Institute of Mental Health

Individual Abstract: In 2015 the Institute of Medicine introduced the concept of learning healthcare where "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience." Four year later, the National Institute of Mental Health established the Early Psychosis Intervention Network (EPINET), the first large-scale learning healthcare system for persons with serious mental illness in the United States. EPINET followed the rapid expansion of evidence-based interventions for first episode psychosis in the US, with over 300 programs operating nationwide. This presentation describes how EPINET stakeholders – researchers, service users, family members, front-line clinicians, and administrators – are working together to implement learning healthcare principles across 100+ early psychosis clinics. It will highlight key innovations that promote learning healthcare, including (1) standard clinical measures that balance rigor and practicality; (2) uniform data collection as part of routine care; (3) systematic analysis of pooled data for quality improvement purposes; and (4) research embedded in care delivery to address gaps in knowledge. It will explain how health informatics and data science expertise in the EPINET data coordinating center will identify best practices across eight regional hubs, explore precision medicine strategies for personalizing services, and promote scientific exchange among research studies operating on the platform. Finally, it will discuss opportunities for aligning EPINET with similar international efforts that aspire to high quality, continuously improving, and sustainable mental health care.

Concurrent Symposia

40. RACIAL DISPARITIES IN FUNCTIONAL OUTCOMES AMONG INDIVIDUALS WITH PSYCHOTIC DISORDERS

Michael Green

University of California, Los Angeles

Overall Symposia Abstract: Racial differences in the prevalence of psychotic disorders, expression of psychotic symptoms, and pathways to treatment have been well-documented internationally. Due to structural racism and other forms of disadvantage that racial minorities encounter, it is important to consider race when studying functional outcomes in psychosis. However, we know remarkably little about racial disparities in functional outcomes among individuals with psychotic disorders. For example, we do not know how these differences may manifest across various types of functional outcomes (e.g. social versus vocational). Further, we do not know whether the predictors and determinants of functional outcomes (such as nonsocial cognition, social cognition, and motivation) vary by race. At a time of heightened

awareness of racial health disparities across society, it is imperative that we take a race-conscious approach in understanding functional outcomes for psychotic disorders.
The goal of this symposium is to bring together investigators from multiple cities and countries who have examined racial differences in functional outcomes in the psychosis spectrum. All four presenters in this symposium are early-career researchers, all are people of color, and three of them are women.

Dr. Das-Munshi will present data from a large electronic health records cohort (about 20,000 patients) from the United Kingdom to examine associations between race with periods of unemployment after a schizophrenia spectrum or bipolar disorder diagnosis. She will describe a novel text-mining machine learning approach to identify indicators of employment within the health records that differ between Black Caribbean and White British participants.

Dr. Nagendra will present findings from a study of race and domains of functioning in a sample of 108 non-Hispanic Black and 61 non-Hispanic White individuals with schizophrenia spectrum disorders. Among the findings are that Black participants showed lower scores than White participants on measures of non-social cognition, social cognition, and functional capacity, but interestingly not on a measure of community functioning. Analyses indicated that neighborhood socioeconomic status explained 21% of the relationship between race and non-social cognition. Additional models with race as a moderator were evaluated.

Dr. Novacek will present findings from an ongoing prospective study of the effects of the COVID-19 pandemic on clinical and functional outcomes in Black and White U.S. Veterans with psychotic disorders and a comparison group. The findings so far indicate no significant differences between Black and White Veterans in terms of psychiatric symptoms, risk/protective factors, or functional outcomes within the psychosis or comparison group, perhaps due to supports that Veterans receive. However, there were correlations between symptoms and risk factors and functional outcomes that were specific to Black Veterans with psychosis.

Ms. He will present findings from a study on first-episode psychosis. The focus of this study is to identify sociodemographic disparities in duration of untreated psychosis and functional outcomes in a first-episode sample. Key demographic variables to be discussed will include immigrant generational status, race/ethnicity, gender, and socioeconomic status.

The discussant will be Sir Robin Murray who will provide a broad perspective on the presentations based on his many years of examining racial differences in psychotic disorders in the United Kingdom.

40.1 RACE/ ETHNIC INEQUALITIES IN PERIODS OF UNEMPLOYMENT FOR PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS: A LARGE-SCALE SURVEY OF ELECTRONIC HEALTH RECORDS FROM LONDON, UK

Jayati Das-Munshi*[1], Natasha Chilman[1]

[1]*Institute of Psychiatry, Psychology & Neuroscience, King's College London*

Background: Unemployment rates remain high for those with schizophrenia and bipolar affective disorders (severe mental illnesses), which have significant individual and societal impacts. Retaining competitive employment may also be an important indicator of recovery and social inclusion. Therefore, it is important to understand predictors of unemployment for

people with severe mental illnesses, however previous research has often been limited to small samples with little exploration of inequalities due to race/ ethnicity.
The objective of this study was to investigate the sociodemographic and clinical predictors of unemployment in patients with severe mental illness, with a focus on race/ ethnicity.

Methods: Electronic health records from South London & Maudsley Trust, a near-monopoly provider of secondary mental health care services to a catchment of 1.3 million people resident in a diverse urban area in southeast London, UK, were used for the analyses. We created a cohort of people with severe mental illnesses (schizophrenia-spectrum and bipolar affective disorders according to International Classification of Mental and Behavioural Disorders-10 (ICD-10)), who were followed up from time of diagnosis after 2007 until 30th July 2019. Sociodemographic and clinical data were extracted from de-identified electronic health records. Health records generally lack information on employment status, however to deal with this, we used a validated Natural Language Processing (NLP) text-mining algorithm to successfully identify mentions of unemployment and employment from the free text in the records. Patients were split into two groups: patients who had experienced unemployment, and patients who had only been employed. We assessed the association of race/ ethnicity and other clinical/ demographic associations with periods of unemployment in the cohort using multivariable logistic regression approaches.
Results: A total of 19,768 patients formed the basis of analysis in the cohort, contributing a median time of 4,969 days (13.6 years) (IQR: 3407, 6620 days) to the cohort. Consistent with previous evidence, the majority had experienced unemployment at least once (16,788; 84.87%). Results of logistic regression analyses showed that compared to White British patients, Black Caribbean patients had a significantly higher odds of experiencing unemployment (OR 1.99, 95% CI 1.80-2.20). After adjustment for age, gender, marital status, deprivation, diagnosis (affective/non-affective), age at diagnosis, and inpatient bed days, this association was reduced (aOR 1.33, 95% CI 1.19-1.49). We also found that patients were more likely to experience unemployment if male, single or divorced, and if living in areas of higher deprivation, diagnosed with a non-affective disorder, or diagnosed with severe mental illness at a 'working' age (<64 years). Patients with at least one psychiatric hospital admission were more likely to have experienced unemployment compared to patients with no admissions (aOR 4.20, 95% CI 3.72-4.73). Patients who had been involuntarily detained were also more likely to have experienced unemployment (aOR 3.60, 95% CI 3.16-4.09).
Conclusions: We utilised novel text-mining methodologies which enabled assessment of periods of unemployment, in a large cohort of patients with severe mental illness. Black Caribbean patients were more likely to have experienced unemployment compared to White British patients over the observation window. In future work, mediators of this association will be explored to inform the development of potential interventions.

40.2 NEIGHBORHOOD SOCIOECONOMIC STATUS AND RACIAL DISPARITIES IN SCHIZOPHRENIA: AN EXPLORATION OF DOMAINS OF FUNCTIONING

Arundati Nagendra*[1], Tate F. Halverson[2], Amy E. Pinkham[3], Philip D. Harvey[4], L. Fredrik Jarskog[5], Amy Weisman de Mamani[6], David L. Penn[7]

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Background: Black Americans diagnosed with schizophrenia experience worse objective functional outcomes than their White counterparts, as indexed by rates of hospitalization, homelessness, incarceration, and employment. However, we have a limited understanding of the pathways through which Black Americans with schizophrenia reach worse objective outcomes. This study evaluates domains of functioning known to be associated with long-term outcomes, including (a) social and community functioning (e.g., interpersonal relationships, work skills); (b) neurocognition (NC); (c) social cognition (SC); (d) social skills; and (e) everyday living skills (i.e., "functional capacity"). These domains have been studied extensively in schizophrenia research and may be more amenable to direct intervention than distal outcomes like hospitalization and incarceration. Thus, this study had three aims. First, we evaluated whether there are Black-White racial differences in measures of NC, SC, social skills, social and community functioning, and everyday living skills. Second, prior research has established that NC, SC, social skills, and everyday living skills predict community functioning in individuals with schizophrenia. We evaluated whether the relationships between these domains are comparably strong across Black and White Americans. Third, we examined the extent to which individual and neighborhood socioeconomic status (SES) explained observed relationships between race and functioning.
Methods: This was a secondary data analysis of the Social Cognition Psychometric Evaluation (SCOPE) study. The sample consisted of 108 non-Hispanic Black and 61 non-Hispanic White individuals with schizophrenia-spectrum disorders (mean age = 43.11 years, SD = 11.65). Domains of functioning were assessed with established role-play tasks, cognitive tests, and informant ratings. Individual SES was measured through participant education, and neighborhood SES was assessed using a geocoded composite of neighborhood income, education, and employment. Study hypotheses were evaluated with MANOVA, mediation, and moderation analyses.
Results: First, Black participants showed lower scores than White participants on measures of NC, SC, and everyday living skills, but not social skills or community functioning. Second, neighborhood SES explained 21% of the relationship between race and NC, but did not mediate the relationship between race and SC or everyday living skills. Finally, race did not moderate the relationships of NC, SC, social skills, or everyday living skills to community functioning.
Conclusions: Our findings suggest that NC, SC, and everyday living skills may be important domains to explore in regard to racial disparities in schizophrenia, especially given that they predicted functioning comparably in Black and White Americans. Moreover, neighborhood characteristics may be a valuable avenue for understanding why disparities emerge, especially for NC. Regardless, even after considering individual education, and accounting for neighborhood income, employment, and education, the majority of the relationship between race and NC remained unexplained. Moreover, neighborhood SES did not mediate the relationship between race and SC or everyday living skills. More research, especially incorporating nuanced race- (e.g., experiences of racism) and SES- (e.g., education quality) related variables, is needed to understand how to best intervene and improve real-world outcomes for Black Americans with schizophrenia.

40.3 FUNCTIONING, PSYCHIATRIC SYMPTOMS, AND RISK/PROTECTIVE FACTORS AMONG BLACK AND WHITE U.S. VETERANS WITH AND WITHOUT PSYCHOSIS IN THE COVID-19 PANDEMIC

Derek Novacek*[1], Michael Green[1], Amanda Mccleery[2], Jonathan Wynn[1], Eric Reavis[1]

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Background: The coronavirus disease (COVID-19) pandemic has had disproportionate effects on Black Americans in terms of higher rates of infection and mortality. These disparities occur in the context of systemic inequities in healthcare, employment, housing, and education. The disproportionate impact on Black Americans could have significant consequences in terms of psychiatric symptoms and functional outcomes for already vulnerable populations such as Veterans with psychosis. The present study examined whether there were racial differences in functional outcomes, psychiatric symptoms, and risk/protective factors between Black and White Veterans with and without psychosis during the COVID-19 pandemic. Correlations between psychiatric symptoms, risk/protective factors, and functional outcomes were also examined.
Methods: Participants were recruited through VA administrative databases and by contacting Veterans who have participated in previous studies. Participants were administered self-report questionnaires and interviews over the phone by trained research staff. The sample consisted of 46 Black Veterans and 26 White Veterans with a psychotic disorder diagnosis as well as 30 Black Veterans and 37 White Veterans without psychosis. Participants were administered self-report measures of depression, anxiety, paranoia, loneliness, perceived stress, coping, and resilience. Clinician-rated measures of social/role functioning and independent living/self-care were also conducted. Data was collected from mid-May through mid-August of 2020.
Results: There were no significant differences between Black and White Veterans in psychiatric symptoms, perceived stress, coping strategies, and functioning within either group. Within the psychosis group we found some correlations that were specific to Black Veterans with psychosis, that is, generalized anxiety symptoms were associated with more impairment in relationships with family and independent living, higher perceived stress was associated with worse work integration, and higher levels of paranoia and defeatist beliefs were associated with worse relationships with friends. For White Veterans with psychosis, motivation and pleasure were correlated with better relationships with friends and family.
Conclusions: There were no significant differences in functioning between Black and White Veterans with or without psychosis. The findings suggest that the wrap-around services offered by the Veterans Health Administration mitigate racial disparities in psychiatric and functional outcomes one might expect given the disparities in COVID-19. There were, however, differential associations between functioning and both psychiatric symptoms and risk/protective factors that have implications for treatment throughout the pandemic. Given that these data were collected towards the early stages of the COVID-19 pandemic in the United States, it will be important to investigate whether or not racial disparities emerge as the pandemic unfolds.

40.4 RACIAL DISPARITIES IN DUP AND FUNCTIONAL OUTCOMES IN A U.S. SAMPLE

Emily He*[1], Emily Kline[2], Esteban V. Cardemil[1], Matcheri Keshavan[2], Vinod Srihari[3]

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Background: Early intervention with psychosis specialty care can support positive long-term functioning by addressing modifiable prognostic factors such as reducing symptom relapse, substance misuse, social withdrawal, cognitive decline (Barder et al., 2013; Green, Kern, & Heaton, 2004), and reducing duration of untreated psychosis (DUP) (Correll et al., 2018; Melle et al., 2004). Even for those admitted to psychosis specialty care, data from a U.S. early

intervention clinic showed that about 50% of individuals had a DUP longer than 3 months, 60% dropped out of school or work, 45% had a substance use disorder, and 10% had attempted suicide (Srihari et al., 2014).
Examination of disparities by race/ethnicity and immigrant status may be especially fruitful since immigrants from countries where the population is predominately Black are at elevated risk for developing psychosis (Cantor-Graae & Selten, 2005). Social adversity may contribute to elevated psychosis risk for racial/ethnic minorities and immigrants (Cantor-Graae & Selten, 2005; Morgan et al., 2010). Following psychosis onset, racial/ethnic minorities and immigrants may further experience treatment disparities, increasing risk for poor outcomes and treatment disengagement (Martin et al., 2018; Anderson et al., 2014; Leclerc et al., 2015; Penttilä et al., 2014; Schimmelmann et al., 2008). The current study will identify sociodemographic disparities in DUP and functional outcomes in a U.S. First Episode sample. Key variables include race/ethnicity, immigrant status, gender, and income. Outcome variables include DUP, social functioning, role functioning, and symptom severity/impairment.

Methods: Participants were young adult and mostly male. Black/African/Caribbean participants made up the largest racial/ethnic group in the sample followed by White/European. Less than a quarter of the sample were immigrants to the U.S. Participants were receiving outpatient treatment in one of two early intervention clinics in the Northeastern U.S. Exclusion criteria for the study were: affective psychosis, psychosis secondary to substance use or a medical illness, unable to communicate in English, eligibility for the U.S. Department of Developmental Services, legal mandate to enter treatment, and unstable medical illness. Outcome measures include: Global Functioning Social and Role Scales (Cornblatt et al., 2007); Global Assessment of Functioning (DSM-IV-TR); DUP-Med (endpoint as adequate medication adherence); DUP-Service (endpoint as admission to specialty care).
Results: Planned analyses will include: the impact of race/ethnicity, immigrant status, age, gender, and income on the relationship between functioning and duration of untreated psychosis.
Conclusions: Findings from the current study will have implications for tailoring early intervention practices targeted to groups disproportionately affected by access and treatment disparities.

41. CURRENT STATUS OF MODEL/HYPOTHESIS-DRIVEN RESEARCHES OF SCHIZOPHRENIA IN THE AGE OF RDOC

Jun Miyata
Kyoto University

Overall Symposia Abstract: Schizophrenia has been believed to be heterogeneous. Meanwhile, diagnosis of psychiatric disorders including schizophrenia has been made upon operational diagnostic systems such as Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD), which are based on subjective symptoms and observable signs. However, biological research evidence such as genetic overlap among multiple psychiatric disorders including schizophrenia, bipolar disorder, and autism, casts doubt about the validity of such diagnostic systems.
Arising from these backgrounds, the National Institute of Mental Health (NIMH) has developed the Research Domain Criteria (RDoC), based on current neuroscience research findings. RDoC consists of a matrix of 6 research domains (Negative and Positive Valence

Systems, Cognitive Systems, etc) and 8 units (levels) of research (Genes, Circuits, Behaviors etc). By applying data-driven approach to data from studies based on this matrix, RDoC aims to reconstruct psychiatric diagnostic framework (Insel and Cuthbert, Science 2015). In agreement with this move, the Society for Neuroscience has changed its annual meeting themes since 2016: theme C has been changed from "Disorders of the Nervous System" to "Neurodegenerative Disorders and Injury", and psychiatric disorders are classified as subcategories of other themes such as "Motivation and Emotion" and "Cognition".

Then, what is the importance and current status of pathophysiological hypothesis/model-driven researches of schizophrenia, as opposed to data-driven approach, in the age of RDoC? In this symposium, young and mid-carrier researchers, who are vigorously conducting hypothesis/model-driven studies of schizophrenia, will present their latest findings. Their theme and approaches are diverse: Jun Miyata, the first speaker and chair of this symposium, will talk about extension of aberrant salience hypothesis, which was first described by Kapur (2003). Ana Pinheiro will give a talk about forward model of hallucination. Andreea Diaconescu will explain her computational model to integrate theory of mind deficit in schizophrenia and persecutory delusion. And Alan Anticevic will mention to excitation-inhibition balance and functional MRI (fMRI). Finally, Akira Sawa will close the symposium with overall discussion.

Through this symposium, we aim to shed light on the importance of pathophysiological hypothesis/model-based researches, as building blocks to reconstruct RDoC itself. This is already happening: RDoC is reformed to consist of 6 domains in 2019, from former 5 domains.

41.1 EXTENDING ABERRANT SALIENCE HYPOTHESIS OF PSYCHOSIS

Jun Miyata*[1]

[1]*Kyoto University*

Background: The midbrain-striatum dopamine neurons are known to code salience of stimuli. In psychosis, hyper-dopaminergic state of the striatum is considered to cause aberrantly heightened salience attribution to daily-life stimuli, leading to formation of delusion and hallucination (aberrant salience hypothesis: Kapur, 2003). Increasing evidence shows that the medial temporal lobe (MTL) structures drive this striatal hyper-dopaminergic state. Separately, neuroimaging studies have revealed that the insular-anterior cingulate cortex salience network (SN) is underlying the processing of stimulus salience (Seeley et al, 2007). The relationship between these two mechanisms and its impact in different stages of psychosis remained unclear.

Meanwhile, delusion is one of the most cardinal symptoms of psychosis, found in approximately 95% at their first episode (Lemonde et al, 2020). People with delusions and/or schizophrenia are known to need less amount of evidence for decision making compared with healthy people. This cognitive bias is called as the jumping to conclusions (JTC) bias (Garety et al, 1991). On the other hand, healthy people's decision making is known to be conservative, needing more amount of evidence than rational reasoning expects. This tendency is called as the conservatism bias (Phillips and Edwards, 1966). The neural correlates of JTC and conservatism bias, and their relationship with aberrant salience were unclear.

Further, salience processing is not limited to the MTL-midbrain-striatum system and the SN, and visual and auditory salience has been extensively studied, in separate background. From an evolutionary psychological point of view, it was unlikely that these different salience systems exist independently, but rather likely that they interact each other.

We tried to answer to these three questions using structural and functional connectivity analyses.

Methods: For the first question, we used resting-state functional magnetic resonance imaging (rsfMRI) of the ultra-high risk (UHR), first episode (FEP) and chronic schizophrenia (ChrSZ) people. We used functional connectivity analysis to investigate the association between the MTLN-midbrain-striatum system and the SN and psychopathology.
For the second question, we used structural, diffusion and rsfMRI data as well as probabilistic reasoning task to investigate the association between structural and functional connectivity and JTC/conservatism bias.

For the third question, we used functional connectivity analysis of rsfMRI to investigate the association among 4 different salience systems.

Results: For the first question, we revealed that 1) the midbrain-striatum dopaminergic network and the two networks are functionally connected, and 2) their abnormalities were associated with diagnosis and positive symptom severity, most prominently in the early stages of psychosis, and 3) correlation between connectivity and positive symptom was ameliorated by medication.
For the second question, we revealed that 4) reduced/increased structural and functional connectivity of the default mode network and the striatum was associated with JTC/conservatism bias, respectively.

For the third question, we preliminarily revealed that 5) these four salience systems tended to co-fluctuate.

Conclusions: Our series of data provide a novel view of psychosis, extending aberrant salience hypothesis.

41.2 CEREBELLAR CIRCUITRY IN AUDITORY VERBAL HALLUCINATIONS

Ana Pinheiro*[1]

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Background: Auditory verbal hallucinations (AVH) - experienced as voice hearing independent of a corresponding external sound source - are a cardinal symptom of psychosis. AVH are transdiagnostic as they feature in other psychiatric (e.g. bipolar disorder) and neurological disorders (e.g. epilepsy), as well as in 6-13% of the general population without need for psychiatric care. Despite many efforts to explain this puzzling phenomenon, the neural substrates of AVH remain largely elusive. One influential hypothesis claims that AVH result from altered sensory feedback, a central concept in theories of cerebellar function. However, research utilizing multiple neuroimaging methods has rendered results on the specificity of cerebellar contributions to AVH unclear.
Methods: To examine the reliability and regional specificity of cerebellar changes in AVH, a systematic search of electronic databases was conducted to identify a broad range of cerebellar neuroimaging studies in psychotic patients or nonclinical participants. Twenty-six studies were selected. The consistency of cerebellar changes and their relationship with sociodemographic and clinical measures were meta-analyzed. Activation Likelihood Estimate analysis (ALE)

examined the reported coordinates for reduced vs. increased volume, fractional anisotropy, or connectivity.
Results: A random-effects model with small sample size correction identified consistent changes in cerebellar connectivity in participants with AVH, which were not moderated by age, sex, medication, or symptom severity. The ALE meta-analysis revealed opposite change patterns in anterior (decreased vol-ume/connectivity) and posterior (increased volume/connectivity) cerebellar lobes. A regional pattern of preferential affectedness showed more consistent effects of AVH on Lobule V and Crus I.
Conclusions: Connectivity changes in the cerebellum might indicate a specific liability for AVH, particularly in sensorimotor (lobule V) and cognitive (Crus I) zones. Cerebellar dysconnectivity may contribute to altered sensory feedback and, consequently, to aberrant prediction in AVH, suggesting operational changes in the forward model.

41.3 COMPUTATIONAL MODELS OF PERSECUTORY IDEATION IN EARLY PSYCHOSIS

Andreea Diaconescu*[1], Daniel Hauke[2], Michelle Wobmann[2], Stefan Borgwardt[3]

[1]*Centre for Addiction and Mental Health, University of Toronto,* [2]*University of Basel,* [3]*University of Lübeck*

Background: Schizophrenia is a severe mental illness characterised by psychosis symptoms including hallucinations and delusions. These symptoms constitute a severe burden for the individual as they are associated with diminished levels of social functioning and drastic reductions in life expectancy. A recent approach to treatment of schizophrenia has focused on early detection and prevention in individuals considered to be at clinical high risk (CHR) for developing psychosis. Prevention treatment is however particularly challenging because even when risk of transitioning to psychosis is quantified, there are no clinical tests to guide treatment. To overcome this challenge, we propose a computational modelling framework that employs immersive probabilistic learning tasks targeting persecutory ideation - beliefs that others are deliberately intending to cause harm - in adults at risk of developing psychosis and first episode psychosis patients (FEP).
Methods: Using an advice-taking task to examine persecutory beliefs, we invited participants to perform a binary lottery as they were given advice from a more informed agent (the adviser) about which options to choose. In order to perform well, participants not only had to predict the accuracy of advice, but also the adviser's intentions. Three groups of participants were recruited via a specialised service dedicated to early detection and intervention in Basel (Basel Early Treatment Service, BEATS). These included (i) clinical high-risk of psychosis individuals (N = 15, mean age 23 ± 2 years) according to the at-risk criteria based on the the Structural Interview for Prodromal Syndromes (SIPS), (ii) FEP patients (N = 13, mean age 24 ± 3 years), and (iii) healthy controls (N = 19, mean age 22 ± 2 years) matched for age, gender, and cannabis consumption. We applied a set of computational models to explain participants' trialwise behaviour and examined possible reasons for group differences in advice-taking behaviour. The model space consisted of four model families: (i) the hierarchical Gaussian filter (HGF), (ii) a mean-reverting HGF which included Ornstein-Uhlenbeck process in discrete time, (iii) a non-hierarchical Bayesian model, and (iii) a Rescorla-Wagner reinforcement learning model.
Results: Persecutory ideation in patients was associated with reduced learning about changes in intentions. We observed reduced effects of volatility on advice-taking behaviour in FEP compared to CHR and control individuals ($F = 3.11$, $p = 0.05$). Furthermore, we identified the mean-reverting HGF as the winning model representing participants' behaviour. The group

differences in advice-taking behaviour were explained by an increased perception of the volatility of intentions in CHR and FEP patients compared to controls ($F=3.84$, $p = 0.03$).
Conclusions: In comparison to controls, FEP patients show disruptions in advice-taking as a function of volatility. Both CHR individuals and FEP patients exhibit an increased perception of contextual change (i.e., volatility) leading to aberrantly large learning rates and belief updating about the adviser's fidelity, even when the advice is helpful and stable. These findings may provide the basis for the development of cognitive assessments using mobile probabilistic learning tasks for early psychosis prevention.

41.4 MAPPING BRAIN-BEHAVIORAL RELATIONSHIPS FROM A LOW-DIMENSIONAL SYMPTOM GEOMETRY FOR PERSONALIZED PATIENT SEGMENTATION

Alan Anticevic*[1], Jie Lisa Ji[1], Joshua Burt[1], Clara Fonteneau[2], John Krystal[3], John Murray[1]

[1]*Yale University,* [2]*Centre Hospitalier Le Vinatier,* [3]*Yale University School of Medicine*

Background: Mental illness is still diagnosed at the syndrome-level, which imposes limits for quantifying symptom-relevant - and therefore neural - individual variation. Continued failed attempts to rationally develop therapies for specific patients underscores a neuro-behavioral mapping knowledge gap in psychiatry, particularly apparent along the 'psychosis' spectrum disorders (PSD).
Methods: We characterized 436 PSD patients across measures of psychosis and cognition, along with 202 healthy controls. We discovered and replicated a data-driven low-dimensional PSD symptom space, which captures variation across both psychosis, mood and cognitive symptoms. Next, using resting-state fMRI, we show how this reduced symptom variation reveals a novel, replicable and individually stable neural mapping, which could not be captured by a priori clinical assessments or categorical diagnoses.
Results: We show that recent multivariate solutions lack the power for personalized behavioral-to-neural prediction. We developed an optimized univariate neuro-behavioral mapping, explicitly leveraging reduced symptoms dimensionality, which replicated at the single patient level. In turn, we related stable individual neuro-type profiles (NTP) with molecular neuro-pharmacological maps quantifying serotonin (via LSD) and glutamate NMDA (via ketamine) manipulation. Finally, using the Allen Human Brain Atlas (AHBA) gene transcriptome maps, we quantified NTP spatial patterns with neural gene expression implicated in PSD (i.e. serotonin, GABA and interneuron transcripts).
Conclusions: Collectively, these results highlight a novel, symptom-optimized and replicable neuro-behavioral mapping along the psychosis spectrum, which cuts across traditional psychiatric diagnoses and "biotypes" that are unanchored in symptom variation. This opens an actionable path, at a single patient level, that can be quantitatively optimized for rational therapeutic selection and design.

42. DIGITAL MENTAL HEALTH IN EARLY INTERVENTION FOR PSYCHOSIS

Charlotte Gayer-Anderson

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Overall Symposia Abstract: Digital technology presents us with new opportunities to deliver services for individuals with psychosis, or those at risk of developing psychosis, differently, hopefully enabling more people to access the treatment and support they need. This symposium

will present the outcomes of four trials, all of which capitalise on digital technologies (smartphone applications, online social media therapy, virtual reality assisted therapy) to improve clinical and functional outcomes in individuals with psychosis.
Inez Myin-Germeys will present the results from two randomised trials to test the feasibility and implementation of a newly developed mobile health intervention, 'ACT in Daily Life (ACT-DL)', which uses an Experience Sampling (ESM) app to improve real-world delivery of Acceptance and Commitment Therapy (ACT) for youth with subthreshold psychopathology (SmartScan Study), and in patients with At Risk Mental State or a first episode of psychosis (INTERACT Study). Mario Alvarez-Jimenez will discuss a randomised controlled trial which assessed the effectiveness of a novel moderated online social media therapy (HORYZONS) designed to enhance social and vocational functioning and maintain clinical gains from specialist FEP services. Sandra Bucci will present the results from a randomised controlled trial of the feasibility and acceptability of a newly developed theory-informed smartphone app (Actissist) which targets early psychosis relapse indicators. Lucia Valmaggia will discuss findings from a study which tests the feasibility and implementation a Virtual Reality Assisted Therapy that aims to help people with psychosis to overcome their anxiety and distress in social situations. The discussion will be led by Ulrich Reininghaus, and will focus on the benefits and opportunities afforded by digital technologies, which might provide scalable and person-tailored options for early intervention, and allow us to rethink current service design and delivery.

42.1 ACT IN DAILY LIFE FOR PEOPLE WITH EARLY DEPRESSION AND PSYCHOSIS: THE FEASIBILITY OF AN ECOLOGICAL MOMENTARY INTERVENTION APPROACH

Inez Myin-Germeys*[1], Evelyne van Aubel[1], Jindra Bakker[2], Thomas Vaessen[1], Tim Batink[3], Therese van Amelsvoort[2], Ulrich Reininghaus[4]

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Background: This paper will discuss a blended ACT in Daily Life therapy, using an Experience Sampling app to improve real-world delivery of Acceptance and Commitment Therapy in two samples: 1) young people with subthreshold depressive and/or psychotic complaints, and 2) individuals with an At Risk Mental State (ARMS) and First Episode of psychosis (FEP).
Methods: In the SmartScan study, 55 youth (age 16-25) with subthreshold psychopathology were randomized to ACT-DL (n=27) or to active control (n=28). In the INTERACT study, ACT-DL was tested in a multi-center randomized clinical trial in 78 ARMS and 62 FEP patients
Results: Smartscan: Participants filled in on average 69 (48%) of signal-contingent beep-questionnaires, agreed to 15 (41%) of offered beep-exercises, initiated 19 on-demand exercises, and rated ACT-DL metaphors moderately useful. Relative to active control, interviewer-rated depression scores decreased significantly in ACT-DL participants (p=.027). Decreases in self-reported depression, psychotic-related distress, anxiety, and general psychopathology did not differ between conditions. INTERACT: Participants with ARMS and FEP evaluated the overall training (M=5.63; SD=1.17), the ACT therapy sessions (M=5.63; SD=1.36), and the exercises (M=4.81; SD=1.69) as useful on a scale from 1 (not useful) to 7 (very useful). Furthermore,

they evaluated the app as useful (M=4.56; SD=1.69), but also as burdensome (M=4.44; SD=1.66). Data from the qualitative study confirm these findings.
Conclusions: ACT-DL is a promising new treatment approach that is feasible in patients in the early phases of depression and psychosis, although adaptations in future research may improve delivery of and compliance with the intervention. There were mixed findings for its efficacy in reducing subthreshold psychopathology. The RCT in participants with psychosis is collecting its final data which will be available at the time of the conference.

42.2 THE HORYZONS STUDY: A RANDOMISED CONTROLLED TRIAL OF A NOVEL ONLINE SOCIAL THERAPY TO SUSTAIN TREATMENT EFFECTS FROM EARLY PSYCHOSIS SERVICES

Mario Alvarez-Jimenez*[1], Sarah Bendall[2], Peter Koval[3], Simon Rice[2], Daniela Cagliarini[2], Lee Valentine[2], Simon D'Alfonso[2], Christopher Miles[2], Penni Russon[2], Jessica Phillips[2], Reeva Lederman[4], Eoin Killackey[2], Catherine Mihalopoulos[5], Helen Herrman[2], Shalini Lal[6], Patrick D McGorry[2], John F Gleeson[7]

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Background: The benefits of First Episode Psychosis (FEP) services may not be sustained after patients are transferred to regular care. We have developed a novel online platform (HORYZONS) designed to enhance social and vocational functioning and maintain clinical gains from FEP services. HORYZONS merges: (i) peer-to-peer social networking; (ii) tailored therapeutic interventions; (iii) expert support by clinicians and vocational workers; and (iv) peer-moderation. The aim of this trial was to determine whether, following 2 years of specialised support, an 18-month online intervention (HORYZONS) was superior to Treatment as Usual (TAU).
Methods: This study was a single-blind RCT (N=170 FEP patients). Treatment conditions included HORYZONS+TAU or TAU alone. Primary outcome was social functioning at 18 months with secondary outcomes including vocational status, rate of hospital admissions and visits to emergency services, cost-effectiveness, depression, loneliness, anxiety, quality of life, and positive and negative psychotic symptoms.
Results: 60% of HORYZONS participants remained engaged in the intervention over 18 months. There were not significant differences between groups in social functioning scores. Participants in the HORYZONS group were more likely to find employment ($p<0.05$) as well as less likely to be admitted to hospital and visit emergency services ($p<0.05$) over the 18-month course of the study. There were no significant differences between groups on other secondary outcomes.
Conclusions: HORYZONS is an effective intervention in improving vocational recovery and reducing the rate of visits to emergency services and hospital admissions in FEP patients.

42.3 THE ACTISSIST STUDY: A CBT-INFORMED SELF-MANAGEMENT APP FOR EARLY PSYCHOSIS

Sandra Bucci*[1], Natalie Berry[1], John Ainsworth[1], Shon Lewis[1], Matthew Machin[1], Katherine Berry[1], Dawn Edge[1], Richard Emsley[2], Gillian Haddock[1]

[1]*University of Manchester,* [2]*King's College London*

Background: Psychosocial interventions are recommended for the treatment of psychosis; however, only a small proportion of service users have access to intervention packages offered by mental health services. Given advancements in mobile phone technology, we have developed a theory-informed smartphone app, Actissist, targeting early psychosis relapse indicators. This paper will report the usage statistics of the digital health intervention we have developed and its impact on clinical outcomes
Methods: We conducted a single-blind randomised controlled trial comparing the Actissist app plus Treatment As Usual (TAU) with a symptom monitoring software application (ClinTouch) plus TAU in early psychosis over a 12-week intervention period. We randomly assigned 170 participants registered with early intervention services across the North West of England, UK into each arm of the trial. We recorded usage rates of the digital health intervention over the 12 week intervention period and administered measures over three time points.
Results: We will report the results of the outcome of the trial, service user engagement with the intervention, and implications for the digital mental health research and clinical field.
Conclusions: Rigorously designed clinical trials in the digital mental health field are needed. This is one of the largest studies worldwide to evaluate a digital health intervention for severe mental illness using a randomised controlled design and an active control group. Implications for taking the digital mental health field forward will be discussed.

42.4 THE IMPLEMENTATION OF VIRTUAL REALITY THERAPY FOR PSYCHOSIS IN CLINICAL PRACTICE

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[1]*Institute of Psychiatry, Psychology and Neuroscience, King's College London,* [2]*South London and Maudsley NHS Trust*

Background: Psychotic disorders are characterised by a range of difficulties, which can affect social interactions. When experiencing core symptoms of psychosis, including hallucinations and delusions, social settings become stressful and distressing, and service users report high levels of anxiety in these situations. Avoidance of social situations can become a maintaining factor of anxiety. Virtual reality (VR) generates virtual environments that feel immersive and realistic and VR assisted therapy (VRT) can be used to help people to overcome their anxiety and distress in social situations.
Our VR Lab has developed a number of VR scenarios that have been used for the assessment of positive and negative symptoms, and to deliver VRT in a research setting. We are currently carrying out a number of implementation studies to introduce the use of VRT in daily clinical practice.

Methods: Participants were recruited from two South London Early Intervention mental health teams for people experiencing a FEP. Participants received a course of 10 sessions of individual formulation-driven VRT with a focus on improving social functioning.The VR environment was used to conduct exposures, behavioural experiments and to practice coping strategies, which were then translated into the individuals' real-life environments. A psychometric assessment was conducted with each participant pre- and post-therapy. A feasibility assessment was conducted, regarding the process of recruitment and retention, required resources and barriers to implementation. To examine acceptability participants also provided qualitative feedback during and after their experiences, and completed an 'unwanted effects' questionnaire.

Results: Eleven participants were recruited to the study, which was above the target of 6-10. There was an 82% retention rate; although several participants therapy was somewhat affected by the Covid-19 pandemic and adjustments had to be made to their participation in the study. Comparison of the pre- and post-therapy psychometric assessment scores revealed a reliable change on some of the assessed domains for all participants. Participants reported few or no unwanted effects and provided positive feedback about the inclusion of VR in the therapy.
Conclusions: VRT can be implemented in clinical setting using commercially available VR headsets and by providing the right training of therapist. It appears to be feasible and acceptable to participants, and potential benefits were derived. However, a number of challenges to implementation were identified that should be carefully considered before further piloting or trailing is attempted.

43. WHAT IS THE FUTURE OF TELEHEALTH FOR YOUNG PEOPLE IN THE EARLY STAGES OF PSYCHOSIS? LESSONS LEARNED DURING THE COVID-19 PANDEMIC

Joseph DeLuca
Icahn School of Medicine at Mount Sinai

Overall Symposia Abstract: The coronavirus 2019 (COVID-19) pandemic has significantly impacted how mental health services are provided worldwide, leading many providers to adapt their traditional in-person services by implementing telehealth services (e.g., videoconferencing platforms). For many providers, patients, and families, the implementation of telehealth services is long over-due and welcomed. Telehealth services can provide greater access to mental health care, particularly specialized care which may have been too geographically distant for patients/families to reach before. Beyond the immediate need of telehealth services for personal health and safety reasons during the pandemic, telehealth services have the power to meet the unique needs of youth and young adults with early psychosis experiences (e.g., psychosis-risk and first-episode psychosis) and can be embedded within such specialized programs once social distancing regulations are no longer in effect. The full power of telehealth services in this area should be harnessed through international experiences in order to sustain the benefits of these services.
Many individuals in the early stages of psychosis face environmental and individual-level barriers to service use, including clinic location and transportation issues, stigma, and symptoms (e.g., emerging paranoia; avolition) that may make traditional in-person help-seeking and engagement more difficult. For youth/young adults and their families, some of these barriers have become exacerbated during the pandemic. However, few studies to date have evaluated the use of videoconferencing interventions with youth in the early stages of psychosis. Patients with early psychosis experiences, being young and help-seeking, are an ideal population to use such services since they tend to be highly engaged with the virtual world already. These youth also often face significant socialization issues that can be addressed through virtual treatment (e.g., individual, family, and group therapy sessions). Aligned with the theme of the 2021 SIRS conference of “Bringing Precision Medicine to Mental Health Services”, a timely focus on telehealth services can help us to understand how to best target the unique needs of heterogeneous patients with early psychosis experiences through virtual treatment, as well as how to personalize virtual services for youth and families worldwide.

This symposium includes research specifically on best practices for telehealth with young people with early psychosis experiences in general and during the pandemic, experiences implementing first-episode psychosis services in three countries (China, Israel, United States) during the pandemic, and telehealth implementations of interventions for youth at risk for psychosis and their families during the pandemic.

First, Dr. Joseph DeLuca will discuss systematic review findings on telehealth for youth in the early stages of psychosis, methodological issues and future research directions, and global best practices during the COVID-19 pandemic. Second, Dr. Piper Meyer-Kalos will discuss telehealth suggestions and recommendations from first-episode psychosis programs in three countries, based on her experiences with training and implementation during the pandemic. Third. Dr. Yulia Landa will describe her work in adapting and implementing telehealth versions of treatments for youth at risk for psychosis and their families, while also discussing future directions in this area. Fourth, Dr. Shaynna Herrera will discuss a telehealth adaptation of a psychoeducational intervention for youth at risk for psychosis and families. Dr. Kim Mueser will be the discussant and can provide expertise on early psychosis treatment and context in respect to telehealth implementations of psychological interventions.

43.1 A SYSTEMATIC AND CRITICAL REVIEW OF TELEHEALTH INTERVENTIONS FOR YOUNG PEOPLE IN THE EARLY STAGES OF PSYCHOSIS

Joseph DeLuca*[1], Therese Todd[1], Matthew Dobbs[1], Rachel Jespersen[1], Shaynna Herrera[1], Nicole Andorko[2], Doha Chibani[2], Samantha Jay[2], Pamela Rakhshan Rouhakhtar[2], Emily Petti[2], Mallory Klaunig[2], Elizabeth Thompson[3], Zachary Millman[4], Kathleen Connors[5], LeeAnn Akouri-Shan[2], John Fitzgerald[2], Samantha Redman[2], Caroline Roemer[2], Miranda Bridgwater[2], Jordan DeVylder[6], Cheryl King[7], Steven Pitts[2], Shauna Reinblatt[5], Heidi Wehring[8], Kristin Bussell[9], Natalee Solomon[10], Sarah Edwards[5], Gloria Reeves[5], Robert Buchanan[8], Jason Schiffman[2], Yulia Landa[1]

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Background: Telehealth interventions can address individual-level and environmental-level barriers to mental health services for youth/young adults with early psychosis experiences and their families, beyond barriers related to the COVID-19 pandemic. Although early psychosis telehealth services have proliferated during the pandemic, telehealth interventions appear to be currently understudied and underutilized for this group. There is a need to better understand the use of these services (including feasibility and acceptability) and to establish global best practices.

Methods: A systematic review was conducted with the PubMed and SCOPUS databases, as well as a manual search (e.g., via Google Scholar and other sources). Texts published up until October 14, 2020, were included in this review. Studies that were focused on psychosis-risk,

first-episode psychosis, and early psychosis (and synonyms), in addition to telehealth (i.e., videoconferencing), were sought out.
Results: Only four relevant articles (three review articles and one case study) were identified in this systematic review (all published in 2020). Two review articles were published by North American-based researchers and one review article was published by international researchers who focused on three different countries – China, Israel, United States. The case study was published by clinicians and researchers in Singapore. Based on these articles, videoconferencing interventions do appear to be safe, feasible, and acceptable to young people experiencing early psychosis-spectrum symptoms and their families. Clinical considerations and advantages and disadvantages of telehealth approaches for this group were discussed. Clinical considerations highlighted the importance of recognizing the heterogeneity of young people with psychosis experiences and individualizing virtual treatment for youth and families (including using tailored clinical strategies and taking advantage of videoconference platform options to increase engagement). Increased access to care and family involvement were identified as potential advantages, while technological issues and potential loss of human connection with in-person therapist were identified as potential disadvantages. Best practice guidelines were noted, including from the World Health Organization and the American Academy of Child and Adolescent Psychiatry.
Conclusions: The results of this review indicate an urgent need for comprehensive research on telehealth interventions (videoconferencing) for young people with early psychosis experiences and their families. To date, no empirical studies have been conducted on early psychosis and videoconferencing. This review identified emerging research in this area and summarized best practices from global youth tele-mental health interventions and guidelines. This review also highlighted important clinical considerations (e.g., pros/cons of telehealth) and research considerations (e.g., methodological/design considerations and measurement issues, need to adapt and pilot new interventions, local and global collaborations, etc.). These clinical considerations (including the use of different platforms and their capabilities) and immediate research steps for the field will be discussed during this talk.

43.2 THE RISE OF TELEHEALTH DURING THE COVID-19 PANDEMIC: CHALLENGES AND SUGGESTIONS TO PROVIDING FIRST EPISODE PSYCHOSIS TREATMENT

Piper Meyer-Kalos*[1]

[1]*University of Minnesota Medical School*

Background: The rise of COVID-19 has led to significant and rapid changes to the delivery of mental health services across the world. In response to the pandemic, many first episode psychosis (FEP) programs have transitioned to telehealth services to provide treatment. The traditional face to face delivery of evidence-based interventions shifted and many FEP teams developed new approaches to delivering multi-disciplinary treatment. This presentation aims to (1) outline common challenges individuals with FEP and family members are facing during the pandemic and barriers FEP providers have encountered; (2) offer strategies and adaptations to FEP treatment using telehealth solutions; and (3) provide recommendations to improve communication, reduce stress, and strengthen team cohesiveness for FEP teams.
Methods: The implementation of social distancing in response to COVID-19 has been associated with immediate changes to the engagement of individuals with FEP and delivery of treatment services. As programs transitioned to telehealth, we explored through observations from members of FEP teams how the pandemic has affected persons with FEP including difficulties identifying and enrolling individuals in services, increasing experiences of boredom

and loneliness among individuals with FEP, increases in individual case management needs, increased stress on family supports, and challenges coordinating a FEP team.
Results: As rates of infection continue to spread, individuals with FEP are facing new challenges to recovery and FEP teams are seeing new barriers to engaging individuals in services and delivering standard treatments. In response to the COVID-19 pandemic, FEP programs across the globe have had to rapidly develop new approaches to engagement and implementation of traditional mental health services. We will provide suggestions from FEP programs that address COVID-19 barriers to treatment and discuss recommendations from FEP providers using telehealth service delivery methods. Suggestions will include strategies to address specific roles on an FEP team such as individual therapy, family education, psychopharmacological management, supported employment and education, peer support, and case management. Innovative solutions such as the addition of zoom groups, skills demonstration and practice, and inclusion of family members and support persons to improve engagement will be discussed. Another barrier for individuals with FEP is access to telehealth video services, so we also will review strategies for helping people when they can engage in services on a limited basis or only by telephone.
Conclusions: Lastly, the presentation will discuss the strain of the pandemic on the FEP team and individual staff members. The implementation of social distancing requirements makes it difficult to do many of the activities that insure good communication and operation of an FEP team. As FEP teams move services more remotely, many teams have fewer opportunities to collaborate with other team members. Additionally, team members may be experiencing increased stress associated with caregiving or other family responsibilities. Changes in the ability to provide services can lead to increased frustration in not being able to deliver services in a manner team members are accustomed. This presentation will offer suggestions to address individual team member needs and maintain communication and flexibility in the delivery of services such as providing opportunities for team members to share their concerns with peers while also addressing feelings of "zoom fatigue."

43.3 TELEHEALTH ADAPTATION OF GROUP AND FAMILY BASED COGNITIVE BEHAVIORAL THERAPY FOR YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: The onset of psychosis is often preceded by a clinical high risk (CHR) phase characterized by attenuated psychotic symptoms and decline in psychosocial and cognitive functioning. Among treatments studied for CHR, cognitive behavioral therapy (CBT) and family psychoeducation have the best evidence base for reducing transition to psychosis and improving functional outcomes. We have established a comprehensive Group and Family-Based Cognitive Behavioral Therapy (GF-CBT) program that aims to facilitate psychosocial recovery, decrease symptoms, and prevent or delay transition to psychosis in youth at CHR. GF-CBT is grounded in sociocultural, ecological systems theory, psychosocial resilience models, and research on information processing in delusions. The program has 3 components: (1) CBT Skills Group for CHR Youth designed to boost peer support, reduce isolation, normalize psychotic-like experiences to lessen distress, reduce cognitive biases, facilitate positive beliefs, and enhance reasoning and decision-making; (2) individual sessions focused on tailoring CBT skills to personal goals, facilitating successful interactions with peers, and

providing academic and vocational support; and (3) CBT Skills Group for Families aimed at supporting the learning of CBT skills in CHR youth and teaching effective communication skills for family members.
Methods: Beginning in March 2020 during the COVID-19 epidemic, we have adapted GF-CBT to be delivered virtually in community mental health settings in New York, Delaware, and Missouri, supported by SAMHSA funded grants to develop clinical programs for youth at CHR. This delivery has been guided by telehealth guidelines from the American Psychological Association, telehealth guidelines related to safety, and specific best practices for CHR. Adaptations to GF-CBT included: identifying video-conferencing platforms to use, developed fillable PDF versions of the workbooks used in GF-CBT, creating a digital library of forms/worksheets, adapting group rules to include discussions of virtual/telehealth etiquette, and using screensharing during sessions to highlight key points and maintain participant engagement (e.g., virtual games and icebreakers). We have developed guidelines for clinicians, patients and families on troubleshooting common issues, including how to use the platform and manage connectivity problems, which have been common concerns in past youth/family telehealth studies. Our team has collected data on the feasibility and acceptability of an adapted GF-CBT intervention conducted through telehealth (GF-CBT-TH). We also distributed an anonymous survey to clinicians to learn about their experience with the intervention delivery.
Results: As of today, GF-CBT-TH services were delivered to 29 patients. We have found high rates of enrollment (92%) and attendance (80% to 96% of sessions attended); as well as high family engagement (96% attendance in one clinic), and overall positive feedback from clinicians providing these telehealth services. Clinicians have been delivering GF-CBT-TH using secure videoconference systems, including Zoom for Healthcare, Doxy.me, and VSee. Clinicians have reported that using telehealth had many benefits, including improved access and scheduling, reduced barriers to treatment such as transportation, and more family involvement (particularly if families could not be in the same place all at once, telehealth allows family members to video-conference in). Clinicians also identified intervention elements that made the transition to telehealth easier, including the GF-CBT digitally fillable manuals and handouts. Potential downsides that clinicians identified included: challenges engaging youth and families (e.g., due to connectivity issues, patients becoming easily distracted at home, and/or therapists having a difficult time reading non-verbal cues virtually); and privacy concerns. Despite these challenges, the clinicians surveyed reported that GF-CBT-TH was feasible and acceptable.
Conclusions: Our preliminary findings indicate that GF-CBT-TH has promise for reaching and treating the CHR population. While the importance of telehealth-based services is clearly evident during the COVID-19 pandemic, more broadly there is a need to systematically investigate remote delivery methods as a way of increasing access to critical services for CHR.

43.4 FEASIBILITY OF A PSYCHOEDUCATION INTERVENTION FOR INDIVIDUALS WITH PSYCHOSIS RISK: EVIDENCE FOR CONTINUING TELEHEALTH SERVICES BEYOND THE COVID-19 PANDEMIC

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Background: Young people at risk for psychosis (PR) are increasingly being identified in specialized and community programs. Effective communication about PR through

psychoeducation has the potential to enhance treatment engagement. We developed a brief and structured 5-session psychoeducation intervention for PR entitled, "BEGIN: Brief Educational Guide for Individuals in Need." The goal of this study was to finalize BEGIN's development based on stakeholder feedback and evaluate feasibility, including feasibility of telehealth delivery after a rapid transition to telehealth as a result of the COVID-19 pandemic.
Methods: Materials: BEGIN session topics include: 1) Psychosis Risk Education; 2) Self-Assessment of Symptoms; 3) Individual Goals; 4) Treatment Options; 5) Decision-Making and Next Steps. BEGIN utilizes a slideshow presentation to aid clinicians in presenting educational material and facilitating discussion. Participants: PR individuals ages 15-33 were identified via Structured Interview for Psychosis Risk Syndromes (SIPS). Procedures: Initial stakeholder feedback was obtained from qualitative interviews with PR individuals (n=5) and caregivers (n=5) after reviewing BEGIN's content and materials. Then, PR individuals (n=12) participated in BEGIN either in-person (n=7) or via telehealth (n=5) due to forced limitations of COVID-19. Regarding in-person delivery, BEGIN was presented on iPads and patients engaged with activities on the iPad using an Apple pencil. For telehealth visits, BEGIN was delivered via screen sharing on VSee, a HIPAA-compliant videochat platform, which patients accessed through their computer, phone, or tablet. Data collection/analysis: Enrollment and retention data were collected. Qualitative interviews were conducted to learn about participants' experience with BEGIN, including their experience with telehealth. Interviews were transcribed and analyzed using iterative thematic analysis. Facilitators and barriers to delivering BEGIN via telehealth were documented by the research team.
Results: Dropouts were reduced in the group who completed BEGIN via telehealth (no dropouts) compared to in-person (4 dropouts). Participants completed BEGIN approximately two times faster via telehealth (mean time to completion = 35 days) compared to in-person (mean time to completion = 71 days). Qualitative data revealed that patients and caregivers had a positive impression of BEGIN, a need for PR-specific and general mental health education in order to understand symptoms, and that BEGIN appears to promote agency and elucidate options for getting better. Patients and caregivers, including those who participated in BEGIN prior to COVID-19, reported that the step-by-step structure and slideshow presentation facilitates broad implementation of BEGIN, such as online delivery. PR individuals who participated in BEGIN via telehealth noted the accessibility, convenience, and approachable nature of telehealth services, while some also acknowledged the potential for less interpersonal connection and discomfort discussing sensitive topics online.
Conclusions: This study demonstrated consumer need for PR psychoeducation and that BEGIN appears feasible when delivered in-person and via telehealth, even beyond the context of a pandemic. Some patients prefer telehealth because of its convenience, which may account for fewer dropouts and better attendance. BEGIN also provides a standardized method for clinicians to effectively deliver psychoeducation about PR. Future research will evaluate clinician experience with training and delivering BEGIN, and measure BEGIN's effectiveness in facilitating treatment engagement in a larger sample.

44. DOES GLUTAMATERGIC SYNAPTIC DYSFUNCTION UNDERLIE SCHIZOPHRENIA? FROM GENETICS AND CELLS TO PATIENTS

Adrienne Lahti

The University of Alabama At Birmingham

Overall Symposia Abstract: The glutamate hypothesis and synaptic dysfunction hypothesis are two of the leading theories of the pathoetiology of schizophrenia. Developments in genetics,

imaging and neuroscience provide new approaches to test these hypotheses. This symposium aims to bring together the latest data from these cutting edge approaches to test both hypotheses and, by bringing together data on both, provide a novel, integrative understanding.
Dr. Walters will present the latest, unpublished data from the Psychiatric Genomic Consortium, which is the largest genetic study of schizophrenia to date, identifying ~100 new genome-wide significant loci associated with schizophrenia. He will cover fine-mapping analysis which identifies that genome-wide significant loci are enriched for genes involved in glutamatergic synaptic transmission and synaptic development as well implicating complement C4A expression. Dr. Howes will present new multimodal imaging data, including the first PET imaging of a specific synaptic marker in vivo in patients and integrating this with measures of glutamate and brain connectivity, showing lower synaptic density in schizophrenia and a loss of the normal relationship with glutamate levels. Dr. Lahti will present novel data from a large antipsychotic naïve first episode psychosis study investigating brain functional connectivity and the relationship to glutamatergic function. She will show that connectivity is linked to brain glutamate levels, and that connectivity is reduced and uncoupled from glutamate in first episode psychosis, and that this is associated with symptom severity. Dr. Sellgren will present complementary clinical and preclinical studies on the potential mechanism underlying glutamatergic synaptic dysfunction in schizophrenia that links genetic risk factors to synaptic loss. This includes a study in first episode psychosis showing that higher complement C4 levels in CSF predict the development of schizophrenia, and studies of neuronal organoids derived from patients showing increased synaptic elimination, and that a glutamatergic antagonist increased synaptic elimination, as did other risk factors for schizophrenia (THC and inflammatory cytokines). These studies also identify the potential of minocycline to reduce synaptic elimination in schizophrenia. Finally, Dr. Van Haren will be the discussant, She will consider how the genetic, imaging, biomarker and preclinical data converge, where there are discrepancies and the implications of these new findings for an integrative understanding of the pathoetiology of schizophrenia and developing new treatments.

The symposium includes contributors from six different institutions and five different countries. It also includes gender and career diversity, including leading female researchers and clinicians and early career researchers (Dazzan, Lahti, Sellgren, and Van Haren). In addition, the symposium covers a range of clinical and experimental techniques, including from genetics, structural and functional imaging, drug challenges and neuronal models from patients. It will be an excellent opportunity to consider and integrate findings from across these fields to provide new understanding of the role of glutamatergic connectivity in schizophrenia and the potential to target it with new treatments.

44.1 GWAS FINDINGS FROM THE SCHIZOPHRENIA WORKING GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM

Schizophrenia Working Group of the Psychiatric Genomics Consortium[1], James Walters*[2]

[1]*PGC,* [2]*Cardiff University*

Background: Schizophrenia has a heritability of 60-80%, much of which is attributable to common risk alleles, suggesting genome-wide association studies can inform our understanding of aetiology.

Methods: In the third wave of the Schizophrenia Working Group of the Psychiatric Genomics Consortium we conducted a meta-analytic GWAS in 69,369 people with schizophrenia and 236,642 controls. We used FINEMAP and functional annotation to prioritise genes. We undertook enrichment analyses on bulk brain tissue and single cell expression data as well as on synaptic gene set ontologies. Finally we compared results with those of the Schizophrenia Exome Meta-Analysis Consortium.
Results: We report genome-wide significant associations at 270 distinct loci. Using fine-mapping and functional genomic data, we prioritise 130 genes as likely responsible for these associations. Fine-mapped candidates were enriched for genes associated with rare disruptive coding variants in people with schizophrenia, including the glutamatergic NMDA receptor subunit GRIN2A and SP4, a transcription factor which is regulated by NMDA transmission and also regulates NMDA receptor abundance. In single cell expression analyses schizophrenia associations were enriched in genes with high expression in human cortical inhibitory interneurons and excitatory neurons from cerebral cortex and hippocampus (pyramidal and granule cells) and implicated fundamental processes related to neuronal function, particularly synaptic organisation, differentiation and transmission.
Conclusions: In the largest genetic study of schizophrenia to date we identify biological processes of pathophysiological relevance to schizophrenia, show convergence of common and rare variant associations in schizophrenia, and provide a rich resource of priority genes and variants to advance mechanistic studies.

44.2 SALIENCE NETWORK GLUTAMATE & BRAIN CONNECTIVITY IN MEDICATION-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS – A MULTIMODAL MAGNETIC RESONANCE SPECTROSCOPY & RESTING STATE FUNCTIONAL CONNECTIVITY STUDY

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Background: In schizophrenia, altered functional activation during cognitive tasks and altered functional connectivity during rest have been consistently reported in regions of the salience network (SN). The SN, which includes the anterior cingulate cortex (ACC) and the insula, is responsible for the detection of salient external stimuli and the subsequent allocation of additional resources through interactions with other networks. However, the pathophysiological origin of this altered activation and connectivity is still poorly understood. The goal of this combined fMRI/MR Spectroscopy (MRS) neuroimaging study was to investigate the role of glutamatergic metabolism as putative mechanism underlying functional connectivity alterations within the SN in a group of medication-naïve first episode psychosis (FEP) subjects.
Methods: The FEP cohort consisted of 73 antipsychotic-naïve FEP patients and 54 matched healthy controls (HC). We measured glutamate + glutamine (Glx) from a voxel prescribed in the ACC using a PRESS sequence (TR/TE = 2000/80 ms). We used a one-way ANCOVA controlling for age, gender, and smoking status to compare ACC Glx between groups. The right anterior insula region of interest (ROI) was used to define the resting state functional connectivity (FC) of the SN. Residual time series were extracted and correlated with every other voxel in the brain, creating individual whole-brain z-transformed correlation maps. To restrict all analyses to the SN, a mask was created by thresholding average positive correlation maps for each group at t-value of 10 and a cluster size of 100 voxels. An additional analysis of negative correlations was also performed. For each group, we used multiple regression analyses to test for voxels with a significant relationship between Glx and SN FC. Another regression

tested for the interaction between Glx, SN FC, and groups. Group analyses were performed using small volume correction ($p < 0.01$) and cluster corrected using threshold-free cluster enhancement (TFCE) within each mask. Age, sex, and framewise-displacement were treated as covariates.

Results: In FEP compared to HC, we found reduced FC in the SN in the absence of group differences in ACC Glx levels ($p = 0.45$). Glx-FC group interactions were found in the ACC and bilateral insula for positive FC, and in the lateral parietal cortex for negative FC. In HC, higher Glx levels predicted greater positive FC in the ACC and insula, and greater negative FC with regions of the lateral parietal cortex. These relationships were weaker or not present in FEP; FC extracted from significant SN Glx group interaction locations correlated with symptom severity [Brief Psychiatric Rating Scale (BPRS) Total score ($r = 0.25$, $p = 0.028$) and BPRS Positive subscale score ($r = 0.22$, $p = 0.048$].

Conclusions: Here, we found that both correlations and anticorrelations in the SN are already altered in antipsychotic medication-naïve FEP, underscoring the importance of considering both correlations and anticorrelations for optimal characterization of pathology in this brain network. Our data empirically demonstrate that Glx modulates functional connectivity differently in FEP than in HC, pointing to a possible mechanism underlying dysconnectivity in psychosis.

44.3 THE ROLE OF COMPLEMENT-DEPENDENT MICROGLIAL MECHANISMS AT THE SYNAPSE IN EARLY-ON SCHIZOPHRENIA

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Background: Emerging evidence suggest a role of microglia in the early-on pathophysiology observed in schizophrenia. Recently, we created cellular models of microglial synapse pruning derived from schizophrenia patients to observe excessive synapse elimination. Genetic risk variants increasing complement component 4A (C4A) expression also caused increased neuronal complement deposition and increased microglial engulfment in this model. Further, the small-molecule Minocycline dose-dependently decreased synapse elimination as well as risk of schizophrenia in electronic health records. In our current projects, we are now 1) validating our findings in vivo as well as mechanistically in cellular 3D models more closely mimicking in vivo conditions, and 2) studying the effects of risk factors (cannabis smoking) and established biomarkers on complement-dependent microglial synapse pruning.

Methods: 1. A novel mass spectrometry assay was developed that can differ C4A and C4B unique peptides in cerebrospinal fluid (CSF). CSF was collected from first-episode psychosis (FEP) subjects and healthy controls.

2. We established a protocol to generate cerebral organoids with innately developing microglia and assays to quantify microglial synapse elimination.

3. Patient-derived co-cultures (neurons and microglia) were generated to study how the NMDAR antagonist kynurenic acid (increased in CSF from schizophrenia subjects) modulate synaptic activity and microglial synapse pruning.

4. Patient-derived neuronal cultures were exposed to pro-inflammatory cytokines increased in CSF from schizophrenia subjects and C4A RNA expression was measured.

Results: 1. FEP subjects that later on developed schizophrenia displayed higher C4A protein levels than FEP subjects receiving a non-schizophrenia diagnosis ($P = 0.03$).
2. Cerebral organoids exposed to 2 μM of Minocycline displayed increased spine density as compared to non-exposed ($P = 0.002$). Experiments are ongoing to compare the extent of synaptic pruning in monozygotic twin pairs discordant for schizophrenia.

3. Kynurenic acid (75 μM) decreased neuronal activity and increased microglial synapse elimination ($P = 0.001$). Exposing patient-derived microglia to THC dose-dependently increased the uptake of isolated patient-derived synaptic structures ($P < 0.05$).

4. Interleukin-1beta increased C4A RNA expression across different copy numbers ($P = 0.049$).

Conclusions: Our preliminary data further strengthen the hypothesis that targetable complement-dependent microglial functions at the synapse play a role in the observed decrease in synaptic density in schizophrenia. Studied risk factors, independent of the C4 locus, also seem to converge on this mechanism and contribute to excessive synapse elimination mediated by microglial engulfment of synapses.

44.4 IS THERE LOSS OF GLUTAMATERGIC SYNAPTIC CONNECTIVITY IN SCHIZOPHRENIA AND IS THIS DUE TO ANTIPSYCHOTIC TREATMENT? COMPLEMENTARY IN VIVO CLINICAL AND PRECLINICAL STUDIES

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Background: Pharmacological, post-mortem and imaging studies indicate that synaptic dysconnectivity involving glutamatergic signalling has a key role in the pathophysiology of schizophrenia. However, this has not been directly tested in vivo in patients, and the influence of antipsychotic treatment on synpatic proteins remains unclear. It is now possible to measure levels of a protein, synaptic vesicle glycoprotein 2A (SV2A), in vivo in people using PET imaging. SV2A is ubiquitously expressed in synaptic terminals, providing an in vivo measure of synaptic density. We used this novel technology to address these questions using complementary clinical and preclinical studies.
Methods: Study 1: Forty-six subjects (n=23 schizophrenia; n=23 controls) received PET imaging using [11C]UCB-J with arterial sampling to index SV2A distribution volume ratios (DVR). Subjects also received fMRI to measure resting state functional connectivity in the salience network and MRS imaging to measure glutamate levels in the anterior cingulate cortex and hippocampus, as well as clinical measures. N-acetylaspartate levels were measured with MRS imaging as a negative control for the glutamate-SV2A analyses.
Study 2: Sprague-Dawley rats were randomised to receive either lithium, haloperidol, olanzapine or vehicle for 28 days (n=10-12/group). Synaptic Vesicle glycoprotein 2A (SV2A) markers and Neuroligin (NLGN) clusters were measured in frontal cortex by western blot, quantitative autoradiography using [3H]-UCB-J, or immunostaining and confocal microscopy.

Results: Study 1: [11C]UCB-J DVR was significantly lower in patients relative to controls in the anterior cingulate cortex (ACC, $t = 2.38$, $p = 0.001$, Cohen's $d = 0.8$). In healthy volunteers, but not patients, [11C]UCB-J DVR was significantly positively correlated with glutamate

levels in the ACC (HV, r=0.53, p=0.01; SCZ, r=0.32, p=0.20) and the left hippocampus (HV, r=0.68, p=0.0005; SCZ, r=0.30, p=0.24). Furthermore, in healthy volunteers, but not patients, [11C]UCB-J DVR was significantly positively correlated with Glx/Cr, in both the left hippocampus (HV, r=0.48, p=0.0002; SCZ, r=0.16, p=0.53) and ACC (HV, r=0.72, p=0.0002; SCZ, r=0.05, p=0.86). Functional connectivity between the ACC and other brain regions was lower in schizophrenia relative to controls. There were no significant relationships between [11C]UCB-J DVR and NAA/Cr in the left hippocampus or ACC in healthy volunteers or patients. There was no significant relationship between prior antipsychotic exposure and DVR ($p>0.3$).
Study 2: There was no effect of antipsychotic or lithium treatment on SV2A markers or total synaptic clusters (p values all>0.4). There was a significant group effect on NLGN cluster density ($F(1,28)=8.478$; $p<0.01$) driven by an increase in NLGN in the lithium group.

Conclusions: As SV2A is ubiquitously expressed in synaptic terminals, these data indicate lower synaptic density in schizophrenia and the loss of the normal relationship between glutamate levels and synaptic density in schizophrenia. Together these findings are consistent with loss of glutamatergic synapses leading to dysconnectivity in schizophrenia. Antipsychotic or lithium did not affect synaptic terminal markers, despite lithium increasing post-synaptic marker levels, indicating that findings of lower synaptic density in schizophrenia are unlikely to be due to an effect of antipsychotic treatment.

45. EARLY INTERVENTION FOR PSYCHOSIS SERVICES IMPLEMENTATION: A GLOBAL PERSPECTIVE

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University Hospital of Montreal

Overall Symposia Abstract: Since the inception of the early intervention for psychosis services (EIS) model in the early 1990s, it has evolved and spread worldwide. Initially emerging from research projects and the efforts of highly engaged clinicians, interest among policymakers in several countries and jurisdictions for widespread implementation of EIS has grown in the last two decades. Pioneers of the model and nations which have made efforts to implement this model of care are joining in this symposium: Australia, Denmark, the United Kingdom (England), and the Canadian province of Quebec. This symposium (chaired by Abdel-Baki and Bertulies-Esposito) will offer the perspectives of clinicians and researchers involved in widespread implementation of EIS in each of these jurisdictions, covering the pathway to implementation, with its challenges and successes. Particular attention will be paid to program fidelity to the EIS model and its integration in the implementation process.
First, Killackey (Australia) will present the path towards successfully developing a national network of EIS, which has not been without challenges and setbacks. Although the world-renowned Early Psychosis Prevention and Intervention Centre was implemented in 1992, it is only in the last decade, that the country has shaped a national strategy for EIS implementation, which was adopted in 2013. The development of a fidelity scale, barriers and facilitators in the process, future challenges and program outcomes will also be discussed.

Nordentoft (Denmark) will then present how the OPUS trial demonstrated the superiority of EIS compared to treatment as usual for several key outcome measures and how this led to implementation of the model throughout the country. To enhance implementation outcomes, a variety of tools were put in place, such as manuals, training opportunities, and a fidelity scale.

Furthermore, dedicated funding for EIS implementation was made available to facilitate the process. Today, this model continues to add innovative care components.

England's approach, based on standards of care and yearly program auditing since 2016, will be presented by French. The auditing method relies on patient data and a questionnaire regarding services. In the 2019/2020 audit, 155 programs participated, which shows an improvement in several outcome measures, such as recording patient outcomes, cognitive behavioural therapy for psychosis, and supported employment and education programmes. However, slight decreases in other components of care were noted: family interventions, timely access and clozapine use. Globally, EIS in England provide high-quality evidence-based services, which seem to be appreciated by service users.

Bertulies-Esposito (Canada) will present Quebec's situation where program development and implementation between 1987 and 2017 relied on highly motivated clinicians who lacked institutional support. However, in 2017, the provincial government announced additional and protected funding to expand current EIS and implement programs in all regions. Surveys regarding essential components of care were conducted before (2016) and after (2020) increased government involvement. Factors influencing program implementation quality were also surveyed in the latter.

Finally, Iyer (Canada) will synthesize the four presentations' content and lead a discussion on EIS implementation, including clinical, research and policy implications. This symposium will highlight the critical role of government involvement in widespread implementation of EIS and highlight common and unique mechanisms for such involvement, including frameworks, standards, audits, dedicated funding and implementation support.

45.1 IMPLEMENTATION OF A NATIONAL EARLY PSYCHOSIS SYSTEM IN AUSTRALIA; DEVELOPMENT, BARRIERS, FACILITATORS AND THE FUTURE

Eoin Killackey*[1], Andrew Thompson[1], Heather Stavely[1], Georgia Leslie[1]

[1]*Orygen*

Background: Australia was a pioneer in establishing an early intervention service for psychosis in 1992. The evidence produced from this and other similar services led to international reform and establishment of early intervention services in a number of countries. However, in Australia broader system-change and implementation of a national early intervention system did not occur until over 20 years later. This reform has largely happened in the period from 2010. This presentation will examine a number of instrumental moments in this 10-year period that illustrate the process of developing a national system, identify barriers and facilitators to implementation and discuss the challenges of implementation of a system based on a dynamic and evolving evidence base.

Methods: Development of a national system model:

While there had been advocacy for wide reform of mental health services to include evidence based early intervention services for psychosis, there had been little change to embrace this model. In 2010 the national mental health commission commissioned a report into the feasibility of a national early psychosis model. Such a report would also necessarily specify the type of model. Development of the model incorporated evidence, and consultation with national and international experts, clinicians, service managers, family and those with lived

experience of first episode psychosis. The report also included economic evidence on the model's efficiency.

Advocacy, budget commitment, political wrangling and a path forward:

Based on the model developed in the report, advocacy centred on obtaining funding. This came in the federal government 2012 budget. Initially intended as a matched funding with state governments it would lead to the establishment of 16 early intervention services around the country. Over the next year the states and federal government could not reach agreement and in 2013 the federal government decided to implement the measure unilaterally in 9 sites.

Results: Facilitators of Establishment, development and fidelity of sites:
Over the next two years sites were identified and began the process of establishment. This was assisted by a number of measures. These included a detailed operationalisation of each of the 16 elements of the model and development of a subsequent implementation manual. Based on this a fidelity scale was also developed. Funding was also provided for the creation of in-person and on-line training modules for each of the 16 model components. Further, a support and advice function was also provided to assist sites in setting up. Fidelity ratings were used both to assess the implementation and to identify which specific areas were in need of more development at which sites.

Barriers:

Across the implementation a number of barriers were identified, and these will be discussed. A significant barrier is the nature and security of funding. Further barriers are governance arrangements and interaction with local mental health services.

Conclusions: The future:
Challenges regarding the future have also been identified. Among them are the ongoing issues around funding, incorporation of new innovations into the model and ensuring that fidelity measures are also able to make some measure of quality of service provided.

Outcomes:

Outcomes that have been identified now that the model has been fully operational for some time will also be presented. These include number of young people seen and measures of functional and symptomatic recovery.

45.2 FROM RESEARCH TO PRACTICE: HOW OPUS TREATMENT WAS ACCEPTED AND IMPLEMENTED THROUGHOUT DENMARK

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Background: The early phases of psychosis have been hypothesized to constitute a critical period, a window of opportunity. At the same time, the early phases of psychosis are associated with increased risk of unwanted outcome, such as suicidal behaviour and social isolation. This was the background for the emergence of early intervention services, and in Denmark, the OPUS trial was initiated as part of that process.
Methods: Modified assertive community treatment, together with family involvement and social skills training, constituted the core elements in the original programme. A total of 547

patients with first episode psychosis were included in the trial. After the trial OPUS was implemented as standard care all over Denmark.
Results: To summarize briefly the results of the OPUS trial: OPUS treatment was superior to standard treatment in reducing psychotic and negative symptoms and substance abuse, in increasing user satisfaction and adherence to treatment, and in reducing use of bed days and days in supported housing. Moreover, relatives included in OPUS treatment were less strained and had higher level of knowledge about schizophrenia and higher user satisfaction.
Implementation involved development of a manual, training courses in family involvement and social skills training, and a fidelity scale.

Conclusions: OPUS treatment was implemented throughout Denmark. Training courses were developed and manuals and books published. Regional health authorities had access to national grants for implementing early intervention services; as a result, OPUS teams were disseminated throughout the country. The content of the treatment is now further developed, and new elements are being tried out – such as individual placement and support, lifestyle changes, cognitive remediation, specialized treatment for substance abuse, and different kinds of user involvement.

45.3 EARLY INTERVENTION IN PSYCHOSIS SERVICES IMPLEMENTATION IN ENGLAND: NATIONAL AUDIT OF QUALITY STANDARDS

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Background: In 2016, England developed standards to ensure that people with first episode psychosis (FEP) and their caregivers receive quality care. EIP teams have been audited annually against these standards since 2016. This presentation describes the audit methods and results.
Methods: EIP teams submitted retrospective data on a sample of up to 100 FEP patients on caseload and complete a service-level questionnaire. Data will be presented from the National Clinical Audit of Psychosis hosted by the College Centre for Quality Improvement at the Royal College of Psychiatry.
Results: Data was submitted from 155 EIP teams in England on 10,560 cases that were used in the final analysis. Performance against several standards have improved since the first NCAP EIP Spotlight Audit 2018/2019. The greatest change was seen in performance on recording outcome measures (from 22% to 41%). Improvement was also seen in physical health screening (from 64% to 75%), interventions for abnormal glucose control (69% to 75%) and abnormal lipids (68% to 75%). Provision of other physical health interventions remained similar, as did performance against other standards. Take-up of CBTp increased slightly from 46% to 49%, supported employment and education programmes from 28% to 31%, and carer-focused education and support programmes from 55% to 58%. Small reductions were seen in provision of family intervention (FI) (22% to 21%), timely access (76% to 74%) and interventions received for elevated blood pressure (from 66% to 65%). There was also a drop in those offered clozapine (54% to 52%).
Conclusions: The data collected show that the provision of timely access to evidence-based treatments for people experiencing FEP has generally continued to improve, and that people treated by EIP services largely report satisfaction with the care received. However, more can be done to improve the provision of evidence-based care in line with NICE quality standards.

45.4 EARLY INTERVENTION FOR PSYCHOSIS SERVICES IMPLEMENTATION IN QUEBEC, CANADA: THE STATE OF AFFAIRS

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Background: For the first few decades following the development of the first early intervention for psychosis service (EIS) in 1987 in Quebec, developing and implementing such programs was driven by highly dedicated individual clinicians whose practices were based on a growing body of EIS literature. In 2017, after over a decade of relentless advocacy by a community of practice for EIS, the provincial government committed to implementation of EIS across the province so as to make EIS available to all of its youth. To support this promise, it published provincial EIS standards, and dedicated funding; human resources to support program development and ongoing implementation; and increased training opportunities. Quebec therefore serves as a unique context to study the impact of policy commitment on implementation fidelity of EIS, by comparing adherence to essential components before and after this change.

Methods: An initial survey of EIS was conducted in 2016, reaching 17 of the 18 existing programs at the time. In 2020, a new online survey was conducted to study the effects of the policy shift by comparing adherence to essential EIS components of programs founded after 2017 with that of older programs. Implementation outcomes were also surveyed, including facilitators and barriers to implementation. Twenty-eight of the 33 programs operating in the province responded.

Results: The 2016 survey revealed that most programs offered high-quality clinical services despite the lack of policy support and dedicated funding. However, specific challenges were observed with respect to administrative and organizational components, such as program evaluation, quality assurance, accessibility through open referral policy, and early identification through public outreach and education of referral sources. Rural programs faced additional challenges in adhering to the EIS model. The latest survey shows that government support through financial resources, establishment of local standards of care, and implementation support has allowed new EIS to develop quickly and adhere to essential components of the model. Results also pointed to specific implementation facilitators and barriers such as turnover among team members, perceived institutional support, team cohesion and morale, workload, and access to adequate physical, human and financial resources.

Conclusions: Increased government involvement in the last three years through financial resources, expert counselling for programs and the publication of provincial standards of care has played a significant role in the rapid development of several new programs offering high-quality care to persons suffering of early psychosis. Using this case study, this presentation will discuss the role of facilitating policies and ongoing implementation support for scaling up EIS, while adhering to quality standards.

46. RECONCEPTUALIZING SCHIZOPHRENIA SPECTRUM ILLNESSES AS SYSTEMIC DISORDERS

Christoph Correll

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Overall Symposia Abstract: Patients with schizophrenia spectrum illnesses demonstrate evidence of metabolic abnormalities and elevated biomarkers of oxidative stress and inflammation, which are present even prior to introduction of antipsychotic drug (APD) treatments. Moreover, these early metabolic and inflammatory sequelae are associated with white matter brain changes, abnormal brain connectivity, as well as worse functional outcomes and increased illness severity. Together, this suggests that systemic disturbances are intrinsic to psychotic disorders, potentially representing new treatment targets. In addition, APDs used in the treatment of these disorders are well established to induce severe metabolic adverse effects including dysglycemia, and thus likely exacerbate the intrinsic metabolic symptoms of affected individuals. This may offer novel insights as to why our current treatments, beyond efficacy for 'positive' symptoms of psychosis, largely fail to address disability and poor functional in those who suffer from schizophrenia spectrum illnesses.
This symposium is chaired by Dr. Christoph Correll, a noted expert in schizophrenia therapeutics and APD psychopharmacology, takes a translational approach to dissect an emerging and complex topic: the systemic manifestations of schizophrenia spectrum illnesses and effects of APDs on related metabolic and bioenergetic pathways. Dr. Heline Mirzakhanian (UCSD) will present clinical data examining markers of neuroinflammation using H-MRS between healthy controls and unmedicated first episode psychosis (FEP) patients. Significant associations between cortical thickness, identified neurometabolites and peripheral biomarkers of neuroinflammation will be discussed. Dr. Margaret Hahn (University of Toronto) will present novel preclinical data demonstrating that APDs including olanzapine and haloperidol interfere with central nervous system (CNS) glucose sensing (the key fuel source of the brain), resulting in whole body insulin resistance. These data demonstrate a novel mechanism by which APDs increase risk of type 2 diabetes (T2D) and build on preclinical findings suggesting APDs dysregulate neuronal inflammatory and insulin signaling pathways. Dr. Zachary Freyberg will present new studies demonstrating a key role for non-CNS dopaminergic pathways in peripheral organs including pancreas for metabolic regulation. He shows that APDs directly act on pancreatic dopamine D2-like receptors to disturb dopamine's regulation of insulin and glucagon release. This results in excessive insulin and glucagon, which are postulated to drive insulin resistance and hyperglycemia observed clinically in response to APDs. Dr. Robert McCullumsmith will present a novel transcriptomics approach to identify new signaling pathways altered in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia. He demonstrates altered AMPK and AKT protein kinase activity in the DLPFC and applies a bioinformatics approach to identify drugs that may reverse this disease signature. Lastly, discussant Dr. Matej Oresic will bring his expertise in metabolic phenotypes in psychiatric disorders including associations with T2D.

46.1 ANTIPSYCHOTIC DRUGS DYSREGULATE CENTRAL GLUCOSE SENSING RESULTING IN WHOLE BODY INSULIN RESISTANCE

Laura Castellani[3], Chantel Kowalchuk[1], Roshanak Asgariroozbehani[2], Sandra Pereira[3], William Brett McIntyre[3], Adria Giacca[3], Margaret Hahn*[3]

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Background: Antipsychotics (APs) remain the cornerstone treatment for schizophrenia and are widely prescribed for other conditions. However, their use presents a significant risk for serious adverse glycemic effects. Independent of adiposity changes, APs directly dysregulate whole body glucose metabolism, and this occurs in part through the central nervous system (CNS). To this end, we have recently demonstrated that olanzapine impairs CNS insulin-action, resulting in whole body insulin resistance. In addition to a critical role of hormones such as insulin in the CNS, glucose-sensing at the hypothalamus is also pivotal for the regulation of whole-body insulin sensitivity. Glucose also represents the primary fuel for brain function, and the hypothalamus represents the key brain center (through glucose sensing neurons) to ensure maintenance of key homeostatic systems. In the current study, we set out to examine the effects of a first generation AP (haloperidol) and second-generation AP (olanzapine) on CNS-glucose sensing, 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 glucose or vehicle solution (2mM, 5μL/hour, into the 3rd ventricle). Male rats were co-treated with an acute injection of olanzapine (3mg/kg, S.C.), haloperidol (10mg/kg, S.C.) or weight adjusted vehicle(veh). AP dosing is based on clinical D2 occupancies. Groups included (ICV–peripheral) Veh–Veh (n = 6), glucose (Glu)–Veh (n = 8),Glu–olanzapine(Ola) (n = 6), Veh–Ola (n = 6), Glu-haloperidol (Hal) (n = 6) and Veh-Hal (n = 7). The peripheral glucose infusion rate needed to maintain euglycemia during the clamp was used as a measure of whole body insulin sensitivity. A radioactive tracer (3-H3-glucose) infusion throughout the clamp procedure was used to assess glucose kinetics, including hepatic glucose production and peripheral glucose uptake.
Results: As expected, ICV (central) glucose infusion caused a significant increase in the peripheral glucose infusion rate (mg/kg.min) compared to vehicle (Veh-Veh 2.96±0.72 vs Glu-Veh 9.15±1.41), $p<0.05$). This effect was mitigated by both olanzapine (Glu-Veh 9.15±1.41, Glu-Ola 0.63±0.38, $p<0.05$) and haloperidol (Glu-Veh 9.15±1.41, Glu-Hal 3.00±0.47, $p<0.05$). Compared to vehicle treated animals, ICV glucose significantly suppressed glucose production (clamp relative to basal: Veh-Veh 19.4%± 15.3 vs Glu-Veh 71.2%±14.1, $p<0.05$) and this effect was inhibited by olanzapine (Glu-Ola16.72%±12.62). The ICV glucose did not alter glucose utilization compared to ICV vehicle (clamp relative to basal: Veh-Veh 24.4%±17.27 vs Glu-Veh 17.0%±18.96, $p>0.05$). However, glucose utilization was significantly suppressed following haloperidol treatment (clamp relative to basal: Veh-Veh 24.4%±17.27 vs Glu-Hal (-)24.2%±5.12, $p<0.05$). In summary, olanzapine and haloperidol both impaired central glucose sensing resulting in whole body insulin resistance via alterations in glucose production (olanzapine) and glucose utilization (haloperidol).
Conclusions: Hypothalamic glucose-sensing is critical for the regulation of peripheral glucose homeostasis. This data, for the first time, demonstrates evidence that APs disrupt central glucose-mediated regulation of glucose kinetics. Perturbed glucose-sensing in the CNS is expected to have deleterious metabolic consequences and possibly disrupt other brain glucose-dependent functions such as cognition. The study unveils a novel effect of AP treatment to disrupt brain nutrient-sensing, suggesting this may be a mechanism by which these drugs increase risk of type 2 diabetes.

46.2 PERIPHERAL AND CENTRAL BIOMARKERS ASSOCIATED WITH INFLAMMATION IN EARLY PSYCHOSIS

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Background: Early-life exposure to stress, infection and/or inflammation has the potential to induce systemic changes linked to metabolic abnormalities, enhanced production of pro-inflammatory cytokines and activated microglia. Elevated serum cytokines have been reported in neuropsychiatric diseases including depression, dementia, and psychosis. Pro-inflammatory cytokines inhibit neurogenesis and hippocampal function, induce apoptosis in cortical neurons and oligodendrocytes, and affect synapse formation and connectivity. Elevations in proinflammatory mediators have been shown to influence symptoms of depression via several mechanisms related to monoamine and glutamate neurotransmission. Microglial activation and inflammatory cytokines have also been implicated in the pathogenesis of white matter disorders including the white matter volume reduction and abnormal brain connectivity reported in first-episode psychosis (FEP). Free water imaging of diffusion MRI data has demonstrated a significant increase in extracellular volume in both white and gray matter in patients with schizophrenia suggesting that prolonged inflammation may lead to axonal degeneration and gray matter loss.

We have reported that Clinical High Risk (CHR) for psychosis participants from the North American Prodromal Longitudinal Studies Consortium demonstrate evidence of metabolic abnormalities, before the onset of psychosis or antipsychotic treatment, that are associated with symptoms and poor functioning. Additionally, early life adversity in CHR is associated with plasma biomarkers of inflammation and oxidative stress in new data from our group. In a separate sample of CHR, medicated and unmedicated FEP participants we have found evidence of elevated proinflammatory biomarkers that are greatest in the CHR sample followed by unmedicated FEP.

1H-MRS studies in psychotic illness suggest that neuroinflammation can result in elevated levels of myo-inositol (Ins) and choline-containing compounds (Cho). In the present study, we compared glutamate, Cho, Ins and N-acetylaspartate (NAA) in bilateral dorsal caudate and Medial Prefrontal Cortex (MPF) in 13 antipsychotic-naive FEP participants and 10 healthy controls (HC) ages 14-30 and explored the associations with peripheral inflammatory biomarkers.

Methods: 1H-MRS spectra were obtained using PRESS (TE =35ms) and shimmed to achieve full width at half maximum (FWHM) $\leq$12 Hz and analyzed using LCModel. Neuroinflammatory biomarkers (cytokines, chemokines, markers of vascular injury) were analyzed by commercial ELISA with internal controls. The association between neurometabolite levels that differed significantly between groups and neuroinflammatory biomarkers were analyzed using Pearson correlations.

Results: There were significantly higher levels of Glu in the Left (LC) and Right (RC) caudate in FEP compared to HC ($p < 0.05$) and associated with lower Brain-derived neurotrophic factor (BDNF) ($r=-.81$; $p<0.05$) and Thymus and activation-regulated chemokine (TARC) ($r=-.87$; $p<0.01$) levels in the RC, possibly indicating disruption of neuroprotective, modulatory effects of BDNF on Glu circuitries. FEP also had higher levels of Ins in the RC ($p < 0.05$) associated with lower Macrophage Derived Chemokine (MDC) ($r=-.78$; $p < 0.05$) and in the MPF associated with lower Macrophage Inflammatory Proteins (MIP 1B) ($r=-.77$; $p < 0.05$), possibly indicating a proinflammatory response associated with neuronal insult. Levels of Choline were higher in FEP in all three ROIs and this was associated with lower Eotaxin ($r=-.89$; $p<0.01$) but higher monocyte chemoattractant protein 1 (MCP1) ($r=.82$; $p<0.05$) likely suggesting a neuroinflammatory response at the blood brain barrier. No group differences were found in NAA levels.

Conclusions: Discussion: Our results are in line with previous studies showing neurometabolite changes present at the onset of psychotic illness. New data demonstrates an association between neurometabolites and inflammatory biomarkers, providing preliminary evidence for the interplay of neuroinflammatory and neurodegenerative processes implicated in the emergence of psychotic illness.

46.3 NEW PERIPHERAL PANCREATIC DOPAMINE MECHANISMS OF ANTIPSYCHOTIC DRUG-INDUCED METABOLIC DISTURBANCES

Despoina Aslanoglou[1], Suzanne Bertera[2], Marta Sánchez-Soto[3], R. Benjamin Free[3], Jeongkyung Lee[1], Wei Zong[1], Xiangning Xue[1], Shristi Shrestha[4], Marcela Brissova[4], Ryan W. Logan[1], Vijay Yechoor[1], David R. Sibley[3], Rita Bottino[2], Zachary Freyberg*[1]

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Background: Antipsychotic drugs (APDs) are among the most widely prescribed psychiatric medications today. Yet, these drugs also cause profound metabolic disturbances including weight gain, glucose intolerance, and insulin resistance and increase the risks of developing type 2 diabetes (T2D) and cardiovascular disease. All APDs cause metabolic side effects to differing degrees and current treatments to reduce these metabolic symptoms have limited efficacy. To date, the mechanisms for APD-induced metabolic disturbances are poorly understood. Nonetheless, the single unifying property of all APDs is their blockade of dopamine (DA) D2-like receptors including D2 (D2R) and D3 (D3R) receptors, suggesting a potential role for these receptors in APD-induced metabolic dysfunction. APD-induced changes in glucose homeostasis occur even in the absence of increased food intake or psychiatric disease. This raises the possibility that APDs may act directly on metabolically-relevant peripheral targets to cause metabolic disturbances. Consistent with this, we and others discovered that D2R and D3R are expressed peripherally in both human and rodent insulin-secreting pancreatic beta cells, key regulators of glucose metabolism. While much less studied then beta cells, D2R and D3R are also expressed in glucagon-secreting pancreatic alpha cells. We therefore hypothesize that APD-induced metabolic disturbances are driven by the direct actions of APDs on pancreatic alpha cell and beta cell D2-like receptors.

Methods: Human pancreatic islet transcriptome analysis: De-identified human islet alpha cells and beta cells (n=5: 3 females, 2 males) were purified by FACS sorting; alpha cells and beta cells were distinguished via indirect antibody labeling with alpha- and beta cell markers. For DA measurements, mouse alpha cell-derived alpha TC1-6 cell supernatants and cell lysates were collected and run on HPLC. Insulin and glucagon homogenous time-resolved resonance energy transfer (HTRF) assays: De-identified cadaveric human islets and BALB/c mouse islets were collected and cultured overnight prior to use. Islets were glucose-stimulated and supernatants collected for insulin and glucagon measurement via HTRF. All human and mouse islet studies were IRB- and IACUC-approved.

Results: We conducted a comprehensive transcriptome analysis to characterize the DA signaling and biosynthetic machinery in human pancreatic alpha and beta cells followed by RNAseq. We found that human alpha and beta cells express the complete DA biosynthetic, catabolic and signaling machinery. HPLC analyses demonstrated that alpha cells both synthesize and secrete DA and DA precursor L-DOPA. Our transcriptome data also showed that D2R and D3R are the predominantly expressed DA receptors in both human alpha and beta cells. These data suggest that APDs target these receptors in beta cells and alpha cells.

In human pancreatic islets, we discovered that low DA concentrations potently decreased glucagon release, in addition to DA's inhibition of beta cell glucose stimulated insulin

secretion. These results suggest that DA modulates both glucagon and insulin secretion in islets. We next examined whether APDs disrupt coordinated secretion of glucagon and insulin during glucose stimulation of human islets. We showed that both clozapine and olanzapine substantially increased alpha cell glucagon secretion relative to vehicle controls; haloperidol also raised glucagon secretion, albeit to a lesser degree. All three APDs also significantly increased GSIS from the same islets. Our results suggest that APDs enhance insulin and glucagon release, contributing to systemic metabolic dysfunction.

Conclusions: We show that pancreatic alpha cells may provide a key source of pancreatic DA which signals locally at alpha and beta cell receptors to modulate both insulin and glucagon secretion. APDs disrupt this pancreatic DA signaling via alpha and beta cell DA D2R and D3R to significantly disturb secretion of key hormonal regulators of metabolism. APDs disrupt dopaminergic inhibition of glucose-stimulated insulin secretion in beta cells, leading to excessive insulin secretion in islets – a driver of insulin resistance in type 2 diabetes. Similarly, APD blockade of alpha cell D2R/D3R also elevates glucagon secretion – a key driver of hyperglycemia. Ultimately, our work suggests that APDs act directly on both alpha cell and beta cell DA signaling to significantly disturb metabolism.

46.4 METABOLIC PERTURBATIONS IN SCHIZOPHRENIA: ABNORMALITIES OF INSULIN SIGNALING PATHWAYS AND ENERGY SENSING IN THE FRONTAL CORTEX

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Background: Converging evidence suggests perturbations of metabolic function in schizophrenia. Metabolic function encompasses myriad biochemical systems and processes, including uptake and breakdown of glucose into bioenergetic substrates. Fates of these substrates include production of monocarboxylates (in particular pyruvate and lactate), which in turn are reactants for the production of ATP in brain cells. These processes are tightly controlled on many levels, including gene expression and posttranslational modification of proteins. Phosphorylation via protein kinases has a major role in the modulation of ATP production, as well as in the fate(s) of the monocarboxylates produced via glucose metabolism. In this study, we have assessed several levels of gene expression and function in postmortem brain from subjects with schizophrenia, highlighting the roles of different elements of bioenergetic pathways downstream of insulin signaling.

Methods: We used the Pamgene kinone array, western blot analyses, individual kinase activity assays, and QPCR to assess expression of elements of insulin signaling pathways, including the AKT and AMPK kinases. We used cell culture and siRNA strategies to identify the relevant serine/threonine peptides on kinome array chips. We used bioinformatics to identify pathways, substrates and drugs associated with our disease signatures. We used kaleidoscope (and R shany app developed in our laboratory) to perform confirmation studies in >30 published databases. Finally, we used LCM QPCR to test specific cell-level hypotheses related to AKT isoform expression in neurons in the frontal cortex in schizophrenia. All of our studies were performed in postmortem samples (n = 16-20 per group) from the ACC or DLPFC.

Results: Kinome array studies show AKT and AMPK as major kinase nodes in postmortem samples from subjects with schizophrenia. Selection of specific reporter peptides was confirmed with cell culture over- and under-expression studies run on the array, which confirmed these and other kinases as hits. We found changes at the region and cellular level in the expression of AKT isoforms ($P < 0.05$). We also found a decrease in the expression of

phosphoAKT, along with an increase in AKT specific activity, in the ACC in schizophrenia ($P < 0.05$). We found a decrease in AMPK activity in the DLPFC in schizophrenia ($P < 0.05$). Following this lead, we studied the first committed steps of glycolysis, and found decreased in enzyme activity and gene expression in hexokinase and phosphofructokinase ($P < 0.05$). We also found an increase in the monocarboxylate transporter MCT1 ($P < 0.05$). We next used a bioinformatics approach, leveraging these findings to generate a disease signature in the LINCs database, which allowed us to identify drugs which reverse the disease signature. One of these drugs was tested in an animal model of schizophrenia, and we found an improvement in a working memory task following administration ($P < 0.05$). Finally, we also detected an increase in lactate levels in postmortem brain in schizophrenia ($P < 0.05$).

Conclusions: Taken together, our findings suggest in schizophrenia 1) diminished glycolysis in pyramidal neurons , 2) increased expression of monocarboxylate transporters, 3) increased levels of lactate, not attributable to postmortem factors or antipsychotic treatment, 4) perturbations of kinases in the insulin signaling pathways. We posit these changes represent a shift towards increased utilization by neurons of monocarboxylates from external sources, and diminished utilization of glucose. These findings highlight the burgeoning evidence for bioenergetic dysfunction in schizophrenia and open new avenues for development of interventions for this often devastating illness.

47. LAYERS OF THE REAL WORLD? THE EXTERNAL VALIDITY OF EARLY PSYCHOSIS RESEARCH AND IMPLICATIONS FOR POPULATION HEALTH

Jai Shah

McGill University

Overall Symposia Abstract: Research findings over the past two decades have improved our understanding of schizophrenia and other psychotic disorders, especially its initial onset and course. However, with this interest and growing uptake has come increasing attention to the population health implications of psychosis and the clinical programming that aims to treat it. This symposium reviews convergent evidence from multiple studies and approaches that highlight a pressing need to better understand and improve the representativeness of research and clinical samples in early intervention services for psychosis (EIS). Despite having developed and offered effective intervention packages for at least a decade, it is unclear how generalizable EIS research findings are to the overall clinical population actually being served – nor whether a majority of new-onset cases are identified and treated, even in sites with longstanding, well-known EIS programs. Without this knowledge, it remains difficult to determine whether interventions that are effective at an individual level are actually having an impact at the population level, or alternately whether adverse events could be prevented and outcomes improved by offering clinical programming that reaches the entirety of the population. At the same time, the symposium will suggest specific strategies for overcoming these challenges in research, clinical programming, and outreach activities.

The first speaker (Dr. Kline) will present evidence of “sampling skew” comparing a first-episode psychosis research sample with a clinical sample. These findings suggest greater diagnostic complexity in the clinical sample – as well as poorer social, role, and cognitive functioning compared to the research sample. There was also an over-representation of non-ethnic minority groups in the research sample, highlighting the need to standardize recruitment protocols to increase sociodemographic and clinical diversity.

The second speaker (Dr. Shah) will examine a large, well-characterized catchment-based clinical sample of individuals experiencing a first episode of psychosis (FEP) and the research samples drawn from it. Each of a sequence of filters (inclusion/exclusion criteria, decisions to not approach specific patients, and patient acceptance or refusal) between the starting clinical population and the reported research sample may be exerting influences on the final population being examined, as measured by key service-related indicators. Furthermore, the impact of these filters on representativeness may differ depending on the focus of each research project. These findings suggest specific strategies to improve representativeness and transparency in reporting around it.

The third speaker (Dr. Anderson) will review findings from an ongoing study comparing cases of nonaffective FEP identified from health administrative data who were and were not admitted to EIP services. While those who received EIS had lower mortality and improved outcomes on a range of indicators, over 50% of suspected cases had never been in contact with EIS, and there was evidence of sociodemographic and clinical disparities in access. Dr. Anderson will also present findings on the role of distance to the EIS on these observed disparities in access.

The final speaker (Dr. Srihari) will describe an approach to designing next-generation early intervention services that addresses concerns about population representativeness, the care needs of diagnostically ambiguous populations, and integration with translational research. An exemplar population health based EIS will be presented, with data from ongoing early case identification, DUP reduction campaigns, and other projects that illustrate the value of this platform for improving various aspects external validity raised throughout the symposium.

These findings and the participants' suggestions for furthering external validity will then be appraised and critically integrated by the discussant, Prof Susser.

47.1 NEUROCOGNITIVE, SOCIAL, AND ROLE FUNCTIONING IN FIRST EPISODE PSYCHOSIS POPULATIONS: DO RESEARCH SAMPLES REFLECT THE REAL WORLD?

Emily Kline*[1]

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Background: The external validity or "generalizability" of clinical research hinges on the extent to which participant samples faithfully represent real-world populations of interest. This presentation
examines the issue of external validity by evaluating the similarity of recruited research samples to unselected clinic samples in two studies that recruited first episode psychosis (FEP) patients within the same city (Boston, United States) and clinical center (Massachusetts Mental Health Center, MMHC).

Methods: Study 1 (The Boston Center for Intervention Development and Applied Research [CIDAR], 2007-2012). The "CIDAR" study recruited patients from local clinics and community settings, including the PREP® clinic at MMHC. We compared PREP® clinic patients admitted and assessed during this period who did not participate in research (n=77) to FEP research participants (n=44),
and age-matched controls (n=38) with regard to demographic characteristics, the MATRICS consensus cognitive battery, and global functioning social and role scales. Between-group

differences were assessed via one-way ANOVA and Chi-square analyses. Study 2 (Reducing Duration of Untreated Psychosis [DUP] and its Impact in the United States,

2014-2018). The "DUP" study recruited exclusively from the PREP® clinic at MMHC. Investigators designed the recruitment strategy to maximize the likelihood that the recruited sample would more accurately reflect the treated population: embedding research staff within the clinical team, increasing the compensation available to participants, and offering participants the option of

completing study visits within familiar clinical offices. We then compared demographic

characteristics and, neurocognitive, social, and role functioning between patients who participated in the study (n =54) and those who were admitted to the clinic but did not participate in research (n= 21) using one-way ANOVA and Chi-square analyses.

Results: Study 1. No significant differences were observed between groups with regard to age and gender. The FEP research sample had a significantly higher proportion of white participants, better
social and role functioning, and better neurocognitive performance when compared with the FEP clinical population.

Study 2. No significant demographic, cognitive, or social/role functioning differences were observed between those who did and did not participate in research, suggesting that the strategies to recruit a more representative subsample were successful; however, it should be noted that a substantial proportion of patients were found ineligible and/or declined participation despite the aforementioned accommodations.

Conclusions: Skewed sampling represents a threat to both the generalizability of research findings as well as a violation of the principle of equity: access to research and especially clinical trials
should not be restricted to those with the means or connections to navigate an overly complex bifurcation of "academic" and "community" care networks. Researchers should be aware of how study design and recruitment practices may impact the representativeness of samples. Concerns

highlighted by these studies are equal representation of patients with more severe illness and of racial minorities, particularly in the United States where minorities have been subject to

discrimination and harm in medical research contexts. Co-locating research with clinical services, offering compensation for participants' time and contributions, and assigning research staff to some non-research, therapeutically oriented interactions with patients, can help to promote wider participation.

47.2 REPRESENTATIVENESS IN CONTEMPORARY PSYCHIATRIC RESEARCH VERSUS PRACTICE: EVIDENCE AND IMPLICATIONS FROM AN EARLY INTERVENTION SERVICE

Jai Shah*[1], Michael Groff[2], Genevieve Gariepy[3], Kelly Anderson[4], Ashok Malla[1], Martin Lepage[1], Srividya Iyer[1], Ridha Joober[1]

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Background: Research findings over the past two decades have improved our understanding of schizophrenia and related disorders, including their onset and early course. However, this growing uptake also necessitates attention to the representativeness of research samples in order to ensure that their findings apply to real-world clinical populations. Indeed, a series of sequential 'filters' operates between the index clinical population and derived research samples: inclusion/exclusion criteria, clinical decision to approach a participant or not, and whether a patient accepts or refuses following informed consent. In a longstanding EIS for first episode psychosis (FEP), we therefore compared characteristics of clinical and research participants across each of these filters for a range of demographic and clinical variables.
Methods: Within a well-established FEP clinical research infrastructure operating within a catchment-based service in Montreal, Canada, we examined patients (ages 14-35) who did (n=175) and did not (n=214) participate in a major peer-reviewed services-oriented research project funded by a national health research agency. Group representativeness at each filter-point was assessed across dimensions of affective versus nonaffective psychosis, presence of comorbid substance use disorder, length of prodrome and duration of untreated psychosis (DUP), and symptoms. Between-group differences were assessed using basic descriptive statistics including t-tests, chi-squared tests, and Mann-Whitney U tests, as appropriate.
Results: Significant differences emerged at every filter point between the index clinical population and those removed from consideration for study participation. Those not considered for participation based on exclusion criteria were more likely to have a nonaffective psychosis, a longer prodrome and DUP, and less severe symptoms. Those who were not approached for clinical reasons had significantly greater rates of nonaffective psychosis and less severe symptoms, but equivalent lengths of prodrome and DUP.
Conclusions: Even in longstanding catchment-based EIS settings with an integrated research infrastructure, study samples may be capturing subgroups that are not representative of the index (presenting) clinical population in important yet potentially divergent ways. Given the ascendance of population-based approaches in mental health, researchers should be aware of the possibility of similar discrepancies in their own studies and careful to interpret study findings in light of questions regarding generalizability. Potential interventions to strengthen representativeness at each 'filter point' between the index clinical population and resulting research sample, from service design to the reporting ofresults, will be discussed.

47.3 TAKING A POPULATION-PERSPECTIVE ON EARLY PSYCHOSIS INTERVENTION SERVICES: WHO GETS IN, AND WHO IS LEFT BEHIND?

Kelly Anderson*[1]

[1]*Western University*

Background: The last two decades have seen the widespread implementation of EPI programs around the world. This has led to a corresponding increase in the number of research studies recruiting samples of people with first-episode psychosis from specialized early psychosis intervention (EPI) services. However, what is often lacking in this body of research is a discussion of the external validity of EPI samples – with this comes the implicit assumption that the vast majority of cases of first-episode psychosis are detected and treated by EPI services. This presentation will summarize findings from a series of published studied aimed at: (i) estimating the proportion of incident cases of non-affective psychosis who do not access EPI services; (ii) examining the socio-demographic and clinical factors associated with EPI admission; and (iii) assess the implications of this reliance on EPI samples for our understanding of the epidemiology of psychotic disorders.

Methods: Using health administrative data, we constructed a retrospective cohort of incident cases of non-affective psychosis in the catchment area of the Prevention and Early Intervention Program for Psychoses (PEPP) in London, Ontario between 1997 and 2013. This cohort was linked to primary data from PEPP to identify EPI-users. We used multivariate logistic regression to model socio-demographic and service factors associated with EPI admission. We also used mapping techniques and regression models to estimate the impact of distance from the program on access to EPI care. Finally, we examined the implications of various sample options on incidence estimates and associated risk factors.
Results: Over 50% of suspected cases of non-affective psychosis did not have contact with the EPI program for screening or admission. Our findings suggest a clear gradient by age, with a decreasing odds of being treated in the EPI program with increasing age strata. EPI-users are more likely to be male, and less likely to live in areas of socioeconomic deprivation. EPI-users also had a lower odds of prior alcohol-related and substance-related disorders. Finally, our incidence estimates for the program catchment area were over twice as high as the EPI-treated incidence, with attenuated risk ratios for major risk factors for psychotic disorder, such as sex and migrant status, in the catchment-based sample.
Conclusions: Much of the prior research on EPI services is predicated on the belief that nearly all people with first-episode psychosis are represented in these services, with little discussion or consideration of people who may be receiving care elsewhere in the health system. We need greater consideration of patients with first-episode psychosis who are not accessing EPI services – our findings suggest this group is sizable, and there may be socio-demographic, clinical, and geographic disparities in access, which may consequently bias study findings. Research using samples recruited from EPI services should give greater attention to the extent to which these samples are representative of the broader population of people with early psychosis.

47.4 POPULATION HEALTH: EARLY INTERVENTION SERVICES 2.0

Vinod Srihari*[1], Maria Ferrara[1], Emily Kline[2], Fangyong Li[1], Laura Yoviene Sykes[3], Walter Mathis[1], John Cahill[3], Keith Gallagher[1], Cenk Tek[3], Matcheri Keshavan[2]

[1]*Yale University,* [2]*Harvard Medical School at Beth Israel Deaconess Medical Center,* [3]*Yale University School of Medicine*

Background: Several developments in evidence and policy raise the need for next generation Early Intervention Services (EIS). Promising support for efforts to shorten the Duration of Untreated
Psychosis (DUP) and rigorous support for specialty-based care for first-episode psychosis (FES) should raise expectations for how EIS can respond to local gaps in access and care quality.

Additionally, the Clinical High Risk (CHR) research paradigm has delivered a complex set of results that will require careful interpretation and suggest avenues for future studies that will need to be attentive to issues of sampling that threaten the external validity of findings, while also confronting the more universal need for care amongst help-seeking samples. Services will also need to design for active participation in research focused on discovering causal factors and biomarkers that will be necessary to improve prognosis and treatment.

Methods: A specific strategy to meet the design needs of next generation EIS will be presented. The design feature of Population Health will be introduced, an exemplar PH based EIS will be described and data from several ongoing projects will be presented to illustrate the value of this approach to address the challenges of external validity, stepped care and integration with

translational research. The Program for Specialized Treatment Early in Psychosis (STEP) has delivered FES since 2006, and in 2015 began explicitly modeling a PH based EIS that seeks to improve access, care quality and outcomes for all residents of a defined geographic catchment with recent onset psychosis. The PH framework involves an explicit focus on: non-medical determinants of health (e.g. social, structural) and on a wide range of ecologically salient outcomes relevant to all local stakeholders, and interrogates for disparities in access and care delivery. The FES serves as an integrator of a local network of cross-sector stakeholders (healthcare, criminal justice, education, social services, voluntary and religious organizations) and seeks to transform pathways to and through care and measure outcomes that are responsive to the expectations of all these stakeholders. Additionally, this FES is co-located with a CHR research clinic.

Results: Over 4 years STEP's FES fielded queries from a wide variety of regional takeholders (clinical, education, criminal justice, social services), formally assessed over thousand referrals, and successfully enrolled 146/167 (87%) patients meeting broad eligibility criteria. The sample is representative of the region in comparison to census figures on usual demographic variables, but data will also be presented on relative participation of the local network in referrals and enrollments, in contributing to delay in the pathway to care and the differential routes to care of CHR vs FEP samples.

Conclusions: STEP's PH based model of EIS is feasible and offers one way to provide care across the continuum from prodrome to chronic psychosis, recruiting representative samples for research, and collaborating with research focused on discovering illness etiology and mechanisms.

O1. Oral Session: Risk and Resilience: Insights from Developmental and Environmental Factors

O1.1. RISK OF PSYCHOSIS IN CHILDREN AND ADOLESCENTS WITH AN AT RISK MENTAL STATE

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Background: The "At Risk Mental State" (ARMS) approach to psychosis, also called Clinical/Ultra High Risk, has had a major impact on psychosis services internationally. Despite well-established developmental differences in the prevalence and expression of psychotic symptoms from childhood into adulthood, however, there has been no systematic review of psychosis transitions specifically in children and adolescents up to age 18 years. Evidence for this age group is crucial for developmentally appropriate clinical decision making for Child and Adolescent Mental Health Services, which typically see young people from childhood up to age 18 years.
Methods: We conducted a systematic review and meta-analysis of psychosis risk among children diagnosed with ARMS up to age 18 years. We calculated pooled transition rates to psychosis after 1-year, 2-year and ≥5-year follow up.
Results: We retrieved 1107 records and identified 16 articles from 9 studies, reporting on 436 individuals with ARMS aged 9 to 18 years. The pooled transition rate to psychosis at 1-year was 9.5% (95%CI 5.5%–14.2%, 7 studies included), at 2-years 12.1% (95%CI 6.7%-18.6%, 4 studies included) and at ≥5 years 16.1% (95%CI 5.6%-30.0%, 4 studies included). We did not find evidence that ARMS diagnosis predicted psychosis in excess of the risk associated with study recruitment biases.
Discussion: At 5 year follow up, one in six youths diagnosed with an ARMS had transitioned to psychosis but we did not find evidence that this risk was related to ARMS diagnosis as opposed to sampling/recruitment strategies. Our findings indicate a need for caution in applying ARMS methodology to children and adolescents and highlight the need for developmentally sensitive approaches when considering psychosis risk prediction.

O1.2. MOTOR ABNORMALITIES AND PSYCHOSIS RISK: DEVELOPMENT, SYMPTOM DIMENSIONS AND FAMILIAL RISK

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Background: Motor abnormalities are a strong indicator of emerging neural network abnormalities and may provide critical early indications of psychopathology risk. In fact, motor abnormalities, such as motor slowing and agitation, are widely recognized as features of several neurodevelopmental disorders. However, our understanding of motor pathology in the course of psychosis remains poorly developed.

Methods: 10,835 adolescents from the ABCD study were used to explore the relationship between motor abnormalities and psychosis. These analyses leveraged the rich data available in the ABCD dataset by examining several motor and psychosis metrics. Depression variables included measures of current symptom dimensions, familial risk, and current diagnoses.In a similarly expansive approach, multiple measures of motor abnormalities were assessed, including early motor delay, coordination, motor slowing, and motor agitation. Finally, motor network connectivity assessed whether current psychosis symptoms are associated with motor network abnormalities for 8,940 individuals.
Results: Early developmental motor delays were associated with current psychosis diagnoses, current symptoms, and a familial risk loading for depression. Current motor abnormality symptoms were also each associated with all psychosis metrics, including current diagnoses, current symptoms, and familial risk loading. Motor network connectivity was also related to current psychosis symptom levels. Additionally, risk for depression conferred risk for motor symptoms beyond familial risk for psychosis or depression alone, suggesting multiple genetic vulnerabilities for motor abnormalities.
Discussion: Motor development and symptoms are critically related to psychosis symptoms, diagnoses, and familial risk loading. Critically, this comprehensive approach provides a well-powered assessment of the influence of multiple psychosis risk definitions on multiple types of motor abnormalities. Collectively, findings suggest that motor function may reflect core biological vulnerability to psychosis as evidenced by familial risk and motor network connectivity. Finally, individuals with familial risk for psychosis and depression showed the greatest motor abnormalities both clinically and biologically.

O1.3. 5-YEAR OUTCOMES OF PSYCHOTIC EXPERIENCES ASSESSED IN PREADOLESCENCE: FINDINGS FROM THE COPENHAGEN CHILD COHORT 2000

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Background: Psychotic experiences in childhood are associated with an outcome of psychotic disorders later in life yet have also been described as transdiagnostic markers of severity of non-psychotic psychopathology. Longitudinal studies of psychotic experiences in children and adolescents in relation to healthcare service use are lacking. We aimed to determine adolescent psychopathological and societal outcomes following psychotic experiences assessed in preadolescence.
Methods: Psychotic experiences were assessed by clinician interview in 1632 11-12-year-olds in a general population birth cohort, the Copenhagen Child Cohort 2000. They were subsequently followed for 5 years using register-based data on use of mental and somatic healthcare services and prescription medications, associated healthcare costs, and educational attainment at the final exams of mandatory education at age 16. Sociodemographic- and perinatal adversities and a baseline IQ-estimate were included as covariates.
Results: Compared to individuals without psychotic experiences, preadolescents with psychotic experiences had an increased risk of incident mental illness diagnosed at child and adolescent mental health services across the diagnostic spectrum, adjusted hazard ratio (aHR) 3.13 (95%CI 1.93-5.07), and use of psychotropic medications, aHR 2.70 95%CI (1.46-5.00). Psychotic experiences were associated with approximately three-fold higher total annual healthcare costs: €3779 vs €1159, difference €2619 (95%CI €372-10,991). Detailed analyses showed that costs were increased for mental healthcare services across primary to tertiary care, but not for somatic care. Psychotic experiences were only associated with slightly poorer educational attainment, which did not persist after adjustment.
Discussion: Psychotic experiences in preadolescence constitute an important and robust risk marker of mental illness across diagnostic boundaries and are associated with societal burden. Psychotic experiences should be included in any screening for mental health problems in children and adolescents.

O1.4. PERSISTENCE AND PREDICTION OF PSYCHOTIC EXPERIENCES FROM CHILDHOOD TO EARLY ADOLESCENCE

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Background: Psychotic experiences in childhood are related to adverse mental health outcomes, including psychosis, mood disorders, and suicidality. Risk is particularly increased when psychotic experiences are persistent over time. However, it is still unclear what distinguishes persistent from transient psychotic experiences. This knowledge could be of clinical relevance for the identification of high-risk youth who may benefit from early intervention strategies, and may reduce the risk of over-treatment of transient and benign psychotic experiences. In this large prospective population-based cohort, we aimed to (1) describe the developmental course of psychotic experiences from childhood into early adolescence, (2) compare youth with persistent versus remittent psychotic experiences, and (3) assess a prediction model for persistence.
Methods: This study was part of the Generation R Study, a birth cohort from Rotterdam, the Netherlands. Youth were assessed on psychotic experiences at mean ages 10 and 14 years using

a self-report questionnaire (N=3473). Multi-rated mental health problems, adverse life events, self-esteem, non-verbal IQ, and parental psychopathology were examined in relation to persistent, remittent, and incident psychotic experiences; odds ratios were calculated. We tested a prediction model for persistence of psychotic experiences using multivariable logistic regression analysis. Performance of the model was assessed using Nagelkerke's R2 and the area under the curve (AUC). The model was internally validated using bootstrapping, resulting in an optimism-corrected AUC value.

Results: The majority of children with psychotic experiences at age 10 years did no longer report them at age 14 years, the persistence rate was 20.5%. Over this four-year period, the incidence rate was 8.1%. Youth with persistent psychotic experiences had higher baseline levels of psychotic experiences, emotional and behavioral problems, as well as lower self-esteem and non-verbal IQ scores than youth with remittent psychotic experiences (all p-values < 0.05; corrected for multiple testing). The prediction model for persistence had an explanatory variance of 7.4% and an AUC of 0.66 (AUC-corrected = 0.62), indicating poor discriminatory power.

Discussion: Although only a minority of youth report persistent psychotic experiences between the ages of 10 and 14 years, they exhibit a higher burden of baseline impairment across multiple psychosocial domains. Despite including a wide array of psychosocial parameters, the prediction model discriminated poorly between youth with persistent versus remittent psychotic experiences. These findings are discussed in the context of clinical relevance, the proneness-persistence-impairment model of psychosis, and the challenges of early identification of youth suffering from persistent psychotic experiences.

O1.5. ASSOCIATIONS OF ENVIRONMENTAL RISK FACTORS WITH PSYCHOSIS DIMENSIONS - A TRANSDIAGNOSTIC APPROACH

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Background: The effect of multiple environmental risk factors for psychiatric disorders has been widely established. Such risk factors are often looked at in a disorder-specific context, many seem to have a rather unspecific effect and instead are relevant influences for the development of multiple disorders. Recently, an increasing number of studies have also looked at the influence of effects of such factors in healthy individuals and dimensional phenotypes and find mostly similar, although attenuated, effects. While most previous studies investigated singular factors, the would not be expected to act indepently, but in cumulation with each other. Recently, a composite score for environmental risk factors for psychosis (environmental risk score, ERS) has been developed (Vassos et al., 2019). Here, we investigated the overall ERS scores and the distribution of composing factors in a transdiagnostic cohort and healthy individuals, and tested the association with schizotypy, a trait level phenotypic risk marker for psychosis.

Methods: The sample for this study is drawn from the ongoing cohort study of the FOR2107 research group, a bi-center study recruiting from the areas of Marburg and Münster, Germany and included a total sample of N=1558 (healthy controls HC: 727, major depression MDD: 637, biopolar disorder BP: 102, schizophrenia/schizoafftecitve disorder SZ/SZA: 92). Calculation of the environmental risk score (ERS) was conducted according to the Maudsley Environmental Risk Score for Psychosis (Vassos et al., 2019), in a range from -4.5 (lowest

risk) to 16 (maximum risk), with 0 equalling an average risk for psychosis. Schizotypy was assessed with the Schizotypal Personality Questionnaire-Brief (SPQ-B). All statistical analyses were conducted in R/RStudio. To account for non-normal distribution of ERS scores, we used non-parametric statistical procedures, i.e. robust rank based (aligned rank transformations, ART) ANOVA to analyse mean group differences in ERS sum scores and main and interaction effects of ERS sum scores and diagnostic category on psychometrically-assessed schizotypy, using the R package ARTool.

Results: ERS sum score were lowest in HC (mean (SD) = -1.27 (2.57)), increasing in MDD (mean (SD) = 0.56 (2.89)) and BP (mean (SD) = 0.71 (2.94)), and were highest in SZ/A (mean (SD) = 1.24 (3.10). We found an overall significant effect of group ($F(3,1554) = 64.32$, $p < 2.22\times10\text{-}16$), but only differences between HC and all patient groups were significant after adjusting for multiple comparisons. In HC, MDD, and BP, but not in SZ/A, ERS total score was significantly and positively associated with schizotypy (both total score and dimensions), ranging from $r=0.16\text{-}0.32$ (all $p<0.05$). MDD patients with a lifetime history of psychotic features showed a significantly higher ERS score, and higher levels of positive schizotypy than those without ($p<0.01$).

Discussion: Our study is the first to examine the level and distribution of a cumulative environmental risk score in a large, transdiagnostic cohort. We show that overall ERS scores do not differ significantly between diagnoses, but are elevated in all patient groups relative to healthy individuals. This can be expected as most factors constituting the measure are general (and not disorder-specific) risks for psychopathology. Similarly to genetic risk scores, however, levels of environmental cumulative risk are associated with dimensional characteristics of the schizophrenia spectrum - but only in individuals where risk has not (yet) manifested into a chronic psychotic disorder.

O1.6. SEVERE NEUTROPENIA IN AFRICAN-DESCENT PATIENTS TREATED WITH CLOZAPINE: RESULTS OF A SIX-MONTH, MULTINATIONAL OPEN-LABEL CLINICAL TRIAL

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Background: Although clozapine is the most effective antipsychotic for treatment-resistant schizophrenia, it is markedly underutilized, particularly in the African American (AA) population. Low absolute neutrophil count (ANC), either at baseline or during treatment (ANC < 1500 cells/mm3), has been a significant barrier to clozapine use in AA patients. This low ANC cut-off was developed in White populations. It was recently shown that the "ACKR1-null" C/C genotype (SNP rs2814778) on the ACKR1 gene (previously called Duffy Antigen Receptor for Chemokines (DARC)), more commonly found in AA than in White populations, is associated with a lower normative ANC range as compared with that seen in White

populations. Low ANC associated with this genotype, and without pathophysiological consequences, has been termed benign ethnic neutropenia (BEN). In 2015 (after the beginning of this study), the Food and Drug Administration issued new guidelines (including lower ANC thresholds) for clozapine monitoring in patients with BEN. However, the range of ANC variability and safety of clozapine have not been established in BEN patients or examined prospectively in patients of African descent.

Methods: We recently completed a 6-month,open-label clinical trial of clozapine use in African-descent adult patients with schizophrenia spectrum disorders with or without the "ACKR1-null" genotype, conducted at two sites in the United States (Baltimore, MD; Washington, DC) and one in Lagos. Nigeria. We examined clozapine safety and weekly ANC during clozapine treatment and evaluated ANC variability and ranges by genotype, sex, location, dosing, and other characteristics. Genotype was assayed using TaqManTM technology (Thermo Fisher Scientific, Waltham, MA USA).

Results: We enrolled 274 participants (150 US, 124 Lagos, Nigeria), of whom 227 (82.8%) completed 6 months of clozapine treatment. 47 discontinued clozapine treatment: 14 from adverse events, 15 participant choice, 6 nonadherence, 2 lack of therapeutic response, and 10 lost to follow up/error/prescriber choice. There was one case of severe neutropenia (<500 cells/mm3) (0.36%), which occurred at week 6. The participant recovered without sequelae after discontinuation of clozapine. Of the participants with known genotypes,199/249 (79.9%, including participant with severe neutropenia) had the "ACKR1-null" genotype ("Duffy-null"). This genotype was more common in the Nigerian sample (n=107,100%) compared to the US sample (92/142 (64.8%) ($\square 2=47.14$, df=1, $p<0.0001$).

Discussion: To our knowledge, this is the largest prospective clozapine trial in African- descent patients. Severe neutropenia was very rare (0.36%), despite the expected occurrence of lower ANC and the high prevalence (80%) of the "ACKR1-null" genotype in this study. We will present comprehensive data on ANC ranges and fluctuations by genotype and other characteristics during clozapine treatment.

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O1.7. REPORTED EXPERIENCES OF CHILDHOOD TRAUMA DOES NOT EXPLAIN ALTERED BRAIN NETWORK INTEGRATION OR SEGREGATION DETECTED IN SCHIZOPHRENIA

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Background: Structural brain alterations in both grey and white-matter regions are more pronounced among individuals with schizophrenia with reported experiences of childhood-trauma (CT). Experiences of CT has been repeatedly associated with a continuum of adverse outcomes along the psychosis spectrum. Examining the topological arrangement of connections encompassing both grey and white-matter is key to understanding the role of CT on structural brain network architecture and at a network level may be more informative for examining the mechanisms underlying the additive effects of CT in schizophrenia.
Methods: Retrospective experiences of CT were measured using the 28-item Childhood Trauma Questionnaire. Trauma presence or absence was defined according to cut-off scores of 'none', 'low', 'moderate' and 'severe' for subtypes of abuse/neglect. Participants were categorised as having experienced 'trauma' if they met the cut-off score for 'moderate' or 'severe' abuse and/or was classified as having 'moderate' or 'severe' abuse in addition to a single case of 'moderate' or 'severe' neglect. High resolution T1-weighted structural MR images (IR-SPGR), alongside diffusion-weighted MR images (32-diffusion gradient directions) were acquired for all participants at the Centre of Advanced Medical Imaging, St. James Hospital, Dublin, Ireland using a Philips Achieva 3T MRI scanner. Structural connectivity matrices (AAL-90) were constructed with edges weighted by both fractional anisotropy (FA) and number-of-streamlines (NOS) following constrained spherical deconvolution-based deterministic tractography (CSD). Variance in whole-brain and subnetwork-permutation-based topology (NBS) were investigated in relation to diagnosis, trauma and the trauma-by-diagnosis interaction.
Results: Individuals with a DSM-IV diagnosis of schizophrenia (n=51) relative to psychiatrically healthy controls (n=140, aged 18-65 years) demonstrated impairments across whole-brain efficiency, strength, betweenness, clustering coefficient, path length, and density ($F=4.73\text{-}18.1$, $p<0.001\text{-}0.03$) alongside a disconnected subnetwork (FA/NOS-weighted) involving fronto-temporal, fronto-parietal and occipital connections ($T=3.5\text{-}4.0$, $p=0.001$). Neither the presence (n=55) or absence (n=136) of CT ($F(16,170)=0.47$, $p=0.96$), nor the trauma-by-diagnosis interaction explained any topological variance observed in schizophrenia ($F(16,170)=0.85$, $p=0.63$).
Discussion: We identified disrupted whole-brain measures of integration, segregation, and a differentially connected subnetwork encompassing fronto-parietal and occipital connections in schizophrenia relative to controls. These findings of disrupted whole-brain communication in schizophrenia corroborate a significant body of prior graph theory studies and support the theory that disrupted whole-brain communication may be a core neuroanatomical substrate of schizophrenia as a disorder of whole-brain disconnectivity. However, variance in global nor subnetwork architectural organisation observed in individuals with schizophrenia was not explained by reported experiences of childhood-trauma nor was reported experiences of childhood-trauma associated with any differences in global nor subnetwork structural organisation irrespective of diagnosis. These results suggest that at macro-scale, self-reported experiences of childhood-trauma may not confer a neurobiological vulnerability to schizophrenia via altered neuroanatomical network organisation detectable in the adult human brain.

O1.8. EFFECT OF STRESSFUL LIFE EVENTS ON SCHIZOTYPAL SYMPTOMS AND SUBCLINICAL PSYCHOTIC EXPERIENCES IN FIRST DEGREE RELATIVES AND HEALTHY CONTROLS

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Background: Stress is implicated in the etiology of psychosis. However, the role of stressful life events (SLE's) in this process remains unclear. Moreover, the effect of SLEs has mostly been investigated in the clinical populations, therefore their role in the gradual development of subclinical psychotic symptoms is unknown. Similarly, little attention has been given to the perceived quality of the experienced events, meanwhile the literature suggests a differential effect of SLE's on psychotic symptoms depending on their type. We examined the associations between the number and quality of SLE's and subclinical psychosis in a population at increased familial risk for psychosis and in controls.
Methods: The analyzed data were collected from siblings of individuals diagnosed with a non-affective psychotic disorder (n=731) and controls (n=490) at two time points, 3 years apart (T1, T2). SLE's and their perceived (un)pleasantness, positive and negative schizotypal symptoms, and frequency of psychotic experiences were assessed. To analyze the data, a set of univariate multilevel regression analyses and multivariate regression analyses was conducted controlling for age, sex, ethnicity, and IQ.
Results: At both T1 and T2, siblings reported more SLEs than controls ($p<.05$) and exhibited higher levels of schizotypal symptoms ($p<.05$) but not of psychotic experiences. Exposure to unpleasant SLEs was associated with an increase in both schizotypal symptoms and psychotic experiences ($p<.001$). SLE's rated as pleasant were associated with a decrease in negative schizotypal symptoms ($p<.05$). Familial risk for psychosis did not predict a greater increase in symptoms after exposure to SLE's. Exposure to unpleasant SLE's at T1 predicted an increase in positive schizotypal symptoms ($p<.05$) at T2, and, surprisingly, a decrease in negative schizotypy ($p<.05$).
Discussion: The results indicate that specifically unpleasant SLE's play a role in the development of psychosis. Pleasant SLE's, on the other hand, seem to serve as a protective factor in this process. Possibly, encountering positive events has a buffering effect against negative events in the context of schizotypal symptoms. Although siblings reported more SLE's and higher levels of schizotypy, they were not more prone to developing subclinical psychotic symptoms after exposure to SLEs than the controls. These findings demonstrate that unpleasant SLE's are an important risk factor for psychosis that is not specific to individuals at increased familial risk.

O2. Oral Session: A Search for Biological Markers

O2.1. ULTRA-RARE EXONIC VARIANTS IDENTIFIED IN A FOUNDER POPULATION IMPLICATE CADHERINS AND PROTOCADHERINS IN SCHIZOPHRENIA

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Background: While rare deleterious exonic variants are thought to contribute to risk for schizophrenia, identification of specific genes and pathways has proven challenging. Rare variant studies to date have converged on a few very broadly defined pathways, such as synaptic signaling and FMRP targets, but these gene sets contain hundreds of possible candidate genes. Studies of de novo variation have identified few individual genes that have been tagged by multiple hits, while the power of case-control studies is greatly hampered by the vast multiplicity of variation in the human genome. Consequently, we adopted a novel

analytic strategy utilizing extreme filtering to eliminate all previously observed variants from the gnomAD and TOPMED databases (excluding neuropsychiatric cases). Applying this approach to a cohort of sequenced schizophrenia cases and controls drawn from the Ashkenazi Jewish (AJ) population, we identified several significant new pathways and gene sets with much greater specificity than prior studies.
Methods: High-depth (>30x) whole genome sequencing was performed on the Illumina HiSeq X system; we restricted analysis to the exome in order to capitalize on all available data in gnomAD. After strict QC, data were available from 786 AJ cases and 463 AJ controls. All variants observed even once in gnomAD (non-neuro) and TOPMED databases (total N > 158K) were filtered, resulting in 12,011 novel loss of function and missense (LoFM) autosomal variants in our dataset. These variants were then grouped by gene, and each gene was characterized by the number of cases and controls possessing a novel LoFM variant in that gene.
Results: Cases had greater frequency of novel missense or loss of function (MisLoF) variants compared to controls. Characterizing 141 "case-only" genes (in which ≥ 3 cases had MisLoF variants with none found in controls), we identified cadherins as a novel gene set associated with schizophrenia, including a recurrent mutation in PCDHA3 which results in mislocalized protein that fails to aggregate normally.

Case-only genes also demonstrated significant overlap with neurodevelopmental disorder genes, including a novel association to TSC2. a gene in which mutations (primarily loss of function) are known to cause tuberous sclerosis (TS). A recent survey of a large international cohort of TS patients identified psychosis in 11% of adults; our results suggest that schizophrenia can be the primary presenting feature of TSC2 mutations. Modeling effects of purifying selection demonstrated that deleterious ultra-rare variants are greatly over-represented in the Ashkenazi population, resulting in enhanced power for rare variant association

Discussion: Our novel filtering strategy, combined with the use of an endogamous founder population, appeared to enhance power for ultra-rare variant discovery. Three of the top genes identified by this strategy include known schizophrenia risk genes (SETD1A, TRIO, and XPO7); moreover, several of our identified LoFM variants (e.g., in PCDHA3) were replicated at the variant level in Ashkenazi schizophrenia cases from the SCHEMA Consortium. Identification of cell adhesion genes in the cadherin/protocadherin family is consistent with evidence from large-scale GWAS in schizophrenia, helps specify the synaptic abnormalities that may be central to the disorder, and suggests novel potential treatment strategies (e.g., inhibition of protein kinase C).

O2.2. FRONTO-PARIETAL ATTENTION NETWORK FUNCTION IN THE FIRST-EPISODE SCHIZOPHRENIA SPECTRUM

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Background: Cognitive impairments are observed at disease onset and account for significant morbidity in schizophrenia. Controlled cognitive processes are particularly susceptible and may contribute to well-established selective attention deficits. The present study assessed functioning of the fronto-parietal attention network (FPAN) in schizophrenia spectrum patients at disease onset (FE).

Methods: Magnetoencephalography (MEG) was recorded from 38 FE and 38 matched healthy controls (HC) during a visual search task. MRI was acquired for cortical localization of MEG activity. FPAN activity elicited in response to a feature-based color cue was compared between groups, across FPAN region (frontal eye fields (FEF), inferior frontal gyrus (IFG), anterior cingulate (ACC) and intraparietal sulcus (IPS)). The Scale for the Assessment of Positive/Negative Symptoms (SAPS/SANS) was used to assess symptom burden in FE.
Results: FPAN activity differed between groups based on region ($p<.01$). FE exhibited greater activity in IFG ($p=.045$). HC exhibited no correlations between performance and FPAN activity. In contrast, faster responses were correlated with stronger activation within FEF ($r=-.36$, $p=.03$) and IPS ($r=-.32$, $p=.047$) among FE. Furthermore, weaker FEF ($r=-.33$, $p=.04$), IFG ($r=-.33$, $p=.047$), and IPS ($r=-.41$, $p=.01$) activity was associated with higher SANS scores in patients.
Discussion: FE exhibit more robust recruitment of the FPAN, specifically within the IFG, during cue processing compared to HC. Whereas recruitment of the FPAN was associated with improved performance and decreased symptom burden in FE, HC did not rely on this network for successful task completion. These results suggest a top-down control network engaged in excess of task demands to overcome deficits in the deployment of attention, a compensatory mechanism that may become overwhelmed in more complex real-world environments. In addition, difficulty recruiting this network was associated with larger SANS scores in patients, highlighting the relationship between disruptions in controlled cognitive processes and negative symptoms during early illness stages.

O2.3. THE CLAUSTRUM-MEDIAL PREFRONTAL CORTEX NETWORK CONTROLS ATTENTIONAL SET-SHIFTING

Leon Fodoulian[1], Olivier Gschwend[1], Chieko Huber[1], Sophie Mutel[1], Rodrigo F. Salazar[1], Roberta Leone[1], Jean-Rodolphe Renfer[1], Kazadi Ekundayo[1], Ivan Rodriguez[1], Alan Carleton*[1]

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Background: Cognitive dysfunctions, which are a hallmark of many psychiatric conditions including schizophrenia and attention-deficit hyperactivity disorder (ADHD), represent a major burden in the daily life of patients. Therefore, a better understanding of the brain circuits involved in cognitive functions and/or dysfunctions is critical to better handle psychiatric pathologies and develop new therapies. Prefrontal cortex (PFC) regions have long been recognized as a neuronal hub contributing to various cognitive functions such as planning, attentional processes and working memory. The current study investigates how the claustrum (CLA), a poorly studied brain region known to share dense reciprocal connections with the neocortex, may participate in these cognitive insufficiencies.
Methods: In the present study, we molecularly distinguished CLA neurons from neighboring striatal and insular cortical neurons using single cell RNA sequencing (scRNAseq) and used a Cre-driver transgenic mouse line to specifically study CLA glutamatergic projection neurons. We used conditional viral tracing, microendoscopic calcium imaging and opto/chemogenetic manipulations during cognitive tasks.
Results: We show that specific ensembles of CLA and of medial prefrontal cortex (mPFC) neurons are activated during a task requiring cognitive control such as attentional set-shifting, i.e. the ability to shift attention towards newly relevant stimulus-reward associations while disengaging from irrelevant ones. CLA neurons exert a direct excitatory input on mPFC pyramidal cells, and chemogenetic inhibition of CLA neurons suppresses the formation of

specific mPFC assemblies during attentional set-shifting. Furthermore, impairing the recruitment of specific CLA assemblies through opto/chemogenetic manipulations prevents attentional set-shifting.
Discussion: In conclusion, we propose that CLA ensembles are formed during different cognitive tasks and influence the formation of mPFC ensembles that are necessary to promote attentional set-shifting. Our findings emphasize a potential role of the CLA-mPFC network in attentional dysfunctions observed in neuropathologies such as schizophrenia .

O2.4. CORTISOL LEVELS IN CHILDHOOD ASSOCIATED WITH EMERGENCE OF ATTENUATED PSYCHOTIC SYMPTOMS IN EARLY ADULTHOOD

Alexis Cullen*[1], Helen Fisher[2], Nancy Gullet[1], Elizabeth Fraser[1], Ruth Roberts[1], Uzma Zahid[1], Melody To[1], Nataile Huijing Yap[1], Patricia Zunszain[1], Carmine Pariante[1], Stephen J. Wood[3], Philip McGuire[1], Robin Murray[1], Valeria Mondelli[1], Kristin Laurens[4]

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Background: Subtle deviations in hypothalamic-pituitary-adrenal (HPA) axis function, including elevations in basal and diurnal cortisol, have been observed in individuals with psychosis. Such findings are consistent with the neural diathesis-stress model, which proposes that HPA axis abnormalities render individuals with increased vulnerability for psychosis more sensitive to the effects of psychosocial stress, and in turn, contribute to dopaminergic and glutamatergic abnormalities that give rise to psychotic symptoms. In support of the model, in youth at clinical high-risk (CHR) for psychosis, it has recently been observed that elevated basal cortisol levels predict later onset of the disorder. However, as longitudinal studies to date have largely focused on CHR populations, it is unclear whether cortisol alterations are evident at an even earlier stage. The present study aimed to address this issue by investigating whether cortisol levels in childhood (and their interaction with psychosocial stress) are associated with the emergence of attenuated psychotic symptoms in early adulthood.
Methods: A sample of children (N=109) enriched for psychosis risk factors were recruited from the UK general population at age 9-12 years and assessed at age 11-14 years (T1) and 17-21 years (T2). Measures of psychopathology (internalising and externalising symptoms and psychotic-like experiences), psychosocial stressors (daily stressors and negative life events), and salivary cortisol samples were obtained at T1. Attenuated psychotic symptoms at T2 were assessed using the Prodromal Questionnaire.
Results: The mean age (± SE) at T1 and T2 was 13.21 (± 0.11) and 17.66 (± 0.08) years, respectively and 46% were male. Consistent with our recruitment strategy (enriched for individuals presenting risk factors for schizophrenia), 21% had a family history of illness. In linear regression analyses, diurnal cortisol levels (β = 0.979, 95% CI: 0.134, 1.823), daily stressor exposure (β = 0.050, 95% CI: 0.023, 0.076), daily stressor distress (β = 1.012, 95% CI: 0.370, 1.653), and negative life event exposure (β = 0.319, 95% CI: 0.054, 0.583) at T1 were all associated with attenuated psychotic symptoms at T2, but only diurnal cortisol survived adjustment for concurrent psychopathology (β = 1.067, 95% CI: 0.247, 1.886). Diurnal cortisol was also found to moderate the effect of daily stressor exposure, which was significantly associated with attenuated psychotic symptoms in those with high (β = -0. 045, 95% CI: 0.009, 0.081), but not low (β = -0. 000, 95% CI: -0.069, 0.068), diurnal cortisol.

Discussion: We show for the first time, that higher diurnal cortisol in childhood increases the risk for developing attenuated psychotic symptoms in early adulthood, potentially by increasing sensitivity to psychosocial stressors. Our findings build on those from a recent study which observed that the inclusion of salivary cortisol in multivariable models can improve prediction of psychosis transition in CHR youth. The results of the current investigation suggest that salivary cortisol may have utility at an even earlier stage of illness, potentially offering a means to identify youth in the general population who may be at greater risk of developing attenuated psychotic symptoms if exposed to high levels of daily stress.

O2.5. PLASMA POLYUNSATURATED FATTY ACIDS AND MENTAL DISORDERS IN ADOLESCENCE AND EARLY ADULTHOOD: CROSS-SECTIONAL AND LONGITUDINAL ASSOCIATIONS IN A LARGE GENERAL POPULATION COHORT

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Background: Polyunsaturated fatty acids (PUFA) may be relevant to the development of mental disorders. For example, docosahexaenoic acid (DHA), an omega-3 PUFA, may have anti-inflammatory and neuroprotective properties, whereas omega-6 PUFA may have pro-inflammatory effects. However, it is currently unclear whether polyunsaturated fatty acid (PUFA) abnormalities temporally precede the onset of mental disorders in the general population. Furthermore, these associations have not been extensively studied in adolescence and early adulthood, despite the fact that most mental disorders have their onset during this critical developmental period. We sought to evaluate cross-sectional and longitudinal associations between PUFAs and mental disorders in adolescence and early adulthood in a general population sample.

Methods: Participants in the Avon Longitudinal Study of Parents and Children attended clinics when aged approximately 17 years (n=5215) and 24 years (n=4019) where interviews and blood sample collection were performed. Fasting plasma PUFA measures (total omega-6, total omega-3, omega-6:omega-3 ratio and DHA percentage of total fatty acids) were assessed using nuclear magnetic resonance spectroscopy. Logistic regression was used to determine cross-sectional and longitudinal associations between standardised PUFA measures and three mental disorders (psychotic disorder, moderate/severe depressive disorder and generalised anxiety disorder [GAD]), adjusting for age, sex, BMI and daily tobacco smoking. Missing exposure and confounder data were imputed using multiple imputation. In sensitivity analyses models were further adjusted for a range of prenatal and childhood variables including home ownership in pregnancy, maternal education, parental social class, family income in childhood and IQ at age 8 years.

Results: At age 17 years, 79 of 4718 participants assessed (1.7%) had psychotic disorder; 227 of 4563 (5.0%) had moderate/severe depressive disorder; and 263 of 4563 (5.8%) had GAD. At age 24 years, 47 of 3889 participants assessed (1.2%) had psychotic disorder; 304 of 3966 (7.7%) had moderate/severe depressive disorder; and 386 of 3957 (9.8%) had GAD.

There was little evidence of cross-sectional associations between PUFA measures and mental disorders at age 17. At age 24, the omega-6:omega-3 PUFA ratio was positively associated

with psychotic disorder (adjusted odds ratio [aOR] 1.43, 95% confidence interval [CI] 1.16 – 1.76), depressive disorder (aOR 1.18, 95% CI 1.06 – 1.32) and GAD (aOR 1.14, 95% CI 1.03 – 1.26), while DHA was inversely associated with psychotic disorder (aOR 0.60, 95% CI 0.40 – 0.89). Regarding longitudinal associations, DHA at age 17 was inversely associated with odds of incident psychotic disorder at age 24 (aOR 0.48, 95% CI 0.25 – 0.93). Sensitivity analyses provided little evidence of further confounding for the additional variables examined.

Discussion: Our findings suggest that PUFA abnormalities occur in association with mental disorders in early adulthood. Furthermore, we provide evidence that higher levels of DHA in late adolescence are associated with lower odds of later developing psychosis in early adulthood. These data are supportive of a role for DHA in relation to prevention of psychotic disorders in early adulthood.

O2.6. CAN MEMBRANE LIPIDS HELP PREDICT PSYCHOTIC TRANSITION IN UHR SUBJECTS?

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Background: Since the formulation of the membrane hypothesis of schizophrenia in 1993, our understanding of the pathophysiology of schizophrenia have evolved and Methods: have also made significant advances. It is now possible to explore precisely the lipid composition of the cell membrane. Schizophrenia is now viewed as a progressive disease evolving through different stages: ultra-high risk (UHR), first episode of psychosis (FEP) and chronic schizophrenia. The progression through these stages is non-mandatory and the biological basis determining the different outcome of the UHR and FEP individuals is not yet understood. There is a need for biomarkers to predict psychotic conversion in UHR patients.We hypothesized that membran lipids could be a biomarker.

Methods: We used blood samples from 61 subjects (29 converters and 32 non converters) from ICAAR cohort at inclusion and after psychotic transition or end of follow-up. Membrane lipids (fatty acids and phospholipids and sterols) were analysed using liquid chromatography coupled with mass spectrometry (LC-MS/MS). SPSS software was used for statistical analysis. We do Pearson's correlation between fatty acids, logistic regression and ROC curve to predict psychotic transition.

Results: We found that linoleic acid (LNA, C18:2n6) was negatively correlated with Arachidonic acid (AA, C20:4n-6), eicosapentaenoic (EPA, C20:5n-3) acid, docosapentaenoic acid (DPA, C22:5n-3), docosahexaenoic (DHA, C22:6n-3), and cholesterol and positively correlated with α-linolenic acid (ALA, C18:3n3) and cholestanol. Membrane concentration of LNA at inclusion could help to predict the conversion to psychosis: a higher level increased the risk (AUC=0.654, p = 0.039, IC 95% [0.516; 0.792). When separated in two subgroups based on their LNA levels, converters were more present in the subgroup with higher LNA

levels (Fisher test, p =0.02). The subgroups had also other significatively different membrane PUFA composition (higher levels of omega-6 (AA and docosatetraenoic acid) and omega-3 (ALA and DPA) in the subgroup with the lowest risk of psychotic transition). Ratio cholestanol/cholesterol can also predict psychotic conversion (AUC=0.686, p = 0.011, IC 95% [0.551; 0.821])

Discussion: We were able to confirm the correlation between membrane lipids and to identify differences between converters and non-converters. Our data support the existence of membrane lipid abnormalities in a subgroup of UHR prior to the development of the disease. To our knowledge, we are the first to explore membrane sterols in UHR and to find significant differences. Compared to previous cohort studies, it underlines the importance of having enough patient converters but also of having a homogeneous population (same country) because membranePUFA levels are influenced by the diet.

Because there are correlation between differentes membrane lipids, these results are encouraging to pursuit omega-3 supplementation trials in UHR. But may be in a more personalized way: exploring membrane lipid levels could help to determine which patients should benefit the most from the supplementation.

O2.7. COPEPTIN PREDICTS CLINICAL OUTCOME IN SCHIZOPHRENIA SPECTRUM DISORDER

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Background: Vasopressin is involved in higher brain functions, e.g., cognition, emotion regulation and social functioning, which are impaired in schizophrenia spectrum disorder (SDD) and increased vasopressin levels have been described in these patients. Copeptin is the more stable surrogate marker of vasopressin mirroring its concentrations in the circulation. Copeptin has been shown to predict outcome in somatic diseases such as pneumonia, myocardial infarction and stroke, and increases under psychological stress. Thus, copeptin could be also useful to predict outcome in SSD, where currently no reliable biomarker has proven to be effective. The aim of this study was to investigate whether copeptin can be used as predictor of psychotic relapse in patients with an acute psychotic episode.

Methods: In this prospective, observational study we enrolled patients with acute psychosis either within SSD or affective disorder. On hospital admission, baseline characteristics including current and prior medication, drug use and disease severity, i.e., Positive and Negative Syndrome Scale, Global Assessment of Functioning, Perceived Stress Scale, State-Trait Anxiety Inventory and Beck Depression Inventory, were assessed and fasting serum copeptin and cortisol were sampled. Psychotic relapse, defined as rehospitalization due to disease progression or reporting of psychotic relapse, was assessed one year after inclusion. The primary endpoint was copeptin at inclusion predicting time to psychotic relapse using Cox Proportional Hazard Model.

Results: We included 73 patients (74% male, mean [SD] age 35.3 [9.8] years) of whom 53 were diagnosed with SSD and 20 with affective disorder (n=17 bipolar, n=3 depression with psychotic symptoms). In all patients, serum copeptin predicted psychotic relapse with a hazard ratio (HR) of 2.4 (95%-CI 1.1, 5.5, p=0.03) and in patients with SSD with a HR of 3.6 (95%-CI 1.2, 10.8, p=0.02). Copeptin did not predict psychotic relapse in patients with an affective disorder (HR 1.0, 95%-CI 0.2, 4.6, p=0.9). Neither cortisol, prior or current antipsychotic

medication, trigger of acute psychosis nor psychopathological ratings were significantly associated with psychotic relapse. Diagnosis of cannabis abuse was significantly associated with psychotic relapse (overall: HR 3.1, 95%-CI 1.5, 6.6, p=0.003; schizophrenia: HR 3.3, 95%-CI 1.4, 8.0, p=.005; affective: HR 1.9, 95%-CI 0.3, 10.4, p=0.5). Adjusting for cannabis abuse, copeptin remained significantly associated with psychotic relapse and identified patients with highest risk of relapse (p=0.005).
Discussion: Our study indicates that copeptin is a promising biomarker improving outcome prediction of psychotic relapse in patients with SDD. Our findings may be used to identify patients at risk of psychotic relapse and in need for a more intensive care.

O2.8. PREVALENCE OF BRAIN ABNORMALITIES IN FIRST-EPISODE PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF STRUCTURAL MRI STUDIES

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Background: Among patients presenting with first-episode psychosis, a subset have “organic” abnormalities that may lead to a change in clinical management. However, the proportion of patients with a clinically relevant intracranial abnormality, that is detectable using MRI has never been clearly established. This has lead to a lack of international consensus on whether patients with first-episode psychosis should routinely undergo an MRI. Using a systematic review and meta-analysis approach, we sought to estimate the prevalence of radiological abnormalities in patients with first-episode psychosis.
Methods: A meta-analysis of studies was performed. Investigators searched Ovid MEDLINE, PubMed, Embase, PsychINFO, and Global Health databases for studies published between 1978 to present. The inclusion criteria were studies published in English that reported the prevalence of intracranial abnormalities detected by structural MRI in patients with first-episode psychosis. Study identification and data extraction were independently double-rated. Using a random-effects model, we calculated the proportion of patient with any structural abnormality, as well as any clinically relevant abnormality (defined as a change of diagnosis or management). For each study, proportion and 95% confidence intervals (CI) were calculated. The influence of potential effect modifiers was explored through meta-regression. Statistical analysis was performed using R.
Results: 10 studies (1,000 patients) were included. The prevalence of any intracranial abnormality was 29% (95% CI 18-41%), with a corresponding number needed to scan of 3. The I2 statistic was 93% indicating a high degree of heterogeneity among the included studies. The proportion of clinically relevant abnormalities was calculable for 5 studies. The prevalence was 5% (95% CI 2-8%), with a corresponding number needed to scan of 20. The I2 statistic was 50% indicating a moderate degree of heterogeneity. Metaregression revealed age and duration of psychosis were not associated with the prevalence of radiological abnormalities.
Discussion: In the first meta-analysis of its kind, the estimated overall prevalence of intracranial abnormalities in patients with first episode psychosis was 29%. Furthermore, the estimated prevalence of clinically relevant abnormalities was 5%, suggesting that 1 in 20 patients with first episode psychosis will have a change in management as a result of an MRI scan.Results : highlight the clinical utility of MRI in detecting abnormalities that impact clinical care. These findings support the routine use of MRI, a safe and well-tolerated neuroimaging technique, in patients presenting with first episode psychosis.

O3. Oral Session: A Network Approach to Brain Function in Schizophrenia and High-Risk Groups

O3.1. COGNITIVE NETWORK SEGREGATION REFLECTS DIVERGENT CLINICAL TRAJECTORIES OF INDIVIDUALS AT ULTRA HIGH RISK FOR PSYCHOSIS

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Background: Cognitive dedifferentiation in schizophrenia refers to cognitive structure components becoming more correlated in schizophrenia patients than the normal population. Recent brain and cognition research pointed to similar findings among individuals at the prodromal stage termed ultra-high risk for psychosis (UHR). Cross-sectionally, Wang and colleagues (2017) compared resting-state functional networks among UHR individuals who later converted to psychosis against those who did not. Converters showed loss of brain functional network segregation and disruption of network communities. Longitudinally, Lam and colleagues (2018) identified UHR individuals who either remitted to normal or remained at risk at the 2-year follow-up and compared their cognitive structure changes. Non-remitters showed decrease differentiation of general cognitive function, perception, and social cognition over time, while remitters demonstrated cognitive recovery. Furthermore, aberrant connectivity among cognitive networks, including default mode network, salience network, and control network, has been consistently reported in schizophrenia patients and UHR individuals (e.g., Wotruba et al. 2014; Wang et al. 2016; Manoliu et al. 2013). We hypothesized that brain cognitive network segregation underlies different clinical trajectories among UHR individuals.
Methods: Resting-state fMRI (2.3 seconds TR, 3 mm isotropic) data were acquired from 142 participants (mean age 21.5, 85 males; 40 UHR-R, 51 UHR-NR, and 51 controls) every year for 2 years. We calculated the network-based community segregation (Chan et al., 2014) based on the baseline brain functional communities (Wang et al., 2017) and the functional network parcellations (Yeo et al., 2011).
Results: Comparing the longitudinal changes in network-based community segregation, we found severer segregation loss over time in default mode network, control network, and salience network among the non-remitters compared to the remitters. Importantly, the rate of SN segregation loss was associated with a faster positive symptom increase. The rate of DMN segregation loss was related to a higher rate of at-risk mention state increase.
Discussion: Together, we argue that salience network segregation reflects the divergent clinical trajectories of UHR individuals. Consistent with the dysconnection hypothesis in schizophrenia (Friston, 2016), cognitive network segregation loss might underlie cognitive dedifferentiation in individuals at risk for psychosis.

O3.2. COMPUTATIONAL MODELLING ACROSS MULTIPLE IMAGING PARADIGMS CONSISTENTLY INDICATES LOSS OF PYRAMIDAL CELL SYNAPTIC GAIN IN SCHIZOPHRENIA

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Background: It is widely hypothesised that a fundamental pathology in schizophrenia is the loss of synaptic gain, i.e. the ability to amplify postsynaptic responses to neural inputs, due to hypofunction of NMDA receptors in particular. Most evidence for this is indirect (e.g. genetic or post mortem), however, and it is unclear whether gain in excitatory or inhibitory neurons is most affected, and how this relates to symptoms. Computational modelling of brain imaging data permits in vivo functional analysis of synaptic gain (and other parameters) at the individual subject level, but, in schizophrenia, it has so far been restricted to small samples and single paradigms. Here, synaptic gain was explored in a larger sample of subjects who had each undergone four imaging paradigms.

Methods: Participants (male and female) with schizophrenia (n=108), their relatives (n=57), and controls (n=107) underwent three electroencephalography paradigms (resting, mismatch negativity – MMN, and 40 Hz auditory steady state response – ASSR) and resting state functional magnetic resonance imaging (rsfMRI). We analysed their brain responses using dynamic causal modelling and parametric empirical Bayes.

Results: The schizophrenia group had typical abnormalities in the EEG paradigms: i) in the resting EEG, increased theta (p(corr)=0.035), decreased beta (p(corr)=0.022 and increased gamma (p(corr)=0.040) power; ii) in the mismatch negativity, a decreased mismatch response (SPM analysis, p(unc)<0.001); and iii) in the 40 Hz ASSR, reduced gamma power (p<0.05) and peak frequency (p=0.015). In the modelling analysis, posterior probabilities were derived using parametric empirical Bayes; all robust to age, sex, smoking and medication covariates, as follows:

rsEEG (Con n=98, Scz n=95): group averaged power spectra were simulated using microcircuit models. Only the model with decreased pyramidal synaptic gain reproduced all three Scz data features.

MMN (Con n=93, Scz n=95, Rel n=40): synaptic gain loss in L IFG (p>0.95) and R IFG (p>0.99) in Scz versus Con. In Scz, disinhibition in Broca's area related to auditory hallucinations (p>0.99). In Con, Digit Symbol score related to synaptic gain in L IFG (p>0.99) and R IFG (p>0.95).

ASSR (Con n=92, Scz n=94, Rel n=42): synaptic gain loss in L and R A1 (both p>0.99) in Scz (versus Rel). In Scz, disinhibition in A1 related to hallucinations (p>0.99). In all, synaptic gain in A1 related to Digit Symbol score (p>0.95).

rsfMRI (Con n=85, Scz n=72, Rel n=45): synaptic gain loss in L IFG (p>0.99) and R IFG (p>0.95) in Scz versus Con. In Scz, hallucinations related to disinhibition in L A1 and STG (both p>0.99). In Con, synaptic gain in R IFG related to Digit Symbol score (p>0.99).

Across all four paradigms, the schizophrenia group showed evidence of decreased synaptic gain (i.e. greater self-inhibition) on pyramidal cells. Abnormal auditory perceptions were linked to disinhibition in auditory areas in schizophrenia, and pyramidal cell gain correlated with cognitive performance in controls.

Discussion: First, the loss of synaptic gain on pyramidal cells was a very consistent finding across paradigms, suggesting well-replicated effects in these three EEG paradigms in schizophrenia are all attributable to the same underlying pathophysiology. Second, auditory perceptual symptoms related to disinhibition, not gain loss, in auditory areas in EEG and rsfMRI, and not just auditory but all other positive and negative symptoms also related to disinhibition in the same network in rsfMRI. Psychotic symptoms may therefore result from a restoration of excitatory/inhibitory balance (i.e. disinhibition of pyramidal cells) in neural circuits. Finally, I evaluate synaptic gain's potential as a computational biomarker for schizophrenia.

O3.3. STRIATAL FUNCTIONAL CONNECTIVITY IN PSYCHOSIS RELAPSE: A COMPARISON BETWEEN ANTIPSYCHOTIC ADHERENT AND NON-ADHERENT PATIENTS AT THE TIME OF RELAPSE

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Background: Most individuals with psychotic disorders relapse over their course of illness. The pathophysiology of psychosis relapse is poorly understood, as few studies account for the confounder of antipsychotic non-adherence, which affects most patients with psychosis and is often unnoticed. Functional brain imaging of individuals experiencing a relapse of their psychotic symptoms, for whom their antipsychotic exposure status can be confirmed, can inform models of the mechanism of relapse, which at the moment are lacking

Methods: Here we are presenting data on resting state striatal functional connectivity at the time of relapse among individuals with schizophrenia, schizoaffective, or bipolar disorder with psychotic features, for whom treatment adherence status was confirmed: either positive by ongoing use of long-acting injectable antipsychotics prior to relapse (i.e., breakthrough psychosis) (n=23), or negative by undetectable plasma levels of antipsychotic upon relapse (n=27), as well as in healthy controls (n=26). Given the previously described "normalizing" effect of antipsychotics in striatal functional connectivity associated with treatment response, we hypothesized that such effect would not be maintained in individuals who worsened despite ongoing antipsychotic delivery, and that individuals with breakthrough psychosis would present with the most aberrant striatal functional connectivity, compared to individuals with relapse without antipsychotic exposure and healthy controls. Region of interest (ROI) analyses were conducted to calculate striatal connectivity index (SCI) values, a summary measure of striatal functional connectivity prognostic of treatment response, which was our primary outcome. Group differences in SCI values were compared in a linear regression model adjusted for sex and age. Furthermore, we conducted exploratory voxel-wise analyses by ROI for hypothesis generation purposes

Results: The mean age for the study population was 34.01 years (Standard Deviation [SD]=11.53), and 39 (51%) of the participants were female, with no significant differences between groups. Among patients, the mean BPRS-18 was 42.59 (SD=7.23). There were no significant differences between groups in psychotic (p=0.7), negative (p=0.3), manic (p=0.09) or depressive symptoms (p>0.9), nor in positive urine toxicology screen (p=0.2) at the time of relapse. In the breakthrough psychosis group, all except for 2 participants had been >1 year on the LAI prior to relapse, and the LAIs prescribed at the time of relapse were aripiprazole (n=7; 30%), paliperidone (n=9, 39%), fluphenazine decanoate (n=1;4.3%), haloperidol decanoate (n=6, 26%). As predicted, individuals in the breakthrough psychosis group had lower SCI values at the time of relapse (reflecting most aberrant striatal functional connectivity) than

those who had undetectable antipsychotic plasma levels (ß=0.86, p=0.032) with an effect size of Cohen's d=0.58 , and healthy controls (ß=1.47, p<0.001) with an effect size of Cohen's d=0.99. In exploratory voxel-wise analyses, there was a preponderance of aberrant functional connectivity in the BAMM group in dorsal striatal ROIs

Discussion: These results suggest that, rather than mediated by extra-striatal mechanisms, as it has been previously hypothesized for treatment resistance, relapse despite ongoing antipsychotic exposure may be mediated by striatal mechanisms. Future studies should replicate this finding by comparing striatal functioning of individuals maintaining symptom stability with those relapsing, and by characterizing the trait vs state behavior of striatal functional connectivity as a biomarker of antipsychotic treatment responsiveness

O3.4. HYPERACTIVATION OF POSTERIOR DEFAULT MODE NETWORK DURING SELF-REFERENTIAL PROCESSING IN CHILDREN AT FAMILIAL HIGH-RISK FOR PSYCHOSIS

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Background: Patients with psychotic disorders show disturbances in self-referential processing and associated neural circuits including the default mode network (DMN). These disturbances may predate the onset of psychosis and underlie early social and emotional problems in children who are at risk for psychosis. However, there are few neuroimaging studies in at-risk children, and none that have directly studied neuroimaging correlates of self-referential processing. To address this knowledge gap, we examined self-referential processing in a group of children (7 to 12 years of age) who are at Familial High Risk (FHR) for psychosis because they have a parent or sibling affected by psychotic illness, as compared to a group of healthy control (HC) children.

Methods: A total of 37 children participated in this study, including 17 FHR and 20 age and sex-matched HC children. All participants were assessed for current psychiatric disorders using the SCID for Childhood Diagnoses (Kid-SCID). Internalizing, externalizing, and total problems were assessed using the Child Behavior Checklist (CBCL). To assess self-referential processing, participants performed a self-reference task during functional MRI (fMRI), in which they were presented with a list of adjectives and asked to indicate whether or not the adjectives described them (self-reference condition) or whether the adjectives described a good or bad trait (semantic condition). Three children (two FHR, one HC) were excluded because of chance-level performance on the semantic condition, leaving a total of 15 FHR and 19 HC for final analysis. Brain activation during self-referential versus semantic processing was evaluated using fMRI data acquired on a Siemens Magnetom Trio 3T scanner. A high-resolution T1-weighted scan was collected for anatomical localization. fMRI data was preprocessed with FSL v5.0.9, following best practices for dealing with motion and other nuisance variables. fMRI task-data were analyzed using FSL FEAT v6.00. All analyses were performed on the whole-brain level, using a Z-statistic threshold of $Z > 3$ and (corrected) cluster significance threshold of $P = 0.01$ after correcting for age and sex. Group-differences in brain activation during self-referential processing were assessed for correlations with CBCL scores.

Results: There were no significant group-differences in performance on the semantic condition or on positive and negative self-appraisal (all $p > .5$). Assessing main effects of task (self-reference > semantic) showed activation of medial prefrontal cortex in HC and precuneus/posterior cingulate cortex (PCC) in FHR. Group-comparison yielded significant results for the FHR > HC contrast, with two clusters of hyperactivation in precuneus/PCC ($p = .004$) and anterior cerebellum/temporo-occipital cortex ($p = .009$) in the FHR group. Greater activation in the precuneus/PCC cluster was found to correlate with greater CBCL scores on internalizing ($r = 0.60$, $p = .032$) and total ($r = 0.69$, $p = .009$) problems.
Discussion: This study shows that children, ages 7 – 12 years, with a familial risk for psychosis exhibit DMN hyperactivity during self-referential processing, which resembles findings in patients with established psychotic illness. These results suggest that abnormal DMN activity during self-referential processing predates not just psychosis, but also prodromal symptoms and adolescence. Moreover, our results show that early disturbances in self-referential processing may be related to internalizing symptoms, which is of interest to clinical staging models of schizophrenia. Taken together, this study's findings posit disturbances in DMN-related self-referential processing as a developmental brain abnormality associated with familial risk factors.

O3.5. THE ASSOCIATION BETWEEN THE NEURAL RESPONSE TO PSYCHOSOCIAL STRESS AND AFFECTIVE REACTIVITY TO REAL-LIFE STRESSORS IN EARLY STAGES OF PSYCHOSIS

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Background: Everyday stressful situations elicit affective and psychotic responses in individuals at early stages of psychosis (EP). On the neuronal level, both patients with schizophrenia and individuals at increased risk show aberrations in stress-reactivity in limbic and frontal areas when compared to healthy controls. No study to date has investigated whether stress-related activity in these areas is associated with affective and psychotic reactivity to daily-life stressors in early stages of psychosis.
Methods: 28 EP individuals were administered a stress task in conjunction with functional magnetic resonance imaging. All participants also provided diary data on momentary mood, symptoms, and stressful activities in their everyday environment. Multilevel models were used to estimate if the affective response to daily stressors was moderated by activity in limbic and frontal brain areas.
Results: A higher task-related increase in reported stress levels was significantly associated with a larger momentary increase in negative affect in response to stressful activities in daily life. Lower stress-related activity in the left inferior frontal gyrus, right superior frontal gyrus, and bilateral anterior cingulate cortex (ACC) and higher stress-related activity in the bilateral hippocampus was associated with greater affective and psychotic response to daily-life stressors.
Discussion: Brain signals associated with the experience of acute psychosocial stress in a laboratory environment are predictive of affective and psychotic reactivity to everyday stressful activities. Difficulties with engagement of frontal areas during stress may result in less controlled affective response to stressful situations.

O3.6. INTEGRATED METASTATE FUNCTIONAL CONNECTIVITY NETWORKS PREDICT CHANGE IN SYMPTOM SEVERITY IN CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: The ability to identify biomarkers of psychosis risk is essential in defining effective preventive measures to potentially circumvent transition to psychosis. Advances in functional imaging analysis provides novel methods for interrogating brain network abnormalities in those at risk of psychosis. The present study explored the association of novel functional connectivity (FC) based biomarkers with longitudinal changes in psychosis symptoms and functioning.

Methods: Using samples of people at Clinical High Risk for psychosis (CHR) and Healthy controls (HC) who were administered a task fMRI paradigm, we used a framework for labelling time windows of fMRI scans as 'integrated' FC networks in order to provide a granular representation of functional connectivity (FC). Periods of integration were defined using the 'cartographic profile' of time windows and k-means clustering, and subnetwork discovery was carried out using Network Based Statistics (NBS).

Results: There were no network differences between CHR and HC groups. Within the CHR group, using integrated FC networks, we identified a sub-network negatively associated with longitudinal changes in the severity of psychotic symptoms. This sub-network comprised brain areas implicated in bottom-up sensory processing and in integration with motor control, suggesting it may be related to the demands of the fMRI task.

Discussion: These data suggest that extracting integrated FC networks may be useful in the investigation of biomarkers of psychosis risk in future studies.

O3.7. WHITE MATTER ABNORMALITIES ANTIPSYCHOTIC MEDICATION-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS WITH AND WITHOUT DEFICIT SYNDROME FEATURES

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Background: The deficit syndrome is a clinical subtype of schizophrenia that presents with persistent negative symptoms. However, no studies have contrasted white matter abnormalities

in patients with and without deficit syndrome features in antipsychotic medication-naïve patients.

Methods: We used a human connectome style diffusion-weighted imaging (DWI) sequence to quantify white matter integrity in 63 antipsychotic medication-naïve first episode psychosis patients (21 with deficit syndrome features, 42 without deficit syndrome features) and 67 matched healthy controls. DWI scans were acquired with opposite phase encoding directions [TR/TE: 3230 ms/ 89.20 ms; multiband acceleration factor 4, flip angle: 84°; slice thickness 1.5 mm, 92 slices, voxel size 1.5 mm3, 92 diffusion-weighted images distributed equally over 2 shells with b-values of ~1500 s/mm2 and ~3000 s/mm2, and 7 interspersed b = ~0 s/mm2 images]. Preprocessing of DWI images was performed in TORTOISE (version 3.1.2). This included correction for thermal noise, Gibbs-ringing, high b-value based bulk motion and eddy-current distortions using a MAP-MRI model. DR-BUDDI was used to correct EPI distortions with input from the anatomical image and to combine the two datasets using geometric averaging to generate the corrected dataset. Tensors were computed with DIFF_CALC using a linear fitting algorithm. To spatially normalize images to the Illinois Institute of Technology atlas (IIT2) space, we used a modified version of 3dQwarp in AFNI. We compared voxel wise fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) among groups using (AFNI 3dMVM), with age, gender, and RMSrel as co-variates. We then computed whole brain FA, MD, AD, and RD measures and compared groups using a MANCOVA with the same covariates and used partial correlations to assess relationships between diffusion values and negative symptom severity.

Results: Whole brain diffusion metrics differed among groups when considered jointly ($F=3.044$, $p=0.003$). Between-subjects effects showed a significant difference for whole brain AD ($p=0.003$) and MD ($p=0.004$). Post hoc pairwise comparisons show that whole brain MD for patients with deficit features was significantly lower than patients with non-deficit features ($p=0.041$).

Discussion: Our data showed significant differences in white matter pathology in first episode psychosis patients when contrasting those with and without deficit syndrome features, supporting the deficit and non-deficit distinction in antipsychotic-naïve first episode psychosis patients. Future studies could potentially benefit from stratifying patients accordingly when investigating target engagement and efficacy of novel pharmacotherapies.

O3.8. EFFECT OF OXYTOCIN ON NEURAL CIRCUITRY OF TRUST BEHAVIOR IN SCHIZOPHRENIA

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Background: Clinical features of schizophrenia are often characterized by trust deficits leading to impairment in social functioning. Converging lines of evidence indicate the critical role of neuropeptide oxytocin in modulating social behavior, including trust and cooperation. Several studies have reported abnormalities in the oxytocin system in schizophrenia, and intranasal oxytocin improves symptoms of schizophrenia. However, to date, no study has examined oxytocin's effect on neural processes underlying trust behavior in schizophrenia. For the first time in this study, we examined the effect of single-dose intranasal oxytocin on the neural circuitry underlying trust behavior in patients with schizophrenia using a multi-round trust game.

Methods: Thirty-two male patients with schizophrenia and twenty-five healthy volunteers underwent fMRI scans using a 3T scanner while performing a multi-round trust game. Eighteen patients participated in the second phase of the study in which they underwent two more scans. In the second part of the study, patients received 24 IU of intranasal oxytocin or a saline placebo 30 minutes before the scan. Participants performed a multi-round trust game and invested in a human counterpart or a computer lottery. Feedback was given midway through the game, whether the trust was reciprocated or not. We pre-processed and analyzed the images using General Linear modeling implemented in Statistical Parametric Mapping. We conducted a whole-brain analysis controlled for multiple comparisons with the Family Wise Error (FWE) correction threshold of $p<0.05$. We examined the behavioral data for the effect of trial type (trust vs. risk), intervention (oxytocin vs. placebo), feedback (pre-feedback vs. post-feedback), and group (SCZ, HV) controlling for age and education using linear mixed effect models.
Results: The linear mixed effects analysis of the behavioral data revealed a significant three-way interaction between group, trial type and feedback. Patients with schizophrenia (85.00±21.98), compared to healthy volunteers (94.82±21.28), invested significantly less amount in trust trials ($t = 3.34$, $p=0.001$). This difference was predominantly due to post-feedback trials (SCZ-40.62±12.53;HV-48.89±10.79;). On fMRI analysis, the patient group had higher activation in left insular cortex (BA 13; pcorr=0.04; peak x=-33,y=-19,z=-4; cluster size 38 voxels) and bilateral dorsomedial prefrontal cortex (BA8,9; pcorr =0.04; x=-3,y=41,z=44; clustersize – 83 voxels). In the second part of the study, there was no significant change in the trust behavior with oxytocin. On fMRI analysis, we found increased activation in the left premotor cortex (BA 6, pcorr = 0.01, x=-45,y=-4,z=32; cluster size - 137) and the bilateral visual association cortex (BA 18, pcorr = 0.03; x=3, y=-88,z=29; cluster size =41) in the oxytocin condition.
Discussion: Study findings indicate decreased trust behavior in patients with schizophrenia. Higher activation of the insula in post feedback trials shows higher risk aversion in patients. While single dose oxytocin did not have effects at the behavioral level, brain activation changes during fMRI suggest the possible neuro-modulatory effect of oxytocin. These findings indicate the need for future studies with multi-dose oxytocin administration examining the impact on trust behavior.

O4. Oral Session: Progress in Functional Imaging Biomarkers for Psychosis

O4.1. SUBGROUPING OF ANTIPSYCHOTIC-NAïVE SCHIZOPHRENIA PATIENTS BASED ON FUNCTIONAL CONNECTIVITY DERIVED FROM RESTING STATE ENCEPHALOGRAPHY REVEALS A 'DEFICIT SCHIZOPHRENIA' PHENOTYPE

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Background: Coordinated neural activity measured with EEG and fMRI is disturbed in patients with schizophrenia. More specifically, schizophrenia is associated with abnormal function of the Default Mode Network (DMN), a network found to be hyperactivated and hyperconnected, although findings are not consistent. In order to embrace the heterogeneity of schizophrenia, we have previously applied unsupervised machine learning to identify subgroups of antipsychotic-naïve, first-episode schizophrenia patients based on task-related electrophysiological- and cognitive measures. Here, we aim to extend this work to include measures of resting state electroencephalography (EEG), which is non-task related and therefore potentially more applicable in a routine clinical setting. Specifically, we investigate if resting state EEG functional connectivity within the DMN can be used to identify subgroups with differential psychopathological and cognitive profiles in patients not confounded by medication effects and chronicity.

Methods: We included 51 antipsychotic-naïve, first-episode schizophrenia patients and 104 matched healthy controls recruited in two consecutive cohort studies. The participants underwent resting state EEG (64-channels) and a neurocognitive test battery including subtests from Cambridge Neurophychological Test Automated Battery (CANTAB), as well as several paper- and pencil tests. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). The EEG data was analyzed using exact low-resolution brain tomography (eLORETA) to allow source localization. Functional connectivity within the DMN was estimated using Phase Lag Index as implemented in the MNE Python package. The functional connectivity data was analyzed separately for the delta, theta, alpha, and beta frequency band using in-house Matlab scripts.

First, we applied machine learning algorithms on the functional connectivity data to identify potential subgroups of schizophrenia. Next, we explored subgroup differences regarding psychopathology and cognition. A reduced principal component space based on the strength of the 15 connections within the DMN in both patients and controls was used as input to a Gaussian mixture model to identify subgroups of patients. With support vector machines (SVM), we explored the relation between PANSS sub-scores and the identified subgroups.

Results: We robustly identified two statistically distinct subgroups of patients using the functional connectivity within the DMN in the theta band (4-8Hz). No other frequency band supported the subgrouping of patients. At baseline, these two sub-groups did not differ significantly in univariate analyses of PANSS sub-scores, demography, or substance use. However, the subgroups differed significantly on motor speed ($p=0.03$) and with trend level significance ($p<0.10$) on verbal memory, spatial working memory, and verbal IQ. Using the PANSS sub-scores as predictors in our SVM, the subgroups were predicted with a significant accuracy of 63.4% ($p=0.01$). The prediction was driven by negative and general, but not positive symptoms.

Discussion: Theta band resting state EEG functional connectivity within DMN identified two subgroups of antipsychotic-naïve schizophrenia patients. Our results suggest that our data-driven, unsupervised machine learning approach could identify a subgroup of patients characterized predominantly by negative and general symptoms and possibly cognitive deficits as well as altered theta band connectivity within DMN. Importantly, the subgroups were not explained by apparent demographic differences. The identified subgroup bears resemblance to the clinically descriptive phenotype of 'deficit schizophrenia'.

O4.2. DORSAL STRIATIAL HYPOCONNECTIVITY PREDICTS ANTIPSYCHOTIC MEDICATION TREATMENT RESPONSE IN FIRST EPISODE PSYCHOSIS AND UNMEDICATED PATIENTS WITH SCHIZOPHRENIA

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Background: Multiple lines of evidence implicate the dorsal striatum in the pathophysiology of psychosis spectrum disorders. Striatal abnormalities have been linked to a number of illness symptoms. Meanwhile, striatal dysconnectivity has been widely reported in the literature with many studies reporting caudate and/or putamen dysconnectivity specifically. Given the high concentration of dopamine receptors found in the striatum and its role in the dopamine pathway, striatal dopamine imbalance is a likely cause in cortico-striatal dysconnectivity in psychosis spectrum disorders. Because of this, there has been a great deal of interest in understanding the relationship between striatal abnormalities in psychosis and response to antipsychotic drug (ADP) treatment.

Methods: The goal of this study was twofold. First, we sought to identify patterns of dorsal striatal dysconnectivity in patients with a psychosis spectrum disorder, and second, to determine if these patterns of dysconnectivity were predictive of treatment response (TR). Using resting state functional connectivity we evaluated dorsal striatal dysconnectivity (using separate bilateral caudate and putamen seed regions) in two cohorts of subjects with psychosis spectrum disorders before APD treatment: a cohort of 71 medication-naïve first episode psychosis patients (FEP), and a cohort of 63 unmedicated patients with schizophrenia (SZ) (along with group matched controls for each cohort). We hypothesize that caudate dysconnectivity would show regional significance in areas of the DMN and that putamen dysconnectivity would show regional significance in areas associated the salience network. We further hypothesized that regions of significant dysconnectivity with either seed region would be predictive of response to APD treatment.

Results: Both cohorts showed hypoconnectivity between the bilateral caudate and regions of the default mode network (DMN), anterior cingulate cortex, sensory/motor areas and the temporal gyri as well as hypoconnectivity between the putamen and medial prefrontal cortex. FEP also showed caudate hypoconnectivity to the insula, fusiform gyrus, thalamus and amygdala, along with putamen hypoconnectivity to the hippocampus, insula, sensory/motor cortex, fusiform and temporal gyri, temporo-parietal junction, and dorsolateral prefrontal and dorsal cingulate cortices. Unmedicated SZ showed putamen hypoconnectivity to the parahippocampus, right anterior precuneus, retrosplenial cortex, and posterior cingulate cortex. Additionally, both caudate and putamen dysconnectivity were predictive of TR in both cohorts.

Discussion: These results Results: establish both putamen and caudate dysconnectivity as useful biological markers of psychosis and predictors of response to APD treatment. These results Results: suggest two similar, but distinct patterns of dysconnectivity tied to the dorsal striatum. Caudate hypoconnectivity results Results: were primarily associated with the DMN (more robust among FEP patients). While not as robust, putamen hypoconnectivity was more associated with the insula (particularly within the FEP cohort). Based on these results Results: we speculate that caudate dysconnectivity to the DMN may be a driving factor during early illness that if left untreated could lead to wider striatal dysconnectivity in other networks, such as the salience network, as the illness progresses.

O4.3. THE RELATIONSHIP BETWEEN HIPPOCAMPAL ACTIVITY, STRIATAL DOPAMINE AND ADVERSE OUTCOMES IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Preclinical models suggest that the onset of psychosis involves increased hippocampal activity that drives subcortical dopaminergic dysfunction (Grace, 2012; Lodge & Grace, 2011; Modinos et al., 2015). To date, relatively few studies have directly examined this relationship in patients. However, it is not known whether changes in the hippocampal-striatal relationship are associated with subsequent clinical outcomes. Thus, the present study used multi-modal neuroimaging to examine the relationship between hippocampal regional cerebral blood flow (rCBF) and striatal dopamine synthesis capacity in people at clinical high risk (CHR) for psychosis, and investigated its association with clinical outcomes.

Methods: Ninety-five participants (67 CHR individuals and 28 healthy controls) underwent both pseudo-continuous arterial spin labelling and 18F-DOPA PET imaging at baseline in two independent studies conducted at King's College London. Both studies used the same clinical and neuroimaging methods CHR participants were clinically monitored after a median of 15 months follow-up, and clinical outcomes were assessed in terms of severity of psychotic symptoms (CAARMS criteria) and the level of overall functioning (Global Assessment of Function scale, GAF). Because the PET data were acquired with two different scanners, we used ComBat (Fortin et al., 2017, 2018) to harmonize the respective PET datasets. We included age, sex, outcome, cannabis use, CAARMS, GAF as covariates in the analysis in R. The relationship between hippocampal rCBF and whole striatal dopamine synthesis capacity (Kicer, min-1) by functional outcome group was examined in a voxel-wise ANCOVA using SPM12, dividing the CHR sample into two groups at follow-up: a good functional outcome group (GAF≥65) and poor functional outcome group (GAF<65). Age, sex and mean global CBF were included as covariates of no interest. Effects were considered significant at family-wise error (FWE) $p<0.05$ after small volume correction (SVC) using a pre-specified anatomical mask of the bilateral hippocampus. The relationship between the whole striatal dopamine synthesis capacity x hippocampal rCBF interaction at baseline and subsequent changes in the severity of positive symptoms was investigated using linear regression in SPSS (significance at $p<0.05$).

Results: Of the 67 CHR participants, 50 were followed-up clinically. No significant differences were found in demographic or clinical variables at baseline between functioning groups. CHR participants with a poor functional outcome (n=25) showed higher rCBF in the right hippocampus compared to CHRs with a good functional outcome (n=25) (xyz: 40 -12 -24, k=17, t=3.68, z=3.42, pFWE=0.026). The relationship between right hippocampal rCBF and striatal dopamine synthesis capacity was significantly different between groups (xyz: 40 -12 -24, k=14, t=3.56, z=3.32, pFWE=0.035); the association was negative in CHR with poor outcomes (xyz: 38 -8 -24, k=20, t=3.99, z=3.66, pFWE=0.012), but non-significant in CHR with good outcomes. Moreover, the correlation between rCBF in this right hippocampal region and striatal dopamine function predicted a longitudinal increase in the severity of psychotic symptoms (β=0.296, R2=0.087, df=47, =0.041). The relationship between hippocampal rCBF and striatal dopamine did not differ in the total CHR group relative to controls.

Discussion: These findings suggest that adverse clinical outcomes in the CHR state are linked to aberrant interactions between heightened resting hippocampal activity and striatal dopamine function, and support future research to examine the effect of stabilizing hippocampal hyperactivity to prevent the development of psychosis-related outcomes.

O4.4. CANNABIDIOL MODULATES MEDIAL TEMPORAL AND STRIATAL FUNCTION DURING FEAR PROCESSING IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: People at clinical high risk for psychosis (CHR) show altered neural responses to emotional (particularly fear-related) stimuli in the striatum and medial temporal lobe. Cannabidiol (CBD) is a non-intoxicating constituent of the cannabis plant with antipsychotic and anxiolytic properties. Previous work suggests that CBD modulates activation and functional connectivity of the medial temporal cortex and striatum during numerous emotional/cognitive paradigms and across various healthy and clinical populations. However, the effects of CBD on these specific regions in CHR subjects during fear processing remain 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 were scanned with functional magnetic resonance imaging (fMRI) during a fearful face-processing paradigm. Differences in activation related to the CHR state and to the effects of CBD were examined using a region-of-interest approach.

Results: During fear processing, CHR participants receiving placebo (n = 15) showed significantly greater activation than healthy controls (n = 19) in the parahippocampal gyrus and less activation in the striatum. Within these regions, activation in the CHR group that received CBD (n = 15) was significantly intermediate between that of the CHR placebo and healthy control group.

Discussion: These findings suggest that in CHR patients, CBD modulates brain function in regions implicated in psychosis risk and emotion processing and in a direction indicative of 'normalisation'. These findings are similar to those previously evident using a memory paradigm, suggesting that the effects of CBD on medial temporal and striatal function in CHR individuals may be task independent. Further research should examine whether these acute neurofunctional effects translate into clinical efficacy after a period of treatment.

O4.5. EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON BRAIN FUNCTION IN SCHIZOPHRENIA: DATA FROM A DOUBLE-BLIND, RANDOMIZED, SHAM-CONTROLLED TRIAL

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Background: Cognitive impairment, particularly deficits in working memory, is a core feature of schizophrenia and predict functional outcome. However, there is a paucity of effective therapeutic interventions targeting these deficits. The dorsolateral prefrontal cortex (DLPFC) plays a critical role in working memory performance. Various studies link working memory deficits to alterations in DLPFC structure and function. Based on our pilot study showing that repetitive transcranial magnetic stimulation (rTMS) to the DLPFC in schizophrenia improves working memory performance, a four-week rTMS trial was conducted. As a part of this trial, we used task-based fMRI to examine changes in brain activity during an N-back working memory task following rTMS.
Methods: This double-blinded, sham-controlled trial randomized 81 participants (age 18-59) with schizophrenia or schizoaffective disorder to active or sham rTMS administered bilaterally to the DLPFC five days/week for four weeks (active rTMS at 20 Hz). Participants completed an fMRI letter sequence N-back task (1- and 3-back trials presented as block design) before and after receiving rTMS. Scan data were preprocessed (correction for slice time, motion, and susceptibility distortions; fMRIprep), transformed onto the cortical surface, and smoothed (Ciftify toolbox). N-back fMRI data was available from 34 participants (active/sham: n=16/18) who completed both scans with adequate performance and acceptable motion. Working memory-related activity was identified via the contrast of 3-back vs 1-back. To assess local effects, an 8mm ROI was created bilaterally around the rTMS coordinates, and mean beta weights extracted for each scan. Between-group (i.e. active or sham) difference in change (local activation post - pre rTMS) was assessed via a two-sample t-test. Whole-brain pattern group analysis was performed using 1000 permutations with threshold-free clustering enhancement (FSL PALM), comparing the change in activation (post - pre rTMS) between groups. We also calculated the Correlational distance between each pair of participants. Individual variability was the average distance from each participant to all participants of the same group (i.e. active or sham), with lower distance representing a more 'typical' activity pattern. While paired t-tests were used to assess within-group change (variability post - pre rTMS), between-group (i.e. active or sham) differences in change (variability post - pre rTMS) were assessed via two-sample t-tests.
Results: Our preliminary results show an increase in task-evoked local DLPFC activity in the active (mean change=0.232±0.28) but not the sham (mean change=-0.023±0.44) group; this group difference was significant (t=2.03, p=0.05, df=32). Although we did not observe differences in the whole brain analysis, the active group showed a reduction in variability in their spatial pattern of task-evoked activation following rTMS (t=-3.14, p=0.007, df=15), while sham group did not (t=0.42, p=0.68, df=17); this difference was significant between groups (t=-2.44, p=0.02, df=32).
Discussion: The current study increases our knowledge about how rTMS treatment may change brain function in schizophrenia. Further understanding of how changes in variability of brain function relates to potential clinical changes will be an important next step.

O4.6. CEREBELLO-THALAMO-CORTICAL HYPERCONNECTIVITY CLASSIFIES PATIENTS AND PREDICTS LONG-TERM TREATMENT OUTCOME IN FIRST-EPISODE SCHIZOPHRENIA

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Background: It has previously been shown that cerebello-thalamo-cortical (CTC) hyperconnectivity is a heritable and state-independent neural trait for psychosis (Cao et al., Nat Comm, 2018; Cao et al., Transl Psych, 2019). However, the potential clinical utility of this trait has not yet been evaluated. This study aimed to investigate whether CTC hyperconnectivity would serve as an individualized biomarker for diagnostic classification and prediction of long-term treatment outcome in first-episode patients.
Methods: Resting-state fMRI and clinical data were acquired from 214 untreated first-episode patients with schizophrenia and 179 healthy controls. A subsample of 62 patients was clinically followed-up at least once at the 12th and 24th months after treatment initiation. Cross-validated LASSO regression was conducted to estimate the accuracy of baseline CTC connectivity for patient-control classification, with the generalizability of classification performance tested in an independent sample including 42 untreated first-episode patients and 65 controls. Clinical outcomes for each patient was evaluated using the PANSS scores and linear mixed models, and the predictability of outcomes with baseline CTC was estimated by leave-one-out cross validation.
Results: There was significantly increased baseline CTC connectivity in first-episode patients compared with controls ($P = 0.01$). Measures of CTC connectivity discriminated first-episode patients from controls with moderate classification accuracy ($AUC = 0.67$, $P < 0.001$), and the classification model had good generalizability in the independent sample ($AUC = 0.68$, $P = 0.001$). Higher CTC connectivity at baseline significantly predicted poorer long-term symptom reduction in negative symptoms ($R = 0.30$, $P = 0.01$) but not positive or general symptoms.
Discussion: These findings extend the established "CTC hyperconnectivity" trait for psychosis to the individual level, provide initial evidence for the value of this trait as an individualized diagnostic and prognostic biomarker for schizophrenia, and highlight the potential of CTC connectivity measures in precision psychiatry.

O4.7. RESTING-STATE NETWORKS ASSOCIATED WITH SEVERITY OF PERSECUTORY IDEATION IN PSYCHOSIS

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Background: Persecutory ideation is a common delusion where individuals believe they are being persecuted despite a lack of evidence. It is often seen in patients with psychotic disorders, but it could be present in the general public as well. We were interested in the neural correlates of persecutory ideation, specifically the functional connectivity between the left frontoparietal (lFP) network and the orbitofrontal cortex (OFC). Reduced connectivity between these two networks was found to be associated with increased persecutory behaviors in psychosis patients (Wisner et al., under review) during an economic social decision-making task, and our goal was to replicate this finding in resting-state data.
Methods: 46 patients were recruited for being in the early course of a psychotic disorder. We took behavioral measures of persecutory ideations using the Minnesota Trust Game (MTG; Johnson et al., 2009) and self-reports using the Green et al. Paranoid Thought Scales (Green et al., 2008). Over a 10-minute scan, we examined the resting-state functional (rsfMRI) connectivity across 9 brain networks that overlapped with our regions of interest, selected from 60 co-activated networks (and neuroimaging artifacts) defined by Rueter et al. (2018) using group independent component analysis.

Results: Resting-state networks were found to correlate with both behavioral and self-reported measures of persecutory ideation. We replicated with resting-state data the finding of reduced connectivity between the lFP network and the OFC in patients with increased persecutory behaviors, as measured by the percentage of distrust in the MTG ($r = -.53$; familywise corrected $p = .01$). The self-reported index for persecutory ideation, on the other hand, correlated significantly with the connectivity between the right frontoparietal (rFP) network and the OFC ($r = .32$; familywise corrected $p = .01$).
Discussion: We extended the previous finding of reduced connectivity between the lFP networks and the OFC in patients with elevated persecutory behaviors to the resting-state. Additionally, we observed a hemispheric difference, such that greater rFP-OFC connectivity predicted elevated self-reported persecutory ideation, suggesting potential differences between the lFP and rFP roles in persecutory social interactions.

O4.8. DISENTANGLING ALTERED FUNCTIONAL CONNECTIVITY IN ANTIPSYCHOTIC-TREATED AND ANTIPSYCHOTIC-NAIVE FIRST EPISODE PSYCHOSIS: A LONGITUDINAL TRIPLE-BLIND PLACEBO-CONTROL FMRI STUDY

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Background: Altered functional connectivity (FC) is a common finding in resting-state functional Magnetic Resonance Imaging (rs-fMRI) studies of people with psychosis, yet how FC disturbances evolve in the early stages of illness, and how antipsychotics may influence the temporal evolution of these disturbances, remains unclear. Here, we scanned first-episode psychosis patients (FEP) who were and were not exposed to antipsychotic medication during the first six months of illness at baseline, three months, and 12 months, to characterize the how FC changes over time, during the early stages of illness.
Methods: Sixty-two antipsychotic-naïve patients with FEP received either an atypical antipsychotic or a placebo pill over a treatment period of 6 months. Both FEP groups received intensive psychosocial therapy. A healthy control group (n=27) was also recruited. A total of 202 rs-fMRI scans were obtained across three timepoints: baseline, 3-months and 12-months. Our primary aim was to differentiate patterns of FC in antipsychotic-treated and antipsychotic-naive patients within the first 3 months of treatment and to examine associations with clinical and functional outcomes. We secondarily investigated long-term effects at the 12-month timepoint.
Results: At baseline, we observed a distributed subnetwork of altered FC in antipsychotic-naïve patients, with FC reductions predominantly affecting connectivity between the default mode network (DMN) and limbic systems with the rest of the brain. From baseline to 3 months, antipsychotic exposure largely increased FC primarily between the thalamus and the rest of the brain, contrasting the pattern observed in patients receiving placebo, where FC increases principally affected connectivity between the DMN, limbic areas, and other brain regions. Importantly, longitudinal FC changes within this subnetwork strongly correlated with improved symptom ratings and functional outcomes over time. At the 12-month follow-up, we

observed evidence for a prolonged effect of antipsychotics in increasing FC, primarily in the DMN and limbic systems.
Discussion: Antipsychotic-naïve FEP patients show wide-spread functional dysconnectivity at baseline, with some evidence for an improvement of these changes within the first three months of illness. In particular, we identify limbic and paralimbic networks as playing a major role in FC disruptions. Our results Results: also suggest that antipsychotic medication normalises dysconnectivity in thalamocortical and limbic/paralimbic networks.

O5. Oral Session: Comorbidities, Symptom Dimensions and Clinical Course

O5.1. SMOKING, SYMPTOMS, AND QUALITY OF LIFE IN PATIENTS WITH PSYCHOSIS, SIBLINGS, AND HEALTHY CONTROLS: A PROSPECTIVE, LONGITUDINAL COHORT STUDY

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Background: The self-medication hypothesis postulates that the high prevalence of smoking in patients with psychosis can be explained by the ameliorating effect of smoking on symptoms. However, there are few large prospective studies testing this hypothesis. We aimed to examine the multi-cross-sectional and prospective associations of changes in smoking behaviour with symptoms and quality of life.
Methods: In this prospective cohort study we recruited patients with a non-affective psychosis (n=1094), unaffected siblings (n=1047), and healthy controls (n=579). Patients aged between 16 and 50 years and diagnosed with a non-affective psychosis according to DSM-IV were recruited by clinicians from four university medical centres and 36 associated mental health-care institutions in the Netherlands and Belgium between Jan 13, 2004, and March 6, 2014. Smoking status and number of cigarettes per day were assessed at baseline, and at 3-year and 6-year follow-up using
the Composite International Diagnostic Interview (CIDI). Symptom frequency was self-rated with the Community Assessment of Psychotic Experience (CAPE), and quality of life was assessed by the WHO Quality of Life (WHOQOL) schedule. Multiple linear mixed-effects regression analyses were done accounting for multiple confounders.

Results: At baseline, 729 (67%) of 1094 of patients smoked (mean 17·5 cigarettes per day, SD 8·8) compared with 401 (38%) of 1047 siblings and 145 (25%) of 579 healthy controls. Multi-cross-sectional results of linear mixed-effects analyses showed that smoking in patients and siblings was associated with more frequent positive symptoms (estimate 0·14, SE 0·02, p<0·0001 in patients; 0·03, 0·01, p=0·0019 in siblings), negative symptoms (0·15, 0·03, p<0·0001 in patients; 0·09, 0·02, p<0·0001 in siblings), and depressive symptoms (0·12, 0·03 p<0·0001 in patients; 0·08, 0·02 p<0·0001 in siblings) and lower quality of life (–0·59, 0·11, p<0·0001 in patients; –0·31, 0·09, p=0·0002 in siblings) than non-smokers. In controls, smoking was associated with significantly higher frequency of subclinical positive symptoms (0·03, 0·01, p=0·0016) and depressive symptoms (0·05, 0·03, p=0·0432) than in participants who did not smoke. Patients who started to smoke during follow-up showed a significant increase in self-reported symptoms, particularly positive symptoms (0·161, 0·077, p=0·0381), whereas smoking cessation was not associated with changes in symptoms or quality of life

compared with those who showed no change in smoking behaviour. Similar results were obtained for the changes in the number of cigarettes smoked.
Discussion: Our findings do not empirically support the self-medication hypothesis. The absence of long-term
symptomatic relief from smoking should encourage clinicians to help patients with psychosis to quit smoking.

O5.2. EVIDENCE FOR SHARED GENETIC AETIOLOGY BETWEEN SCHIZOPHRENIA, CARDIOMETABOLIC AND INFLAMMATORY TRAITS: GENETIC CORRELATION AND COLOCALIZATION ANALYSES

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Background: Schizophrenia commonly co-occurs with cardiometabolic and inflammatory disorders, but it is unclear to what extent comorbidity between these traits could be attributable to shared genetic aetiology.
Methods: We used GWAS summary data to estimate potential common genetic aetiology between schizophrenia and twelve cardiometabolic and inflammatory traits including fasting insulin (FI), fasting plasma glucose, glycated haemoglobin, insulin resistance, glucose tolerance, type 2 diabetes mellitus (T2D), lipids, body mass index (BMI), coronary artery disease (CAD), and C-reactive protein (CRP). We examined genome-wide correlation between traits using linkage disequilibrium score regression (LDSC); then stratified by minor-allele frequency (MAF) using genetic covariance analyzer (GNOVA); then refined to the locus-level using heritability estimation from summary statistics (ρ-HESS). Regions showing local correlation were used in hypothesis prioritization multi-trait colocalization (HyPrColoc) to estimate colocalisation supporting shared genetic aetiology.
Results: Schizophrenia was correlated at genome-wide level with T2D (rg=-0.07; 95% C.I., -0.03,0.12; p=0.002) and BMI (rg=-0.09; 95% C.I., -0.06,-0.12; p=1.83x10-5). In MAF-stratified analyses, we found correlation between schizophrenia, CAD, FI, T2D, HDL, LDL, and CRP in the lowest MAF-quartile, which was underpinned by 92 regions of locus-level correlation. We found evidence for colocalisation between schizophrenia and included traits at twelve loci, of which seven had a posterior probability >0.80. Four of those (rs6265 (BDNF); rs8192675 (SLC2A2); rs3800229 (FOXO3); rs17514846 (FURIN)) are implicated in brain-derived neurotrophic factor (BDNF)-related pathways.
Discussion: Common genetic aetiology for schizophrenia, cardiometabolic and inflammatory traits could be predominantly confined to lower-frequency variants. Genes related to BDNF, glucose transport and other pathways may underpin the increased comorbidity between schizophrenia and cardiometabolic disorders.

O5.3. CANNABIS USE AND PSYCHOSIS RISK IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS: THE NORTH AMERICAN PRODROME LONGITUDINAL STUDY (NAPLS-3)

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Background: Cannabis use is more prevalent among youth at clinical high-risk (CHR) for psychosis compared to healthy controls (HC), with almost half of CHR youth reporting that they have tried cannabis in their life. It has been reported that cannabis use is associated with increased symptom severity of the attenuated psychotic symptoms (APS) in CHR youth. There is some evidence that current cannabis abuse or dependence among CHR individuals is associated with the transition to psychosis. This study aims to assess 1) cannabis use differences between CHR and HC, and 2) the role of cannabis use on APS and in the development of psychosis in individuals at CHR.

Methods: Method: Participants in this study were from the North American Prodrome Longitudinal Study-3 (NAPLS-3), a 9-site prospective case-control longitudinal study including 710 help-seeking youth (325 females, 385 females), age 12-30, meeting criteria for a psychosis risk syndrome based on the Structured Interview for Psychosis-risk Syndromes (SIPS), and 96 HC (48 females, 48 males). Cannabis, alcohol, and other substance use in the past month and its frequency was assessed with the Alcohol Use Scale/Drug Use Scale (AUS/DUS) at baseline, 2-, 4-, 6-, 8-, and 12-month follow-ups. Current and past substance use disorders were assessed with the Structured Clinical Interview for DSM-5 (SCID-5) at baseline and 12-month follow-up. The severity of APS was rated on the Scale of Psychosis-Risk Symptoms (SOPS) at baseline, 2-, 4-, 6-, 8-, and 12-month follow-up. Transition to psychosis was based on the SIPS interview, defined as meeting the Presence of Psychosis Syndrome (POPS) criteria.

Results: At baseline, of the 710 CHR participants, 7.4% had a current and 8.7% a past substance use disorder, which were significantly higher than HC (0% and 1%, respectively). The groups did not differ in other substance use disorders. The two groups significantly differed in current cannabis use, with 176 (35%) CHR and 11 (11.5%) HC reporting cannabis use in the last month. There were no differences between the groups in the frequency of use. At baseline, there were significant differences in grandiose ideas and total SOPS symptoms between CHR who reported cannabis use in the last month and CHR who reported no use. The two groups did not differ in positive or the total SOPS symptoms at any follow-up assessment. There was no difference in baseline cannabis use between those who transitioned to psychosis and those who did not transition.

Discussion: Findings suggest that CHR individuals seem to use more cannabis than HC. However, between CHR who use cannabis and those who do not use, we have found differences in the severity of symptoms only for a few APS. These findings seem to be consistent with previous research in the high-risk population.

O5.4. A FIVE-FACTOR MODEL DEFINES THE STRUCTURE OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Negative symptoms are core components of schizophrenia and contribute to poor functioning. Plenty of research has been conducted to differentiate negative symptoms from other symptoms of schizophrenia, and to understand their inner structure which resulted in several factorial models. The recent conceptualization of negative symptoms which shaped new generation assessment measures and is used as part of criteria A for the diagnosis of schizophrenia in the DSM-5, consists of two factors: motivation and pleasure (MAP), and expression (EXP). However, this model has been recently challenged by data supporting the superiority of a five-factor model which includes blunted affect, alogia, avolition, anhedonia and asociality as main components defined by NIMH-MATRICS consensus statement on negative symptoms. Clearly, the structure of negative symptoms is and might be an ongoing debate until further data will be able to corroborate existing evidence. The aim of this study is to define a factorial model of negative symptoms from a representative large sample of patients with schizophrenia, and then to compare it with existing models for determining the best among them.

Methods: This was a multi-site cross-sectional study with 271 participants with schizophrenia from outpatient mental health services. All participants were administered the Clinical Assessment Interview for Negative Symptoms (CAINS) to rate negative symptoms. Principal Component Analysis (PCA) was used to ascertain the number of factors, and factorial models. Next, the models were tested with Confirmatory Factor Analysis (CFA) to examine the goodness-of-fit of the models and to determine the best one. The indexes used to evaluate the model were: the Root Mean Square Error of Approximation (acceptable value <0.08), the Comparative Fit Index and the Tucker-Lewis Index (acceptable values ≥0.95; the Standardized Root Mean Square Residual (≤0.08); the Adjusted Goodness of Fit Index (<0.95); the relative Chi-square (< 3). The Akaike Information Criterion was used to determine the best among competing models (with lower value indicating better fit).

Results: A five-factor model emerged as the most statistically robust one and consisted of the following factors: diminished expression, diminished motivation for recreational activities, diminished motivation social activities, diminished motivation vocational, and diminished motivation close/intimate relationships. All factor loadings were in the high range (≥ 0.80) and between good and excellent Cronbach's alpha values. From CFA, the above five-factor model showed better indexes and therefore goodness-of-fit than the existing two- and the five-factor model (MAP and EXP, and five core factors from NIMH-MATRICS consensus respectively).

Discussion: The current two-factor model (MAP and EXP) and the five core factors suggested by the NIMH-MATRICS for negative symptoms would need to be reconsidered in the light of finding from this study. Our five-factor model underlines the importance of diminished expression as a core component of negative symptoms and draws the attention to the role of motivation across different areas. This finding would support both research and clinical practice by suggesting that a better definition of outcomes in relation to negative symptoms in clinical trials is necessary and that the adoption of distinct types of diminished motivation would help mental health professionals to monitor progression or remission of symptoms. Overall, our results could contribute to improve treatment of schizophrenia.

O5.5. INVESTIGATING THE INFLUENCE OF THOUGHT INTERFERENCE AND SOMATIC PASSIVITY ON OUTCOMES IN PATIENTS WITH PSYCHOSIS

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Background: Of the many studies describing psychotic symptoms in schizophrenia, few have investigated their direct influence on prognosis. We aimed to apply natural language-processing (NLP) algorithms in routine healthcare records to identify reported somatic passivity and thought interference symptoms (thought broadcasting, insertion and withdrawal), and determine associations with prognosis by an analysis of routine outcomes.
Methods: Four algorithms were thus developed on de-identified mental healthcare data from a large south London provider and were applied to ascertain recorded symptoms over the three months following first presentation to that service in a cohort of patients with a primary schizophreniform disorder (ICD-10 F20-F29) diagnosis. The primary binary dependent variable for logistic regression analyses was any negative outcome (Mental Health Act section, >2 antipsychotics prescribed, >22 days spent in crisis care) over the subsequent 2 years, adjusted for age, gender, ethnic group, neighbourhood deprivation, diagnostic group, and recorded paranoia, persecutory delusions or auditory hallucinations.
Results: In 9,323 patients, final models indicated significant associations of this composite outcome with baseline somatic passivity (prevalence 4.9%; adjusted odds ratio 1.61, 95% CI 1.37-1.88), thought insertion (10.7%; 1.24, 1.15-1.55) and thought withdrawal (4.9%; 1.36, 1.10-1.69), but not independently with thought broadcast (10.3%; 1.05, 0.91-1.22).
Discussion: Symptoms traditionally central to the diagnosis of schizophrenia, but under-represented in current diagnostic frameworks, were thus identified as important predictors of short- to medium-term prognosis.

O5.6. CLINICAL RECOVERY IN PSYCHOTIC DISORDERS AT 10-YEAR FOLLOW-UP: CHALLENGING THE EXISTING DEFINITIONS

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Background: Clinical recovery (symptom remission and adequate functioning) from psychotic disorders is more common than previously thought (Hegelstad et al., 2012; Lally et al., 2017). However, with no consensus definition of clinical recovery or psychotic disorders, studies vary in recovery criteria and included diagnoses. This hinders conclusive results on overall recovery rates, and comparisons across bipolar and schizophrenia spectrum disorders. As such, the aims of the present first-episode psychosis (FEP) longitudinal study (TOP 10-year) were to investigate the following:

1. Are the rates of clinical recovery in the previous TIPS 10-year follow-up replicated when using the same definition, and do they differ across bipolar and schizophrenia spectrum disorders?
2. What is the rate of adequate functioning in a healthy control group at 10-year follow-up?
3. How do clinical recovery rates change when altering criteria for symptom remission, adequate functioning and duration?

Methods: 119 FEP participants (30.2% bipolar spectrum; 69.8% schizophrenia spectrum) from the TOP longitudinal study were investigated at 10-year follow-up. 117 matched healthy

controls were also included. Symptoms were measured with the Positive and Negative Syndrome Scale (PANSS), The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and the Young's Mania Rating Scale (YMRS). Functioning was measured with a structured clinical interview. Clinical recovery was defined according to the TIPS 10-year follow-up study (Hegelstad et al., 2012), including duration of at least 12 months of: psychotic symptom remission according to RSWG-criteria (Andreasen et al., 2005) and adequate functioning consisting of full-time employment or study, independent living and weekly social contact.

Results: At 10-year follow-up, 59.7% were in symptom remission with at least 12 months duration. 38.7% of participants were in clinical recovery, with significantly higher recovery rates among those with bipolar spectrum diagnosis (53.4%) compared to schizophrenia spectrum diagnosis (30.2 %) ($\chi 2$ (1, N = 119) = 6.247 $p < .05$). Amongst the healthy controls 86.1% met criteria for adequate functioning compared to 39.5% of the FEP participants. Finally, clinical recovery rates changed with altered criteria, such as including remission of affective symptoms in addition to psychotic symptoms, allowing looser criteria for adequate functioning such as working part-time, and different lengths of duration (final analyses in preparation).

Discussion: The present study found a clinical recovery rate of 38.7% among FEP participants at 10-year follow-up, comparable to the 30.7% from the previous TIPS 10-year follow-up study. The recovery rate for participants with bipolar spectrum disorder was over 20% higher than for schizophrenia spectrum disorders. Although, the majority of healthy controls met the criteria for adequate functioning, almost 14% did not, suggesting that these recovery criteria might be too strict for participants with psychotic disorders. As expected, the rate of clinical recovery was altered with adjusted criteria for symptom remission, adequate functioning and duration. In conclusion, the findings suggest a need for a consensus definition of clinical recovery for individuals with psychotic disorders that adequately captures improvement in outcome without undue stringency.

O5.7. TRAJECTORIES OF PREMORBID FUNCTIONING PREDICT COGNITIVE REMEDIATION GAINS FOR PROCESSING SPEED IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Neurodevelopmental models of schizophrenia suggest that individuals who ultimately develop schizophrenia can show early changes in brain development and cognition, which may be reflected in diverse trajectories of premorbid functioning. Although aspects of post-onset brain development may be shaped by cognitive remediation, few studies to date have investigated whether early behavioral development may predict later cognitive changes following cognitive training. We therefore examined the extent to which pre-onset adjustment trajectories predict post-onset cognitive remediation gains in schizophrenia.

Methods: 94 outpatient participants with first-episode schizophrenia underwent cognitive remediation in one of three randomized clinical trials. Interventions ranged from 6 to 12 months of computerized cognitive remediation combined with a bridging group to facilitate generalization. To classify premorbid adjustment trajectories across childhood, early

adolescence, and late adolescence, we compared the fits of a series of growth mixture models using mean adjustment scores for each period on the Cannon-Spoor Premorbid Adjustment Scale. We assessed cognitive remediation gains based on the difference between T-scores at baseline and at 6-month follow-up for MATRICS Consensus Cognitive Battery domains. We identified cognitive domains for which participants demonstrated mean change after cognitive remediation then examined whether premorbid adjustment trajectories predicted changes in these domains.

Results: Growth mixture models indicated three trajectories of premorbid adjustment: stable-poor adjustment (N=17, 18.1%), gradual-decline adjustment (N=57, p=60.1%), and late-decline adjustment (N=20, 21.3%). Participants with stable-poor adjustment showed poor adjustment from childhood to late adolescence. Participants with early-decline adjustment showed moderate declines from childhood through late adolescence whereas participants with late-decline adjustment showed stable good adjustment from childhood to early adolescence, then showed declines in late adolescence. Participants did not differ on average between clinical trials in cognitive remediation gains, and out of the seven cognitive domains, participants on average demonstrated significant improvements in Speed of Processing, Verbal Learning, and Reasoning and Problem Solving, or Social Cognition. Across the three trajectories, participants demonstrated similar gains for Verbal Learning and Reasoning and Problem Solving. Notably, participants with stable-poor adjustment demonstrated significantly greater improvements in Speed of Processing scores (mean=11.06, s.d. = 11.67) compared to participants with early-decline adjustment (mean=4.47, s.d. = 7.78) or participants with late-decline adjustment (mean=4.40, s.d. = 7.83), ($F(2,91)=1.959$, $p=0.020$).

Discussion: To our knowledge, this is the first study to examine the association between premorbid adjustment trajectories and cognitive remediation gains after psychosis onset, indicating that individuals who show early, stable functional difficulties may reap greater benefits from cognitive remediation for processing speed, compared to individuals who show better early functioning that declines before psychosis onset. Taken together with prior research suggesting that premorbid adjustment is associated with cognitive training gains (Buonocore, et al., 2018), our findings highlight the connection between trajectories of pre-onset and post-onset functioning in schizophrenia and emphasize the utility of considering the lifespan developmental course in efforts to personalize treatments.

O5.8. THE INDEPENDENT AND INTERACTIVE EFFECTS OF MULTIPLE RISK FACTORS FOR SCHIZOPHRENIA SPECTRUM DISORDERS: A COMBINED REGISTER-BASED AND CLINICAL TWIN STUDY

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Background: Research has yielded evidence for numerous factors influencing the risk of developing schizophrenia spectrum disorders, including both genetic and environmental

factors. A recent twin study reported high heritability estimates of 79% for schizophrenia and 73% for the broader category of schizophrenia spectrum disorders. For environmental influences, multiple risk factors occurring both early (during pregnancy or birth) and later in development have been identified. However, the individual effects of the identified environmental risk factors are small, indicating that multiple risk factors occurring during critical periods of neurodevelopment are required, leading to onset of manifest illness once a certain threshold has been reached. The cumulative or interactive effect of multiple risk factors in schizophrenia spectrum disorders is not well elucidated. Twin pairs discordant for the disease offer a unique opportunity to identify environmental factors that differ between the patients and their unaffected co-twin, who are otherwise perfectly matched for age and sex as well as partly for genetic background and early environmental insults.
Methods: Register data from the Danish Birth Register was combined with clinical data for 216 twins comprised of 32 complete monozygotic (MZ) and 24 complete dizygotic (DZ) proband pairs (i.e. with one or both twins having a diagnosis within the schizophrenia spectrum) as well as 29 complete MZ and 20 complete DZ healthy control pairs. Additionally, six twins from proband pairs participated without their sibling. The included risk factors were: The polygenic risk score for schizophrenia, season of birth, paternal age, birth weight, birth complications, maternal smoking during pregnancy, Apgar scores, urbanicity, parental socioeconomic status, premorbid IQ, self-reported childhood trauma and cannabis use. Logistic regression models were applied to predict 1) illness vulnerability (being part of a proband pair vs. a healthy control pair) and 2) illness status (being a patient vs. an unaffected co-twin).
Results: Three risk factors independently predicted illness vulnerability: the polygenic risk score for schizophrenia (odds ratio (OR) 1.6, 95% CI [1.1 – 2.3]), self-reported levels of childhood trauma (OR 4.5, 95% CI [2.3 – 8.8]), and regular cannabis use (OR 8.3, 95% CI [2.1 – 32.7]). Moreover, we observed a significant interaction between childhood trauma and cannabis use (OR 0.17, 95% CI [0.03 – 0.9]). Within proband pairs, using cannabis on a regular basis was the only significant predictor of having a schizophrenia spectrum diagnosis (OR 3.3, 95% CI [1.1 – 10.4]).
Discussion: These findings suggest that several genetic and environmental risk factors show independent effects, but also act interactively to increase the risk of schizophrenia spectrum vulnerability. Moreover, regular cannabis use, an avoidable environmental risk factors, seems to be a main driver in making vulnerable individuals reach the psychosis threshold.

O6. Oral Session: Cognition in Schizophrenia: Advances in Uncovering Mechanisms, Unpacking Heterogeneity, and Developing Interventions

O6.1. DIGITAL SELF-MONITORING, BODIED REALITIES: RE-CASTING APP-BASED TECHNOLOGIES IN FIRST EPISODE PSYCHOSIS

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Background: Smartphone technology has seen expanding interest across nearly all areas of medicine, including psychiatry. And while digital self-monitoring applications exist for nearly all diagnostic categories and across therapeutic modalities, such applications are especially prominent in the area of first episode psychosis.
Methods: This paper discusses ethical issues relating to the burgeoning use of digital technologies for symptom monitoring in the field of first episode psychosis, focusing on ecological momentary analysis (EMA) and experience sampling method (ESM). We draw on

both empirical findings from a three year long ethnographic study of lived experience of first episode psychosis, in Toronto Canada, linking this with a philosophical analysis of ethical considerations surrounding the use of EMA/ESM in this population.
Results: From both our empirical research and the FEP literature, one can trace a rising interest in the use of digital platforms not only for patient self-management, but for the assessment of symptom domains. The latter, in particular, has been increasingly linked to claims that digital care technologies offer a means of giving voice to the heterogeneity of lived experience. Our findings trouble assumptions about what it means to engage lived experience within such technologies. At the same time, ESM/EMA proponents argue in favour of such interventions as a way to avoid the "messiness" and supposed unreliability of subjective experience - arguments that undermine the credibility of claims to supporting deeper understandings of service users' day to day realities.
Discussion: Our findings raise ethical and epistemological challenges for EMA/ESM. We focus on the issue of epistemic injustice within digital technologies, understanding these challenges in relation to intersectional axes of social power. At the same time, this paper pauses to recognize how such technologies might nonetheless offer potentially novel, meaningful forms of health care engagement.

O6.2. COGNITIVE GAINS AS A MECHANISM FOR FUNCTIONAL CAPACITY IMPROVEMENTS IN SCHIZOPHRENIA: RESULTS FROM A MULTI-SITE RANDOMIZED CONTROLLED TRIAL

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Background: Cognitive Enhancement Therapy (CET), a comprehensive social and non-social cognitive remediation approach, has been shown to improve cognitive and functional outcomes among individuals with early course and long-term schizophrenia. Various studies have investigated the relationship between these outcomes and found cross-sectional links, though few have investigated the relationship between change in cognition and change in functioning in the context of cognitive intervention trials. The current study first examines the efficacy of CET on functional capacity for individuals with schizophrenia and then tests whether cognitive gains mediate that relationship. Evidence of specific cognitive mechanisms that form a pathway between treatment and functional capacity can be beneficial for guiding more targeted approaches for rehabilitation in this population.
Methods: Individuals in the early course of schizophrenia (N = 86) participated in an 18-month randomized clinical trial of CET. The UCSD Performance-Based Skills Assessment, the MATRICS Consensus Cognitive Battery (MCCB), and additional measures of social cognition were administered at baseline, 9 months, and 18 months. Mixed-effects models were used to examine the effects of treatment on the financial skills domain, communication skills domain, and total UPSA-B changes at mid-treatment and treatment completion. Next, using a composite index of the MCCB, a mediator analysis using mixed-effects models was conducted to examine the mediating effects of cognitive improvement on changes in functional capacity. Individual neurocognitive and social cognitive domains were also examined using mixed-effect mediator models for 9- and 18-month changes. All analyses were completed in R and the size and significance of mediation effects were estimated using the MacKinnon asymptotic z' test of indirect effects.

Results: Functional capacity effects at mid-treatment showed significant differential benefits favoring CET for total UPSA-B score (d = .25) and the financial domain (d = .28), but less so and non-significantly for the communication domain. CET effects at 18 months increased for all UPSA-B measures but were nonsignificant. Changes in the MCCB overall composite proved to be a significant mediator of CET-related gains in functional capacity, at both 9 months (B = 2.42, z′ = 2.49, p = .006) and 18 months (B = 1.96, z′ = 1.91, p = .042). When examining specific MCCB domains, only attention was a significant mediator at 9 months (B = 1.88, z′ = 2.21, p = .006), but speed of processing and social cognition were trending, with decreased effects at 18 months. Within additional social cognitive measures, the MSCEIT was a significant mediator at 18 months (B = 1.43, z′ = 1.80, p = .039) but not 9 months, whereas the Hinting Task was significant at 9 months (B = 1.70, z′ = 2.05, p = .008) but not 18 months. The ER-40 and TASIT were not significant in the mediator models.
Discussion: This study suggests that CET is an effective intervention for improving functional capacity in individuals with schizophrenia. Furthermore, analyses confirmed that cognitive improvements mediate this relationship. Specifically, attention, speed of processing, and social cognition are promising mechanisms of functional outcomes. The additional exploration of social cognitive areas indicated that improvements in functioning are also partially mediated by emotional intelligence and gistfulness. These findings address essential areas for cognitive intervention researchers to incorporate within rehabilitative approaches.

O6.3. COGNITIVE DEFICITS AND THEIR ASSOCIATION WITH WHITE MATTER IN SCHIZOPHRENIA

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Background: Several previous smaller studies and meta-analyses have shown that individuals with schizophrenia demonstrate widespread cognitive deficits and that cognitive deficits are among the best predictors of real-world functioning and treatment response. Here we combined harmonized cognitive data (n=970) for eight domains (language, processing speed, vigilance, working memory, verbal memory, non-verbal memory, motor function, and executive function) with previously harmonized diffusion MR data. First, we investigated cognitive deficits across the age trajectory, testing for the effects of sex, the presence of a “cognitive deficit subtype,” and the association with clinical variables (symptom severity and medication). Next, we investigated if and how white matter structural abnormalities may explain cognitive deficits in patients with schizophrenia.

Methods: Cognitive, diffusion-weighted, and clinical data were collected from 13 sites, and combined for the purpose of this study. We harmonized data across all sites utilizing T scores for cognitive data and a previously established harmonization method for the imaging data. We applied ANCOVAs to compare all cognitive domains between patients with schizophrenia and healthy individuals, testing for the effects of age and sex. Next, we used regression analyses to describe the association between cognitive deficits and symptom severity/medication in patients. To investigate whether or not white matter abnormalities can explain cognitive deficits, we calculated whole-brain fractional anisotropy (FA) and utilized regression-mediation analyses to model the association between group (patients versus healthy individuals), whole-brain FA, and cognitive performance and the association between group, whole-brain FA, processing speed, and cognitive performance.
Results: ANCOVAs demonstrated significant group differences for all cognitive domains ($p<.006$, Bonferroni-corrected for eight domains). Obtained effect sizes were medium to large ($d=.48$ to $d=1.17$), with the effect size for processing speed being the largest. We also observed an age effect for vigilance and a sex effect for working memory only. We did not find evidence for a "cognitive deficit subtype," although almost all patients demonstrated cognitive deficits in one or more domains. Processing speed, vigilance, working memory, and verbal memory deficits were associated with more severe positive symptoms, and higher medication dose at the time of the scan was associated with fewer vigilance impairments ($p<.006$). Mediation analyses confirmed that whole-brain FA mediated the association between group and language, processing speed, working memory, and non-verbal memory. Moreover, processing speed explained partially the group and FA's influence on language, working memory, and non-verbal memory.
Discussion: Our findings highlight the critical role cognitive deficits play in schizophrenia, as they are present across all domains, across all patients, independent of age and sex. We further showed that white matter abnormalities can partially explain the link between a diagnosis of schizophrenia and all cognitive deficits present in this population, demonstrating the central role of white matter pathology in schizophrenia. Last, we provided evidence for the underlying mechanism: schizophrenia is associated with white matter abnormalities that translate into slower processing speed and, consequently, cognitive deficits. Based on our findings, alternative treatment strategies (including neuroprotective medication and cognitive training) should be developed, to supplement traditional antipsychotic treatment.

O6.4. GLUTAMATE AND COGNITIVE FUNCTION IN ANTIPSYCHOTIC RESPONSIVE AND NON-RESPONSIVE PSYCHOSIS: FINDINGS FROM THE STRATA-1 STUDY

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Background: Impaired cognition in psychotic disorders¬ is central to poor quality of life and reduced functional outcomes. Current antipsychotics primarily act as dopamine antagonists and have little impact on cognitive function. There is increasing consensus of the role of glutamate in cognitive deficits, with some evidence of a positive correlation between glutamate and cognitive function, although results are inconsistent. Further, we have little understanding

about the relationship between glutamate and cognition within treatment responsive and resistant illness groups. One hypothesis is that there is an optimal range of glutamate, whereby a lack or excess in concentration is associated with worse functioning.
Methods: We examined the relationship between glutamatergic neurometabolites and cognition in a sample of 85 participants with non-affective psychotic disorders, recruited across four UK sites. Participants with antipsychotic responsive and non-responsive illness were recruited based on a prior criteria of symptom severity above or below a certain threshold and good treatment adherence. Proton magnetic resonance spectroscopy data were acquired from the anterior cingulate cortex (ACC) and right caudate. Cognitive domains were assessed using the Brief Assessment for Cognition in Schizophrenia (BACS). Linear regression adjusting for age and sex was used to examine the effect of glutamate and Glx (glutamate + glutamine) on total BACS scores, and on performance within cognitive domains. We subsequently tested for an interaction effect of antipsychotic response group (responder versus. non-responder) on the relationship between glutamate and cognition.
Results: ACC glutamate was associated with total BACS score ($\beta = 3.12$, 95% CI = 0.01 – 6.23, $p < 0.04$), such that higher glutamate was associated with better cognitive performance after adjusting for age and sex. Both ACC glutamate and Glx were associated with verbal memory after adjusting for age and sex (Glu, $\beta = 3.74$, 95% CI = 1.23 – 6.20, $p < 0.003$; Glx, $\beta = 3.40$, 95% CI = 0.88 – 5.91, $p < 0.009$). Univariate regression revealed an association between Glx and executive functioning ($\beta = 1.03$, 95% CI = 0.15 – 1.90, $p = 0.02$), although this was not significant after controlling for effects of age ($p = 0.1$). There were no significant effects of antipsychotic response group on the relationship between ACC glutamate and Glx and cognition.
Discussion: Reduced glutamatergic metabolites in the ACC were associated with worse global cognition and verbal memory. Our results add to the literature supporting a role of glutamate in cognitive deficits in psychotic disorders. We found no evidence of an effect of antipsychotic response status on the relationship between glutamate and cognition, although this may be due to methodological factors such as illness chronicity of the sample and ascertainment of treatment response. Further understanding of the relationship between glutamate and cognition in antipsychotic responsive and non-responsive illness could aid stratification of patient groups for targeted treatment interventions.

O6.5. BRAIN STRUCTURAL CORRELATES OF COGNITIVE DEFICITS IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cognitive impairments are strong predictors of overall functional outcomes in schizophrenia (SZ) and are important treatment targets to improve patients' quality of life. Morphological studies have found that SZ is also characterized by several brain structural changes (e.g., reduced volume, cortical thickness, and surface area) that are thought to be the root of cognitive degradation. Extensive research has examined the structural neural correlates of cognitive deficits in SZ. However, there lacks a comprehensive synthesis of this literature that encompasses all cognitive domains and their related morphological changes. Thus, we conducted a systematic review and meta-analysis of the available literature on brain structure and cognition in SZ.

Methods: This study was preregistered on PROSPERO (CRD42020206152). We performed a systematic literature review to identify articles that (a) were peer-reviewed, (b) reported on individuals with a diagnosis of schizophrenia spectrum disorder, and (c) included associations between cognition and brain structure using structural magnetic resonance imaging. Following data extraction of included articles, we performed meta-analyses on brain structures and each of the seven MATRICS cognitive domains (attention/vigilance, reasoning, and problem solving, speed of processing, social cognition, verbal learning and memory, visual learning and memory, and working memory). Then, we conducted a series of subgroup analyses to assess associations between specific structural metrics (i.e., volume, cortical thickness) and brain networks. We also assessed inter-raters reliability (Gwet's AC1 coefficient) during article selection and the quality of included studies (rated LOW/HIGH in bias based on segmentation method, multiple comparisons correction, covariates, and reporting of nonsignificant results.
Results: The systematic literature search retrieved 7,259 articles, only 119 of which followed the inclusion criteria. From those, 97 reported effects that could be included in the meta-analysis. Inter-rater reliability (three raters) was high (0.87-0.88) throughout article selection. For the meta-analyses, we found a significant correlation between cognitive domains and brain structures (Hedge's g= 0.083 for speed of processing to g= 0.647 for social cognition) except for attention/vigilance (g= 0.016). We also found that social cognition and speed of processing were the only two domains affected by risk of bias. Additionally, results.showed that volume (g= 0.228) and cortical thickness (g= 0.146), but not surface area (g= 0.096), significantly correlated with cognition. Finally, we were able to group a sample of structures into the seven Yeo networks, finding significant correlations between cognitive domains and all networks (g= |0.500-0.837|) except the frontoparietal network.
Discussion: Our meta-analysis results bring together the vast literature on brain structure and cognition in SZ and show that social cognition has the strongest association with structures while volume was the structural metric with the strongest correlation with cognition. Grouping brain regions into networks showed important associations between the speed of processing and the dorsal attention network as well as social cognition and the limbic network, among others. Non-significant findings in certain domains/networks may point to a gap in the literature including the lack of studies about attention and brain structures as well as the scarcity of research on cortical thickness and surface area in relation to cognition. This study ultimately provides a reference for brain structure-cognition associations in SZ and a starting point for future research in the field.

O6.6. LONGITUDINAL SYMPTOM SEVERITY AND GLOBAL FUNCTIONING IN DISTINCT COGNITIVE SUBGROUPS OF FIRST-EPISODE PSYCHOSIS: A CLUSTER ANALYSIS

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Background: Cognitive deficits are a core symptom of First Episode Psychosis (FEP) and have been linked to impaired functional outcome over time. FEP patients differ widely in the extend and severity of cognitive deficits, with a significant minority showing no cognitive deficits. A growing interest in data-driven clustering analyses emerged, grouping patients into more homogeneous and treatment-relevant cognitive subgroups. However, how membership of distinct cognitive clusters is related to long-term functional outcome remains poorly understood. This study aimed to investigate the extend of longitudinal symptom severity and global functioning in homogeneous cognitive subgroups of FEP.

Methods: 168 FEP patients and 39 healthy controls between 16-60 years old were included. Hierarchical clustering analysis (Ward's method) was conducted using The Brief Assessment of Cognition in Schizophrenia (BACS). Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) at six- and twelve months follow-up. Self-report of global functioning and disability was assessed using the WHO-DAS 2.0 and objective global functioning using the Global Assessment of Functioning (GAF) at six- and twelve months follow-up.
Results: Three distinct cognitive clusters emerged: one relatively preserved cluster (34%), one moderately impaired cluster (40%) and one severely impaired cluster (26%). Subgroups of cognition were characterized by significant differences in symptom severity with more severe symptoms (PANSS total and PANSS negative) in the severely impaired cluster compared to the relatively preserved cluster, at both six- and twelve months follow-up. No differences in functional outcome (WHODAS 2.0) were present between the groups, but general functioning (GAF) was significantly higher in the relatively preserved cluster compared to the severely impaired cluster, at both six- and twelve months follow-up.
Discussion: The current results confirmed the existence of three distinct subgroups of cognition in a sample of FEP, including one relatively preserved group, one moderately impaired group and one severely impaired group. These subgroups corresponded with clinical and functional outcome as measured by PANSS and GAF, but not as measured by WHODAS, at six- and twelve months follow-up. This suggests that discrete cognitive subtypes could offer relevant information about illness profile and prognosis.

O6.7. VISUAL AFTEREFFECTS IN SCHIZOPHRENIA

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Background: Symptoms of schizophrenia have been explained as a failure to appropriately apply past environmental regularities to predictively guide the interpretation of incoming information, thus leading to abnormal perceptions and beliefs. Here we use the visual system as a test bed for investigating the role of prior experience in shaping perception in individuals with schizophrenia. Specifically, we use visual aftereffects, illusory percepts resulting from prior exposure to visual input, to measure the influence of prior events on current processing. At a neural level, visual aftereffects arise due to attenuation in the responses of neurons that code the features of the prior stimulus (neuronal adaptation) and subsequent disinhibition of neurons signaling activity at the opposite end of the feature dimension.
Methods: In the current study, we measured tilt aftereffects and negative afterimages, two types of aftereffects that reflect, respectively, adaptation of cortical orientation-coding neurons and adaptation of subcortical and retinal luminance-coding cells in persons with schizophrenia (PSZ; n=36) and demographically-matched healthy controls (HC; n=22).
Results: We observed stronger tilt aftereffects in PSZ compared to HC ($p=0.002$), but no difference in negative afterimages ($p=0.32$). Stronger tilt aftereffects were related to more severe negative symptoms ($r=0.50$, $p=0.005$).
Discussion: These data suggest over-sensitivity to recent regularities at cortical, but not subcortical, levels in schizophrenia, which is in line with a growing literature that predictive processes in schizophrenia are altered at multiple cortical levels. More broadly, the results underscore the value of aftereffect paradigms as a tool for the quantitative examination of canonical computations whose dysfunction may underpin symptom genesis in schizophrenia.

O6.8. GENERALIZED REINFORCEMENT LEARNING DEFICITS IN UNMEDICATED SCHIZOPHRENIA PATIENTS ACROSS LEARNING FROM REWARDS AND LOSSES

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Background: Difficulties in reinforcement learning accompanied by reduced neural prediction error signalling are consistently described in schizophrenia patients (Deserno, Boehme, Heinz, & Schlagenhauf, 2013; Maia & Frank, 2017). These deficits were linked to both, positive and negative symptoms (Maia & Frank, 2017). However, there is an ongoing debate whether a more pronounced deficit in learning from wins compared to losses is specifically relevant to apathy (Gold et al., 2012). In this study, we aimed at disentangling learning from wins compared to losses in unmedicated schizophrenia patients and healthy controls while applying computational modelling techniques. fMRI data were collected and analysis of the accompanying learning signals is ongoing.

Methods: Twenty-four unmedicated patients with schizophrenia as well as 25 controls (matched for age and gender) performed a reinforcement learning paradigm during fMRI. In this paradigm, subjects had to choose between two neutral graphic stimuli in order to (1) receive a reward (+ 1 Euro vs. no win, reward condition) or (2) avoid losses (- 1 Euro vs. no win). Contingencies were probabilistic, i.e. the better option led to win (reward condition) or no win (loss condition) in 80 % of trials, while the remaining 20 % of trials led to the opposite feedback ('no win' for reward learning, loss for loss avoidance; anti-correlated pattern for the 'worse' stimulus). In a neutral condition, both stimuli led to the 'no win'-feedback. Contingencies remained stable across 150 trials (60 reward, 60 loss, 30 neutral condition) and conditions were presented in an intermixed pattern. Groups were compared regarding their correct responses by condition (reward, loss avoidance). We applied computational modelling to trial-by-trial choice data in order to investigate the underlying mechanisms for learning from rewards and losses. Data were concurrently fitted to prediction error based learning models (encompassing different learning rates for reward and loss learning as well as single, double and individually weighted update of the unchosen option) with a hierarchical Bayesian inference approach (Piray, Dezfouli, Heskes, Frank, & Daw, 2019).

Results: Healthy controls chose the correct option more often than schizophrenia patients (84 % vs. 67.8 %, $F=13.2$, $p=0.01$). There was a significant effect for condition, indicating that all subjects learned more successfully in the reward condition compared to loss avoidance (78.5 % vs. 73.2 % correct, $F=8.6$, $p=0.005$). There was no interaction between group and condition ($p > 0.4$). As shown by model comparison, subjects learned only about the chosen option (protected exceedance probability for single update model = 99.8 %). Mirroring the behavioural raw data results the learning rate for the win condition was higher compared to the loss learning rate (condition effect on alpha, $F=41.4$, $p<0.001$), again not differing between groups ($p > 0.8$). Patients showed lower betas ($F=11.6$, $p<0.001$), reflecting less exploitation of learned values. Only in controls, betas were higher for reward than for loss learning while they did not differ in patients (interaction group by condition, $F=4.2$, $p=0.046$).

Discussion: We found that schizophrenia patients show generalized difficulties in learning from rewards and losses, without any evidence for a specific deficit in one of these two feedback domains. However, as performance in the task was considerably impaired across the patient group more fine-grained differences might be blunted by this floor effect and subgroup analyses in above chance performing patients are warranted. We will examine task-related fMRI data in future analyses to evaluate associated neural learning signatures, such as expected values and reward prediction errors.

O7. Oral Session: Genomes, Brain and Symptoms

O7.1. DYSREGULATED CXC CHEMOKINE FAMILY MEMBER EXPRESSION IS ASSOCIATED WITH INCREASED MACROPHAGE AND REDUCED INHIBITORY INTERNEURON MARKER EXPRESSION IN THE DORSOLATERAL PREFRONTAL CORTEX IN PSYCHIATRIC DISORDERS

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Background: The CXC chemokine CXCL12 and its cognate receptors CXCR4 and CXCR7 regulate various processes implicated in the pathophysiology of psychiatric disorders. CXCL12 signalling promotes the migration and positioning of cortical inhibitory interneurons. In contrast to these homeostatic functions, CXCL12 expression is upregulated in response to inflammation to facilitate immune cell trafficking for brain repair. We hypothesised that altered CXC chemokine family member expression is associated with elevated pro-inflammatory cytokine expression, increased macrophage marker expression and reduced inhibitory interneuron marker expression in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia and bipolar disorder.

Methods: CXCL12, CXCR4 and CXCR7 mRNAs were measured by qPCR in the DLPFC from 35 schizophrenia, 31 bipolar disorder and 32 control cases from the Stanley Medical Research Institute. Gene expression was analyzed by diagnoses and previously assigned 'low' and 'high inflammation' biotypes based on increased IL1B, IL1RL1, IL6, IL8, SERPINA3 and TNF mRNAs. Semi-partial correlations were used to assess relationships between expression of CXC chemokine family members and markers of macrophages (CD163, CD64, MRC1, FN1) and inhibitory interneurons (PVALB, SST, VIP, NPY, CR, CCK, CB). Cellular localization of CXCR4 and CXCR7 expression was examined by immunohistochemistry.

Results: CXCL12 mRNA was reduced in schizophrenia compared to controls (25%, $p=0.004$). CXCL12 mRNA was further decreased in 'high inflammation' schizophrenia compared to 'low inflammation' controls (25%, $p=0.01$). In contrast, CXCL12 mRNA was increased in 'high inflammation' compared to 'low inflammation' bipolar disorder (40%, $p=0.02$). CXCL12 mRNA positively correlated with macrophage (MRC1, FN1) and inhibitory interneuron marker expression (VIP). CXCR4 mRNA was unchanged in diagnostic groups. CXCR4 mRNA was increased in 'high inflammation' bipolar disorder compared to both 'low inflammation' controls (92%, $p<0.001$) and bipolar disorder (94%, $p<0.001$). CXCR4 expression positively correlated with macrophage (FN1) but negatively correlated with inhibitory interneuron marker expression (VIP, CR, CCK). CXCR4 immunostaining was identified in pyramidal cells, interneurons and glia. CXCR7 mRNA was unchanged in diagnostic groups. CXCR7 mRNA was increased in both 'high inflammation' schizophrenia and bipolar disorder compared to all 'low inflammation' groups (55-105%, all $p\leq0.006$). CXCR7 expression positively correlated with macrophage (CD163, CD64, FN1) but negatively correlated with inhibitory interneuron marker expression (SST, NPY). CXCR7 immunostaining was observed in endothelial cells and glia.

Discussion: We provide the first molecular evidence of disease- and inflammation-specific changes in CXCL12, CXCR4 and CXCR7 expression in the DLPFC in psychiatric disorders. CXCR7 expression by endothelial cells and increased CXCR7 mRNA in 'high inflammation' biotypes indicate altered CXCL12 availability at the blood-brain barrier, which may facilitate

immune cell trafficking into the parenchyma. This hypothesis is supported by the positive relationships between CXC chemokine family members and macrophage marker expression. We identified that altered CXC chemokine family member expression is associated with reduced inhibitory interneuron marker expression, indicating that CXCL12 signaling may modulate neuronal function directly and/ or indirectly through interaction with the immune system. Future studies need to identify the cellular localization of CXCL12 and examine CXCL12 splice variants to further disentangle the role of CXCL12 signaling in the pathophysiology of psychiatric disorders.

O7.2. DOPAMINERGIC ORGANISATION OF THE STRIATUM IS LINKED TO CORTICAL BRAIN ACTIVITY AND BRAIN EXPRESSION OF GENES ASSOCIATED WITH PSYCHIATRIC DISORDERS

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Background: The neuromodulator dopamine strongly influences the ability of neural circuits to control behaviour. Dopamine signalling is constrained to discrete tracts yet has brain wide effects on neural activity. The nature of this relationship between local dopamine signalling and brain wide neuronal activity is not clearly defined and has relevance for neuropsychiatric illnesses where abnormalities of cortical activity and dopamine signalling coexist.

Methods: We employed simultaneous PET-MRI to simultaneously measure striatal D2/3 receptor availability using the radiotracer [11C]-(+)-PHNO, and cerebral blood flow (CBF) using arterial spin labelling . 52 scans were obtained from 28 healthy volunteers, with one scan following placebo administration and the other following administration of 0.5 mg/kg of dexamphetamine.

We integrated the high-dimensional data from PET and MRI in an unbiased manner with the use of canonical correlation analysis to identify a mapping between striatal dopamine function and cortical activity. We next examined whether this mapping linked changes in striatal dopamine and cortical activity following amphetamine administration. Finally, we investigated how this mapping related to gene expression data obtained from the Allen Human Brain Atlas, and whether genes implicated were overexpressed in several psychiatric disorders.

Results: We identified a strong mode of covariation between striatal dopamine signalling and cortical blood flow (out of sample cross validation $p<0.001$), and demonstrated that spatial patterns of striatal dopamine signalling predict patterns of cortical blood flow (accuracy 81%, $p<0.001$). This mapping linked amphetamine induced changes in striatal dopamine receptor availability to changes in brain wide blood flow ($p=0.04$). Striatal gene expression patterns were associated with this mapping ($p=0.04$), and the implicated genes overlapped significantly with genes upregulated in schizophrenia, bipolar disorder and autism ($p<0.001$).

Discussion: These results advance our knowledge of the relationship between cortical function and striatal dopamine, with relevance for understanding pathophysiology and treatment of diseases in which simultaneous aberrations of these systems exist.

O7.3. ASSOCIATIONS OF AGGRESSION AND SELF-HARM BEHAVIORS WITH CARDIAC-RELATED POLYGENIC SCORES IN A LARGE SCHIZOPHRENIA SAMPLE

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Background: Over decades, research has linked hostility, anger, and aggression with heart disease and cardiovascular events in non-clinical samples. More focused work is beginning to uncover similar associations in psychiatric disease, including psychotic illness. The explosion of genome wide association studies (GWAS) – combined with methods for using GWAS summary statistics to create polygenic scores (PGS) for diverse phenotypes – offers new strategies for studying broad genetic influences on behavior. In a large schizophrenia sample, we studied the associations of PGS for cardiac disease and related somatic conditions, on the one hand, with behaviors related to aggression and suicide, on the other hand. Our main hypothesis, based on prior literature, was that cardiac genetics would be related to aggression. We selected a range of genetic and behavioral variables for analysis in order to test this hypothesis and better understand its specificity.

Methods: For 532 people with schizophrenia, we coded medical records to capture documented instances of non-physical and physical aggression, destructive behavior, non-suicidal self-injury, and suicide attempts. Blood samples were obtained from which genotype information was derived. We used summary statistics from multiple reference GWAS conducted in the massive UK Biobank sample to generate diverse PGS for our schizophrenia cases. We generated separate PGS for mild and severe cardiac illness, high blood pressure, elevated cholesterol, and diabetes. Using logistic regression, we tested associations between these cardiac-related genetic scores and aggression and suicide related behaviors, controlling for age, sex, and population stratification. Based on sex-specific findings in the literature, we also tested for sex differences in these associations in separate, but parallel, analyses.

Results: Results identified a constrained set of significant associations of PGS for serious cardiac disease with physical aggression and non-suicidal self-harm. For example, the association between any documented history of physical assault and PGS for major cardiac events was Wald= 13.935, p= .000189, OR= 1.464, 95% CI= [1.199,1.789], and ES= .035. Additionally, the association between any non-suicidal self-injury and PGS for coronary atherosclerosis was Wald= 14.129, p= .00017, OR= 1.455, 95% CI= [1.197,1.769], and ES= .038. These associations were not apparent between PGS for other somatic markers, including blood pressure, diabetes, and cholesterol, or for other behaviors including non-physical aggression, destructive behavior, and suicide attempts. A sex-specific pattern of associations emerged. The association of PGS for serious cardiac disease with aggression was driven by males (e.g., for physical aggression and major cardiac event PGS, Wald= 19.073, p= .000013, OR= 1.719, CI= [1.348, 2.193], and ES= .067) but was not present for females. In contrast, the association of PGS for serious cardiac disease with self-harm was quite strong in females (e.g., for any non-suicidal self-injury and coronary atherosclerosis PGS, Wald= 8.511, p= 0.00353, OR= 1.759, CI= [1.204, 2.572], and ES= .078) but only marginally significant in males.

Discussion: In a large schizophrenia sample, we found a statistically robust pattern of behavioral associations to multiple PGS reflecting significant cardiac illness. Males drove an association between PGS and physical aggression. Females showed stronger associations between PGS and non-suicidal self-injury. Effect sizes are modest, but our confidence in the is enhanced by the sex-specific pattern of results and the lack of associations between other somatic PGS and other facets of behavior.

O7.4. STRUCTURAL CEREBELLAR CORRELATES OF PSYCHOTIC AND SUBTHRESHOLD PSYCHOTIC SYMPTOMS IN THE 3Q29 DELETION SYNDROME

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Background: The 3q29 deletion is a recurrent copy number variant (CNV) caused by a 1.6 Mb hemizygous deletion with a population prevalence of ~1 in 30,000 individuals. The deletion confers a ~40-fold increased risk for schizophrenia (SZ), the largest known effect size for any SZ-associated genetic variant. Recent findings by the Emory 3q29 Project (http://genome.emory.edu/3q29/) revealed that cerebellar hypoplasia is a common feature of 3q29 deletion syndrome. This is coincident with evidence from studies in SZ and related disorders that implicate the cerebellum as a central site of neuropathology. In light of the increasing recognition of the cerebellum as key to higher-order processing, we sought to investigate the relationship between cerebellar volume and psychotic and sub-threshold psychotic symptoms (the prodrome) in 3q29 deletion syndrome.

Methods: 17 individuals with 3q29 deletion (mean age = 17.71 years, SD = 9.06; 59% male) participated in this study. Dimensional and diagnostic assessment of psychotic and subthreshold psychotic symptoms were evaluated via the Structured Interview for Prodromal Syndromes (SIPS). T1- and T2-weighted magnetic resonance imaging (MRI) scans were acquired by a Siemens Magnetom Prisma 3T scanner, using 3D MPRAGE and SPACE sequences. The pipeline developed by the Human Connectome Project was used for data preprocessing and extraction of total cerebellar, cerebellar cortex and cerebellar white matter volumes. Linear regression was used to model the relationship between domain-specific SIPS ratings (positive, negative, disorganized, and general) and global and tissue-specific cerebellar volumes. Logistic regression was used to determine whether cerebellar volumes predict the diagnostic absence/presence of either a psychotic disorder or the prodrome. Age and sex were treated as covariates.

Results: Six subjects (35%) met diagnostic criteria for a psychotic disorder or the prodrome. Cerebellar cortex volume was found to be a significant predictor of the severity of SIPS symptom ratings in the positive domain (B = -0.43, 95% CI = -0.78 – -0.07, p = 0.02). Smaller cerebellar cortex volumes were associated with more severe positive symptoms. In the same model, sex was found to be a significant predictor, with males demonstrating more severe positive symptoms than females (B = 9.70, 95% CI = 1.76 – 17.65, p = 0.02). This relationship was not observed when total cerebellar or cerebellar white matter volumes were evaluated as predictors or when other SIPS domains were treated as outcome variables. Logistic regression indicated no evidence of a predictive relationship between cerebellar volume and the absence/presence of the evaluated diagnoses.

Discussion: These findings constitute the first reported investigation of the neuroanatomical correlates of psychopathology in the 3q29 deletion syndrome. We identified a predictive relationship between cerebellar volume and severity of positive symptom ratings determined by the gold-standard SIPS interview for early identification of prodromal symptoms. Our data suggest a dimensional, rather than diagnostic, relationship between cerebellar volume and psychosis proneness, that was restricted to the positive symptom domain. This relationship was exclusively driven by the cerebellar cortex (gray matter), the central functional unit of which is inhibitory Purkinje neurons. Post-mortem work in idiopathic SZ and related disorders

revealed morphological alterations of Purkinje cells. Future studies should investigate whether Purkinje cell pathology is a common molecular denominator between idiopathic SZ and the 3q29 deletion syndrome and whether cerebellar pathology lies in the causal pathway to psychosis in this CNV.

O7.5. DISC1 GENE AND BRAIN ACTIVITY: A GENETIC NEUROIMAGING ASSOCIATION STUDY

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Background: The DISC1 protein and its interactome have critical roles in brain development and function, such as being involved in neuronal migration and maturation and acting as central coordinator of neuronal trafficking (Thomson et al. 2013; Tomoda et al. 2017). DISC1 gene and has been consistently associated with schizophrenia (SZ), both at a single nucleotide polymorphisms (SNP) and haplotype levels (Hennah et al. 2005; Ma et al. 2018; Sachs et al. 2005). While several studies have investigated the role of DISC1 gene SNPs on brain functional data (Duff et al. 2013), there is scarce evidence on the modulation role of risk haplotypes in fMRI measures. Therefore, we aimed: i) to conduct a genetic association analysis to identify DISC1 risk haplotypes for SZ, ii) to investigate the brain functional correlates of the detected risk haplotype by means of neuroimaging genetics approach.
Methods: First, a genetic association approach was performed in 238 patients with SZ and 138 healthy subjects (HS) by genotyping a set of SNPs selected according to their involvement in risk haplotypes described in previous studies: HEP3 (rs751229 and rs3738401) and HEP1 (rs667581, rs999710 and rs1000731) (logistic regression; PLINK) Second, a subsample of 70 HS and 70 SZ patients (matched for age, sex and premorbid-IQ) was used for the neuroimaging association study. All had fMRI data while performing the N-back task (two levels: 1-back, 2-back). A whole-brain approach was used to study the interaction between the risk haplotype x diagnosis on brain function (ANOVAs; FSL).
Results: The genetic association study revealed that the haplotype HEP3 was associated with the risk for SZ; with the A-A combination being more frequent in patients than in controls (OR=2.28, 95%CI [1.45-2.71], p=0.012). According to this result, the neuroimaging genetic approach was focused on the HEP3 A-A x diagnosis interaction in response to working memory function (2-back vs. 1-back). These analyses showed a significant interaction in two clusters: 1) the middle and superior frontal cortex bilaterally (1218 voxels, peak activation at MNI [30,52,44], Zmax=4.11, p=0.0005) and, 2) the right dorsolateral and ventrolateral prefrontal cortex (585 voxels, peak activation at MNI [48,44,-16], Zmax=3.83, p=0.04). In both clusters, regardless the diagnosis, subjects not carrying the risk haplotype depicted a similar activation profile, whereas subjects with SZ carrying the HEP3 A-A showed an opposite pattern as compared to HS with the same haplotype.

Discussion: To our knowledge, these results are the first to show the diagnosis-based differential effect of a DISC1 risk haplotype on working memory-related brain function. The most distinctive activity pattern between HS and SZ patients is observed in the presence of the risk haplotype; also, the implicated regions (the ventrolateral and dorsolateral prefrontal cortex) have been previously associated with the disorder (Minzenberg et al. 2015). This emphasizes the role of DISC1 and its interactome in the pathophysiology of SZ.
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O7.6. GLOBAL AND SPECIFIC CORTICAL THICKNESS-COGNITION ASSOCIATIONS IN FIRST-EPISODE PSYCHOSIS

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Background: Schizophrenia involves widespread brain abnormalities and severe cognitive deficits. Brain-cognition associations are robustly observed in schizophrenia; however, the few first-episode psychosis (FEP) studies on this topic are equivocal. Moreover, clear findings of overall decreases in brain structure (e.g., mean thickness, total volume) and a general cognitive deficit in psychosis bring into question global versus specific structure-cognition associations in FEP. We sought to identify reliable associations between global and specific cortical thickness and cognition using a multivariate partial least squares (PLS) approach across two well-characterized FEP samples.
Methods: Cortical thickness (CT) was calculated from 1mm3 T1-weighted MRIs of 167 FEP patients (sample 1: n = 115; sample 2: n = 52) and 134 healthy controls (sample 1: n = 81; sample 2: n = 53). Cognition was assessed across six domains (verbal/visual/working memory, processing speed, attention, and executive function) using sample-specific control-normalized z-scores. CT-cognition associations were assessed in patients only using PLS to optimize covariance patterns. Global and specific CT-cognition associations were assessed by regressing mean CT and/or a general cognitive index (mean domains) from CT prior to analysis. Thus, four models were tested separately in each sample: global CT-global cognition (no covariates); global CT-specific cognition (covariate: general cognitive index); specific CT-global cognition (covariate: mean CT); specific CT-specific cognition (covariates: mean CT, general cognition). Significance of latent variables and predictors were assessed via permutations and bootstrapping with 1000 samples. Only significant, replicated findings are reported.
Results: FEP patients showed impaired verbal/visual/working memory and executive function as well as a trend towards decreased mean CT versus controls. Both global CT models (global and specific cognition) showed overall reduced CT driven by reduced mean CT as well as a processing speed deficit that did not persist after covarying global cognition. Male sex and older age predicted this pattern for specific cognition only. Specific CT-global cognition revealed a pattern of general cognitive deficit (all domains but processing speed) associated with increased CT in left middle and superior frontal gyrus, which was more prevalent in patients with decreased IQ and less education. Specific CT-specific cognition associations involved a partially replicated pattern of decreased verbal memory, increased processing speed, and more severe negative symptoms, which was associated with decreased left ventral temporal cortex CT and increased right precuneus CT as well as right handedness. No patterns were associated with antipsychotic medication.

Discussion: Reliable global and specific CT-cognition associations were observed in FEP. Global CT-cognition associations were most strongly indicated by processing speed deficits. Increased prefrontal CT associations with a general cognitive deficit could indicate abnormalities in maturational pruning or early compensatory mechanisms. Decreased ventral temporal and increased parietal associations with increased processing speed and verbal memory deficits might reflect the speed-accuracy trade-off observed in schizophrenia. Results highlight distinct structural cognitive network alterations in FEP over and above global thickness reductions, suggesting that frontal regions underlie a processing speed driven general cognitive deficit and ventral temporal and parietal regions underlie specific alterations in verbal memory and processing speed, the domains most strongly implicated in schizophrenia.

O7.7. MULTIVARIATE ASSOCIATIONS AMONG WHITE MATTER MICROSTRUCTURE, NEUROCOGNITION, AND SOCIAL COGNITION IN PEOPLE WITH A SCHIZOPHRENIA SPECTRUM DISORDER AND HEALTHY CONTROL PARTICIPANTS

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Background: A growing consensus of behavioural research has shown dissociability between neurocognitive and social cognitive performance in schizophrenia spectrum disorders (SSD). However, the extent to which neurocognitive and social cognitive performance might be associated with shared vs. distinct neurocircuitry remains an open question, with mixed preliminary evidence. Here, we used canonical correlation analysis (CCA) to examine the doubly-multivariate associations among white matter microstructure, and neurocognition and social cognition, across the healthy-to-schizophrenia spectrum.

Methods: We derived a test and replication sample from the multi-centre 'Social Processes in Neurobiology of the Schizophrenia(s) (SPINS)' study, based on scanner hardware. The test sample was comprised of n=135 (89 SSD) from a single site, who underwent diffusion imaging on a GE Discovery scanner; the replication sample was comprised of n=173 (91 SSD) from three sites, who underwent a matched diffusion acquisition on prospectively harmonized Siemens PRISMA scanners. The CCA model's predictor set consisted of 19 fractional anisotropy features derived from white matter tracts of hypothesized relevance to cognition in SSD (5 bilateral association, 1 bilateral projection, and 7 commissural), estimated via UKF tractography. The criterion set consisted of 16 features: 6 neurocognition factor scores from the MATRICS MCCB, and 10 social cognition scores from a task battery.

Results: We observed a high canonical correlation between the predictor and criterion set in both the test and replication samples (Rc_test=.71; Rc_replication=.72); correlation values across all variates were stable in the face of iterative feature removal. Permutation testing (B=500) showed the full canonical models to be significant using the Lawley-Hotelling trace statistic (T2_test=3.65, p=.044; T2_replication=3.33, p=<.001). Within the full models, only the first canonical variates met significance (F_test(304,1570)=1.18, p=.02; F_replication(304,2178)=1.49, p=<.001). The structure coefficients of the respective first variates showed identical valence and commensurable magnitudes, though some variation was observed in features meeting conventional thresholds for interpretation. The body of the corpus

callosum and the right uncinate fasciculus contributed highly to the predictor set in both samples; additionally, the left inferior longitudinal fasciculus contributed highly in the test sample, and the right arcuate and left uncinate fasciculi contributed highly in the replication sample. There were several shared contributions in the criterion sets: neurocognition MATRICS MCCB factor scores of Processing Speed, Verbal Learning, and Visual Learning, and the social cognition TASIT 3 'sarcasm' subscale score.
Discussion: Our results suggest a significant association among white matter microstructure, and neurocognition and social cognition, and help clarify which tracts may be most prominently involved in neurocognitive and social cognitive performance, in SSD and HC participants. Further analyses will clarify the shared and unique variance among these relationships.

O7.8. DEVELOPMENT OF PROTEOMIC PREDICTION MODELS FOR TRANSITION TO PSYCHOTIC DISORDER IN THE CLINICAL HIGH-RISK STATE AND PSYCHOTIC EXPERIENCES IN ADOLESCENCE

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Background: Biomarkers that are predictive of outcomes in individuals at risk of psychosis would facilitate individualized prognosis and stratification strategies. The objective of this research was to investigate whether proteomic biomarkers may aid prediction of transition to psychotic disorder in the clinical high-risk (CHR) state, and adolescent psychotic experiences (PEs) in a general population sample.
Methods: This research comprised 2 case-control studies. These were nested within the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) and the Avon Longitudinal Study of Parents and Children (ALSPAC). EU-GEI is an international multisite prospective study of participants at CHR referred from local mental health services. ALSPAC is a United Kingdom–based general population birth cohort. Included were EU-GEI participants who met CHR criteria at baseline and ALSPAC participants who did not report PEs at age 12 years.

In EU-GEI, transition status was assessed using the Comprehensive Assessment of At-Risk Mental States or via contact with clinical services. In ALSPAC, PEs at age 18 years were assessed using the Psychosis-Like Symptoms Interview. Proteomic data were obtained from mass spectrometry of baseline plasma samples in EU-GEI and plasma samples at age 12 years

in ALSPAC. In both studies, support vector machine learning algorithms were used to develop predictive models.

Results: The EU-GEI subsample (133 participants at CHR; mean [SD] age 22.6 [4.5] years; 68 [51.1%] male) comprised 49 (36.8%) participants who developed psychosis and 84 (63.2%) who did not. A model based on baseline clinical and proteomic data demonstrated excellent performance for prediction of transition outcome (area under the receiver operating characteristic curve [AUC], 0.95; positive predictive value [PPV], 75.0%; and negative predictive value [NPV], 98.6%). Functional analysis of differentially expressed proteins implicated the complement and coagulation cascade. A model based on the 10 most predictive proteins accurately predicted transition status in training (AUC, 0.99; PPV, 76.9%; and NPV, 100%) and test (AUC, 0.92; PPV, 81.8%; and NPV, 96.8%) data.

The ALSPAC subsample (121 participants from the general population with plasma samples available at age 12 years; 61 [50.4%] male) comprised 55 participants (45.5%) with PEs at age 18 years and 61 (50.4%) without PEs at age 18 years. A model using proteomic data at age 12 years predicted PEs at age 18 years with an AUC of 0.74 (PPV, 67.8%; and NPV, 75.8%).

Discussion: In individuals at risk of psychosis, proteomic biomarkers may contribute to individualized prognosis and risk stratification strategies, in line with a precision medicine-based approach. These findings suggest that detectable dysregulation of the complement and coagulation cascade occurs prior to the development of early psychosis outcomes. The results have clinical implications for service development in the fields of psychosis prevention and early intervention, as well as etiological implications regarding the pathophysiology associated with early psychosis phenotypes.

O8. Oral Session: Mapping Risk, Early Course, and Illness Progression

O8.1. STRUCTURAL COVARIANCE OF DEPTH-DEPENDENT INTRACORTICAL MYELINATION IN THE HUMAN BRAIN AND ITS APPLICATION TO DRUG-NAIVE SCHIZOPHRENIA: A T1W/T2W MRI STUDY

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Background: Intracortical myelination (ICM) plays an important role in effective signal transformation in central nervous system. Studying myelination in a specific cortical lamina is not practicable with magnetic resonance imaging (MRI). However, A depth-dependent manner could be a feasible alternative.

Methods: A total of 106 first-episode treatment-naive schizophrenia patients and 126 healthy controls were enrolled. We used T1w/T2w ratio as a proxy of ICM, parcellated cortex into 11 equivolumetric layers and mapped depth-specific T1w/T2w ratio to each layer. Source-based morphometry was used to generate depth-dependent structural covariance networks (dSCNs) of ICM and produce network-level ICM scores. Partial least squares correlation (PLSC) was conducted for inter-group comparison of ICM and correlation between ICM and clinical symptoms of schizophrenia.

Results: We found that dSCNs were highly reproducible in two independent samples of healthy controls (adjusted rand index = 0.46). Network-level ICM was reduced in prefrontal and cingulate cortex and increased in perisylvian cortex in first-episode treatment-naïve

schizophrenia patients (permuted p-value < 0.05, all bootstrap ratios > 1.96). Those deficits happened in early stage of schizophrenia and was not caused by antipsychotic medication. All the abnormal ICM could link to clinical symptoms of schizophrenia. Correlation patterns revealed by PLSC indicated a different factor structure from conventional three or five-factor structure of Positive and Negative Symptom Scale.
Discussion: We offer a feasible and sensitive framework to study depth-dependent ICM and relationship between brain structure and clinical symptoms. Through this framework we can understand the disruption of ICM and its related phenotypes in schizophrenia further.

O8.2. AGE-DEPENDENT EFFECTS OF SCHIZOPHRENIA GENETIC RISK ON CORTICAL THICKNESS AND CORTICAL SURFACE AREA: EVALUATING EVIDENCE FOR NEURODEVELOPMENTAL AND NEURODEGENERATIVE MODELS OF SCHIZOPHRENIA

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Background: Cumulative risk for schizophrenia peaks during late adolescence and early adulthood, a critical period for brain development. Schizophrenia-specific brain changes may occur early in development, as suggested by early neurodevelopmental models (Murray & Lewis, 1987; Weinberger, 1987), closer to schizophrenia onset, as suggested by late neurodevelopmental models (Feinberg, 1983), and/or continue with increasing duration of illness after schizophrenia onset, as suggested by neurodegenerative models (Lieberman, 1999). Although prior studies of familial risk and schizophrenia polygenic risk in unaffected individuals have some relevance, such investigations have not focused specifically on these developmental questions. Thus, given that the age of clinical onset of schizophrenia peaks in young adulthood, we sought to identify the age periods at which schizophrenia genetic risk affect brain structures.
Methods: As part of the Multiplex Genetic Investigation of Schizophrenia (MGI study), 506 participants, including 200 individuals at genetic high-risk for schizophrenia (age range: 12-85 years) from 32 families with at least two first-degree schizophrenia relatives and 276 unrelated controls, underwent magnetic resonance imaging (MRI). Quantitative genetic variance decomposition analyses were conducted on cortical thickness (CT) and cortical surface area (CSA) measures across 34 regions to distinguish among schizophrenia developmental neurogenetic effects that are salient before schizophrenia peak age of risk (age under 22 years: early neurodevelopmental effects), during peak age-of-risk (age 22-42 years: late neurodevelopmental effects), and after peak age-of-risk (age older than 42 years: neurodegenerative effects).
Results: During the early neurodevelopmental period, genetic correlations with schizophrenia were high (Rg > 0.7) and significant for three CSA traits (rostral middle frontal, pars orbitalis, and insula) but not for any CT traits. During the late neurodevelopmental period, genetic correlations with schizophrenia were also high and significant for total CSA and for frontal (superior frontal, rostral middle frontal, pars opercularis, medial orbitofrontal), parietal (superior parietal), and occipital (lateral occipital, lingual) CSA traits. During the neurodegenerative period, only two traits (parahippocampal CT and superior parietal CSA) showed significant genetic correlations with schizophrenia; both correlations were moderate

(Rg = 0.4-0.5). Importantly, these developmental neurogenetic effects were diagnostically specific to schizophrenia and not found in non-psychotic depression.
Discussion: To our knowledge, this is the first study to systematically evaluate early neurodevelopmental, late neurodevelopmental, and neurodegenerative hypotheses of schizophrenia neurodevelopment. Overall, CSA traits were more associated with schizophrenia risk than CT traits, particularly during the period around the peak age of schizophrenia onset and in frontal regions. To the extent that schizophrenia genetic risk may be associated with changes in brain development through biological mechanisms such as synaptic pruning, these effects may be more evident for cortical surface area than for cortical thickness. Our findings highlight the potentially dynamic nature of schizophrenia genetic effects across the lifespan and further emphasize the utility of integrating developmental behavior genetic approaches to understand the ontogeny of schizophrenia.

O8.3. SCHIZOPHRENIA GENETIC RISK AFFECTS CORTICAL SURFACE AREA BUT NOT CORTICAL THICKNESS: A MULTIPLEX, EXTENDED PEDIGREE STUDY

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Background: Despite schizophrenia's high heritability (h2 = .80) and regionally reduced cortical volumes, the effect of schizophrenia genetic risk on the cerebral cortex is poorly understood. To address this question, we employed a multiplex (two schizophrenia probands per family), extended pedigree (first to fourth degree relatives of probands) design (the Multiplex Genetics Investigation, MGI) that allowed the estimation of genetic correlations between schizophrenia and cortical measures in one of the largest such studies to date.
Methods: A total of 506 participants provided satisfactory MRI scans, consisting of 230 relatives (30 with schizophrenia) from 32 multiplex, extended pedigrees and 276 unrelated controls. Cortical thickness and surface area were estimated using Free-Surfer for 34 bilateral cortical regions. Quantitative genetic analyses used the SOLAR program with False Discovery Rate correction. In order to examine diagnostic specificity, genetic correlations between major depression and cortical measures were also computed.
Results: Cortical thickness and surface area for all cortical regions were significantly heritable. Although nine regions showed significantly lower cortical thickness in schizophrenia, regional thickness was not significantly genetically correlated with schizophrenia for any region. In contrast, 18 regions had significantly lower surface area in schizophrenia patients and seven regions' surface areas were significantly genetically correlated with schizophrenia. Four of these were in the frontal lobe. None of the genetic correlations between major depression and any cortical measure were significant.
Discussion: These results indicate that schizophrenia genetic risk primarily affects the cortex's surface area, not thickness, and primarily in regions of the frontal lobe. This argues for a focus on specific genetic effects on surface area, which largely reflects the number of cortical columns. These schizophrenia genetic cortical effects showed diagnostic specificity compared to non-psychotic depression.

O8.4. PROGRESSIVE CHANGES IN GLUTAMATE CONCENTRATION IN EARLY STAGES OF SCHIZOPHRENIA: A LONGITUDINAL 7-TESLA MRS STUDY

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Background: Progressive reduction in glutamatergic transmission has been proposed as an important component of the illness trajectory of schizophrenia. Despite its popularity, to date, this notion has not been convincingly tested in patients in early stages schizophrenia.
Methods: In a longitudinal 7T magnetic resonance spectroscopy (1H-MRS), we quantified glutamate at the dorsal anterior cingulate cortex in 21 participants with a median lifetime antipsychotic exposure of less than 3 days and followed them up after 6 months of treatment. Healthy controls were also scanned at two time points. We studied time by group interaction on glutamate after adjusting for gender and age. Bayesian ANCOVA was also used to evaluate whether groups differed in effect of time on follow-up glutamate concentration measurements.
Results: While patients had significantly lower overall glutamate levels than healthy controls ($F(1,27) = 5.23$, $p = 0.03$), we did not observe a progressive change of glutamate concentration in patients ($F(1,18) = 0.47$, $p = 0.50$), and the group by time interaction was not significant ($F(1,27) = 0.86$, $p = 0.36$). On average, patients with early psychosis receiving treatment showed a 0.02 mM/year increase, while healthy controls showed a 0.06 mM/year reduction of MRS glutamate levels.
Discussion: Bayesian analysis of our observations does not support early, post-onset glutamate loss in schizophrenia. Interestingly, it provides evidence in favour of a lack of progressive glutamate change in our schizophrenia sample – indicating that the glutamate level at the onset of illness was the best predictor of the levels 6 months after treatment. A more nuanced view of glutamatergic physiology, linked to early cortical maturation, may be required to understand glutamate-mediated dynamics in schizophrenia.

O8.5. CORTICAL NEUROANATOMICAL SIGNATURES OF SUBCLINICAL NEGATIVE SYMPTOMS IN SCHIZOTYPY - AN ENIGMA CONSORTIUM META-ANALYSIS

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Background: Negative symptoms can be seen to represent a continuum from subclinical manifestations in the general population to severe symptoms in schizophrenia. Neuroanatomical studies show evidence of prefrontal structural abnormalities linked to negative symptoms in patients with schizophrenia (Walton et al. 2018). However, it remains an open question whether these structural associations are also observed in ostensibly healthy individuals reporting subclinical negative symptoms. The present study used structural T1-weighted brain imaging data from the ENIGMA Schizotypy Working Group to investigate the relationship between subclinical negative symptoms and cortical neuroanatomical measures.
Methods: We included 2619 healthy unmedicated individuals with varying levels of schizotypy from 23 centres around the world. The complete sample had a weighted mean (range) age of 29.52 (12-68) and 53.04% (51%–100%) were male. Subclinical negative symptoms were assessed at each site separately using factor scores from self-report schizotypy questionnaires (i.e., the Community Assessment of Psychic Experiences, the Oxford-Liverpool Inventory of Feelings and Experiences, or the Schizotypal Personality Questionnaire). Based on prior studies in schizophrenia (Walton et al. 2018), we obtained cortical thickness from 18 prefrontal regions-of-interest (ROIs) using FreeSurfer. We performed meta-analyses of effect sizes (standardized regression coefficients) from a model predicting mean cortical thickness by subclinical negative symptom scores, adjusting for age, sex, and site. These models were repeated in an exploratory whole-brain analysis to investigate potential associations with subclinical negative symptoms in non-prefrontal cortical regions.
Results: Meta-analyses revealed significant positive associations between subclinical negative symptoms and cortical thickness of the right medial orbitofrontal cortex (βstd=0.075; pFDR=0.007), the right rostral anterior cingulate cortex (βstd=0.053; pFDR=0.048), and the left frontal pole (βstd=0.056; pFDR=0.048). Exploratory whole brain analysis revealed a positive correlation between subclinical negative symptoms and the right temporal pole (βstd=0.086; p=0.003).
Discussion: Using a large sample of healthy unmedicated individuals with varying levels of schizotypal personality traits, this ENIGMA meta-analysis showed that subclinical negative symptoms are associated with thicker prefrontal cortex. The present data are contrary to previous findings in schizophrenia, which demonstrates a relationship between negative symptoms and lower prefrontal cortical thickness (Walton et al. 2018) but consistent with recent reports of thicker OFC in individuals with high schizotypy. These divergent neural correlates suggest that thicker cortex could be a potential compensatory mechanism preventing individuals with schizotypy from the clinical manifestation of severe negative symptoms. Alternatively, greater prefrontal cortical thickness could also be associated with pathological processes along the negative symptom continuum prior to clinical manifestation.

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O8.6. WHITE MATTER DISRUPTION IN THE EARLY PHASE OF PSYCHOSIS

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Background: Abnormalities of white matter (WM) microstructure have been reported across all phases of psychosis. However, results have not always been consistent, which may reflect the use of modest sample sizes. We sought to address this issue by examining WM microstructure in relatively large samples of subjects in the clinical high risk (CHR) and first episode phases of psychosis.

Methods: We studied a total of 585 subjects, comprising 212 CHR subjects, 252 patients with first-episode psychosis (FEP), and 121 healthy controls (HC). Participants were recruited from 18 sites in Europe, Asia, Australia, and the Americas. At baseline and at follow-up, all subjects were assessed using the same acquisition protocol on 3T MRI scanners. Diffusion-weighted images were processed through a robust pipeline involving distortion correction, quality control (single-subject and study-wise level), tensor fitting, tract-based image registration and transformation (TBSS), and post-processing multi-site harmonization (ComBat). We also extracted 25 ROI-averaged measures of fractional anisotropy (FA) from each individual WM skeleton following the ENIGMA DTI-protocol. In this preliminary analysis, which was restricted to baseline data, between-group comparisons of skeletonized FA maps were conducted using randomization tests with the TFCE method and FWE correction for multiple comparisons. The influence of potentially confounding covariates was assessed through comparison of mean FA of ROIs using GLM and FDR correction for multiple comparisons.

Results: The groups differed in gender (female: CHR 45.8%; FEP 31.7%; HC 40.7%; $P<.05$) and age (mean: CHR 22.1; FEP 24.6; HC 23.4; $p<0.001$). TBSS analyses of FA skeletonized maps showed widespread reductions of FA in both the CHR and FEP groups relative to HC. ROI analyses showed that gender was the only covariate globally affecting FA measures (age, handedness, and site had no effect). After controlling for gender effects, the FEP group had lower FA than HC in the anterior limb of internal capsule (ALIC) and posterior corona radiata. The CHR group also had lower FA than HC in the posterior corona radiata, and lower FA measures than both HC and FEP in the splenium of corpus callosum.

Discussion: Our findings confirm that alterations in the WM are evident at both the CHR and FEP stages of psychosis. The extent to which these baseline findings are static or progress over time will be investigated in longitudinal analyses of the DWI data from these subjects.

O8.7. EFFECTIVE CONNECTIVITY OF FRONTO-STRIATO-THALAMIC SYSTEMS ACROSS THE PSYCHOSIS CONTINUUM

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Background: Aberrant dopaminergic activity within dorsal and ventral fronto-striato-thalamic (FST) circuits is thought to play a prominent role in the pathogenesis of psychosis. It remains unclear whether the primary abnormality lies in bottom-up signalling of subcortical areas or impaired top-down regulation by cortical regions. The present study aimed to map causal interactions (effective connectivity) within and between dorsal and ventral FST circuits across different stages of the psychosis continuum and to identify specific connections associated with striatal dopamine synthesis capacity.

Methods: Spectral dynamic causal modelling (DCM) for resting-state functional magnetic resonance imaging (fMRI) data was used to model FST effective connectivity in three datasets: (1) 46 antipsychotic-naïve patients with first-episode psychosis (FEP) (mean age [SD]= 19.12 [2.97]; 20 males) and 23 healthy controls (HCs) (mean age [SD] = 21.74 [1.92]; 14 males); (2) 36 patients with established schizophrenia (SCZ) (mean age [SD] = 35.81 [8.49]; 26 males) and 100 HCs (mean age [SD] = 30.6 [8.87]; 55 males); and (3) 33 healthy adults (mean age [SD] = 22.30 [2.21]; 15 males) recruited from a non-clinical community sample assessed for psychosis-like experiences (PLEs), who completed concurrent [18F]DOPA positron emission tomography (PET). The DCM of FST systems included 47 connections linking 8 regions that spanned across the dorsal and ventral circuits, including the dorsolateral and ventromedial prefrontal cortices, dorsal caudate, nucleus accumbens, anterior hippocampus, amygdala, thalamus, and the midbrain. Differences in effective connectivity between patients and controls were assessed in FEP and SCZ groups using a parametric Bayesian model. Separate Bayesian general linear models estimated associations between FST connectivity and symptom severity in in all cohorts. Associations between FST connectivity and ventral and dorsal striatal [18F]DOPA uptake were estimated in the PLE group.

Results: FEP and SCZ patients showed disinhibition of the midbrain and reduced top-down influence of thalamus on nucleus accumbens. Cortical dysfunction was only apparent in established illness. Positive symptoms were primarily associated with bottom-up connectivity in FEP and a mixture of bottom-up and top-down connectivity in the SCZ and PLE groups, with disinhibition of ventromedial prefrontal cortex and extrinsic connectivity of the midbrain implicated across all cohorts. Thalamic and midbrain connectivity were closely associated with dorsal and ventral [18F]DOPA uptake. Ventral striatal [18F]DOPA uptake was associated with the influence of midbrain on dorsal caudate.

Discussion: Our results identify a primary role for subcortical dysconnectivity in early illness phases, centered on the midbrain and thalamus, with cortical dysfunction emerging in established schizophrenia. Effective connectivity of the midbrain and thalamus are strongly linked to positive symptom severity and striatal dopamine synthesis capacity, suggesting that they represent key elements of FST involvement in the pathogenesis of psychotic symptoms. Striatal dopamine synthesis is closely tied to thalamic and midbrain connectivity, with ventral striatal dopamine synthesis related to dopamine signalling in the dorsal striatum.

O8.8. BRAIN NETWORK DYSCONNECTIVITY AND CORTICAL GLUTAMATE IN ANTIPSYCHOTIC-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Human connectome studies have provided rich data consistent with the hypothesis that dysconnectivity is predominant in psychosis spectrum disorders. Converging lines of evidence suggest that cortical glutamate may play an important modulatory role in brain network dysconnectivity, but empirical data on this topic remains sparse. The present study used resting state functional connectivity (FC) and magnetic resonance spectroscopy (MRS) to investigate how measurements of Glutamate + Glutamine (Glx) in the anterior cingulate cortex (ACC) relate to FC in medication-naïve first episode psychosis (FEP) patients compared to healthy controls (HC). Based on our previous findings, we hypothesized that HC would show correlations between Glx FC in the default mode (DMN), dorsal attention (DAN), and executive control networks (ECN), but these relationships would be altered in FEP.
Methods: Data from 60 antipsychotic-medication naïve FEP (age = 24.08 ±6.29, 38M/22F) and 53 HC (age = 24.70 ±6.23, 34M/19F) were analyzed. MRS data were acquired from a voxel in the ACC (PRESS, TR/TE = 2000/80ms). Metabolite concentrations were quantified with respect to internal water using the AMARES algorithm in jMRUI. FC data were processed using a standard preprocessing pipeline in the CONN toolbox We assessed positive and negative (anticorrelations) connectivity of the DMN, DAN, and ECN using seed-based analyses. We then performed a series of linear regressions to assess associations between Glx and positive and negative FC in each group, and then examined Glx-FC group interactions. FC and Glx-FC analyses were controlled for age, gender, and motion when applicable; small volume correction was performed as well [($p < 0.01$, threshold-free cluster enhancement corrected (TFCE)].
Results: We found alterations in both positive and negative FC in all networks in FEP. Glx modulated positive and negative FC in HC, but this relationship was attenuated in the ECN and DAN and absent in the DMN in FEP patients. When contrasting the Glx-FC relationships between groups, we found inverse associations between these variables in FEP patients compared to HC in both correlated and anticorrelated networks (all analyses pTFCE corrected).
Discussion: We demonstrated that both correlations and anticorrelations in three large-scale resting state networks are already altered in antipsychotic-naïve FEP, underscoring the importance of also considering anticorrelations for optimal characterization of large-scale brain networks. Our data also adds to the growing body of evidence supporting a role of cortical glutamate as a mechanism underlying alterations in functional connectivity.

O9. Oral Session: Accessing Care, Service Use and Treatment Outcomes

O9.1. DISENGAGEMENT FROM EARLY PSYCHOSIS INTERVENTION SERVICES: ELICITING PATIENT AND FAMILY PERSPECTIVES TO IDENTIFY TARGETS FOR IMPROVEMENT

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Background: While evidence suggests that young people with psychosis can achieve superior outcomes in early psychosis intervention (EPI) services, approximately 30% disengage from services prematurely. Much of the literature on service engagement in EPI is drawn from observational cohort studies. Little EPI research, with the exception of a few qualitative studies,

has elicited patient and family perspectives on service engagement. We sought to understand patient and family perspectives on service engagement in an EPI program and use these findings to highlight factors associated with EPI disengagement in a cohort of patients in the same program.

Methods: We recruited patients aged 16-29 consecutively referred for assessment in a large EPI program and their families to complete a web-based survey on facilitators and barriers to service engagement between July 2018-February 2020. We calculated descriptive statistics, identifying the top-endorsed facilitators, barriers, and suggestions for improvement. We conducted a prospective chart review of a cohort of 225 patients aged 16-29 consecutively enrolled in the same EPI program from July 2018-April 2019. Patients were observed in their first 9 months of treatment. The primary outcome of interest was risk of premature disengagement, defined as discharge with no transition to other mental health care, or nonattendance for at least 3 months. Trained abstractors extracted demographic, clinical, and service use data. Informed by findings in the patient and family survey, we examined the relationship between treatment-related factors, including lack of family involvement in care, medication nonadherence, and lack of engagement in rehabilitation services, namely, individual psychotherapy and supported employment and education (SEE), and risk of disengagement. Logistic regression was used to estimate odds of disengagement in univariate and multivariate models.

Results: The survey was completed by 167 patients and 79 family members. The top endorsed engagement facilitators related to the therapeutic relationship in both patients (47% cited their clinician speaking to them about their personal goals and thoughts on treatment) and family members (43% cited the patient's positive impression of the clinician). The top endorsed barrier to engagement was medication side effects, cited by both patients (29%) and families (39%). Forty-three percent of family members suggested that more family involvement would improve service engagement. Among patients consecutively admitted to EPI services in 2018-2019 (n=225), 153 (68.0%) had family involved in care, 106 (47.1%) had been nonadherent to medication, 112 (49.8%) engaged in individual psychotherapy, and 89 (39.6%) used SEE services in the first 3 months of care. At 9 months, 38 (16.9%) had disengaged prematurely. In univariate logistic regression, the two service components, use of individual psychotherapy (OR 0.29, 95% CI 0.13-0.65) and SEE (OR 0.42, 95% CI 0.19-0.93) were associated with lower odds of disengagement. In multivariate logistic regression, only use of individual psychotherapy was associated with significantly decreased odds of disengagement (OR 0.35, 95% CI 0.15-0.83).

Discussion: Patients with psychosis and their family members regard the therapeutic relationship as key to service engagement, a finding that was reflected in the fact that early use of individual psychotherapy in EPI was associated with a nearly fourfold decrease in risk of disengagement. These findings may help inform targets in EPI programs to promote early service engagement.

O9.2. CHARACTERISTICS OF HISPANICS REFERRED TO COORDINATED SPECIALTY CARE FOR FIRST EPISODE OF PSYCHOSIS AND FACTORS ASSOCIATED WITH ENROLLMENT

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Background: The Early Program provides Coordinated Specialty Care (CSC) services to young adults in New Mexico, aged 15-30 years who have experienced a First Episode of

Psychosis within the past year. The objective of this research was twofold. The first objective was to examine referral sources, demographics, and clinical and socio-environmental characteristics among Hispanics referred to, or enrolled in, the Early Program compared to other racial/ethnic groups. The second object was to explore which factors (demographic, clinical and socio-environmental) were associated with eligible referrals enrolling into the Early Program.

Methods: A retrospective review was conducted on all individuals referred to the Early Program over a two-year period. Extracted data included referral sources, demographics and clinical characteristics. Zip code-level data from publicly available sources were cross-referenced with each individual record. Over the two-year period, the Early program received 224 referrals. For the first objective, referrals still in process (n=5) and referrals with unknown race or ethnicity (n=39) were excluded. Among the remaining 180 referrals, 32.2% (n=58) were ineligible and 67.8% (n=122) were eligible for services. Of the eligible referrals, 61.5% (n=75) enrolled and 38.5% (n=47) individuals never enrolled. Among those referred, 41.1% (n=74) were Hispanic, 37.2% (n=67) were non-Hispanic white, and 21.7% (n=39) were other minorities. Non-parametric tests and appropriate secondary analysis were used to determine significant differences across racial/ethnic groups referred to or enrolled in the Early Program. For the second objective, eight eligible referrals were excluded due to missing data resulting in a final data set of 114 of which, (65.8% enrolled and 34.2% never enrolled). A Random Forest model was used to determine which factors or interacting factors were associated with eligible referrals enrolling in services.

Results: Compared to non-Hispanic whites, Hispanic individuals were more likely to be referred from inpatient or outpatient mental health providers and not from other sources within the community (OR=0.30(0.13, 0.68), p=0.004). In addition, Hispanic referrals were more likely to live in areas with higher rates of Spanish spoken in the home (MdD=7.41(1.13, 9.15), p=0.012). The random forest model identified that Hispanics or non-Hispanic whites were more likely to enroll compared to other minorities (OR=4.97(1.82, 13.55), p=0.0009) and (OR=4.42(1.52, 12.87), p=0.006), respectively. Finally, a significant interaction emerged in classifying enrollment. Despite Hispanic referrals living in areas with higher rates of Spanish spoke in the home, compared to non-Hispanic whites and other minorities, eligible Hispanics were 2.4 times more likely to be enrolled if living in areas with a lower prevalence of Spanish speaking (p=0.025).

Discussion: Results suggest a need for community outreach and psychoeducation programs targeting Spanish-speaking communities in New Mexico to increase referrals directly from community sources. In addition, further work is needed to explore the pathways to care for Hispanic individuals and how primary language affects referral process and enrollment rates for different race/ethnicity groups. The Early Program in New Mexico has an opportunity to contribute to knowledge of FEP in Hispanic youth that otherwise is underrepresented by nationwide clinical and implementation research. Continued exploration of factors associated with referral and enrollment processes for the growing Hispanic ethnic group in the US can help to determine best steps for developing CSC programs.

O9.3. ABSTRACT WITHDRAWN

O9.4. SAR-PEP: A RAPID LEARNING HEALTHCARE SYSTEM FOR EARLY INTERVENTION FOR PSYCHOSIS PROGRAMS

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Background: Although the literature highlights essential elements for EIS (eg. easy and rapid access to reduce DUP), an important heterogeneity remains in the extent to which they are implemented. A learning healthcare system can improve the uptake of clinical guidelines and evidence-based medicine in clinical settings and the translation of knowledge into practice and therefore improve the quality of health care

Methods: Grounded in the Integrated Knowledge Translation (iKT) approach that actively involves knowledge users throughout the design and implementation of the entire research process, with the overarching goal to improve the quality of care for patients with first-episode psychosis, this project aims to determine the feasibility of implementing a rapid learning health system (RLHS). Built in collaboration with all stakeholders (clinicians, user and family representatives, researchers, decision makers, the National center of excellence in mental health (CNESM), and the Quebec association of first episode programs (AQPPEP) this RLHS draws on real-time, user-and program centered indicators and capacity-building activities across 11 EIS in diverse settings of the Quebec province (Canada). Other aims are to determine its acceptability and impact on user outcomes (i.e., patient and family satisfaction); compliance to essential EI components, and decision-making at local and provincial levels.

Results: The implementation of the RLHS proved to be feasible, despite different challenges linked to 1)involvement of many stakeholders from different cultures and Backgrounds, 2)the lack of existing systematic, reliable, and clinically appropriate data collection procedures, 3)the lack of required resources (exacerbated during COVID-19 pandemic) paired to willingness to change and 4) accurate understanding of the model that may not be shared by all decidors and/or clinicians. The RLHS was deployed on multiple phases over 2 years and regular meetings were held to receive and give feedbacks on the RLHS and adapt it regularly with all stakeholders comments. The implementation steps were: 1)The identification and priorisation of indicators in collaboration with all stakeholders including service users and families, through surveys and both in person and virtual meetings. 2) The development of a health technology platform to allow real-time clinical data (indicators) to be routinely collected and entered by clinical teams 3-monthly, and continuously by users and family members. 3) Data collection implementation on all sites from early in 2020 every 3 months. 4) Diffusion to individual programs of personalized feedback on fidelity to indicators, electronically produced showing each program progression over time and comparing it to the mean of all programs. with comments to suggest improvement targets, 5) Capacity-building activities (eg. webinars, development and training on new tools, and individual mentoring) tailored to evolving needs of individual programs as identified by RLHS, are offered partly through an electronic platform embedded in the RLHS. 6) And the cycle goes on measuring again the same indicators to determine areas of achievements and those who need further efforts

Discussion: The RLHS can increase capacity for providing evidence-based care, monitoring performance, setting targets for improvement, using data to make program-level decisions, for collaborative learning and multi-stakeholder interactions so that patient-centered care in EIS can be achieved . The next implementation step involves the scale-up of the RLHS model across the whole province of Quebec or in other provinces and its implementation in other complex mental health services (e.g., ACT teams).

O9.5. USING BIOTYPE COGNITIVE AND CLINICAL SUBTYPES TO IMPROVE PROBLEM-SOLVING AND SOCIAL SKILLS TREATMENT OUTCOMES

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Background: The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) has proposed three biotype subgroups of psychosis with neurocognitive and symptom homology. These neurobiologically driven biotypes depict unique cognitive and clinical characteristics that provide stronger discrimination than symptom-based DSM diagnoses (Clementz et al., 2016; Pearlson & Stevens, 2020). The eventual goal is to test biotype-specific, tailored/individualized treatment advances up to and including treatment strategies suggested by the biotype characteristics themselves; or in this case, whether traditional treatment can be facilitated simply by separating patients by biotype characteristics in ways expected to influence therapeutic milieu. Many psychosocial treatment programs enroll patients into group treatment cohorts based on DSM diagnosis, which results in mixed groups containing all three biotypes. We conducted a pilot to examine whether separating group therapy patients into BSNIP biotype cohorts would enhance treatment outcomes compared to the usual approach of providing a group treatment to a heterogeneous cohort comprised of all three biotypes.

Methods: Participants were 59 adult patients with schizophrenia (SCZ) enrolled in a 4-month cognitive compensatory and social skill group as part of their intensive outpatient program. Biotype 1 Groups (B1G, n=19) consisted of only patients impaired on the Stroop Task and WAIS PSI (<1.50 SD), with significant negative symptoms (PANSS Negative subscale >16), and poor social function on the Social Functioning Scale (SFS raw score<116). Biotype 2 Groups (B2G, n=13) had below average scores on the Stroop and WAIS PSI (0 to -1.50 SD), moderate negative symptoms (PANSS Neg subscale 10-16), and mild to moderate social function (SFS=116-130). Biotype 3 Groups (B3G, n=11) had relatively normal or better Stroop and WAIS PSI scores (>0 SD), mild negative symptoms (<10), and relatively intact social function (SFS=131+). Heterogeneous Groups (HG, n=18) had a mixture of biotypes in each group cohort (33% Biotype 1, 39% Biotype 2, 38% Biotype 3). Assessments of executive ability (Penn Conditional Exclusion Test; Stroop), social function (SFS), symptoms (PANSS), and real-world problem-solving skills (Independent Living Skills-Problem Solving module; ILS-PS) were conducted at baseline, mid-point (2 mo), and post (4 mo).

Results: There was a clear functional outcome advantage when groups were separated into biotypes, with all three biotype groups showing substantial gains on the PCET and ILS-PS from pre to post compared to HG (F=9.10-16.27, p's<0.016). Between group pre-post effect sizes on the ILS-PS ranged from HG (0.37), B1G (0.49), B3G (0.50), and B2G (0.58). Only B2G showed gains on the SFS (F=6.41, p=0.008). No changes on the Stroop, PSI, or PANSS were found in any of the groups (p's>0.09).

Discussion: The benefits of cognitive and social skill group therapy were enhanced when patients were assigned to treatment groups by biotype. When patients with the same diagnosis but different biotypes are enrolled in groups, treatment progress may be hindered due to different treatment needs. For example, those with more impairment may need repetition of group content, while those with less impairment may require less repetition, but instead move

more quickly through the lessons and cover the content in more detail. Debriefing with therapists and their anecdotal reports raises several reasonable possibilities that could explain these outcome differences. These include group therapists reporting the biotype groups were more efficient in covering lesson material and "much easier to plan."

O9.6. THE ASSOCIATION OF A LONGITUDINALLY DEFINED STRESS-SENSITIVITY PHENOTYPE WITH PSYCHOSIS-PRONENESS

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Background: Stress-sensitivity is defined as a trait of individual differences and considered a mechanism mediating the association between early-life adversity and psychosis through a process of psychobiological sensitization to stress. However, the critical assumption that stress-sensitivity is a stable trait over time has been largely unexamined. Thus, we investigated whether stress-sensitivity reflects a stable response to stress across measurements spanning 4,5 years as well as the existence of different developmental patterns and the association with levels of positive and negative schizotypy. It was hypothesized that a subset of individuals would present with a pattern of stable high stress-sensitivity and that this subset would also present with high schizotypy.

Methods: This study is part of Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013). From a large pool of unselected non-clinical young adults, a selected subgroup oversampled for schizotypy scores continued regular follow-ups. Stress-sensitivity was measured at three waves (spanning 4.5 years) with the Perceived Stress Scale (PSS). A subsample of 102 participants completed PSS at T3 (M=23.49yrs/SD=2.55), N=89 at T4 (M=24.84 yrs/SD=2.67), and 168 at T5 (M=28.02yrs/SD=2.41). Latent Growth Curve Modeling (LGCM) and Latent Class Analysis (LCA) were used to assess individuals' trajectories of stress over time and to group individuals. Schizotypy was measured with the Wisconsin Schizotypy Scales (WSS), obtaining dimensional scores of positive and negative schizotypy.

Results: LGCM showed a positive and significantly different from 0 mean latent intercept (M=19.75, p<.001) and a non-significant mean latent slope (M=0.15, p=.670) thus indicating an absence of significant overall change over time. LCA identified two classes with different stress-sensitivity trajectories. The first class (67%), Low-stress-sensitivity group (M=13.91), presented slightly significant increase of perceived stress across time (0.93, p=0.046), whereas the second class (33%), High-stress-sensitivity group (M=27.87), showed no significant changes of perceived stress across time (-0.60/p=0.390). Both positive (t=-3.67, p <.001) and negative (t=-2.34, p=.020) schizotypy levels differed between groups. The high-stress-sensitivity group presented significantly higher positive (M=.85/SD=1.47) and negative (M=.46/SD=1.24) schizotypy scores as compared to the low-stress-sensitivity positive (M=.09/SD=.97) and negative (M=.03/SD=1.14) schizotypy group; the difference for positive (d=0.61) was greater than for negative schizotypy (d=0.36).

Discussion: These findings support the assumption that high stress-sensitivity is a stable trait. Whereas individuals with low sensitivity to stress exhibited a slight increase in stress responses over time (possibly related to a developmental stage that entails the increasing challenge of building a professional career and becoming fully-independent), those already highly sensitive

to stress at baseline responded with no changes over time, indicating the stable nature of the trait. As expected, individuals with high stress-sensitivity presented with higher positive (in particular) and negative schizotypy, which is consistent with previous research showing that heighted stress-sensitivity is more prevalent in psychosis samples (and more strongly related to the dimension of reality distortion).

O9.7. THE EFFECTS OF SOCIAL COGNITION AND SOCIAL PROBLEM SOLVING SKILLS TRAINING ON WORKPLACE SOCIAL SKILLS AND JOB TENURE IN VETERANS WITH PSYCHOTIC DISORDERS

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Background: Employment difficulties are common to many Veterans with schizophrenia. Despite progress at increasing job obtainment rates through supported employment services, job tenure remains highly variable with shorter tenure frequently associated with interpersonal difficulties in the workplace. The present study sought to address this problem by examining the efficacy of separate, sequential social cognition skills training and social problem solving interventions (SCST) added to usual VA vocational rehabilitation services (VR) in a sample of Veterans with schizophrenia and other psychotic disorders.

Methods: The study included 91 Veterans recently enrolled in one of three types of VA employment services (incentive therapy, compensated work therapy, supported employment). Following a baseline assessment, participants were matched according to overall levels of social and non-social cognition and then randomized 1:1 to either SCST+VR or VR within a cohort of 14-16 subjects. Of the 91 enrolled participants, 13 dropped out of the study prior to filling all of the slots within their respective cohort plus an additional 10 subjects (4 SCST+VR subjects; 6 VR subjects) failed to attend any training sessions leaving 68 randomized participants who received training (SCST+VR = 34; VR = 34). Data analyses were conducted on these 68 subjects. Training for the SCST+VR group included 12 weeks of SCST (during job search phase) followed by 6 weeks of work-related social problem solving training (after getting a job); training for VR included usual vocational rehabilitation services plus a comparison control intervention matched to the two SCST+VR interventions in training format and number and length of training sessions. All participants received a baseline and post-training assessment of social cognition and, for those who got jobs, a pre- and post-training assessment of work behavior. The primary outcome measures were an overall composite of social cognition, a social skills total score derived from the Work Behavior Inventory to assess functioning in the work setting, and job tenure measured in weeks worked over the 12-month follow-up period. For social cognition and workplace social skills, the data were analyzed using a 2 (group) x 2 (time) repeated measures ANCOVA using the SPSS linear mixed model procedure. For job tenure, we conducted a survival analysis using the Kaplan-Meier procedure to estimate the overall survival functions (rates across time) for each group and the Log-Rank test to compare the groups. The target event was job loss.

Results: Results showed a significant group x time interaction favoring SCST+VR over VR on social cognition ($p < .001$; $d = .67$) and workplace social skills ($p < .04$; $d = .57$), but there were no significant group differences from the survival analyses of job tenure ($p = .19$).

Discussion: This two-phase psychosocial intervention yielded medium effect size improvements in social behavior in the workplace, a common area of impairment among Veterans with psychotic disorders and one linked to early unsatisfactory job termination. The absence of a training effect on job tenure in this study may have been due, in part, to the high

ceiling effects observed in weeks worked across the three types of employment service programs. Future studies may target a single type of employment service program that characteristically has more variability in job tenure (e.g., supported employment) to better gauge SCST and social problem solving training effects on this area of work outcome.

O9.8. COGNITIVE ADAPTATION TRAINING (CAT) IN THE AGE OF COVID-19

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Background: Cognitive Adaptation Training (CAT) is an evidence-based psychosocial intervention using environmental supports established in a person's home environment to bypass cognitive and motivational impairments. Support such as signs, alarms, calendars, checklists and pill containers and the reorganization of belongings are used to prompt and sequence adaptive behaviors directed toward an individual's recovery goals. Supports are set up and maintained or altered on weekly home visits based upon a comprehensive behavioral, cognitive, functional and environmental assessment. Due to the international pandemic, CAT processes had to be significantly modified for delivery in Community Mental Health Centers and other programs.

Methods: Using CAT principals and the circumstances of individual CAT participants, we formulated a Remote CAT program which uses telephone and telemedicine platforms for visits and delivery of supports to the home via mail. In R-CAT providers work with the individual by phone to set up the supports that have been delivered. Approximately 35 individuals were participants in CAT as part of an 8-site effectiveness study conducted in CMHCS in multiple states at the start of pandemic lockdowns. In addition, we had 30 members of managed care participating in a UT run CAT program for high utilizers called the Familiar Faces Program. With the shut down there was an abrupt switch to Remote CAT. We were interested in identifying challenges to R-CAT delivery, examining characteristics of the treatment that changed, retention of individuals already in CAT and the engagement of new participants.

Results: Challenges included the low level of skill/comfort with technology in older participants preventing them from video conferencing or in some cases even taking pictures. This led to difficulty assessing the home environment as well as in monitoring medication follow-through. In general, for those with video capability, CAT assessment and intervention was delivered in a similar way to in-person CAT. There was a shift in the focus of sessions away from recovery goals such as job seeking that were put on hold due to the pandemic toward maintaining productive activity and enhancing leisure activities not requiring in-person social contact. This required a high level of creativity on the part of providers who engaged participants in video yoga/exercise, virtual country and museum tours, cooking with videos, and multiple art projects. Providers helped participants to structure their children to assist with home schooling, and did more training in health and safety measures; such as hand washing and mask use. Supplies provided included more smartphones, paying for data plans, craft supplies and having groceries delivered for those testing positive for the COVID-19 virus. None of the 35 participants in the multi-site study at the start of COVID dropped. Only 9 new participants were recruited during the long months of social distancing reflecting the burden of the pandemic on community agencies. For the Familiar Faces program, we added an additional 30 referrals during the pandemic; 4 individuals dropped out and we were unable to contact 9 of the referrals leaving us with 46 of 50 contacted who have remained in the program. In the past if we would have made home visits to the nine we could not find but this was not possible during the pandemic.

Discussion: Remote delivery of CAT is feasible particularly for those with access to video conferencing via smart phone or computer. Mail delivery and set up over the phone appears to feasible. Retention appears to be good in R-CAT. It remains unclear whether CAT or R-CAT would be preferred by this population following the pandemic.

O10. Oral Session: Epidemiological Correlates of Psychosis

O10.1. PSYCHOTIC DISORDERS AND ANTIPSYCHOTIC MEDICATIONS USE AS A RISK FACTOR FOR SARS-COV-2 INFECTION AND SEVERITY OF COVID19 ILLNESS: A CASE-CONTROL STUDY

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Background: People with chronic psychosis have higher rates of physical illness and respiratory infections than the general population. In addition, their symptoms may reduce their ability to comply with infection-restrictive measures such as isolation, physical distancing, wearing masks and maintaining personal hygiene. Furthermore, the course of infections, as well as other medical illnesses, is less favourable in this population

Methods: To determine if psychotic disorders or the use of antipsychotic medications are risk factors for infection with COVID-19, and for a more severe course of illness and mortality.

A case-control study using a large database of all members of an HMO who were tested for SARS-CoV-2 respiratory PCR between 1.3.2020 and 31.8.2020. The prevalence of psychotic disorders and use of antipsychotic (APD) medications was compared between cases (COVID-19 infection) and controls (negative test results.The presence of a psychotic disorder was explored as a predictor of hospitalization and death during follow-up among COVID-19 positive patients and controls, using a series of binary logistic models adjusted for confounding demographic, clinical and medical variables.

Results: Among 554,287 people tested for SARS-CoV-2 PCR, 33,287 (6%) were found positive. The use of psychotropic medications use were associated with lower incidence of infection (adjusted OR=0.95 95% CI [0.93-0.97]). After adjusting for medical comorbidities, psychotic disorders were found to be associated with increased risk for hospitalization due to COVID-19 (OR 1.99 95%CI [1.44 – 2.54]) and death (OR 1.91 95% CI [1.25 – 2.54]) in comparison to controls

Discussion: Individuals with psychotic disorders are at a lower risk for COVID-19 infection, but once infected, they are two-fold more vulnerable for hospitalization and mortality. This calls for appropriate prevention, and measures for detection and provision of care for people with severe mental illness.

O10.2. PREDICTIVE PERFORMANCE OF EXPOSOME SCORE FOR SCHIZOPHRENIA IN THE GENERAL POPULATION

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Background: Previously, we established an estimated exposome score for schizophrenia (ES-SCZ) as a cumulative measure of environmental liability for schizophrenia to use in gene-environment interaction studies and for risk stratification in population cohorts. Hereby, we examined the discriminative function of ES-SCZ for identifying individuals diagnosed with schizophrenia spectrum disorder in the general population. Furthermore, we compared this ES-SCZ method to an environmental sum score (Esum-SCZ) and an aggregate environmental score weighted by the meta-analytical estimates (Emet-SCZ). We also estimated the association between ES-SCZ and psychiatric diagnoses and other medical outcomes.
Methods: Baseline data (n = 6646) were utilized from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), a prospective general population cohort. Using the log odds from our previous report, we generated the ES-SCZ by summing log odds weighted environmental exposures (cannabis use, winter birth, hearing impairment, and childhood adversities [emotional neglect, psychological abuse, physical abuse, sexual abuse, and peer victimization]). For comparison, Esum-SCZ was generated by adding each binary exposure per individual as 0 = absent and 1 = present (ranging from 0 to 8) and an aggregate environmental score weighted by the meta-analytical estimates for each exposure were generated. To determine the discriminative function of ES-SCZ for identifying individuals diagnosed with schizophrenia, receiver operating characteristic (ROC) analysis was performed that applies a nonparametric estimator of the 95% confidence intervals around the area under the ROC curve (AUC) using a bootstrap method (n = 1000 repetitions). We performed multinomial logistic regression models to analyze the association of ES-SCZ at optimal cut-point with psychosis risk strata (no risk, low-risk, moderate-risk, high-risk, and clinical psychosis strata). Finally, we applied logistic regression models to test the association of ES-SCZ with 33 psychiatric diagnoses and other medical outcomes.
Results: ES-SCZ showed a good discriminative function (AUC=0.84) and statistically significantly performed better than both Esum-SCZ (AUC=0.80; x2 = 6.66, P = 0.010) and Emet-SCZ (AUC=0.80; x2 = 7.29, P = 0.007). At optimal cut-point, ES-SCZ showed similar performance in ruling out (LR− = 0.20) and ruling in (LR+ = 3.86) schizophrenia. ES-SCZ at optimal cut-point showed also a progressively greater magnitude of association with increasing psychosis risk strata. With the 'no risk' as reference group, the low-risk, moderate-risk, high-risk, and clinical psychosis strata showed a relative risk ratio of 1.53 (95% CI: 1.23; 1.90), 2.79 (95% CI: 2.17; 3.89), 4.06 (95% CI: 3.15; 5.23), 7.27 (95% CI: 3.58; 14.73), respectively. Among all psychiatric diagnoses and other medical outcomes, the association between ES-SCZ and schizophrenia spectrum disorder indicated the highest odds ratio (OR = 2.76 [95% CI: 2.20; 3.46]) with an explained variance of 14%. This was followed by bipolar disorder (OR = 2.61 [95% CI: 2.19; 3.10], R2 = 13%), suicide plan (OR = 2.44 [95% CI: 2.16; 2.75], R2 = 12%), suicidal thoughts (OR = 2.39 [95% CI: 2.19; 2.60], R2 = 14%), and suicide attempt (OR = 2.24 [95% CI: 1.95; 2.57], R2 = 9%).
Discussion: Our findings from an epidemiologically representative general population cohort demonstrate that an aggregate environmental exposure score for schizophrenia constructed using a predictive modeling approach—exposome score for schizophrenia—has the potential to improve risk prediction and stratification for research purposes and may help gain insight into multicausal etiology of psychopathology.

O10.3. PRENATAL AND PERINATAL RISK FACTORS FOR PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Over fifty years of research implicates prenatal and perinatal risk exposures in the later onset of psychosis. The meta-analytical evidence for associations between prenatal and perinatal risk and protective factors and psychotic disorders has not been updated for nearly two decades.

Methods: In this systematic review and meta-analysis, we quantified the consistency and magnitude of associations between prenatal and perinatal factors and psychotic disorders. Web of Science including PubMed/MEDLINE was searched up to 20th July 2019. We selected cohort and case-control studies examining the association between prenatal and perinatal factors and any ICD or DSM non-organic psychotic disorder with a (preferably) healthy comparison group. The primary outcome was the association (odds ratios (OR) and 95% CIs) between exposure to prenatal or perinatal risk or protective factors and psychotic disorders. Independent data extraction performed according to EQUATOR and PRISMA guidelines. Data were synthesised using random-effects pairwise meta-analyses, Q statistics, I2 index, assessment of study quality and publication biases.

Results: 152 studies relating to 98 factors were included. Significant risk factors were: maternal ages <20 (OR=1.17) and 30–34 (OR=1.05), paternal age <20 (OR=1.31) and >35 (OR=1.28), any maternal (OR=4.60) or paternal (OR=2.73) psychopathology, maternal psychosis (OR=7.61) and affective disorder (OR=2.26), 3 or more pregnancies (OR=1.30), herpes simplex 2 (OR=1.35), maternal infections not otherwise specified (NOS) (OR=1.27), suboptimal number of antenatal visits (OR=1.83), winter (OR=1.05) and winter-spring (OR=1.05) season of birth in northern hemisphere, maternal stress NOS (OR=2.40), famine (OR=1.61), any famine/nutritional deficits in pregnancy (OR=1.40), maternal hypertension (OR=1.40), hypoxia (OR=1.63), ruptured (OR=1.86) and premature rupture (OR=2.29) of membranes, polyhydramnios (OR=3.05), definite obstetric complications NOS (OR=1.83), birthweights <2000g (OR=1.84), <2500g (OR=1.53), 2500–2999g (OR=1.23), birth length <49cm (OR=1.17), small for gestational age (OR=1.40), premature birth (OR=1.35) and congenital malformations (OR=2.35). Significant protective factors were: maternal ages 20–24 (OR=0.93) and 25–29 (OR=0.92), nulliparity (OR=0.91), and birthweights 3500–3999g (OR=0.90) and >4000g (OR=0.86).

Discussion: Numerous prenatal and perinatal factors are associated with the later development of psychosis. This updated knowledge may help to refine our understanding of psychosis pathogenesis, enhance risk prediction and inform the selection of potentially modifiable risk factors for future preventative intervention.

O10.4. IMPACT OF SUBSTANCE ABUSE AND OTHER RISK FACTOR EXPOSURES ON CONVICTION RATES BY PEOPLE WITH A SEVERE MENTAL ILLNESS AND OTHER MENTAL DISORDERS

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Background: Previous studies have shown an increased risk of criminal offending by persons with a severe mental illness (SMI). Some suggest other risk factors such as substance abuse,

victimisation and parental history of offending may be associated with the increased risk. However, few studies have had the capacity to model a wide range of risk factors for offending in people with SMI using population-based data. This paper examines the impact of substance abuse and other risk factors on conviction rates in people with SMI and other mental disorders (OMD) compared to those with no mental disorder (NMD).

Methods: This research is part of a longitudinal record-linked population-based study of 467,945 children born in Western Australia (WA) between 1980 and 2001. This cohort was identified through linkages between the WA psychiatric case register, WA corrective services data and other statewide registers. This study explores the impact of exposure to a variety of risk factors on conviction rates by people with a mental illness. To ensure enough follow up time for a severe mental illness (predominantly psychotic disorders) to be recorded and for risk factors to be observed, the cohort was restricted to those born 1983 to 1991. The final cohort consisted of 184,147 people with a follow up time of 18 to 26 years.

Results: There were 11,836 people (6.4% of the cohort) with at least one conviction. People with a SMI and OMD had higher conviction rates than those with NMD, with unadjusted incidence rate ratios (IRR) of 3.98 (95% CI 3.67-4.32) for SMI and 3.18 (95% CI 3.03-3.34) for OMD. Three percent (3.1%) of the cohort had recorded substance abuse and these were 7.7 times more likely to have a conviction than those with no substance abuse. Rates of conviction were also found to be higher for males, those who were Aboriginal, those born in areas of greatest disadvantage and those with a history of childhood abuse. Having a parent with an offence history also elevated the risk of conviction. Adjusting for substance abuse reduced the IRRs by 60% in SMI and 30% in OMD: IRRs 1.59 (95% CI 1.45-1.74) and 2.24 (2.12-2.37), respectively. Minimal change was seen when adjusting for other potential risk factors (including socio-demographics, victimisation and parental offending) in those with a SMI (IRR 1.58; 95% CI 1.43-1.74), whereas the rate ratio in those with an OMD decreased a further 15% to an IRR of 1.90 (95% CI 1.80-2.02).

Discussion: Our analysis shows that people with a mental illness have higher rates of conviction than those with no mental disorders and substance abuse has a major impact on these rates. This study highlights the importance of risk exposures other than mental illness, especially substance abuse, and shows that the impact of substance abuse is even greater for people with a severe mental illness compared to those with other mental disorders. Results suggest the need for a greater investment in programs addressing the issue of comorbid substance abuse with a view to reducing the rate of convictions in this population. Better integration of drug and alcohol services with psychiatric treatment services might be one way of achieving this.

O10.5. HALLUCINATIONS ACROSS THE LIFESPAN - PREVALENCE AND PSYCHOPATHOLOGIC SIGNIFICANCE IN A LARGE COMMUNITY SAMPLE OF 16- TO 95-YEAR OLDS

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Background: Research over the past 15 years has highlighted that hallucinations occur in a significant proportion of the population, outside of the context of psychotic disorder. Studies have shown that these experiences are associated with increased risk of a wide range of mental

disorders, as well as increased suicidal ideation, suicide attempts and suicide deaths. Most research to date, however, has focused on young people. Using a large representative sample of the general English population aged 16 to 95 years, we investigated the prevalence and psychopathologic significance of hallucinations across the lifespan.
Methods: We used data from 'the Adult Psychiatric Morbidity Survey', a stratified, multi-stage probability sample of households, which assessed a range of general medical conditions, mental disorders, and a range of demographic, service use, and social variables every 7 years in the UK. We combined data from the 2000, 2007 and 2014 datasets, giving a total of 23,338 participants. Hallucinations were assessed using the Psychosis Screening Questionnaire. Mental health disorders were assessed using the Clinical Interview Schedule Revised, which assessed for depression, phobia, panic disorder, obsessive compulsive disorder (OCD), mixed anxiety and depression, and generalised anxiety disorder.We calculated the prevalence of hallucinations in the following age groups: 16-19, 20-29, 30-39, 40-49, 50-59, 60-69 and 70+. We then used logistic regression to investigate the relationship between hallucinations and 1) mental disorders, 2) suicidal ideation and 3) suicide attempt in each of the following age categories: 16 to 34 years, 35 to 54 years, 55 to 64 years, 65 to 74 years, and 75 years+.
Results: The prevalence of past year hallucinations was 6% in 16-19 year olds, 4.8% in 20-29 year olds, 4.4% in 30-39 year olds, 4.6% in 40-49 year olds, 4.4% in 50-59 year olds, 3.4% in 60-69 year olds and 2.7% in those aged 70+ years plus. The past-year prevalence of hallucinations decreased significantly with age. However, the psychopathologic significance of hallucinations was consistent across age groups – for all age categories, hallucinations were associated with a marked increase in the odds of having one or more mental disorders. There was no interaction between hallucinations and age in terms of risk for mental disorder. Hallucinations were consistently associated with increased suicidal ideation and suicide attempt across all age categories, a finding that was not fully explained by co-occurring mental health symptoms.
Discussion: The prevalence of hallucinations varies significantly across the lifespan, becoming less prevalent with age, but the psychopathologic significance is consistent from one age group to the next. Hallucinations are associated with significantly increased odds of a range of mental disorders from the teenage years to old age. What is more, hallucinations are robustly associated with suicidal behaviour not just in youth but through middle age and into old age. Our findings extend research on young people to the full adult life span and highlight an unusual degree of developmental continuity in that hallucinations retain similar psychopathologic significance regardless of whether they are reported in a 19 year old or a 90 year old.

O10.6. THE INCIDENCE OF NON-AFFECTIVE PSYCHOTIC DISORDERS IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: There is a robust, replicable and varied distribution of the incidence of non-affective psychotic disorders (NAPD): rates elevated in those under the age of 35 as well as in

men, and rates are consistently elevated in ethnic minority populations. Closer inspection of the studies which have contributed to this epidemiological landscape reveals these are predominantly conducted in high-income countries in Northern Europe, North America and Australia. To broaden our knowledge about the basic epidemiology of NAPD, we sought to systematically review and meta-analyse all incidence studies conducted in low- and middle-income countries (LMICs).

Methods: We systematically searched PubMed, PsychINFO, Web of Science and Embase. Our search strategy covered the terms non-affective psychotic disorders, incidence and LMICs. Citations were eligible for inclusion if they were published between 1 January 1960 and 31 December 2019, where wholly or partially conducted in an LMIC and contained data on the incidence of NAPD in the general adult population. We placed no restriction on language of publication, study design or publication states. Study selection was carried out in duplicate, and two authors carried out data extraction. Our primary outcome was incidence per 100,000 person-years of NAPD. Two independent raters assessed study quality according to previously published criteria. We conduced a narrative synthesis and carried out random-effects meta-analyses if >5 studies were available . Our primary outcome was incidence per 100,000 person-years of NAPD (International Classification of Disease [ICD]10: F20-F25). Our secondary outcomes were incidence per 100,000 person-years of all psychotic disorders (ICD10: F20-F33) and of schizophrenia (ICD10:F20). We chose not to display pooled incidence rates, but instead our interpretation focussed on the observed variation.

Results: We retrieved 6596 records of which 17 met inclusion criteria, and 12 had sufficient data available for meta-analysis. These studies were conducted in eight (former) countries. Quality of studies ranged between 2.5 (out of 7) to 6 point, with 6 being the mode score. Incidence of NAPD was derived from seven citations and varied around 3.5 times from 9.0 (95% confidence interval [CI]: 7.2- – 11.2) in India to 31.5 (95%CI: 27.0- – 36.8) in South Africa . Incidence of sSchizophrenia was available for seven settings derived from five citations and varied around 20 times from 1.74 (95%CI: 1.437-2.241) in Nigeria, Africa to 35.00 (95%CI: 21.10-58.106) in India, Asia. Incidence of all psychotic disorders (including NAPD) was available for four settings derived from three citations and varied from 10.0(95%CI: 8.8-11.4) in Brazil to 27.5 (95%CI:19.9-38.0) in India.

Discussion: Our study highlights the dearth of evidence on even the basic epidemiology of NAPD in LMICs. This makes it impossible to draw any conclusions about the distribution of NAPD in the majority of the world and to assess if the received wisdom about the epidemiological landscape of NAPD holds is truly global or biased due to being based on only a small subset of the global population .

O10.7. REGISTER-BASED METRICS OF YEARS LIVED WITH DISABILITY ASSOCIATED WITH MENTAL AND SUBSTANCE USE DISORDERS

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Background: Mental and substance use disorders are common, often have their onsets in young adulthood, and can be associated with recurrent or persistent periods of disability. These disorders, and schizophrenia specifically, account for a substantial proportion of the years lived

with disability (YLDs) globally. To date, these estimates have been calculated 'top down' based on summary statistics. We had the opportunity to calculate YLDs and a novel related measure (Health Loss Proportion, HeLP) for schizophrenia and 17 other mental and substance use disorders, based on person-level register data ('bottom up').
Methods: We conducted a nationwide register-based cohort study comprising of 7.0 million current and historical Danish residents and identified individuals diagnosed with a mental or substance use disorder (n=411,900) between 1995 and 2015 in the Danish Psychiatric Central Research Register. YLDs (the duration of disease multiplied by a disability weight) were calculated for the disorder of interest (index disorder) and for comorbid mental and substance use disorders. HeLPs were estimated as all YLDs (index YLDs and comorbid YLDs) in persons diagnosed with the index disorder divided by total person-years in those with the index disorder. Disability weights, health states and recovery rates were modelled according to protocols from the Global Burden of Disease Study and all analyses were adjusted for observed mental and substance use comorbidity using a multiplicative model for disability weights.
Results: Major depressive disorder was the most prevalent disorder, while schizophrenia was the leading cause of YLDs, for all ages and both sexes (YLDs in males: 322.6 [95% CI: 274.1-370.7] per 100,000 person-years; females: 225.0 [95% CI: 190.0-258.09]). The highest rates of disability in people diagnosed with schizophrenia were experienced in ages 35-39 years in males and 45-49 years in females. People diagnosed with schizophrenia lost the equivalent of 73% (HeLP=0.73, 95% CI, 0.63-0.83) of healthy life due to mental and substance use disorders, the largest HeLP of all mental and substance use disorders. Comorbidity of mental and substance use disorders accounted for 81-83% of HeLPs in people with cannabis and cocaine use disorder and ADHD. In contrast, comorbidity explained 11-23% of the HeLPs in people with schizophrenia, autism spectrum disorder, and conduct disorder.
Discussion: Mental and substance use disorders are associated with substantial health loss varying across age, sex and disorder. Schizophrenia was the leading cause of health loss in terms of YLDs and HeLPs. Moreover, comorbidities accounted for little additional health loss in people diagnosed with schizophrenia. In general, the new HeLP metric complements the traditional YLD metric by revealing the proportion of non-fatal health loss related to the index disorder versus comorbid conditions and register-based studies of non-fatal health loss can improve the methodology by incorporating observed comorbidity.

O10.8. CHILDHOOD TRAUMA AS A MEDIATOR OF THE ASSOCIATION BETWEEN AUTISTIC TRAITS AND PSYCHOTIC EXPERIENCES: EVIDENCE FROM THE ALSPAC BIRTH COHORT

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Background: There is increasing evidence suggesting associations between childhood autistic traits and psychotic experiences in adolescence. However, the mechanisms for such associations are currently unknown. For example, it is unclear whether these associations persist into adulthood, are confounded by a genetic risk for schizophrenia, and/or are mediated by childhood traumatic experiences. Here we examine the associations between childhood autistic traits with psychotic experiences in young adulthood, and the influence of childhood trauma on this association. Moreover, we evaluate the role of genetic confounding by schizophrenia polygenic risk scores (PRS).

Methods: We conducted a longitudinal study in the population-based ALSPAC birth cohort based in South West England. We used four dichotomised (upper 10% of the distribution) measures of autistic traits (social communication, assessed at 7 years; coherence, assessed at 9 years; repetitive behaviour, assessed at 5 years; and sociability, assessed at 3 years). Psychotic experiences were assessed at ages 18 and 24 using the semi-structured Psychosis-Like Symptoms interview (PLIKSi) and categorised as distressing or frequent (which represents a phenotype more strongly indexing schizophrenia liability). Traumatic experiences (between ages 5 to 11) were assessed by parental questionnaires and interviews about domestic violence, physical abuse, emotional abuse, emotional neglect, sexual abuse, and bullying victimization. We calculated schizophrenia PRS using the results of the Schizophrenia Working Group of the Psychiatric Genomics Consortium schizophrenia GWAS (2014) as our discovery sample.
Results: The maximum sample with complete data was 3,410 for the autistic traits-psychotic experiences analyses and 3,327 for the mediation analyses. Childhood social communication difficulties were associated with distressing and/or frequent psychotic experiences measured until age 24 (adjusted odds ratio = 1.61, 95% CI 1.01–2.56, p = 0.05). In mediation analysis, traumatic experiences in childhood explained a substantial proportion of the association between social communication and later psychotic experiences (approximately 36%). The associations were not confounded by schizophrenia PRS.
Discussion: Childhood autistic traits of social communication are associated with psychotic experiences by age 24. This association is substantially mediated by childhood traumatic experiences and not confounded by schizophrenia PRS. Experience of trauma may be an important, potentially modifiable pathway between autistic features and later onset of psychotic psychopathology where interventions could be targeted.

O11. Oral Session: Advancements in Clinical Trials in Schizophrenia: Novel Pharmacotherapies and Cognitive Remediation

O11.1. EFFICACY AND SAFETY OF ANTI-INFLAMMATORY AGENTS IN TREATMENT OF PSYCHOTIC DISORDERS - A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Antipsychotic effects of immunomodulating drugs have been suggested; however, a thorough, comprehensive meta-analysis on the effect and safety of anti-inflammatory add-on treatment on psychotic disorders is lacking.
Methods: Multiple databases were searched up until February 2020. Only double-blinded, randomized, placebo-controlled clinical trials (RCTs) were included. Primary outcomes were change in total psychopathology and adverse events. Secondary outcomes included amongst others, positive and negative symptoms, general psychopathology and cognitive domains. We performed random-effects meta-analyses estimating mean differences (MD) and standardized mean differences (SMD) for effect sizes.
Results: Seventy RCTs (N=4104) were included, investigating either primarily anti-inflammatory drugs, i.e. drug developed for immunomodulation, such as NSAIDs, minocycline

and monoclonal antibodies (k=15), or drugs with potential anti-inflammatory properties (k=55), e.g. neurosteroids, N-acetyl cysteine, estrogens, fatty acids, statins, and glitazones. Antipsychotics plus anti-inflammatory treatment, compared to antipsychotics plus placebo, was associated with a PANSS scale MD improvement of -4.57 (95%CI= -5.93 to -3.20) points, corresponding to a SMD effect size of -0.29 (95%CI= -0.40 to -0.19). Trials on schizophrenia (MD= -6.80; 95%CI, -9.08 to -4.52) showed greater improvement ($p<0.01$) than trials also including other psychotic disorders. However, primarily anti-inflammatory drugs (MD=4.00; 95%CI= -7.19 to -0.80) was not superior ($p=0.69$) to potential anti-inflammatory drugs (MD=4.71; 95%CI= -6.26 to -3.17). Furthermore, meta regression found that smaller studies showed significantly larger effect sizes than the larger studies ($p=0.0085$), and only 2 studies had low risk of bias on all domains. Small but significant effects were found on negative symptoms (MD= -1.29), positive symptoms (MD= -0.53), general psychopathology (MD= -1.50) and working memory (SMD= 0.21). No differences were found regarding adverse events, but only 26 studies reported hereon.

Discussion: Anti-inflammatory add-on treatment to antipsychotics showed improvement of psychotic disorders; however, no superiority was found in primarily anti-inflammatory drugs raising the question of the mechanism behind the effect, and treatment effect might be overestimated due to the large number of small studies.

O11.2. SIMVASTATIN AUGMENTATION FOR PATIENTS WITH EARLY PHASE SCHIZOPHRENIA-SPECTRUM DISORDERS: A DOUBLE-BLIND, RANDOMISED PLACEBO-CONTROLLED TRIAL

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Background: Schizophrenia-spectrum disorders (SSD) are associated with increased inflammatory markers in both brain and periphery. Augmentation with drugs that lower this pro-inflammatory status may improve clinical presentation. Simvastatin crosses the blood-brain barrier, has anti-inflammatory effects in the brain, and reduces metabolic syndrome. We investigated if simvastatin augmentation for 12 months can improve symptoms and cognition in patients with early SSD.

Methods: This double-blind placebo-controlled trial included SSD in- and outpatients across the Netherlands. Patients were <3 years after diagnosis, without contraindications for statin use. Patients were randomly assigned 1:1 to simvastatin 40mg or placebo. Online randomisation was stratified for sex and site, with study personnel blind to allocation. Primary outcomes were symptom severity and cognition. Depression, symptom subscores, general functioning, metabolic syndrome, movement disorders and safety were secondary outcomes. Intention to treat analyses were performed, using linear mixed models and ANCOVA. Trial registration: ClinicalTrails.gov:NCT01999309;EudraCT-number:2013-000834-36.

Results: Between December 2013 and December 2019, 127 patients were included and 119 were randomised (placebo n=58, simvastatin n=61). Ninety patients completed the treatment

phase. No main effect of simvastatin treatment was found for total symptom severity over 12 months of treatment (X2(1)=0.01,p=.90). Group differences did vary over time (treatment*time X2(4)=11.2;p=.025), with significantly lower symptom severity in the simvastatin group after 6 months treatment (mean difference=-4.8; p=.021;95%CI:-8.8 to -0.7) and at 24 months follow-up (mean difference=-4.7;p=.040;95%CI:-9.3 to -0.2). No main treatment effect was found for cognition (F(1,0.1)=0.37,p=.55) or the secondary outcomes. SAEs occurred more frequently with placebo (19%) than with simvastatin (6.6%).
Discussion: Simvastatin augmentation did not improve symptoms nor cognition after 12 months of treatment, while tolerability was high.

O11.3. CONFIRMATORY EFFICACY OF COGNITIVE ENHANCEMENT THERAPY FOR EARLY COURSE SCHIZOPHRENIA: FINAL RESULTSFROM A MULTI-SITE RANDOMIZED CONTROLLED TRIAL

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Background: The early application of cognitive remediation interventions has provided some of the greatest optimism for reducing long-term disability among people with schizophrenia. Cognitive Enhancement Therapy (CET) is an 18-month comprehensive cognitive remediation intervention designed to improve cognition and functioning in the early course of the condition. The current study sought to confirm previously observed benefits of CET on cognitive and behavioral outcomes in early course schizophrenia in a larger multi-site clinical trial.
Methods: A total of 102 early course schizophrenia outpatients were randomized to either 18 months of CET (n = 58) or an Enriched Supportive Therapy (EST; n = 44) comparison treatment. Participants completed a comprehensive battery of commonly used measures (i.e., MATRICS Consensus Cognitive Battery) to assess cognition, social adjustment, and symptoms at baseline, 9 (mid-treatment), and 18 months (end of treatment). Composite indexes were calculated for cognition, social adjustment, and symptomatology. Intent-to-treat mixed-effects models adjusting for study site were used to investigate differential change in outcomes between CET and EST. Due to the high level of attrition (49%), sensitivity analyses were performed to test for any potential differences in the findings between the intent-to-treat sample (N = 102) and those who completed treatment (N = 49). All reported p-values are one-tailed for both intent-to-treat and completer analyses because of the confirmatory nature of the trial.
Results: The effect of CET on improved cognition was confirmed in both the intent-to-treat and treatment completer samples, with particularly favorable effects on social cognition [d (intent-to-treat) = .52, p (one-tailed) = .033] and attention/vigilance [d (intent-to-treat) = .46, p (one-tailed) = .017]. The social adjustment effect was not confirmed in the intent-to-treat sample, but among participants who completed treatment (n = 49) a differential effect favoring CET was observed on improved social adjustment [d (completer) = .51, p (one-tailed) = .057]. Both groups demonstrated similar symptom improvements.

Discussion: Overall, these findings confirm the reliable and beneficial cognitive effects of CET in early course schizophrenia, and indicate that the greatest functional benefits are gained among those who complete the full treatment. In addition, opportunities to further optimize CET for this population were identified, including developing strategies to increase treatment engagement and completion.

O11.4. EFFICACY OF ADD-ON SULFORAPHANE FOR IMPROVING SYMPTOMS AND COGNITION IN SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND STUDY

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Background: The consumption of cruciferous plants such as broccoli and cauliflower has been associated with a reduced risk of cancer and other chronic diseases. This beneficial effect has been ascribed largely to the plants' high content of glucosinolates which are converted to isothiocyanates such as sulforaphane. Sulforaphane crosses the blood brain barrier and has antioxidant and anti-inflammatory activities. A previous trial in males with autism found that adjunctive sulforaphane was associated with improvements in some indicators of social functioning and aberrant behavior. The primary aim of the current study was to evaluate the safety and efficacy of an adjunctive sulforaphane nutraceutical for individuals with schizophrenia in a placebo-controlled, randomized double blind trial.

Methods: Individuals with schizophrenia or schizoaffective disorder, most of whom had long-standing illness and who had residual psychotic symptoms of at least moderate severity were randomized to receive 6 tablets per day of 16 mg of glucoraphanin, which is metabolized following ingestion yielding approximately 100 micromoles of sulforaphane, or identical-appearing placebo added to usual psychiatric medications. The study duration was 16 weeks following a 2 week placebo run-in. The primary outcome was change in the severity of psychiatric symptoms, measured biweekly by the Positive and Negative Syndrome Scale (PANSS) over the double-blind phase. The secondary outcome was change in cognitive functioning, measured by the MATRICS Consensus Cognitive Battery (MCCB), from the beginning to the end of the trial. Mixed effects models were used to evaluate the relationship between the administration of the sulforaphane precursor and change in symptoms or cognitive functioning during the study period. Exploratory analyses were performed to examine the association between levels of the sulforaphane metabolite, dithiocarbamate, in urinary samples and changes in the outcome measures.

Results: A total of 64 participants were randomized (mean age 44.0 (±12.0) years); 58 participants, 29 in the active arm and 29 in the placebo arm, completed the 18 weeks of the trial. There were no significant differences in the change of positive, negative, general, or total PANSS symptom scores between groups including all of the randomized participants or the subgroup of individuals who completed the study. There was also no significant improvement in MCCB total or domain scores by treatment group in the entire cohort. However, there was a significant association between glycophorin treatment and improvement in the MCCB working memory domain in individuals with urine concentrations of dithiocarbamate of > 1 mmol/L . Reasons for the differences in sulforaphane metabolism are not known with certainty but may be related to host genetics, the composition of the gastrointestinal microbiome, or medication compliance. The study medication was well tolerated with no significant difference in the number of adverse events between groups.

Discussion: The trial did not demonstrate an overall benefit of adjunctive sulforaphane for psychiatric symptoms or cognition in schizophrenia. Sulforaphane may result in improvement

in working memory for the subset of persons who generate dithiocarbamate following treatment

O11.5. OLANZAPINE/SAMIDORPHAN MITIGATES WEIGHT GAIN ACROSS SUBGROUPS OF PATIENTS KNOWN TO BE AT INCREASED RISK FOR WEIGHT GAIN WITH OLANZAPINE TREATMENT

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Background: Treatment with olanzapine is associated with clinically significant weight gain. Certain patient characteristics are associated with a greater propensity for olanzapine-associated weight gain, including younger age, being female, being of non-white race, and having a low body mass index (BMI). A combination of olanzapine and samidorphan, an opioid antagonist (OLZ/SAM) has been developed to mitigate weight gain associated with olanzapine treatment while maintaining antipsychotic efficacy. In a phase 3 study in outpatients with schizophrenia (ENLIGHTEN-2), OLZ/SAM treatment significantly mitigated weight gain versus olanzapine over 24 weeks. Here, we present previously unreported prespecified subgroup analyses based on demographics and baseline patient characteristics to determine if any differential treatment effects exist in these subgroups.

Methods: The phase 3 multicenter, randomized, double-blind study enrolled adults (18–55 years) diagnosed with schizophrenia (DSM-5 criteria) who were outpatients, had a BMI of 18–30 kg/m2 and stable body weight (self-reported change ≤ 5% for at least 3 months before study entry). Patients were randomized 1:1 to OLZ/SAM or olanzapine for 24 weeks. Co-primary endpoints were percent change in body weight and proportion of patients with ≥10% weight gain at week 24. In this report, exploratory subgroup analyses were conducted by sex, age, race, and BMI. Percent change in weight from baseline was evaluated by analysis of covariance model, and the proportion of patients with ≥10% weight gain was analyzed by logistic regression model. Missing postbaseline data were imputed by multiple imputation.

Results: A total of 538 patients were included (OLZ/SAM: n=266; olanzapine: n=272). Baseline demographics were similar across treatment groups. OLZ/SAM was associated with a lower percent change in weight vs olanzapine at week 24 across all subgroups evaluated, with least squares mean differences (95% CI) of −2.38% (−3.88%, −0.88%) in the overall population, −2.73% (−4.45%, −1.01%) for males (n=391), −1.53% (−4.43%, 1.38%) for females (n=147), −3.43% (−7.00%, 0.13%) for age <30 years (n=98), −2.14% (−3.78%, −0.51%) for age ≥30 years (n=440), −2.37% (−4.10%, -0.63%) for black patients (n=392), −2.41% (−5.28%, 0.46%) for non-black patients (n=146), −2.17% (−4.10%, −0.24%) with BMI <27 kg/m2 (n=327), and −2.70% (−5.01%, −0.39%) with BMI ≥27 kg/m2 (n=211). The proportion of patients with ≥10% weight gain was smaller in each subgroup treated with OLZ/SAM versus those treated with olanzapine. Relative to olanzapine, the odds ratios (95% CI) for having a ≥10% weight gain from baseline at week 24 with OLZ/SAM treatment were 0.50 (0.31, 0.80) in the overall population, 0.41 (0.23, 0.73) for males, 0.68 (0.30, 1.55) for females, 0.65 (0.25, 1.70) for age <30 years, 0.46 (0.27, 0.78) for age ≥30 years, 0.47 (0.27, 0.82) for black patients, 0.55 (0.24, 1.30) for non-black patients, 0.57 (0.32, 1.00) with BMI <27 kg/m2, and 0.38 (0.16, 0.87) with BMI ≥27 kg/m2.

Discussion: In this exploratory analysis of the 24-week, phase 3 study of patients with schizophrenia, the combination OLZ/SAM treatment mitigated weight gain associated with

olanzapine across several patient subgroups, including groups of patients who are known to be at higher risk for weight gain with olanzapine based on sex, race, age, and baseline BMI.

O11.6. RELATIONSHIP BETWEEN THE SHORT-FORM 12 (SF-12) AND SCHIZOPHRENIA SYMPTOM RATING SCALES IN A RANDOMIZED CONTROLLED CLINICAL TRIAL OF PALIPERIDONE PALMITATE 3 MONTHLY FORMULATION

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Background: There is increasing emphasis on understanding the impact of core symptoms and functioning on well-being and quality of life (QOL) to achieve holistic outcomes in schizophrenia. The short-form-12 (SF-12) is a widely used generic measure of self-reported health-related QOL (HRQOL). The relationship of SF-12 as an outcome measure of HRQOL in patients with schizophrenia with clinically relevant symptom rating scales for schizophrenia was evaluated.

Methods: Post-hoc analyses were conducted from a randomized, placebo-controlled, relapse prevention phase 3 study (NCT01529515) of paliperidone palmitate 3-monthly (PP3M) in patients with schizophrenia (DSM-IV-TR). Patients received flexible doses of paliperidone palmitate 1-monthly (50, 75, 100, or 150 mg eq) during a 17-week open-label (OL) transition phase, followed by a single dose of PP3M during a 12-week OL maintenance phase; stabilized patients were randomized to a fixed dose of PP3M (175, 263, 350, or 525 mg eq) or placebo during a 29-week double-blind (DB) phase. The SF-12 (version 2.0) was administered upon entry to the transition phase (OL baseline) and at the end of the DB phase or upon withdrawal from the study. The SF-12 subscales (bodily pain, general health, mental health, physical health, vitality, role physical, role mental, social functioning) and summary scores (mental component summary [MCS], physical component summary [PCS]) were normalized with a range of 0-100 and a population mean (SD) of 50 (10). Linear regression for change in SF-12 and common schizophrenia symptom rating scales (Positive and Negative Syndrome Scale [PANSS], Personal and Social Performance [PSP], Clinical Global Impression – Severity [CGI-S] and measure of caregiver burden [Involvement Evaluation Questionnaire, IEQ]) on change in MCS/PCS, with baseline MCS/PCS added as a covariate, were conducted.

Results: Patients (n=205) included in the post hoc analysis had mean (SD) age of 36.7 (10.93) years and were mostly men (71.2%). Improvements in the positive ($p<0.0001$; $R2=0.330$) and negative ($p=0.002$; $R2=0.305$) symptom subscale of the PANSS were significantly associated with improvements in the MCS scores. Improvements in PSP ($p< 0.0001$; $R2=0.326$) and CGI-S ($p=0.0034$; $R2=0.302$) scores were also significantly associated with improvements in MCS scores. Improvements in PANSS (negative: $p=0.786$; $R2=0.163$; positive: $p=0.501$; $R2=0.165$), PSP ($p=0.345$; $R2=0.167$) and CGI-S ($p=0.9268$; $R2=0.163$) scores were not significantly associated with improvements in PCS scores of SF-12. Improvements in IEQ urging component were significantly associated with improvements in mental health subscale score ($p=0.0143$; $R2=0.2564$).

Discussion: A clear and significant relationship was observed between the SF-12 MCS score and the validated psychiatric rating scales (PANSS, PSP and CGI-S) of schizophrenia. Other components and subscales of SF-12 did not show a clear relationship. Change in schizophrenia symptoms as measured by the SF-12 MCS may reflect a change in patient's QOL.

O11.7. PRELIMINARY EVIDENCE FOR THE PDE4 INHIBITOR, ROFLUMILAST, IN AMELIORATING COGNITIVE FLEXIBILITY DEFICITS IN PATIENTS WITH SCHIZOPHRENIA: A PHARMACOLOGICAL FMRI STUDY

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Background: Cognitive flexibility deficits in patients with schizophrenia are severe and are strong predictors of functional outcome, yet currently have no targeted pharmacological treatments. This study aimed to investigate whether the phosphodiesterase type 4 (PDE4) inhibitor, roflumilast, can improve cognitive flexibility performance and functional brain activity in patients with schizophrenia.

Methods: This was a within-subject, randomised, double-blind, placebo-controlled study using an fMRI-optimised version of the Intradimensional/Extradimensional (ID/ED) task in 10 patients with schizophrenia after receiving placebo, 100µg or 250µg roflumilast for 8 days. Data from an additional fMRI ID/ED study of 18 healthy controls on placebo was included to contextualise the schizophrenia-related performance and activations. Behavioural performance and functional scans were analysed to investigate the cognitive cost and neural correlates of solution search, attentional set shifting and reversal learning across groups and drug conditions. Functional analyses included a-priori-driven region of interest (ROI) analysis of the dorsal frontoparietal attention network.

Results: Patients with schizophrenia on placebo made more errors than healthy controls whilst searching for the target, shifting attentional sets and engaging in reversal learning, suggesting a broad deficit in cognitive flexibility. These behavioural impairments were accompanied by preserved network activity for solution search but reduced activity in the left ventrolateral prefrontal cortex and posterior parietal cortex (PPC) for attentional set shifting and reduced activity in the left dorsolateral prefrontal cortex (DLPFC) for reversal learning. ROI deficits during attentional set shifting and reversal learning were ameliorated by 250µg roflumilast, although this was not associated with any behavioural improvement. Conversely, during solution search, 100µg roflumilast reduced activity in the left orbitofrontal cortex (OFC), right DLPFC and bilateral PPC, and this was associated with an improvement in the formation of attentional sets.

Discussion: The results suggest roflumilast has dose-dependent cognitive enhancing effects on the ID/ED task in patients with schizophrenia, and provides sufficient support for larger studies to test roflumilast's role in improving cognitive flexibility deficits in this clinical population.

O12. Oral Session: Digital Health Technologies, Brain Imaging and Outcome

O12.1. ASSESSING PSYCHOSIS RISK USING QUANTITATIVE MARKERS OF DISORGANISED SPEECH

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Background: Recent work has suggested that disorganised speech might be a powerful predictor of later psychotic illness in clinical high risk subjects (Mota et al 2017, Corcoran et al 2018). To that end, several automated measures to quantify disorganisation of transcribed speech have been proposed. However, it remains unclear which measures are most predictive of psychosis-onset, how different measures relate to each other and what the best strategies are to elicit disorganised speech from participants.

Methods: Here, we first assessed the ability of twelve automated Natural Language Processing (NLP) markers to differentiate transcribed speech excerpts from subjects at clinical high risk for psychosis (CHR-P), first episode psychosis (FEP) patients and healthy control subjects (N=53 in total). Ten of these markers were taken from the literature, and we also proposed two novel markers of repetition and whether speech was on topic. Second, we investigated whether different NLP measures were correlated with each other across subjects, to assess whether they provided complementary or overlapping information. Finally, we compared the ability of transcribed speech generated using different tasks to differentiate the three groups.

Results: In-line with previous work, several of the twelve NLP measures employed showed significant differences between groups, including semantic coherence (Iter et al 2018, Corcoran et al 2018) and speech graph connectivity (Mota et al 2018). Our new measure of whether speech was 'on-topic' also exhibited significant reductions in both CHR-P subjects and FEP patients compared to healthy control subjects, outperforming the prior, related measure of tangentiality (Iter et al 2018). We therefore believe this on topic measure merits inclusion in future research studies. We observed some significant correlations between the different NLP measures examined, but most were only weakly related to each other. Finally, speech generated from picture descriptions of the Thematic Apperception Test (Murray et al 1943) and a story re-telling task showed greater group differences than free speech excerpts.

Discussion: Our results have a number of implications for translating NLP markers of disorganised speech to clinical applications. First, they suggest that different NLP measures may provide complementary information, perhaps capturing different aspects of psychosis, and that combining different measures could give additional power to predict future disease trajectories for CHR-P subjects. Future studies should examine multiple NLP measures concurrently in larger samples, to test this hypothesis. Second, our results suggest that certain tasks may be better suited to eliciting disorganised speech from patients for NLP analysis than others. This observation is in-line with previous work (Mota et al 2014) and implies that the tasks used to generate speech should be considered carefully.

Overall, quantitative speech markers represent a promising direction for future diagnostic applications.

O12.2. REAL-WORLD IMPLEMENTATION OF PRECISION PSYCHIATRY: TRANSDIAGNOSTIC RISK CALCULATOR FOR THE AUTOMATIC DETECTION OF INDIVIDUALS AT-RISK OF PSYCHOSIS

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Background: Risk estimation models integrated into Electronic Health Records (EHRs) can deliver innovative approaches in psychiatry, but clinicians' endorsement and their real-world usability are unknown. This study aimed to investigate the real-world feasibility of implementing an individualised, transdiagnostic risk calculator to automatically screen EHRs and detect individuals at-risk for psychosis.
Methods: Feasibility implementation study encompassing an in-vitro phase (March 2018 to May 2018) and in-vivo phase (May 2018 to April 2019). The in-vitro phase addressed implementation barriers and embedded the risk calculator (predictors: age, gender, ethnicity, index cluster diagnosis, age*gender) into the local EHR. The in-vivo phase investigated the real-world feasibility of screening individuals accessing secondary mental healthcare at the South London and Maudsley NHS Trust. The primary outcome was adherence of clinicians to automatic EHR screening, defined by the proportion of clinicians who responded to alerts from the risk calculator, over those contacted.
Results: In-vitro phase: implementation barriers were identified/overcome with clinician and service user engagement, and the calculator was successfully integrated into the local EHR through the CogStack platform. In-vivo phase: 3722 individuals were automatically screened and 115 were detected. Clinician adherence was 74% without outreach and 85% with outreach. One-third of clinicians responded to the first email (37.1%) or phone calls (33.7%). Among those detected, cumulative risk of developing psychosis was 12% at six-month follow-up.
Discussion: This is the first implementation study suggesting that combining precision psychiatry and EHR methods to improve detection of individuals with emerging psychosis is feasible. Future psychiatric implementation research is urgently needed.

O12.3. IDENTIFYING CLINICAL CLUSTERS WITH DISTINCT TRAJECTORIES IN FIRST-EPISODE PSYCHOSIS

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Background: The extreme variability in symptom presentation reveals that individuals diagnosed with a first-episode psychosis (FEP) may encompass different sub-populations with potentially different illness courses and, hence, different treatment needs. The identification of early clinical and sociodemographic features may be important in identifying subsets of patients with similar characteristics, facilitating personalised treatment approaches. Previous studies have shown that sociodemographic and family environment factors are associated with more unfavorable symptom trajectories. The aim of this study was to examine the dimensional structure of symptoms and to identify individuals' trajectories at early stage of illness and potential risk factors associated with poor outcomes at follow-up in non-affective FEP.

Methods: One hundred and forty-four non-affective FEP patients were assessed at baseline and at 2-year follow-up. To assess cognitive reserve (CR) we have used the three most commonly proposed proxy indicators of CR in psychiatry which include premorbid intelligence quotient, education and lifetime participation in leisure, social and physical activities.

A Principal component analysis has been conducted to identify dimensions, then an unsupervised machine learning technique (fuzzy clustering) was performed to identify clinical subgroups of patients. We performed Dann and Gamma Indexes to verify the quality of clustering at baseline as well as at follow-up. Furthermore, we performed a Discriminant function analysis (DFA) using package 'MASS' (version 7.3-53) to confirm the clusters retained and to investigate the predictive power of the clustering of each subject's psychopathological dimensions to the clinical cluster.

Results: Six symptom factors were extracted (positive, negative, depressive, anxiety, disorganization and somatic/cognitive). Three distinct clinical clusters were determined at baseline: mild; negative and moderate; and positive and severe symptoms, and five at follow-up: minimal; mild; moderate; negative and depressive; and severe symptoms. Four-trajectory groups were described as "excellent prognosis", "remitting course", "clinical worsening" and "chronic course". Patients with an excellent prognosis trajectory were those who exhibited mild symptoms at baseline and minimal or mild symptoms at follow-up, whereas those with remitting course had moderate or severe symptoms at baseline and minimal or mild symptoms at follow-up. Patients with a clinical worsening trajectory exhibited mild symptoms at baseline and negative/depressive or severe symptoms at follow-up. Finally, patients with a chronic course trajectory showed moderate/severe symptoms at baseline and negative/depressive or severe symptoms at follow-up. Receiving a low-dose antipsychotic, having a more severe depressive symptomatology and a positive family history for psychiatric disorders were risk factors for poor recovery, whilst having a high cognitive reserve and better premorbid adjustment may confer a better prognosis.

Discussion: The current study provided a better understanding of the heterogeneous profile of FEP. Not only positive but also negative and depressive symptoms are common in patients with FEP and are highly involved in their clinical trajectory. Early identification of patients who could likely present poor outcomes may be an initial step for the development of targeted interventions to improve illness trajectories and preserve psychosocial functioning. Thus, this study highlights the importance of addressing depressive and negative symptoms, cognitive reserve and premorbid adjustment in the early stages of psychosis.

O12.4. ABERRANT TRIPLE-NETWORK CONNECTIVITY PATTERNS DISCRIMINATE BIOTYPES OF FIRST-EPISODE MEDICATION-NAïVE SCHIZOPHRENIA IN TWO LARGE INDEPENDENT COHORTS

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Background: Schizophrenia is a complex disorder associated with aberrant brain functional connectivity. This study aims to demonstrate the relation of heterogeneity of symptomatology in this disorder to distinct brain connectivity patterns within the triple network model.
Methods: The study sample comprised 300 first-episode antipsychotic-naïve patients with schizophrenia (FES) and 301 healthy controls (HC). At baseline assessment, resting-state functional magnetic resonance imaging data were captured for each participant, and concomitant neurocognitive functions were evaluated outside the scanner. Clinical information of forty-nine FES in the discovery dataset were reevaluated at a 6-week follow-up. Differential features were selected from triple-network connectivity profiles between FES and HC. The cutting-edge unsupervised machine learning algorithms were used to define patient subtypes. Clinical and cognitive variables were compared between patient subgroups.
Results: Two FES subgroups with differing triple-network connectivity profiles were identified in the discovery dataset and confirmed in an independent hold-out cohort. One patient subgroup appeared to have more severe clinical symptoms was distinguished by salience network (SN)-centered hypoconnectivity, associated with greater impairment in sustained attention. The other subgroup exhibited with hyperconnectivity and manifested greater deficits in cognitive flexibility. Compared to the hyperconnectivity subgroup, the SN-centered hypoconnectivity subgroup had more persistent negative symptoms at a 6-week follow-up.
Discussion: The present study illustrates that clinically relevant cognitive subtypes of schizophrenia may be associated with distinct differences in connectivity in the triple-network model. This categorization may foster further analysis of effects of therapy on these network connectivity patterns, which may help to guide therapeutic choices to the goals of effective personalized treatment.

O12.5. BRAIN NETWORK ARCHITECTURE INTRICATELY LINKED TO MORPHOLOGICAL ABNORMALITIES IN MAJOR PSYCHIATRIC DISORDERS

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Background: Schizophrenia (SCZ) is associated with widespread neuroanatomical abnormalities. Recent studies suggest a link between disease effects in SCZ and brain network architecture. The identification of the exact relationship between network architecture and morphological abnormalities associated with SCZ could further elucidate the pathophysiological mechanisms of the disease. In our cross-sectional mega-analysis, we tested the hypothesis that cortical and subcortical connectivity architecture is linked to structural abnormalities, through the lens of nodal interconnectedness in SCZ. Using ENIGMA meta-analytic findings, we then replicated our findings for SCZ and extended the analysis to other major psychiatric disorders.

Methods: Structural brain imaging data from 1,566 adults with SCZ and 1,682 healthy controls from 16 international sites of the ENIGMA SCZ Working Group were compared using a surface-based linear model and related to normative connectivity data obtained from the Human Connectome Project. We adopted an approach recently applied to the common epilepsies, and tested two network-based nodal susceptibility models: (1) nodal stress models, which correlated nodal centrality metrics, computed using the Brain Connectivity Toolbox with the morphological abnormality map to assess a selective vulnerability of hub regions, and (2) epicenter models, where nodal connectivity profiles were related to the spatial distribution of structural brain abnormalities. In both cases, model fit was evaluated against null models with equivalent spatial autocorrelation. Robustness of findings was confirmed using meta-analytic results of the latest ENIGMA SCZ study; network analysis was then also applied to ENIGMA meta-analytic findings in Bipolar Disorder (BIP) and Major Depressive Disorder (MDD).

Results: Highly interconnected cortical hub regions displayed higher disease-specific atrophy in SCZ ($p_{func} = 0.005$, $p_{struc} = 0.043$) and BIP ($p_{func} = 0.07$, $p_{struc} = 0.01$) whereas the opposite trend was observed in MDD ($p_{func} = 0.07$, $p_{struc} = 0.64$). We further identified unique sets of brain regions whose connectivity profiles were anchored to disorder-specific morphological abnormalities. Cross-disorder comparisons revealed substantial overlap in cortical network involvement in SCZ and BIP, but pointed to a more specific distribution of temporo-limbic localized neuroanatomic epicenters in SCZ.

Discussion: Our findings provide significant evidence that brain network architecture is intricately linked to brain structural abnormalities in SCZ and other major psychiatric disorders, with nodal centrality emerging as a fundamental component of this relationship. We extend prior research by implicating distinct sets of brain regions in the disease processes of each disorder and by revealing shared and distinct substrates of network pathology.

O12.6. ASSOCIATION BETWEEN MENTAL DISORDERS AND SUBSEQUENT YEARS OF WORKING LIFE. A NATIONWIDE, REGISTER-BASED COHORT STUDY BASED ON 5.1 MILLION INDIVIDUALS LIVING IN DENMARK

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Background: The impact of mental disorders on workforce participation can vary from unemployment and periods of sick leave, to exit from the workforce via disability pension or voluntary early retirement. Although it is well established that mental disorders are associated with reduced workforce participation, previous studies are based on small samples with short follow-up, and often present relative risks. Thus, the actual number of working years lost for people with mental disorders has not previously been quantitated. The aim of this study was to estimate the association between different types of mental disorders across the whole spectrum and working years lost, defined as the number of years not being actively working or enrolled in an educational program. Additionally, we aimed to describe the contribution of different factors on these estimates (sickness absence, unemployment, starting on a disability benefit, voluntary early retirement, and premature mortality).

Methods: We conducted a population-based cohort study including all 5,163,321 persons aged 18-65 years living in Denmark in 1995-2016. Information on mental disorders and workforce participation was obtained from Danish registers. Individuals were assumed to be in the labour market until their 65th birthday (age of scheduled retirement), or until permanent premature exit (if they died or experienced early retirement). In order to estimate periods of temporary exit from – or delayed entry to – the labour market, individuals were classified as being enrolled in an educational program, employed, unemployed, or in sickness absence. For individuals diagnosed with each mental disorder (defined by the ICD-10 diagnoses and subchapters), we estimated average working years lost after disease diagnoses compared to the general population of same sex and age, and divided it according to specific causes of not being in the workforce.

Results: Individuals with mental disorders were on average actively working or enrolled in an educational program for an additional 12.8 years after diagnosis, compared to 23.3 years in the Danish population of same sex and age; consequently, they lost on average 10.5 years of working life. When looking at specific mental disorders, working years lost ranged from 6.7 years for eating disorders to 25.5 years for intellectual disabilities. Those with schizophrenia lost on average 18.9 working years. Individuals with mental disorders left the labour market permanently 19.0 years after diagnosis, 7.8 years earlier than the Danish population of same sex and age. More specifically, those with mental disorders experienced a reduction of 7.5 years of working life through being awarded a disability pension; and 0.9 years due to premature mortality; however, they were part of the labour market 0.6 years longer than the general population by not benefiting from a voluntary early retirement.

Discussion: This study is the largest and most detailed to quantify the impact of mental disorders on working life to date. We report novel estimates that take into account the observed age at onset of the disorder, instead of focusing on specific ages. The findings showed that individuals with mental disorders left the workforce earlier than the general Danish population. Additionally, they also experienced a larger amount of years being unemployed or in sickness absence before retirement. All types of disorders were associated with shorter working life

compared to the general population. We hope that this research will motivate effective interventions to promote employee's mental health and support individuals with mental disorders throughout their working life.

O12.7. THICKNESS AND SURFACE AREA DIFFERENCE IN SCHIZOPHRENIA STRATIFIED BY DURATION OF ILLNESS IN THE GENUS DATASET

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Background: Schizophrenia (SZ) is a serious mental disorder with complex and diverse symptomatology. The heterogeneity that characterizes SZ indicates that many different psychopathologies may underlie its symptomatology. Abnormalities of several brain regions have been identified; nonetheless, the neural mechanisms underlying psychosis are largely unknown. We have previously shown cortical thickness (CT), but not surface area (SA), abnormalities in attention and language network regions in young subjects at clinical high risk for psychosis. Here, utilizing the large, deeply phenotyped GENUS dataset, we investigate CT and SA in relation to duration of illness in subjects affected by schizophrenia and matched on age, sex and race. We predicted that morphometric abnormalities of global CT and SA and of language/attention regions will be associated to illness duration when controlling for aging effects, with CT as the stronger direct correlate for duration of illness.
Methods: Subjects were: Familial high risk (FHR, n=329); SZ: Early Course < 3 years from first hospitalization (EC, n=346), Middle > 3 years < 10 years (MC, n=216), and Chronic course > 10 years (CC, n=378); and controls (HC) (n=1313). T1-MPRAGE scans were processed using FreeSurfer 5.3 and total mean CT and total SA measurements, as well as CT and SA for the following regions: the banks of superior temporal sulcus, the middle temporal, the fusiform, the Heschl, the inferior parietal, the supramarginal, the pars opercularis, and the pars triangularis extracted according to the Desikan-Killiany Atlas (DKT). Probands-control comparisons were carried out after propensity matching on age, sex, race, and effect sizes of group comparisons (p (FDR)<0.05) are false discovery rate (FDR) corrected.
Results: The EC, MC, and CC groups had diminished global CT and SA (pfdr<0.05, -d= -0.16 to -0.47) compared to controls. Only CT, but not SA, distinguished SZ from FHR. Effect sizes for SZ CT difference with HC were increasingly stronger from EC to MC to CC, for both global CT and CT of language/attention network regions. However, there were no significant findings for the between-SZ group comparisons.
Discussion: By employing a large, deeply phenotyped dataset, the GENUS, we identify and confirm CT as the main brain measure affected across different stages of SZ. We also determine that thinner CT present in the early course of the illness continues to thin with illness duration, significantly widening the gap with age matched controls, indicating both neurodevelopmental but also neurodegenerative processes at play during the course of the illness.

O12.8. EXTRAPOLATING CLOZAPINE TREATMENT START AND STOP DATES BY MERGING BLOOD TEST DATA WITH ELECTRONIC HEALTH RECORDS DATA

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Background: While clozapine is the best treatment for treatment-resistant schizophrenia, it is one of the most underused medications in psychiatry. This is because it has a rare but potentially fatal side effect, agranulocytosis, a severe form of neutropenia. Clozapine-induced agranulocytosis occurs in less than 1 percent of clozapine users but since there is no way of predicting it, all clozapine users are required to undergo regular blood test monitoring throughout their course of treatment. The majority of clozapine-induced agranulocytosis occurs in the first 18 weeks of clozapine therapy, therefore, in the UK, clozapine users are required to have a blood test every week for 18 weeks, then fortnightly until 1 year, and every four weeks thereafter.

Methods: In order to study the incidence of agranulocytosis in patients taking clozapine, we combined data from a blood monitoring database with electronic health records to obtain accurate start and stop dates of clozapine treatment. The South London and Maudsley (SLAM) NHS Trust uses the Zaponex Treatment Access System (ZTAS) to record and monitor the blood tests of clozapine patients. There are 19 years of blood test data in SLAM's ZTAS database with over 210,000 blood test records on over 2000 patients. Also, SLAM uses the Clinical Record Interactive Search (CRIS) database system to anonymize SLAM's electronic health records data and make it available for research use. Using SQL and python programming languages, the dates of blood tests were extracted from the ZTAS database. Then the intervals between consecutive tests were calculated. These intervals were compared against the frequency of blood tests expected depending on the duration of treatment, and anomalies were examined. Rules were coded in to accommodate planned increases in the frequency of blood tests, for example, if a result in the amber range, then mandating that the next blood test should occur sooner. Unexpected gaps between tests were identified and data from electronic health records were used to fill in these gaps, for example (1) Pharmacy dispensary data (2) clozapine clinic attendance data (3) Positive mentions of clozapine use in the clinical narratives. A merged dataset of blood test data and electronic health records data was generated. From this merged dataset, clozapine treatment start and stop dates were extrapolated by setting rules such as (1) a gap of more than 35 days is considered a break in clozapine treatment (2) all new episodes of clozapine treatment start with weekly tests.

Results: There were 210,273 blood tests from 2,028 SLAM patients in ZTAS database, from 2001 to 2019. Only around 25% of blood tests followed the expected frequency pattern of starting with weekly tests, then fortnightly after 18 weeks then monthly after a year of clozapine treatment. These tests came from 1,375 (68%) unique patients. The remainder of the blood test data needed to be combined with electronic health records data. After removing tests with no consecutive tests, we extrapolated 2,828 clozapine treatment segments in 1,729 patients. These comprised of 174,839 tests.

Discussion: We show that it is possible to extrapolate clozapine start and stop dates by merging blood test results data with prescription data, clozapine Clinic attendance data and text mined data from free-text clinical narratives. This data can help us to closely study the side effects of clozapine.

Sunday Poster Session

S1. INFLUENCE OF SOCIAL EXCLUSION FACTORS ON PREDISPOSITION TO A FIRST PSYCHOTIC EPISODE

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Background: There is a growing interest in identifying individuals at high risk for developing psychosis. The social defeat hypothesis postulates that the long-term experience of being excluded from the majority group puts the individual at increased risk for a psychotic disorder. The aim of the present study was to investigate possible interactions between factors of social exclusion in the occurrence of first episode psychosis.
Methods: Over a three-year period, we analyzed a sample of 197 incident cases of psychosis and 300 controls. The adverse experiences evaluated were: social disadvantage index (calculated by the sum of school delay, unemployment, marital status, social support, living alone and not owing home), bullying, discrimination and childhood trauma, adjusted by commonly known psychosis predictors as sex, age, ethnicity and cannabis use in life. The data were analyzed using the multivariate logistic regression method.
Results: In the complete logistic regression model, we observed increase in the chance of occurrence (odds ratio) of psychosis associated to the investigated adverse experience variables, exception done to bullying. There were increase of 1.81 (95% CI: 1.50-2.19) for increase of each unit in the disadvantage index, 2.05 (95% CI: 1.24-3.35) and 2.46 (95 % CI: 1.57-3.85), respectively, to whom were victims of discrimination and trauma in childhood. The experience of bullying lost the association significance in the full model (OR = 1.39, 95 % CI: 0.81-2.38).
Discussion: In this case-control study, we found association between the chance of psychotic disorders and different variables of environmental disadvantages, possible proxies of social defeat.

S2. REDUCED RISK ACROSS MULTIPLE CARDIOMETABOLIC RISK FACTORS WITH OLZ/SAM COMPARED WITH OLANZAPINE: RESULTS FROM A 24-WEEK PHASE 3 STUDY

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Background: The olanzapine and samidorphan (OLZ/SAM) combination was developed to mitigate olanzapine-associated weight gain while maintaining antipsychotic efficacy. In the phase 3 ENLIGHTEN-2 study, patients gained significantly less weight with OLZ/SAM compared with olanzapine. We present post hoc analyses from ENLIGHTEN-2 assessing the effects of OLZ/SAM versus olanzapine across multiple cardiometabolic risk factors.
Methods: The phase 3, 24-week, randomized, double-blind study enrolled adults with schizophrenia (18–55 years; body mass index [BMI] 18–30 kg/m2). Patients were randomized

1:1 to OLZ/SAM (10/10 or 20/10 mg/day) or olanzapine (10 or 20 mg/day). Post hoc analyses evaluated changes in BMI, risk of obesity (BMI ≥30), changes in blood pressure, and risk of blood pressure shifts from normal to hypertensive (all at week 24), and risk of developing metabolic syndrome (last on-treatment assessment).
Results: OLZ/SAM (n=266) was associated with smaller BMI increases, least squares (LS) mean difference (95% CI): −0.65 kg/m2 (-1.01, -0.28); reduced risk of obesity, odds ratio (95% CI): 0.52 (0.32, 0.82); smaller increases in blood pressure, LS mean difference [95% CI] in systolic (-2.63 mmHg [-4.78, -0.47]) and diastolic (-0.75 mmHg [-2.31, 0.80]) blood pressure; and a reduced risk of blood pressure shifts from normal to hypertensive, (OR [95% CI]: 0.48 [0.24, 0.96]) vs olanzapine (n=272) at week 24. The risk of developing metabolic syndrome per ATP III criteria was also reduced with OLZ/SAM (OR [95% CI]: 0.55 [0.31, 0.99]).
Discussion: Patients in ENLIGHTEN-2 were less likely to experience worsening of certain cardiometabolic risk factors when treated with OLZ/SAM.

S3. INTERPERSONAL TRAUMA, SOCIALLY ANXIOUS BELIEFS, AND POSITIVE AND NEGATIVE SYMPTOMS OF PSYCHOSIS

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Background: Trauma exposure is common in people with psychosis, with almost 60% of those with schizophrenia spectrum disorders experiencing physical abuse and over 30% experiencing sexual abuse (Mauritz et al., 2013). Prior research has also established that interpersonal trauma significantly predicts positive symptoms of psychosis (Bailey et al., 2018; Honings et al., 2017). However, findings have been mixed regarding the relation between interpersonal trauma and negative symptoms (Bailey et al., 2018; Van Dam et al., 2014). Social anxiety seems to be related to both interpersonal trauma (Cougle et al., 2010; McMillan & Asmundson, 2016) and psychosis (Pontillo et al., 2017; Voges & Addington, 2005), but these findings are not uniform (Gumley et al., 2004; Kuo et al., 2011). Additionally, prior research has not addressed how trauma may be related to anxiogenic beliefs thought to underlie social anxiety. This poster will test the hypothesis that interpersonal trauma and psychosis are related to both symptoms and beliefs associated with social anxiety.
Methods: The current poster aims to 1) replicate prior findings regarding interpersonal trauma and positive symptoms of psychosis, 2) explore mixed findings between interpersonal trauma, social anxiety, and positive and negative symptoms, and 2) explore the role of socially anxious beliefs in these relations. Participants were a transdiagnostic sample of 117 adults with psychosis. The Trauma History Questionnaire (THQ; Hooper et al., 2011) was used to measure variety of types of physical and sexual trauma experiences (e.g., forced touching of private body parts, assault with a weapon), regardless of number of instances of each type. The Self-Beliefs Related to Social Anxiety Scale (SBSA; Wong & Moulds, 2009) measured high standards ("I must get everyone's approval"), conditional beliefs ("If I make mistakes, others will reject me"), and unconditional beliefs ("People think I'm inferior"), and the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998) measured social anxiety symptoms. Lastly, the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) was used to measure symptoms of psychosis.
Results: More types of physical/sexual experiences endorsed on the THQ were significantly associated with greater scores for SBSA conditional beliefs ($r = .29$, $p = .002$), SBSA unconditional beliefs ($r = .28$, $p = .002$), total SIAS ($r = .35$, $p < .001$), and total BPRS ($r = .25$,

p = .006). However, the association between THQ scores and BPRS positive symptoms did not reach significance (r = .18, p = .051). More SBSA conditional beliefs were significantly correlated with total BPRS scores (r = .30, p = .001) and BPRS positive symptoms (r = .19, p = .03). More SBSA unconditional beliefs were correlated with total BPRS scores (r = .36, p < .001) and BPRS positive symptoms (r = .30, p = .001). However, more SBSA high standard beliefs were only significantly associated with total BPRS scores (r = .19, p = .04). Finally, greater SIAS scores were significantly related to total BPRS scores (r = .48, p < .001), BPRS positive symptoms (r = .38, p < .001), and BPRS negative symptoms (r = .23, p = .01).
Discussion: These results may reflect a mediational role of social anxiety symptoms and beliefs in the relation between interpersonal trauma and psychosis. This directionality and potential causal relation cannot be confirmed by the current poster due to the limitations of a cross-sectional design. Therefore, future research should seek to replicate these findings in a longitudinal design to test for mediation. If this is found to be the case, then intervening in socially anxious beliefs following interpersonal trauma could hold promise as a method for preventing later conversion to psychosis.

S4. ANALYSIS OF MIRNA EXPRESSION ASSOCIATED WITH A COGNITIVE DEFICIT SUBGROUP OF SCHIZOPHRENIA IN THE PERIPHERAL BLOOD

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Background: Schizophrenia (SZ) is a neurodevelopmental psychiatric disorder that affects nearly 1% of the population and permanently disables more young people than any other illness. Currently, the diagnosis is based on signs and symptoms, but understanding the molecular mechanisms of the disease and particularly the cognitive symptoms, might enable us to identify diagnostic biomarkers and direct treatments to its underlying causal factors. microRNAs (miRNAs) are known to be associated with the disorder and their altered expression may also be associated with the severity of cognitive symptoms.
Methods: Small RNA-Sequencing was conducted on peripheral blood mononuclear cells (PBMCs) from a subgroup of cases with severe (CD) and moderate (CS) cognitive deficits from the Australian Schizophrenia Research Bank (ASRB). Sequencing data analysis was performed by a customised pipeline comprised of FASTQ, Cutadapt, HISAT2, and HTSeq-count bioinformatic tools, followed by differential expression analysis by the R package edgeR. TargetScan database and ToppFun online tool were used for identifying the predicted targets of differentially expressed (DE) miRNAs as well as exploring their enrichment in various cellular functions and diseases, respectively. Finally, SH-SY5Y-derived neuron-like cells were transfected with mimics and inhibitors for DE miRNAs, and the resultant changes in their transcriptome were investigated.
Results: 15 miRNAs showed expression dysregulation (PValue<0.05), of which only hsa-miR-3175, with a 12-fold down-regulation in CD cases, survived multiple testing correction (FDR<0.05). Predicted targets of this miRNA contribute to neurogenesis, synaptic signalling, and synaptic plasticity regulation, and are associated with various neurodevelopmental diseases, including SZ. Mimic and inhibitor oligonucleotides of miR-3175 caused differential expression of 68 and 895 genes, respectively, in neuron-like cells, with 56 genes common between the two conditions. 16 of these 56 common genes are predicted targets of miR-3175, of which 12 are known to be associated with psychiatric

diseases and 14 are related to the immune system. Gene Set Enrichment Analysis (GSEA) revealed that the common genes were involved in many biological processes and signalling pathways related to the immune system, and were linked to autoimmune disorders, which have well-established associations with psychiatric diseases.
Discussion: Collectively, our results collectively suggest that hsa-miR-3175 might be an interesting candidate biomarker for cognitively impaired subtype of SZ.

S5. AUDITORY MISMATCH NEGATIVITY DEFICITS IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS THEIR CORRELATION SYMPTOM SEVERITY AND COGNITIVE DYSFUNCTION

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Background: Sensory processing deficits are core features of schizophrenia, reflected in impaired generation of EEG-derived event-related potentials such as the auditory mismatch negativity (MMN). The MMN is elicited by deviant stimuli in an auditory oddball paradigm, and it is a robust predictor of psychosis onset in clinical high risk (CHR) cohorts. Herein, we examined auditory MMN in two CHR cohorts, one collected at Columbia University Medical Center and the other at the Icahn School of Medicine at Mount Sinai, and assessed which MMN deviants were abnormal in CHR patients and association of MMN with prodromal symptom severity and cognition.
Methods: Participants included fifty-two CHR and 27 healthy controls (HC) from two sites (Columbia & Mount Sinai) who completed an auditory MMN paradigm with deviants in duration, frequency, intensity, frequency modulation, and change of location (right and left). Positive and negative symptom severity in CHR were assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS) and Cognition measured by MATRICS. Group differences were assessed using the multivariate analysis of covariance and MMN association with clinical symptoms were determined using partial correlations, with data acquisition sites as covariates of no-interest.
Results: Results showed significantly reduced MMN in CHR for the duration deviant (p=.009), Decreased Intensity (p=.049), and Right Change of location (p=.023). Among CHR patients, MMN Increased duration is correlated with higher SIPS total positive (p=.006), Negative Symptoms (p=.006), total General symptoms (p=.024), and Global Assessment of Functioning scores (p=.018). MMN Right change of location with negative symptoms Social Anhedonia (p=.041).
Discussion: Data collection is ongoing. Our main finding to date is that duration, Decreased Intensity, and Right change of location MMN is significantly reduced in CHR patients. Although these findings replicate other studies that identify that duration MMN is among the most replicated biomarkers of psychosis risk, current results extend our understanding regarding MMN to other deviants (e.g., frequency, intensity Frequency Modulation& Change of Locations) and their association with more severe SIPS Negative and General clinical symptoms.

S6. NEUROLOGICAL SOFT SIGNS PROGRESSION IN TREATMENT-RESISTANT SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia patients exhibit neurological soft signs (NSS) which appears to fluctuate along the course of schizophrenia. Previous studies suggest that NSS could predict end-point diagnosis and treatment response in first-episode psychosis patients. However, it is unclear whether NSS could predict treatment resistance in first-episode schizophrenia patients.
Methods: This longitudinal study recruited first-episode psychosis patients, and administered the abridged version of Cambridge Neurological Inventory at baseline, the sixth month, and the fifth year. We compared the levels of NSS at different time-points between 29 treatment-responsive schizophrenia patients and 23 treatment-resistant schizophrenia patients.
Results: Our results showed that treatment-resistant schizophrenia patients exhibited similar levels of NSS as treatment-responsive schizophrenia patients, but the former group had increased NSS whilst the latter group had reduced NSS. The group difference in NSS progression over the 5 years remained significant, even after age and estimated IQ were controlled for.
Discussion: NSS may reflect the development of neuropathology in schizophrenia, and appeared to be more severe in schizophrenia patients who developed treatment resistance. The potential clinical utility of NSS as a predictor of treatment response should be further studied, using larger samples.

S7. EXAMINING THE ASSOCIATION OF HAIR CORTISOL LEVELS WITH A COMPREHENSIVE AND LONGITUDINALLY-DEFINED PHENOTYPE OF PERSISTENT STRESS-EXPOSURE AND STRESS-RELATED SYMPTOMS IN SCHIZOTYPY

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Background: There is clear evidence on the association between psychotic-spectrum disorders and elevated HPA activity, suggesting the HPA axis as a mediator of the effects of stress on psychotic symptoms. Specifically, elevated hair cortisol concentrations (HCC) have been found in clinical samples of persons with schizophrenia and bipolar disorder, First Episode of Psychosis (FEP) and clinical risk for psychosis. However, poor concordance between psychosocial stressors, stress-related phenotypes and cortisol levels has been found across high-risk and diagnosed psychosis groups. Consistently, Torrecilla and Barrantes-Vidal (2020) described for the first time that HCC was not cross-sectionally associated with a wide range of adversity measures and stress-related phenotypes in a sample with elevated schizotypy. It has been suggested that one of the explanations underlying this lack of psychoendocrine covariance might be that samples comprise individuals exposed to either very high or very low stress levels (clinical versus “super normal controls”, respectively). Additionally, there is scant research examining longitudinally the persistence of stress, which might be an essential feature for the disruption of the HPA axis and to make HCC a reliable indicator. Thus, we investigated the association between HCC and longitudinal trajectories of persistent perceived stress, recent life events, anxiety, depression and suspiciousness in a sample of nonclinical young adults oversampled for schizotypy.
Methods: This study is embedded in the ongoing Barcelona Longitudinal Investigation of Schizotypy Study (BLISS). From a large pool of unselected youngsters, a selected subgroup

oversampled for schizotypy scores continued regular follow-ups. A subtotal of 112 nonclinical young adults (mean age=27.93, SD= 2.29) had valid HCC data and completed assessments at three different time points (T1, T2, T3) for stress measures (perceived stress, threatening life events) and stress-related phenotypes (depression, anxiety and suspiciousness). Latent Class Analyses (LCA) were used to group individuals' longitudinal trajectories for each of the stress measures and stress-related phenotypes assessed and the classes obtained were compared on HCC with independent t-tests.

Results: One participant was excluded for abnormally increased HCC (244.6 pg/mg). Mean cortisol levels of the final sample of 111 participants were 6.44 pg/mg (SD= 5.17). There were not significant differences in HCC between males and females. LCA revealed two classes of longitudinal trajectories for each of the variables assessed (perceived stress, life events, depression, anxiety and suspiciousness): a Low versus Persistent group. However, neither the Persistent nor the Low groups of the different measures were significantly associated with HCC.

Discussion: The present results extent previous findings by adding evidence to the lack of concordance found between cortisol levels and stress-related measures, both cross-sectional and longitudinally assessed, in a sample of young adults oversampled for schizotypy scores. Still, supports previous evidence on the poor relationship between psychosocial stressors and cortisol found across other manifestations of the psychosis continuum such as clinical high-risk groups or established psychosis. Further studies across the nonclinical manifestation of psychosis are needed to study the predictive ability of hair cortisol and its relationship with stress, affective and psychotic spectrum related measures.

S8. TOXOPLASMA GONDII INFECTION AND CLINICAL CHARACTERISTICS OF PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Schizophrenia is associated with an increased prevalence of IgG antibodies against T.gondii (T.gondii seropositivity), whereby the infection seems to precede the disorder. However, it remains unclear whether a T.gondii infection affects clinical characteristics of schizophrenia. Therefore, a systematic review and meta-analysis was conducted following PRISMA guidelines examining the association between T.gondii seropositivity and severity of total, positive, or negative symptoms or age of onset in schizophrenia.

Methods: PubMed, Embase and PsycInfo were systematically searched up to 23rd of June 2019 (PROSPERO #CRD42018087766). Random effects models were used for analysis. Furthermore, influence of potential moderators was analyzed. Indications for publication bias were examined.

Results: From a total of 934 reports 13 studies were included. No overall effect on severity of total, positive or negative symptoms was found. However, in patients with a shorter duration of illness T.gondii seropositivity was associated with more severe positive symptoms (Standardized Mean Difference (SMD)= 0.32; $p< 0.001$). Similar but smaller effects were seen for total symptoms, while it was absent for negative symptoms. Additionally, a significantly higher age of onset was found in those with T.gondii seropositivity (1.8 years, $p= 0.015$), although this last finding was probably influenced by publication bias and study quality.

Discussion: Taken together, these findings indicate that T.gondii infection has a modest effect on severity of positive and total symptoms in schizophrenia among those in the early stages of the disorder. This supports the hypothesis that T.gondii infection is causally related to schizophrenia, although more research remains necessary.

S9. GLI3 AS A MODULATOR OF BRAIN AND FACE DEVELOPMENT IN SCHIZOPHRENIA

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Background: Brain and face are both derived from the same ectodermal layer, thus, alterations in the brain may be reflected on the face. Disruptions in Sonic Hedgehog (Shh) signalling pathway, which is involved in brain and face development (Gallet, 2011), are suggested to leave an imprint in brain and face morphogenesis, acting as a risk factor for neurodevelopmental disorders such as schizophrenia (SZ) (Weinberger & Levitt, 2011). Within the Shh pathway, the GLI3 gene is responsible for Shh target genes downregulation (Sharan et al. 2017) and has been associated with the risk for SZ (Chen et al. 2015). Therefore, the study of Shh signalling pathway and the GLI3 gene, can improve the understanding of the integration between brain and face development and its implications for SZ.
This study aimed to assess the association between facial shape and neuroanatomical measures in patients with SZ and healthy controls (HC) and to test whether GLI3 modulates such relationship.

Methods: The sample comprised 134 subjects: 67 HC and 67 SZ patients matched by age, sex and premorbid IQ. Facial 3D reconstructions and neuroanatomical measures were obtained from 1.5T MRI scans. To capture facial morphological variation, we recorded the 3D coordinates of 20 anatomical facial landmarks in each facial reconstruction using Amira 5.2. Neuroanatomical measures (thickness, volume and area) were obtained from the grey-matter segmentation of 34 ROIs performed with FreeSurfer. In 96 subjects (45 HC and 51 patients), the SNP rs3735361 (located in the 3'-UTR region of GLI3) was genotyped with TaqMan qPCR. Geometric Morphometrics and multivariate statistical techniques were used to assess the influence of cortical regions on facial shape between SZ patients and HC. A three-way interaction between genotype, cortical regions and diagnosis on global facial shape was also tested by Procrustes ANOVA tests.

Results: The analyses revealed significant associations of specific brain measures with facial shape, such as superiorfrontal region thickness ($p=0.044$) and volume ($p=0.035$), which explained 1% of facial shape variance. These associations were not conditional to the diagnosis. When the GLI3 genotype was included in the ANOVA model, a significant interaction effect of superiorfrontal area, diagnosis and genotype on global facial shape was found ($p=0.001$). This interaction explained up to 4.8% of total facial shape variance.

Discussion: Our findings on the relationship between superiorfrontal region thickness and volume with global facial shape support the notion of global facial shape as an indirect

neuroanatomical marker. The detected three-way interaction of brain superiorfrontal area, diagnosis and GLI3 gene on facial shape suggests the role of this gene as a modulator of brain and face development in SZ. These results are in line with previous evidence on the impact of disruptions in the expression of GLI3, as well as in its epistasis with SHH gene, on alterations in the cytoarchitecture of the neocortex during mid-gestation (Shimada et al. 2019). Further analyses with larger samples are needed to confirm that alterations in the expression of genes that control neurogenesis and corticogenesis processes may result in subtle brain alterations, which later may become a risk factor for SZ (Clifton et al., 2019).
Acknowledgements: i) CP20/00072 contract to MF-V (ISC-III, ERDF/ESF "Investing in your future") and, ii) the Comissionat per a Universitats i Recerca del DIUE, of the Generalitat de Catalunya regional authorities (2017SGR1271 and 2017SGR1630 research groups; AGAUR). (* N Martínez-Abadías and M Fatjó-Vilas share senior authorship).

S10. NEGATIVE SYMPTOMS IN LATER-ONSET FIRST-EPISODE PSYCHOSIS: THE RELATIONSHIP WITH DOPAMINE SYNTHESIS CAPACITY

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Background: Elevated dopamine synthesis capacity (DSC) has been demonstrated in first-episode later-onset psychotic disorders, such as in schizophrenia (SZ) and delusional disorder (DD). DSC has been linked to the severity of positive symptoms and level of responsiveness to treatment. Negative symptoms represent important features of psychotic disorders and one of the key determinants of long-term outcomes, it is yet uncertain how DSC may be associated with negative symptoms in later-onset psychosis patients.
Methods: Using a prospective cohort of 23 patients with first-episode psychosis (12 SZ and 11 DD, age- and gender- matched) who received an 18F-DOPA positron emission tomography (PET) scan within one month of antipsychotic treatment, we tested the relationship between baseline striatal DSC (Kocc;30–60 value) in the putamen and caudate regions and negative symptoms (total and subscale scores of the Scale for the Assessment of Negative Symptoms, SANS) at baseline and at 3-month and 6-month follow-up.
Results: In SZ patients, Kocc;30–60 in the putamen region showed a positive trend with baseline SANS Avolition-Apathy subscale score (rho=0.527, p=0.078), while Kocc;30–60 in the caudate region showed a negative trend with baseline SANS Affective Flattening (rho=-0.503, p=0.095). At three months, significant negative correlations were observed between Kocc;30–60 and SANS total (average caudate: rho=-0.800, p=0.010), as well as the SANS subscales of Anhedonia (average putamen: rho=-0.684, p=0.042), Attention (average caudate: rho=-0.730, p=0.025), and Affective Flattening (average caudate: rho=-.839, p=0.005). Importantly, the relationship between DSC and negative symptoms (indexed by SANS total) was still observable at 6-month follow-up in the putamen region (rho=-0.632, p=0.050). No such relationships were observed for DD patients (p>0.05).
Discussion: Striatal dopaminergic function in first-episode psychosis plays an important role in determining negative symptoms in SZ patients. Our data suggests that DSC levels are related to negative symptom outcomes in later-onset SZ. The relationship between DSC and negative

symptoms is less clear at baseline, possibly reflecting the impacts of positive symptoms on secondary negative symptoms expression. The relationship became clearer as the psychosis subsided and it appeared to be specific to SZ and is not shared in DD. Our findings added to existing studies to show that in addition to the expected role of dopamine in determining positive symptoms, DSC is also predictive of negative symptom outcomes in later-onset SZ.

S11. PATTERNS OF BRAIN STRUCTURE AND COGNITION IN TREATMENT RESISTANT SCHIZOPHRENIA AND HEALTHY CONTROLS - A MULTIBLOCK PARTIAL LEAST SQUARES CORRELATION ANALYSIS

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Background: Schizophrenia is a heritable brain disorder with brain structural deficits and cognitive dysfunction as independent predictors for poor clinical outcome. In those with severe and chronic schizophrenia, the interplay between patterns of cognitive deficits and brain structural abnormalities remain unclear.

Our aim was to investigate brain structural-cognitive patterns in patients with treatment-resistant schizophrenia (TRS), non-affected, first-degree relatives (NAR) and matched healthy controls (HC) by employing a multiblock partial least squares correlation (PLS-C) technique, which is an extension of the commonly used 2-block PLS-C method. Multiblock PLS-C enables to detect multivariate structure-cognition patterns across ≥2 groups, by constructing multiple latent variables (LVs) (weighted combinations of original variables) whilst allowing for covariate representation in the latent space. The detailed description of multi-block PLS-C can be found elsewhere (Syeda et al, to be submitted to ISMRM-21). Here, we present findings from the two-group (HC/TRS) and three-group (HC/NAR/TRS) PLSC-C analyses.

Methods: Forty-one TRS patients (age 38.6±9.1, 30 males (M), 11 females (F)), 45 HC (age 40.3±10.7, 29 M; 16 F), and 23 NAR (age 47.5±15.5, 7 M, 16 F).

Structural magnetic resonance images were acquired using a 3T Siemens Trio scanner. Regional volumes were estimated using FreeSurfer and Desikan-Killiany atlas (68 regions). Seven variables from CANTAB covering four cognitive domains were included: Intra-Extra Dimensional Set Shift (IED), Paired Associates Learning (PAL), Spatial Span (SSP), Spatial Working Memory (SWM).

Group differences were initially tested using univariate methods controlling for age and gender where appropriate. Two-group (HC/TRS) and three-group (HC/NAR/TRS) multiblock PLS-C analyses were performed to identify differences in patterns along latent structure-cognition dimensions. Age, gender, total intracranial volume, body mass index and premorbid IQ were used to construct covariate blocks.

Results: Compared to HC and NAR, individuals with TRS displayed significantly lower brain volumes across various 46/48 brain regions (p-values <0.05), and worse performance in all cognitive domains (p-values <0.05).

The two-group PLS-C analyses between regional brain volumes and cognitive variables were significant (omnibus test, p<1e-6. Two significant LVs explained 93.2% of block covariance in total.

LV1 (p<1e-6, variance explained: 83.3%) showed similar volume-cognition patterns between groups, with the majority of brain regions and all cognitive variables contributing reliably to the pattern.

LV2 (p=0.001, 9.9% of variance) showed a strong differential (orthogonal) pattern of associations distinguishing TRS patients and HC. The pattern of LV2 showed that PAL and IED intra-dimensional set shifting mapped strongly to widespread brain regions.

Three-group PLS-C identified a single significant LV (p=1e-6, variance explained: 73.23%), with IED, SWM and SSP variables mapping strongly to the pattern of regional volumes.

Discussion: Our multiblock PLS-C analyses suggest a widely shared pattern of cortical-cognitive relationship in TRS patients and HC, which explained >80% of the variance. However, 10% of the cortical-cognitive relationship revealed a differential pattern of relationships between TRS and HC. This pattern appears specifically driven by PAL and IED across multiple brain regions, which are more severely affected as the illness becomes more chronic and deteriorate over time. These findings provide evidence of a dissociable pattern of brain structure to cognitive in schizophrenia which may provide a marker of TRS.

S12. IDENTIFICATION OF PANSS ITEMS OF PARTICULAR CHALLENGE TO RATERS IN ADOLESCENT SCHIZOPHRENIA CLINICAL TRIALS: EXPANSION OF INITIAL FINDINGS

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Background: Global regulatory initiatives have resulted in an increasing number of psychopharmacology trials in the pediatric age range. Among the challenges in ensuring valid and reliable data in such trials are developmental limitations in symptom description, the need to integrate and weight information from varied sources including parents/caregivers and other informants, and the global shortage of child-trained clinical investigators (Busner, 2013; Farchione, 2013). Moreover, few efficacy measures have been developed and validated specifically for pediatric trials. As a result, measures designed for and validated in adults such as the Positive and Negative Syndrome Scale (PANSS) are frequently used in adolescent schizophrenia trials. The PANSS is a complex 30-item measure that has been extensively studied and shown to pose ratings challenges even in the adult patients for whom it was designed (e.g., Daniel and Dries, 2013).
To identify PANSS items for which raters in pediatric trials might have particular difficulty, we examined and reported PANSS item scoring variability of 171 worldwide raters from several large adolescent schizophrenia trials who had watched one of two standardized patient videos (Busner, Daniel, Findling, 2013). We have since secured data from 2 additional sponsors' international adolescent schizophrenia trials, with 2 additional standardized videos and 237 additional raters, allowing for new analyses and expansion of our initial findings.

Methods: Using data from multiple adolescent schizophrenia clinical trials by multiple sponsors, standard deviations were calculated for each of the 30 PANSS items scored by 408 clinical trials investigators/raters from 23 countries who had viewed one of four separate

standardized adolescent patient videos as part of the qualification process for their respective clinical trial. The clinical trials investigators/raters had been trained extensively in live sessions on adolescent-specific conventions immediately prior to viewing and scoring the video. PANSS item standard deviations from each video, separately, were calculated and rank ordered from lowest to highest variability. The variability rank order of the 30 PANSS items for each of the 4 videos was then compared across videos using Kendall W.

Results: The variability (SD) rankings of the 30 PANSS items for the 4 videos was statistically similar, Kendall W=0.57, p<.0001. Three PANSS items were ranked among the 10 most variable in all 4 videos: N4 (Passive/apathetic social withdrawal), P7 (Hostility), and P4 (Excitement), and two PANSS items were ranked among the 10 least variable in all 4 videos: P3 (Hallucinatory Behavior), and G14 (Preoccupation).

Discussion: Scoring variability of a standardized video reflects lack of agreement among raters and suggests challenges in item scoring. Identification of PANSS items that reflect scoring challenges and scoring disagreement for pediatric trials investigators allows targeted training and in-study intervention to help improve consistency. The work extends our earlier findings despite the addition of 2 new videos and 11 new countries. Item variability rankings across four different adolescent videos were statistically similar, suggesting that scoring ease or difficulty of individual PANSS items is independent of the specifics of the patients rated. As occurred with our earlier work, the high variability items in these adolescent videos continue to differ from those noted in with videos of adults (Daniel and Dries, 2013), making even more clear the need for focused attention and perhaps modification for these items when applied to the pediatric age range.

S13. DECREASED TEMPORAL ACUITY WITHIN AND ACROSS VISUAL AND AUDITORY MODALITIES IN ADOLESCENTS WITH EARLY-ONSET SCHIZOPHRENIA

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Background: Individuals with schizophrenia have difficulties in integrating multisensory information into coherent perceptions. One form of multisensory dysfunction is a bias to perceive temporally separate events as occurring simultaneously. This widened temporal binding window (TBW) (i.e., lower sensitivity of detecting asynchrony) may contribute to abnormal perceptual experiences and disorganized symptoms. However, previous studies primarily focus on adult patients with schizophrenia. Given the developing sensory system in children and adolescents, it is worthwhile to investigate whether multisensory temporal integration is altered in adolescents with early-onset schizophrenia (EOS).

Methods: Thirty-one patients with EOS (Mean age = 14.84 years, S.D. =1.37; 10 males) were compared with 30 age-matched typically-developing (TD) controls (Mean age = 14.20 years, S.D. =1.32; 11 males) using temporal order and simultaneity judgement tasks within and across visual and auditory modalities. Eye-tracking data were also acquired when participants were viewing a split-screen video of two identical females speaking side-by-side, with only one of the speaker's mouth movements in synchrony with the sound track. The synchrony might change between the two sides every few seconds and participants were asked to look for and watch the synchronous speaker.

Results: Compared with TD individuals, patients with EOS required longer time intervals to correctly tell the temporal order of unisensory stimuli (Cohen's d = 0.64 and 1.06 for visual and auditory temporal acuity, respectively). They also exhibited abnormally widened audiovisual TBWs for both non-speech (Cohen'd = 1.78) and speech (Cohen'd = 1.52) stimuli, which could not be fully explained by slower unisensory temporal processing. Wider multisensory TBWs were correlated with lower IQ in the EOS group (r = -0.53 and -0.50 for non-speech and speech stimuli, ps < .01) but not in the TD group. When watching videos of fluent speech, EOS patients viewed significantly less at the synchronous speaker than their TD peers and spent more time gazing at irrelevant non-facial regions. Percentage of viewing time at the synchronous speaker was negatively correlated with the severity of negative symptoms (r = -0.579, p =.006; n = 21), especially avolition (r = -0.566, p =.008) of the SANS.
Discussion: Reduced temporal acuity is a general feature of patients with EOS, ranging from unisensory to multisensory modalities, and also from non-speech to speech stimuli. Moreover, impaired audiovisual temporal integration is not just a reflection of altered unisensory temporal function but also an indicator of impaired general cognitive abilities in schizophrenia. Using complex and ecologically-valid linguistic stimuli, patients with EOS fail to show a preference for temporally congruent audiovisual information, which may have a cascading effect on negative symptoms of schizophrenia.

S14. PERIPUBERTAL STRESS PRODUCES AGE-DEPENDENT, STRESSOR-SPECIFIC, AND SEXUALLY-DIMORPHIC CHANGES IN DOPAMINE SYSTEM RESPONSIVITY AND CORTICOAMYGDALAR CONNECTIVITY

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Background: Early-life stress is associated with increased risks for schizophrenia. Our previous work suggested that adolescence might be a critical period for stress to induce long-term dopamine hyperresponsivity resembling psychosis. However, the temporal boundaries and the potential sex differences of this developmental vulnerability are unclear.
Methods: Male and female Sprague-Dawley rats were stressed over a 10-day period during prepuberty (postnatal day [P] 21-30) or postpuberty (P41-50). The stress protocols involved either repeated daily foot-shock (FS; 1 mA/2 s, 20–60 s random interval; 25 sessions), one-hour restraint stress (RS), or their combination (FS+RS). At 1-2 and 5-6 weeks post-stress, dopamine system responsivity in the ventral tegmental area (VTA) and prefrontal inhibitory control of the putative pyramidal neurons in the basolateral amygdala (BLA) were assessed by in vivo electrophysiology.
Results: In males, prepubertal FS or FS+RS increased dopamine population activity in the VTA 1-2 and 5-6 week post-stress, consistent with observations in models of schizophrenia. In contrast, postpubertal FS+RS decreased VTA DA neuron population activity only at 1–2 week post-stress, consistent with observations in animal models of depression. Moreover, none of the P41-50 stressors was able to alter dopamine neuron population activity in adults, suggesting overall male resilience to the long-term effects of postpubertal stress. In females, both prepubertal and postpubertal FS or FS+RS produced estrous cycle-dependent changes in the VTA dopamine system 1-2 and 5-6 week post-stress, and an increase in dopamine neuron population activity was present only in peripubertally stressed females at proestrus and estrus stages.
To assess adaptive stress responses in the amygdala, the inhibitory control of the medial prefrontal cortex (mPFC) over the BLA pyramidal neurons was measured. In naive males and

females, high-frequency stimulation (HFS) of the mPFC induced long-term depression (LTD) of evoked spikes in the BLA pyramidal neurons in adults (P65-74) but not in adolescents (P37-44), indicating maturational changes of the mPFC-BLA inhibitory circuitry. In contrast, our preliminary data suggest that prepubertal FS or FS+RS stress induced an adult-like mPFC-BLA LTD 1-2 week post-stress (P37-44) but an LTD deficit 5-6 weeks post-stress (P65-74). Moreover, in males and females exposed to postpubertal FS or FS+RS stress, only a transitory reduction in the mPFC-BLA LTD was found 1-2 weeks post-stress (P57-64), which did not persist after 5-6 weeks (P85-92).

Discussion: This dataset indicated that prepuberty and postpuberty might represent two distinct windows of vulnerability to stress-induced, psychosis-related dopamine dysregulation. Moreover, the stress-induced pathophysiology in the dopamine system in females appeared to be more pronounced in proestrus and estrus stages with presumably high levels of circulating sex hormones. Prepubertal stress induced precocious maturation of the mPFC-BLA circuit, which might contribute to the adult deficits in the PFC-BLA inhibitory control. Altogether, this dataset revealed that age, stressor-type, and sex might be important determinants of the susceptibility to psychosis-related dopamine dysregulation.

S15. COMPARISON OF MEAN SEVERITY OF THE PANSS AT SCREENING IN SCHIZOPHRENIA TRIALS PRIOR TO AND AFTER ONSET OF THE COVID-19 PANDEMIC

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Background: The impact of the COVID-19 pandemic on the severity and stability of psychopathology in schizophrenia and other psychiatric disorders is sparsely addressed in the current psychiatric literature. There is considerable potential for pandemic induced changes in psychopathology to influence both routine clinical treatment as well as clinical trial outcomes and interpretation. As part of our initial exploration of this issue we compared the severity of screening PANSS scores in schizophrenia clinical trials before and after the onset of the COVID pandemic.

Methods: Data were collected from currently ongoing schizophrenia clinical trials that started before the COVID-19 outbreak. Data were pooled together irrespective of schizophrenia subtype. We arbitrarily set the reference date to separate pre-COVID-19 data from those after COVID-19 outbreak to be the date when WHO declared the pandemic, March 11, 2020. To assess the impact of COVID pandemic on the symptom presentation at screening we utilized Wilcoxon rank-sum test for equality of distributions.

Results: The current dataset consists of 2,232 datapoints collected in the screening period, 1,253(56%) collected before and 979(44%) collected after the reference date. Significant differences in item severity distributions between data collected before and after the COVID-19 pandemic declaration were identified in 24/30 PANSS items, of those the average symptom severity did increase in 23 items and decreased in 1 item.

Discussion: After the onset of the COVID-19 pandemic we observed a statistically significant increase in severity of schizophrenic psychopathology across multiple symptom domains in the PANSS. The etiology is unclear. Among the potential explanations are the impact of social distancing or other psychosocial or environmental factors. An impact of the COVID-19 virus directly on psychopathology in a subgroup of subjects cannot be ruled out. Our analysis is preliminary and will be updated with larger samples.

S16. LONG-TERM SAFETY OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 2 AND 3 STUDIES

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Background: Antipsychotic medications are commonly used in maintenance therapy regimens for a variety of psychiatric conditions. As a result, patients may require chronic treatment; therefore, it is critical to evaluate safety and tolerability of new antipsychotic treatments over extended durations. A combination of olanzapine and the opioid antagonist samidorphan (OLZ/SAM) is being developed for the treatment of schizophrenia and bipolar I disorder. OLZ/SAM provides the efficacy of olanzapine while mitigating olanzapine-associated weight gain. Here, the long-term safety and tolerability of OLZ/SAM (up to 3 years) are reported from a pooled analysis of patients with schizophrenia from 6 clinical studies.

Methods: Data for patients exposed to OLZ/SAM in 1 of 3 blinded controlled studies and/or in 3 associated open-label safety extension studies were pooled and integrated to evaluate the long-term safety profile of OLZ/SAM. Baseline refers to pre-treatment status before initiating treatment with OLZ/SAM. Safety assessments reported here include adverse events (AEs), vital signs, and laboratory evaluations.

Results: Safety data from 831 patients (mean age, 41.4 years) were included. The median (range) OLZ/SAM exposure was 324.0 (1–1126) days. A total of 541 patients (65%) received OLZ/SAM for ≥6 months; 386 patients (46.5%) received OLZ/SAM for ≥52 weeks. The overall exposure to OLZ/SAM from baseline up to the data cutoff date of April 1, 2019 was 814.5 patient-years. AEs occurred in 67.7% of patients; those reported by ≥5% of patients included weight increased (18.9%), somnolence (12.8%), dry mouth (7.3%), headache (6.5%), and extra dose administered (5.1%; these extra doses were accidentally taken by patients and reported as AEs). In the majority of patients, AEs were mild or moderate in severity (35.5% and 27.8%, respectively). The onset of most AEs occurred between 4 and 24 weeks from OLZ/SAM initiation. Severe AEs were reported by 4.5% of subjects. AEs leading to treatment discontinuation occurred in 10.0% of patients; those occurring in ≥1% of patients included worsening/exacerbation of schizophrenia (1.6%) and glycosylated hemoglobin (HbA1c) increased (1.3%; HbA1c ≥6.5% was a discontinuation criterion). Serious AEs (SAEs) were reported in 37 (4.5%) patients, most commonly exacerbation of schizophrenia (1.4%). Evaluation of AEs of special interest, based on the known risks of olanzapine and effects associated with opioid antagonists, did not suggest any increased risks associated with OLZ/SAM compared with the known risks of olanzapine. Weight increased over the first 4 to 6 weeks of treatment and then stabilized, with limited subsequent weight gain (mean change was 1.73 kg at week 6, 2.20 kg at week 52, and 3.13 kg at week 104). Changes in metabolic laboratory parameters were generally small and stabilized with long-term treatment.

Discussion: OLZ/SAM was well tolerated in adults with schizophrenia for up to 3 years of treatment.

S17. VIRTUAL REALITY FOR IMPROVING SOCIAL ACTIVITIES AND PARTICIPATION (VR-SOAP): DEVELOPMENT OF A NEW TREATMENT FOR YOUNG PEOPLE WITH PSYCHOSIS

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Background: Young people with a psychotic disorder have the same social goals as their healthy peers, but their social networks are smaller, they participate less often in leisure activities and are less successful in work and education. Current treatments have only moderate effects on social functioning. Virtual Reality (VR) has a great potential to improve the social functioning of young people with psychosis. With VR, individuals can practice with simulations of difficult social situations in a safe and personalized way. Therefore, we aimed to develop and investigate feasibility of a novel VR treatment (VR-SOAP) for improving social contacts, leisure activities and social participation of young people with a psychotic disorder.
Methods: As a first step, a literature search of causes of impaired social functioning was conducted. Underlying relationships and mechanisms of the causes were identified. The causes of impaired social functioning were translated into concepts for the VR modules. The concepts were translated into requirements for the VR modules. Subsequently, the software and the treatment manual were developed in an iterative process with a team of experiential experts, psychosis therapists, researchers, VR experts and software engineers. The final prototype will be tested in a small pilot study with three therapists and six patients. In order to determine the feasibility and acceptability of the treatment and to evaluate and improve the treatment protocol using input from therapists and patients.
Results: Several determinants of impaired social functioning were identified: negative symptoms, impaired social cognition, paranoid ideations, social anxiety, low self-esteem, self-stigma and poor communication skills. These causes are multifaceted, but at the same time interrelated and overlapping. VR-SOAP was designed as five modules that address these causes, four optional modules (1-4) and one fixed module (5). The treatment is personalized and takes the specific individual contributing causes into account. Patient and therapist select two out of four optional modules. In module 1 (Negative symptoms) patients will focus on increasing their motivation and pleasure in dealing with amotivation and anhedonia. In module 2 (Social cognition) patients will practice with recognizing facial emotions and interpreting social situations. Module 3 (Paranoid ideations) consists of exposure exercises and behavioural experiments testing harm expectancies. In module 4 (Self-esteem and self-stigma) patients will focus on positive aspects of the self and challenge self-criticism. All patients will end with module 5 (Communication and Interaction skills), in which experiences, knowledge and skills from other modules are integrated and applied in role-plays. Currently, the pilot feasibility study is ongoing. Preliminary results will be presented.
Discussion: VR-SOAP is a promising new intervention for enhancing the social functioning of young adults with psychosis. VR is very useful for practicing new social behaviour. It enables patients to practice with real-world social situations in a safe and gradual way. In the coming years, a single-blind randomized controlled trial will be conducted to test the effect of VR-SOAP on social contacts, leisure activities and social participation.

S18. DIURNAL VARIATION OF SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Altered levels of morning cortisol (Berger et al 2016; Girshkin et al 2014) and sleep abnormalities at night (Kaskie et al 2017) have been reported in individuals with schizophrenia and linked to prominent features of the disease, such as psychosis, emotional reactivity, social withdrawal, and psychomotor agitation. These factors may influence severity of symptoms; however, there has been limited systematic investigation of schizophrenia symptoms at different times of day. The current study aims to examine the symptom severity of schizophrenia in the morning compared to afternoon, using a dataset derived from a double-blind, active-controlled, fixed-dose, randomized, global clinical trial in patients with treatment-resistant schizophrenia. To establish presence of treatment resistance, subjects had to have a documented lack of response to an antipsychotic treatment trial within the previous two years. Washout of disallowed medications was initiated after informed consent had obtained. Each subject had a Positive and Negative Syndrome Scale (PANSS) total score of ≥80 and a score of ≥4 on at least 2 of the following PANSS items at screening and at baseline visits: P2-Conceptual disorganization, P3-Hallucinatory behaviour, P6- Suspiciousness/persecution, G9-Unusual thought content.
Methods: There were 1508 subjects in the study, and 1106 of them completed both screening and baseline visits. Since exposure to the assigned drug treatment might affect the PANSS scores, only screening and baseline visits were included in this analysis. In addition, we focused on 16 PANSS items (P2, N1, N3, N5, N6, N7, G1, G2, G3, G4, G9, G10, G11, G12, G13, and G15) that are rated based only on observation during the interview. The other items are rated based on the behavior that occurred over the past week and not relevant to this study. The start times were separated in two groups: Morning (prior to noon) and Afternoon. First, ANOVA tests were conducted to examine the difference of PANSS scores across groups at different visits and with different start times. Then, for each visit, PANSS item scores between morning and afternoon groups were analyzed by t-test.
Results: Eight items rated based on observation during the interview (P2, N1, N3, N6, N7, G11, G13, G15), PANSS Total, PANSS Negative Total and PANSS General Total score are significant for main effect of start time ($p<.05$). All of those interaction effects are insignificant from screening to baseline, which shown a consistent trend of difference between two start time groups across visits. While Items; P2, N6, G11, G13, G15, PANSS Total, PANSS Negative Total, PANSS General Total scores were significantly higher in the morning ($p<.05$) during the screening visit, no significant difference in scores between morning and afternoon were found at Baseline. The results show that eight items are sensitive to time of day and they tend to have higher scores in the morning.
Discussion: Observational items were found to have significant differences based on the time of day that the PANSS was administered, suggesting time as a variable could be an influential factor on total score and item severity scores. Limitations to the study include that time of medication administration was not controlled on the day of screening and baseline visits and these findings may be applicable to only certain groups of schizophrenia patients with treatment resistance.

S19. ATHENS MULTIFAMILY THERAPY PROJECT

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Background: The Athens Multifamily Therapy Project (A- MFTP) aims to provide systemic multifamily group therapy to youths who experienced a first psychotic episode (FEP) and their families. During the Covid-19 pandemic, the provision of therapy to the current groups continued through online sessions.
Methods: The participants were recruited from the longitudinal study, Athens FEP Project, which aimed to investigate the involvement of genetic and environmental determinants on psychosis risk. Since the beginning of the project in 2017, we run four groups. Each of them included four to six families attending a 2-hour group session twice a month. Sessions were conducted by two therapists plus one therapist with the role of external observer and session notes keeper. Supervision meetings to the team were provided once a month. Among other questionnaires, participants were asked to answer qualitative questions on the perceived effectiveness of the therapy on their life as well as on the presenting problem(s) at three time points: middle, end of therapy and 6-month follow-up.
Results: The families' social network increased and perceived social isolation decreased. Participants reported they mostly learned through the experience of others. The therapeutic process developed with active involvement of all participants: the patients, their parents and siblings, and the therapeutic team. It might be described as a immediate, humane and democratic therapy, which conveys the message that families are all "on the same boat", with the therapists taking a dialogical role beside them, on the same level, learning from their stories.
Discussion: Psychosis can affect all aspects of a person's life and, without support and appropriate care, it can place considerable weight on the patient's relatives, as well as the community in general. Our suggestion is that MFGT can be a viable way to support the whole system facing psychosis, with the aim of preventing relapse and implementing quality of life of all the participants.

S20. EFFICACY OF LUMATEPERONE (ITI-007) IN DEPRESSION SYMPTOMS ASSOCIATED WITH SCHIZOPHRENIA

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Background: In patients with schizophrenia, depression symptoms are often prevalent, even in stable patients following antipsychotic treatment. Depression associated with schizophrenia is linked to poorer patient outcomes, including increased risk of relapse and suicidality, worse functioning, and decreased quality of life. Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel agent for the treatment of schizophrenia that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. This mechanism of action may confer beneficial effects in treating depression symptoms associated with schizophrenia.
The efficacy, safety, and tolerability of lumateperone in schizophrenia was established in randomized, placebo-controlled studies. An open-label study (Study 303) in stable schizophrenia patients switched from prior antipsychotic (PA) treatment to 1 year of lumateperone 42 mg further supported the long-term effectiveness and safety of lumateperone.

This post hoc analysis of Study 303 evaluated the effects of lumateperone 42 mg across the range of depression symptoms in stable patients with schizophrenia.

Methods: Depression symptoms in Study 303 were assessed using the Calgary Depression Scale for Schizophrenia (CDSS). This scale comprises 9 items that are scored 0 (absent) to 3

(severe). Analyses were conducted in patients with moderate-to-severe depression symptoms (CDSS≥6) at baseline. Mean change from baseline was analyzed with a paired t-test. A responder analysis (≥50% improvement from baseline) was also conducted.
Results: The overall population comprised 602 stable schizophrenia patients, of these, 80 patients had moderate-to-severe depression symptoms (CDSS score ≥6). Mean CDSS score in these patients was 7.6 (range 6-16). At the end of treatment (EOT) mean change from baseline was −4.8 (P<.0001); mean CDSS score was 2.4. In stable patients with CDSS score ≥6 at baseline, 50% responded by EOT. Improvements were seen in patients with and without concomitant antidepressant treatment.
Depression (Item 1) and Early Awakening (Item 7) were the most prominent symptoms at baseline (mean scores 1.5 and 1.1, respectively); Suicide (Item 8) was the least severe (0.1). At Day 75 (earliest on-treatment assessment), all CDSS items showed significant improvement (P<.05 to P<.0001) from baseline. The magnitude of improvement for all items increased from Day 75 to EOT (Day 368). The largest improvement was for Item 2 (Hopelessness; change from baseline=−0.8); 5 CDSS items showed marked improvements (−0.6) including Item 1, Item 3 (Self Depreciation), Item 5 (Pathological Guilt), Item 6 (Morning Depression), and Item 7.

Discussion: In stable schizophrenia patients with moderate-to-severe depression, lumateperone 42 mg significantly improved a broad range of depression symptoms. Clinically meaningful improvement of depression symptoms was achieved in 50% of patients. These results support the benefits of lumateperone 42 mg in treating depression symptoms associated with schizophrenia.

S21. REDUCED HIPPOCAMPAL VOLUME AND IMPAIRED VERBAL MEMORY FOLLOWING A FIRST-EPISODE PSYCHOSIS

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Background: Research on schizophrenia has shown significant impairment of verbal memory and a reduction in hippocampal volume, yet it is unclear when these changes occur. Longitudinal examination in a cohort of young people who have experienced a first episode of psychosis (FEP) allows us to better determine the onset of such phenomena. Our main objective was to examine whether verbal memory performance and volume of the hippocampus and subfields change over time in FEP patients compared to controls. We hypothesized that patients would show a more pronounced decrease in verbal memory performance and in hippocampal volume than controls.
Methods: FEP patients, followed by the PEPP-Montreal clinic (N = 55), and controls (N = 54) completed a 3T MRI scan and a neurocognitive evaluation (CogState) at 3 and 6 months after admission.
Results: Multilevel analyses revealed a significant difference between patients and controls at baseline in verbal memory performance; t(71.6795) = - 4.926, p = 5.22e-06, with patients showing a lower performance compared to matched controls. Significantly reduced volume was observed in the right dentate gyrus subfield when comparing time point 1 and 2; t(83.502) = - 2.098, p = 0.0389, with a reduced subfield volume after 6 months in patients.

Discussion: Knowledge of a significant reduction in hippocampal volume at the onset in FEP shows that it is crucial to provide treatment at the onset of the first psychotic symptoms, which may not only reduce cognitive deficits but also eventually restore damaged neuronal pathways. Future research over a longer period of time may be needed to allow a more in-depth understanding of structure-function relationships with verbal memory. An exploration of brain plasticity following FEP may also be useful, since the detection of the disease and the introduction of an early treatment program can optimize the outcome of this debilitating disorder.

S22. COGNITIVE REMEDIATION ENHANCED BY AEROBIC EXERCISE CAN IMPROVE NEGATIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA: A RCT

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Background: Meta-analyses have shown that the effects of cognitive training in schizophrenia patients go well beyond improvement in cognition to include benefits such as negative symptom reduction and improvements in functioning. In addition, evidence from a meta-analysis demonstrates the potentially beneficial effects of exercise on symptoms in individuals with schizophrenia. We examined the effects of combining cognitive training plus aerobic exercise compared to cognitive training plus healthy living training on symptoms in first episode schizophrenia patients.

Methods: A RCT was used to compare Cognitive Training Plus Exercise (CT&E) to Cognitive Training Plus Healthy Living training (CT&HL) in 53 patients who had a first psychotic episode within two years of study entry, 64% of whom were male. The patients had a mean age (study entry) of 23.1 (4.4) years and a mean of 13.6 (1.9) years of education. The average age of onset of first psychotic symptoms was 21.5 (4.4). All participants were provided four weekly sessions of internet-based cognitive training and were randomized to receive (simultaneously) an aerobic exercise program or training in healthy living over a 6-month period. The two conditions were matched for time in the intervention. The expanded Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS) were administered by trained raters every 2 weeks to assess negative and positive symptoms.

Results: Using General Linear Mixed Models, the trajectory (slope) over the 6-month intervention showed improvement (decrease) that favored CT&E as compared to CT&HL for BPRS Negative Symptoms (Mean change = -0.29 vs +0.02, p=0.04) and for the SANS Experiential Symptom domain comprised of Avolition/Apathy (Mean change = -0.31 vs +0.74, p = 0.01) and Anhedonia/Asociality (Mean change = -0.55 vs +0.09, p=.02). SANS Affective Flattening showed a strong tendency in the same direction (Mean change = -0.44 vs +0.02, p = 0.06). However, there was no significant difference in the trajectory (slope) of positive symptoms over time (Mean change +0.01 vs +0.02, p = 0.66).

Discussion: Our findings suggest that the enhancing effect of adding aerobic exercise to cognitive training appears to extend to negative symptom improvement. Given these reductions in key negative symptoms that are related to motivation and social functioning, the chances of promoting recovery through this combined intervention is very promising in first episode schizophrenia patients.

S23. EXAMINING THE ROLE OF RACE IN THE RELATIONSHIP BETWEEN DISORGANIZATION AND COGNITIVE CONTROL PROCESSES ACROSS THE PSYCHOSIS SPECTRUM

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Background: Disorganization symptoms, such as formal thought disorder, are associated with a variety of cognitive impairments (Ventura et al., 2010). However, despite theoretical similarities, there is little evidence of a unique relationship between disorganization and cognitive control – executive processes that enable the regulation, coordination, and sequencing of thoughts and actions (Cohen et al., 1999; Miller & Cohen, 2001). This uncertainty is exacerbated by possible clinical rater bias. Research suggests patients with ethnic minority and immigrant identities are more likely to be diagnosed with schizophrenia than White counterparts with similar symptoms, and tend to receive higher severity ratings within the same diagnosis (Olbert et al., 2018; Schwartz & Blankenship, 2014; Strakowski et al., 1996). These disparities appear largely predicated on disorganization ratings that may reflect linguistic and behavioral deviations from the dominant culture, instead of pathological thought processes (Jongsma et al., 2020; Schwartz et al., 2019). Consequently, studies with inflated disorganization ratings for ethnic minority participants may suffer from increased false positives that suppress results Thus, this study aimed to examine the effect of controlling for race while examining the relationship between disorganization and cognitive control processes in the Dot Pattern Expectancy Task (DPX; MacDonald et al., 2008).

Methods: Analyses took place within an initial sample of 116 patients with schizophrenia (56 male, 44 Non-Hispanic White), 60 patients with schizoaffective disorder (46 male, 34 Non-Hispanic White), and 62 participants with bipolar disorder with psychotic features (22 male, 39 Non-Hispanic White). symptom severity was measured with the Brief Psychiatric Rating Scale (Overall & Gorham, 1962; Ventura et al., 1993). Participants completed 4 blocks of the DPX following the 'A-then-X' rule, in which 'target' sequences depicted an 'A' cue followed by an 'X' probe, and all other sequences were to be indicated as 'nontarget'. Goal maintenance was measured with d' context, the normalized difference between AX hits and BX false alarms (Servan-Schreiber et al., 1996). Prepotent response inhibition was measured with AY interference, the averaged difference between AY and AX hits (MacDonald et al., 2005).

Results: Preliminary findings indicate that the schizoaffective disorder group had the most severe ratings for each symptom category. Moreover, White schizoaffective disorder patients had significantly lower disorganization ratings than their Non-White counterparts. Future analyses will examine if the relationship between disorganization and DPX metrics changes with increasing psychosis severity, and if controlling for race affects these relationships.

Discussion: To our knowledge, this is the first study to systematically address racial bias as a source of noise for understanding the relationship between clinical symptoms and cognitive performance. By extension, this study will comment on the extent to which patterns in clinical ratings of psychosis severity might explain variance in subsequent findings.

S24. IDENTITY RECOGNITION FROM FACES AND BODIES IN SCHIZOPHRENIA

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Background: There is substantial evidence that individuals with schizophrenia have deficits in face recognition and processing. Previous research has revealed that the body is also an important factor in identity recognition, and is especially important in viewing conditions in which facial features are more difficult to detect (Rice, Phillips, Natu, An, & O'Toole, 2013). Given these findings, we hypothesized that individuals with schizophrenia would present with deficits in body perception as well and that these deficits would correlate with poorer emotion recognition.
Methods: Sixty-five individuals with schizophrenia and 49 non-psychiatric controls completed three versions of a person recognition task in which they attempted to match identities of unknown persons. Conditions included original photos, photos of bodies only, and photos of faces only (Rice et al., 2013). Individuals also completed assessments of emotion recognition from faces, the Penn Emotion Recognition 40 Task (Kohler et al., 2003), and bodies, the Body Emotion Recognition Task (Hajduk et al., 2020).
Results: Results showed that healthy controls performed significantly better than individuals with schizophrenia across all conditions ($F(1,112) = 149.29$, $p = <.001$). We also found that performance in both groups decreased across the three conditions ($F(1,112) = 429.153$, $p = <.001$), with performance being best when full bodies and faces were presented together and worst when bodily information was erased and only faces were shown. Performance for bodies alone was intermediary. Additionally, across groups, performance on each of the three conditions significantly correlated with better performance on both face and body emotion recognition tasks.
Discussion: These discoveries extend previous research indicating that patients with schizophrenia may have deficits in whole person recognition, rather than just face recognition. Findings also reveal relationships between identity recognition, emotion recognition, and body perception warranting further analysis into how these deficits may affect overall social functioning in individuals with schizophrenia.

S25. THE ATTENTIONAL CAPTURE OF SOCIAL VERSUS NONSOCIAL STIMULI IN SCHIZOPHRENIA: AN ERP STUDY

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Background: People with schizophrenia experience disturbances in social motivation that result in poor social functioning. One proposed mechanism underlying these disturbances is reduced social attention, defined as the bias to attend to social aspects of the environment. Studies of social attention in schizophrenia have not examined how social attention unfolds over time across multiple stages of processing. The current study examined specific processing stages associated with social versus nonsocial attention in schizophrenia using event-related potentials. We examined these three stages using a cued target detection task: (1) attentional orienting to social/nonsocial stimuli (indexed by the N1pc), (2) sustained attention and target response preparation (contingent negative variation [CNV]), and (3) target evaluation and response execution (P3). Additionally, we analyzed correlations between the ERP indices of attentional processing and participants' response time (RT) to the targets.
Methods: Electroencephalography from 36 clinically-stable outpatients with schizophrenia and 20 healthy participants was recorded. The cued target detection task had three conditions: social, nonsocial, or scrambled. Trials began with two images presented on opposing sides of

a central fixation cross. Social and nonsocial trials included one non-scrambled image with identifiable social or nonsocial information, along with a scrambled image. Scrambled trials included two scrambled images without visually identifiable information. After the images disappeared, participants were asked to identify the location of a target (two dots) on the right or left of the screen with a button press, as quickly and accurately as possible. The non-scrambled images appeared with equal probability on the left and right sides, as did the target. **Results:** First, both groups demonstrated larger N1pc to social and nonsocial vs. scrambled images (i.e., intact attentional orienting). Second, both groups had larger CNV (i.e., greater sustained attention) to social vs. nonsocial or scrambled images when preparing for the target [$F_{2,108} = 46.988$, $p < .001$, $\eta p2 = .465$]. However, participants with schizophrenia had lower CNV amplitudes to all stimulus types, compared with healthy participants [$F_{1,54} = 5.437$, $p = .023$, $\eta p2 = .091$]. Third, when locating the target and executing a response, both groups exhibited larger P300 amplitudes to social vs. nonsocial or scrambled trials [$F_{2,108} = 35.821$, $p < .001$, $\eta p2 = .399$]. Lastly, greater sustained attention (CNV) was associated with quicker RTs to the target for healthy participants (r's > .67), but not schizophrenia participants (r's < .21).
Discussion: Our study found aspects of social attention that were preserved in schizophrenia. Similar to healthy participants, schizophrenia participants oriented their attention to social stimuli (N1pc), showed a greater sustained attention to social images (CNV) than other image types, and were more primed for target evaluation and response execution on social trials (P3) than other trial types. However, some aspects of attentional processing were impaired. Schizophrenia participants showed diminished overall sustained attention (CNV) during the task, compared with healthy participants. Furthermore, greater sustained attention (CNV) was not associated with improved behavioral performance (faster RTs), as was the case for healthy participants. Together, these findings suggest there is a general deficit in sustained attention in schizophrenia, which may have implications for goal-directed social behaviors and real-world social motivation.

S26. PREMORBID IQ AND AGE OF ONSET CONTRIBUTION TO FUNCTIONAL, SYMPTOM AND COGNITIVE OUTCOMES IN FEP INDIVIDUALS

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Background: Heterogeneity in clinical, functional and cognitive outcomes among individuals with a first episode of psychosis (FEP) has been evidenced. Presenting with an early age of onset of psychotic (EOP) symptoms or a low average premorbid IQ (pIQ) have been associated with worse functional prognosis [1]. However, it is still unclear the longitudinal contribution of both factors over functional, clinical and cognitive performace over time. To clarify this issue, the present study aims to characterize FEP individuals in subgroups based on EOP and

pIQ and to examine functional, clinical and neurocognitive outcomes of participants at two-years follow-up.

1. Immonen, J., Jääskeläinen, E., Korpela, H., & Miettunen, J. (2017). Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. Early intervention in psychiatry, 11(6), 453-460.

Methods: A total of 326 healthy controls and 255 individuals with FEP (age 9-35) who completed the correspondent 2-year follow-up assessments from two Spanish clinical cohorts were included. Age of onset was recorded and estimation of premorbid IQ was conducted at baseline using the Spanish version of the vocabulary subtest of the WISC-IV (Wechsler, 1997) or WAIS-III (Wechsler, 2003) according to the age of participants. General functioning was assessed through the Global Assessment of Functioning Scale (GAF) [4] or the Children Global Assessment of Functioning Scale [5] respectively Clinical assessment was conducted using the Positive and Negative Symptom Scale PANSS [6]. Cognitive assessment was conducted using a extensive battery specifically designed to evaluate attention, processing speed, working memory, executive function and verbal memory domains. Raw scores were converted to z-scores relative to the healthy control group. The whole sample was divided in four subgroups based on both premorbid IQ (<85; Low-IQ; LIQ/ ≥85; normal IQ; NIQ) and the age of onset of positive symptoms (<18; early age of onset; EO/ ≥18; adult onset; AO). Clinical and neuropsychological outcomes were compared among the resulting groups (EO-LIQ; AO-LIQ; EO-NIQ; AO-NIQ) using ANOVA and chi-square tests, as appropriate.

Results: The EO-LIQ group presented with lower global functioning at baseline ($F=22.15$ $p < .001$) and at the 2-years follow-up ($F=6.64$ $p < .001$), higher positive ($F= 10.94$ $p < .001$) and total psychotic symptoms ($F= 6.66$ $p < .001$) at baseline, and higher positive ($F=3.03$ $p=.03$), negative ($F=3.88$ $p=.01$), general ($F=15.07$ $p < .001$) and total symptoms ($F=2.91$ $p=.03$) at 2-years follow-up in comparison to AO-NIQ and AO-LIQ. All FEP individuals demonstrated a cognitive performance 0.8-1.8 s.d below controls in attention, processing speed and executive functions domains. The AO-NIQ group demonstrated significantly better performance in all cognitive domain, whereas the EO-LIQ group displayed a widespread cognitive deficit profile with lower memory deficits (i.e. >2 s.d. below controls) than any of the other groups.

Discussion: Our results suggest that early presentation of psychotic symptoms in patients with under-average premorbid IQ may be an indicator of worse functional and symptom outcomes 2-years after the illness onset. Furthermore, these results suggest that verbal learning and memory impairments might aim to differentiate outcome trajectories in subjects presenting with FEP. According with our results age of onset and premorbid IQ at the moment at first episode of psychosis can be used as clinical reliable indicators of longitudinal functional prognosis.

S27. COGNITIVE SUBTYPES IN FIRST-EPISODE PSYCHOSIS PATIENTS AND THEIR RELATIONSHIPS WITH CLINICAL AND FUNCTIONAL VARIABLES

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Background: Cognitive impairment is a core feature of psychotic disorders and is associated with functional disability. Literature indicates that patients with psychotic disorders exhibit generalized cognitive dysfunction encompassing multiple cognitive domains. The current study aimed to clarify and disentangle the heterogeneity of cognitive impairment in first-

episode psychosis (FEP), as well as to investigate the relationships between cognitive subtypes and clinical and functional variables.
Methods: Three hundred and sixty Chinese adult patients aged 26-55 years, presenting with FEP to specialized early intervention program for psychosis (Jockey Club for Early Psychosis, JCEP program) in Hong Kong were recruited. A comprehensive clinical and cognitive assessments were conducted. Standardized z-score for each of the cognitive tests was computed based on performance of fifty healthy controls. Hierarchical agglomeration cluster analysis with Ward method was performed to identify separable cognitive sub-groups, which were then validated by external variables including demographics, premorbid adjustment, onset profiles, symptoms and functioning among clusters using analysis of variance.
Results: A total of 289 patients completed cognitive assessment and constituted the final study sample. Cluster analysis revealed three cognitive sub-groups. Patients in Cluster 1 (n=101) exhibited the worst cognitive performance across all cognitive tests, including severe impairment in digit span (WAIS-R), Modified Wisconsin Card Sorting test (MWCST) and category verbal fluency (1-1.5 SD below mean), and moderate impairment in digit symbol (WAIS-R), verbal and visual memory (WAS-R logical memory and visual reproduction subtests) (within 1 SD below mean). Cluster 2 (n=76) was characterized by normal cognitive performance in all domains (0-1 SD above mean). Patients in Cluster 3 (n=112) showed mild-to-moderate impairment in digit symbol, verbal memory and verbal fluency (within 1 SD below mean), but no deficits in other cognitive domains (0-0.5 SD above mean). Comparison analyses revealed that patients in Cluster 1 had significantly older age at onset of psychosis, lower educational attainment, greater positive, negative and disorganization symptom severity, poorer insight and lower levels of functioning than those in Cluster 2. Patients in Cluster 2 also displayed significantly better functioning and higher education levels than the counterparts in Cluster 3. Compared with Cluster 3, Cluster 1 was associated with significantly greater severity in positive symptoms, disorganization and amotivation.
Discussion: Cognitive sub-grouping provides a clinically useful approach in reducing heterogeneity of FEP patients. Differential relationships between cognitive subtypes and clinical and functional variables facilitate early identification of patient subgroup with potentially poorer prognosis with subsequent provision of effective intervention to promote early functional recovery.

S28. PRELIMINARY STUDY ON PREFERENCE FORMATION UNDER TWO DIFFERENT TASKS (LIKING AND SHOPPING) AMONG HEALTHY CONTROLS

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Background: The fundamental premise of eye-tracking methodology is that a subject is mentally and visually processing an onset stimulus. Visual behaviour paradigms can reveal information that conventional self-report methods would miss. Therefore, eye-tracking is useful when measuring visual attention and understanding its role in decision-making processes. Previous research suggests gaze bias expressing and indicating preference. According to the supposition, known as the gaze cascade hypothesis, the longer a participant looks at an object, the more likely she is to develop a preference for it. Yet, little investigations have been done taking advantages of the eye-tracking technique to study judgements in clinical populations; presented framework is a preliminary study to start to fill this gap.

Methods: Since food reward mechanisms are mediated by either "liking" (positive affect) or volitional "wanting" (motivation), in this study, evaluative responses toward food images under two different mind-sets (Liking and Shopping) were investigated. Furthermore, to investigate the relationship between preference and actual viewing time, the assessment process was supported with an eye-tracking device (EyeLink1000). In the Liking task, healthy controls (n=26) were asked to rate each food image from 1 ("not like at all") to 3 ("like very much"). In the Shopping task, participants were asked to express their judgement by picking maximum 7 food images to their 'shopping basket', with three response options: 1 ("leave it"), 2 ("postpone judgement"), and 3 ("put in"). Exposure time and response were recorded. Moreover, to compute the actual viewing time (of the displayed food pictures), eye positions beyond the image area and eye blinks were removed.
Results: The presented data indicate that longer viewing does not intrinsically lead to a higher evaluation. In the Liking task, the Authors found that longer viewing duration was associated with lower ratings. However, in the Shopping task an inverted U-shape trend appeared, where images labelled as 'postponed-judgement' were associated with the longest actual viewing time duration. The Authors suggest that the observation of slow viewing for the middle category may represent the extended information gathering phenomena. By this interpretation, the longer viewing durations may reflect doubt or indecisiveness (i.e., participants being unable to reach a quick positive or negative judgement). The present finding provides further evidence that increased liking from longer viewing does not hold true in a single-exposed image paradigm.
Discussion: Implementation of eye-tracking technology, to capture subconscious and unbiased data of healthy controls, is a growing trend in psychological experiments. In addition to loss of food-derived satisfaction among clinical populations, examining food preferences may elucidate processes that contribute to poor physical health and loss of social autonomy.

S29. THE RELATIONSHIP BETWEEN THE BIAS AGAINST DISCONFIRMATORY EVIDENCE, FORMAL THOUGHT DISORDER AND DELUSIONS IN PSYCHOSIS – A PRELIMINARY ANALYSIS

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Background: Positive symptoms such as delusions are considered a core feature of psychotic disorders. However, their etiology remains poorly understood. Presently, it is hypothesized that they originate from an interaction between dysregulated striatal dopamine, cognitive biases (CB), and environmental factors. Recently, a relationship has been observed between the bias against discriminatory evidence (BADE) and delusions in psychosis. This bias is known to decrease the likelihood of rejecting incorrect hypotheses in the face of contradictory evidence and has been linked in several studies to the formal thought disorder (FTD), a psychotic symptom characterized by an impairment in thought expressed by a disorganized speech. Given that both BADE and aspects of FTD depict disordered reasoning processes and the presence of a relationship between FTD and both delusions and the BADE, we hypothesized that FTD might mediate the relationship between BADE and delusions in psychosis.
Methods: We recruited 31 participants with (n=16) and without (n=15) psychotic disorders. We assessed cognition (Brief Cognitive Assessment Tool for Schizophrenia) and cognitive biases using a computerized BADE task. Psychiatric history (controls; SCID-NP) or symptoms (patients; Scales for the Assessment of Positive/Negative Symptoms) were measured via semi-structured interviews. Groups were compared on sociodemographic variables and cognitive biases by means of t-tests and Chi-square as appropriate. Due to the pandemic, we were unable

to recruit the number of patients needed to proceed with a mediation analysis. Thus, we ran Spearman correlations in the clinical sample to examine relationships between BADE, FTD, and delusions.
Results: The patient group presented mild levels of FTD (x = 1.06, sd = 1.24), moderate levels of delusions (x = 2.31, sd= 1.54) and a higher intensity of the BADE (t=2.094, p= .04). Groups did not significantly differ on age, sex, education, or cognition, with the exception of the digit symbol subtest, on which patients scored significantly lower than controls (t=-2.188, p=.037). In the patient group, we detected a positive, though non-significant correlation between BADE and FTD (r =0.159, p=.56), no correlation between BADE and delusions (r =0.001, p=.99), and a negative non-significant correlation between FTD and delusions (r =-0.430, p=.09). While the nonsignificant association between BADE and FTD is in line with previous research, we did not replicate the association between BADE and delusions nor the expected association between delusions and FTD.
Discussion: Our patient group showed deficits in processing speed and a greater BADE than controls, hence confirming the role of the BADE as cognitive indicator of psychosis. However, although some associations between the BADE, FTD, and delusions were observed, these were not in the expected direction for the association between the two symptom measures and did not reach significance in our sample. The failure to observe significant positive relationships between BADE and delusions may be explained by our small sample and its low level of positive symptoms. FTD might also be more accurately assessed with objective speech-related measures rather than subjective ratings. Following resumption of data collection, we will test the mediation model and distinguish between positive FTD (incoherence) and negative FTD (poverty of speech) using linguistic analysis. A better understanding of the relationships between cognitive biases, FTD, and delusions could inform cognitive bias-based interventions for psychosis, such as metacognitive training, in that inclusion of FTD-related content could improve efficacy of these interventions.

S30. GENDER DIFFERENCES IN COGNITION AND METACOGNITION IN FIRST-EPISODE PSYCHOSIS

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Background: Impairments in cognition and metacognition are core factors in psychosis, and already exist in first-episode psychosis. Gender differences in neurocognition have been widely explored, but some findings remain unclear. Regarding social cognition and metacognition, gender differences have been little explored and also show mixed results. The current study explored gender differences in a wide range of neurocognition, social cognition and metacognition domains in a sample of first-episode psychosis.
Methods: A cross-sectional descriptive study was performed. A total of 191 patients (129 men, 62 women) with first-episode psychosis were recruited from several public mental health services in Spain. Participants were assessed with the Beck Cognitive Insight Scale, the Beads

Task, the Faces Test, the Internal, Personal and Situational Attributions Questionnaire, the Hinting Task and a wide neuropsychological and clinical battery.
Results: Women had a better performance in verbal learning and memory than men, specifically in immediate recall (p=0.013) and long-term memory (p=0.017). Men had more intrusions (p=0.014) and more false positives in recognition (p=0.033) than women. On the other hand, women used more semantic strategies, both in short-term (p=0.007) and long-term memory (p=0.008), while men used more serial strategies in short-term memory (p=0.0015). No gender differences were found in other neurocognitive domains, metacognition or social cognition.
Discussion: Our results suggest that women with first-episode psychosis have better verbal learning and memory than men. Also, men and women tend to use different strategies for short-term and long-term memory. However, no other gender differences were found. Early interventions should address cognitive and metacognitive abilities and may take into account potential gender differences in order to meet gender specific needs.

S31. ALTERATIONS IN REWARD REPRESENTATION AND SUBSEQUENT ANTICIPATORY RESPONSE IN SCHIZOPHRENIA RATHER THAN SCHIZOTYPY

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Background: Anticipatory anhedonia has been reckoned as a prominent manifestation `of emotional difficulties in schizophrenia (SCZ) and schizotypy, thereby exerting a detrimental impact on their psychsocial outcomes. However, it remains largely unclear about the mechanism underpinning this alteration in schizophrenia and schizotypy. The present study aimed to examine reward representation maintenance and its subsequent relation to anticipatory pleasure in SCZ patients and individuals with schizotypy.
Methods: We recruited 32 patients with SCZ, 27 individuals with schizotypal trait and 28 healthy controls (HC) with well-matched age and gender. Schizophrenia was diagnosed by using the Structured Clinical Interview for DSM-IV Axis I Disorders while individuals with and without schioztypy were identified according to the screening criteria of Schizotypal Personality Questionnaire. The Reward Representation Maintenance (RRM) Task, which is a newly developed paradigm, was administrated to all the participants to assess the capacity of reward representation maintenance as well as subsequent anticipatory pleasure under the conditions where maintenance process was or was not required.
Results: A Maintenance x Price x Group three-way repeated measure ANOVA revealed a significant main effect of Group on the mismatching rate for the two successive rewarding cues ($F(2,84) = 3.653$, $p = .03$), with SCZ patients showing higher mismatching rate than HC ($p = .036$) but individuals with schizotypy displaying no difference from HC ($p = .99$). These results indicate that patients with SCZ but not schizotypy are impaired in the reward representation ability, independent of the representation maintenance process. Regarding anticipatory

pleasure response, we observed significant Group x Price interaction effects on the averaged number ($F(4,168) = 5.267$, $p = .001$) and standardized deviation ($F(4,168) = 2.881$, $p = .024$) of button presses towards the target, respectively. Further simple effect demonstrated that patients with SCZ exhibited exceptionally larger and more highly varied number of button-presses in the condition of small price as compared to HC ($ps < .05$), but no group differences were revealed between schizotypal individuals and HC. These results suggest that people with SCZ rather than schizotypal trait exhibited altered anticipatory pleasure response no matter when representation maintenance process was involved.

Discussion: Our findings suggest that reward representation processes and subsequent anticipatory pleasure response were overtly impaired in SCZ patients but not in schizotypy individuals. In contrast to our expectation, the representation maintenance may not be the only reason that explains SCZ patient's distorted anticipatory pleasure response. These may offer a new perspective on the nature of anticipatory anhedonia in schizophrenia spectrum disorder.

S32. SEMANTIC MEMORY IMPAIRMENT ACROSS THE SCHIZOPHRENIA CONTINUUM: A META-ANALYSIS OF CATEGORY FLUENCY PERFORMANCE

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Background: Semantic memory (SM) impairments are a core feature of schizophrenia and are present along the psychosis continuum. It is, however, unclear whether the degree of SM impairments vary along this continuum and if demographic and clinical factors affect impairment severity. This study performed meta-analyses of category fluency task performance (a task commonly used to assess SM) in 4 groups along the schizophrenia continuum: high schizotypes (HSZT), first-degree relatives (FDR), recent onset patients (≤2 y; ROP) and chronic patients (CSZ).

Methods: Electronic databases were searched for relevant studies published up to October 2019 resulting in the inclusion of 48 articles out of an initial 5,552 results Studies were included if they: (1) examined schizophrenia spectrum disorder patients at both the first episode/recent-onset stage and later in the illness course, and/or FDRs of schizophrenia patients, and/or HSZT individuals; (2) had a healthy control group comparison; (3) limited participants to between 16 and 65 years of age inclusive; (4) used at least one 1-minute semantic fluency task (no language specifications); (5) reported sufficient data to calculate effect sizes for meta-analysis; (6) were peer-reviewed and published in English; (7) were not case reports, reviews or other meta-analyses. Articles were also excluded if participants had co-morbid Axis I disorders or a history of neurological disorders. The main analyses assessed fluency productivity scores in 2978 schizophrenia spectrum disorder patients, 340 first-degree relatives of schizophrenia spectrum disorder patients, and 3204 healthy controls. Further analyses assessed errors, mean cluster size, and switching data that were available in the CSZ group only. Meta-regression analyses explored the influence of age, age of onset, illness duration, years of education, premorbid IQ, and symptomatology. Mean effect sizes for the groups were also compared using equivalence testing.

Results: Results revealed significant impairments in fluency productivity were present in the FDR, ROP, and CSZ groups relative to healthy controls, but not in HSZT. In the CSZ group, significant differences relative to healthy controls were also observed in non-perseverative errors, mean cluster size, and number of switches. No meta-regressions were significant. Only the mean effect size differences between the ROP and CSZ could be considered equivalent.

Discussion: The findings collectively suggest that SM deficits are present at each stage of the continuum and are exacerbated post-illness onset. They also support the centrality of SM impairments in schizophrenia and most elevated risk groups, with a degree of genetic liability. Future studies with a more comprehensive range of category fluency metrics and more diverse measures of SM function are needed to further characterize and understand this major cognitive deficit.

S33. DIFFERENTIATING OVER-MENTALISING IN PATIENTS WITH DELUSIONS

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Background: Delusions in patients commonly involve some intentional Other. Despite perceived intentions, about half of the external agents in delusions are not recognizable human figures already in the patients' social life. One explanation for this phenomenon is "over-mentalising", i.e., excessive mappings between representations of hidden mental states and overt actions. This view is contrary to the "deficit" perspective on social cognition in patients. The current study tested the over-mentalising hypothesis by using pre-determined, delusion-neutral animations. It was hypothesised that compared with non-clinical controls, patients' understanding would contain more mental state attributions.

Methods: Adult outpatients (18-65 years of age) with non-organic psychosis ever experiencing delusions in their life were compared against non-clinical participants without any psychiatric disorder. Affective states, intelligence, overall psychopathology, and severity of delusions were measured. Over-mentalising was assessed by the Frith-Happé Animations task, which consists of 12 animations of triangles moving (1) randomly, (2) in a goal-directed manner (e.g., following), or (3) in a way that requires referring to mental states to understand (ToM; e.g., persuading). Each participant verbally described in Cantonese what happened in each animation. Responses were audio-recorded and rated in terms of mental state complexity in the verbs (intentionality) and accuracy in understanding the overall animation (appropriateness). Raters were blinded to the group conditions.

Results: Thirty-seven patients (15 females, PANSS P1 = 3.24 ± 1.53) and 37 non-clinical participants (17 females) matched on gender and age were included. Patients were significantly lower in estimated intelligence (94.43 ± 10.21 vs. 105.32 ± 11.33, $t(72) = 4.34$, $p < .001$, Cohen's $d = 1.01$), generalised anxiety (6.24 ± 5.25 vs. 10.70 ± 5.65, $t(72) = 3.52$, $p < .001$, Cohen's $d = 0.82$), and depression (7.76 ± 4.90 vs. 12.78 ± 6.55, $t(72) = 3.74$, $p < .001$, Cohen's $d = 0.87$). Interrater-reliability of the animation scores ranged 0.91-0.93.

Across all animations, there was a significant difference in appropriateness ($t(72) = 4.40$, $p < .001$, Cohen's $d = 1.02$) but not intentionality ($p > .05$). For random animations, patients scored lower on appropriateness than controls (1.49 ± 0.80 vs. 2.21 ± 0.68, Mann-Whitney $U = 340.00$, $p < .001$, rank biserial $r = 0.50$), but they were comparable on intentionality ($p > .05$). Lower appropriateness (i.e., understanding the random animations with more purposefulness) was correlated with higher intentionality (i.e., using verbs indicating more complex mental states) (Spearman's $\rho = -0.59$, $p < .001$). The group difference remained significant after controlling for intelligence or affective states.

For goal-directed and ToM animations, patients were also lower on appropriateness than controls (Mann-Whitney $U = 443$, $p = .009$, rank biserial $r = 0.35$, and Mann-Whitney $U = 461$, $p = .015$, rank biserial $r = 0.33$, respectively), suggesting a tendency to misinterpret the pre-determined theme. Patients also showed lower intentionality in goal-direct animations ($t(72) =$

2.20, p = .031, Cohen's d = 0.51). However, these group differences disappeared after controlling for estimated intelligence.

Discussion: Patients with delusions tended to understand random actions with a greater sense of purpose, without necessarily attributing to more specific and complex mental states. Additionally, the processes underlying this tendency might differ from those involved in understanding behaviours commonly perceived as intentional. With limitations and interpretation cautions in mind, our study supports differentiable facets of mentalisation in delusion research.

S34. DOES A COMPUTERIZED SOCIAL COGNITIVE INTERVENTION IMPROVE IMPLICIT OR EXPLICIT THEORY OF MIND IN INDIVIDUALS WITH PSYCHOSIS?

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Background: Theory of mind (ToM) is a critical component of social interaction used to understand the behavior of others and plan one's own behavior accordingly. Measures of ToM can be explicit, which involves interpreting the mental states of others when cued to do so, or implicit, which require the individual to understand and attend to the mental states of others without being prompted to do so. Individuals with schizophrenia have repeatedly been found to exhibit ToM difficulties when compared to healthy controls, and these difficulties could lead to deficits in social functioning. Computerized targeted social cognitive training (TSCT) interventions have produced improvements in different domains of social cognition but changes in explicit versus implicit ToM have not been assessed directly. This study measured changes in implicit and explicit ToM in individuals with schizophrenia who were randomized to either TSCT or a computer games control condition to evaluate the effect of social cognition training on ToM as well as the relationship to overall social functioning.

Methods: Individuals who met DSM-5 criteria for schizophrenia enrolled in the study were randomized into either the active experimental treatment group (n= 21) or the control treatment group (n=24). Implicit ToM was measured using the Spontaneous Theory of Mind Protocol (STOMP), which is designed to assess an individual's focus on others' thoughts and emotions based upon unprompted descriptions of video clips involving characters undergoing mental state change. Explicit ToM was measured via the Awareness of Social Inference Test (TASIT), during which participants watch 16 short videos that involve lying and deception and are then asked a series of yes/no questions regarding the characters' internal states. In addition, participants were administered the Social Functioning Scale (SFS) to measure overall social functioning.

Results: Three separate analysis were done to look at each of three outcome variables: STOMP index score, total TASIT score, and SFS scaled scores were tested using hierarchical mixed-effects models to assess the main effects of study visit and treatment group status, the interaction of study visits and treatment group and the impact of covariates including IQ and symptom severity. The hierarchical model testing implicit theory of mind showed a significant treatment group by visit interaction ($\chi 2$ (3) = 13.94, p = .003). The experimental group showed a significant change in performance (b = .05, t(64.86) = 6.2, p < .001) indicating that they focused more on emotions and thoughts relative to physical descriptions following TSCT. The hierarchical model testing explicit ToM and social functioning revealed no simple effects of visit or treatment group or a significant interaction of visit and treatment group.

Discussion: The results revealed that individuals in the experimental treatment group exhibited greater change on the measure of implicit ToM compared to individuals in the control group. The groups did not exhibit any significant performance differences on explicit ToM or social functioning, which do not support the hypothesis of training related changed in those domains. This study demonstrates that individuals with schizophrenia who undergo targeted social cognitive training increase their rate of spontaneous ToM focused on other's thoughts and emotions.

S35. EXAMINING NEUROCOGNITIVE AND FUNCTIONAL SUBGROUPS IN SCHIZOPHRENIA

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Background: Neurocognitive impairments are a core feature of schizophrenia. However, there is considerable variability in neurocognitive functioning within this population, and 20-25% of individuals demonstrate intact neurocognitive performance. A range of neurocognitive subgroups have been identified, varying from severe global impairment to normative performance. Despite the strong association between neurocognition and community functioning, it is unknown whether distinct subgroups emerge when considering functioning across both of these domains. This could identify if there are individuals who functionally over- or under-perform their cognitive ability. The current study sought to identify subgroups of schizophrenia based on neurocognitive and community functioning.
Methods: The current sample includes participants from three studies: the Social Cognition Psychometric Evaluation study; the Validation of Everyday Real-world Outcomes study; and a study done at the Epidemiology-Genetics Program at the Johns Hopkins School of Medicine. The final sample consisted of 1028 participants with schizophrenia or schizoaffective disorder. Neurocognition, community functioning, and psychiatric symptoms were analyzed. Two distinct sets of classification were employed. First, participants were classified into neurocognitive subgroups based on current neurocognitive functioning, estimated premorbid IQ, and degree of deterioration relative to premorbid function using predetermined z-score cut-offs. Second, participants were classified into functional subgroups based on their neurocognitive performance and community functioning using cluster analysis.
Results: The first analysis identified five subgroups: 1) Compromised, with low premorbid and current neurocognition; 2) Compromised & Deteriorated, with low premorbid and current neurocognition plus decline; 3) Preserved, with intact premorbid and current neurocognition; 4) Preserved & Deteriorated, with intact premorbid and current neurocognition plus decline; and 5) Declined, with intact premorbid and low current neurocognition, indicating a decline. Both of the Compromised subgroups had poorer community functioning and more severe psychiatric symptoms compared to the Preserved groups. The Declined group was intermediate across nearly all measures. The second analysis identified three subgroups: 1) Overperforming, with impaired neurocognition but higher community functioning; 2) Higher Functioning, with intact neurocognition and higher community functioning; and 3) Impaired, with impaired neurocognition and community functioning. Both the Overperforming and Higher Functioning groups had less severe psychiatric symptoms as compared to the Impaired group, with the exception of negative symptoms. In this case, the Overperforming group was still less severe than the Impaired group, but worse than the Higher Functioning group.
Discussion: The sample was neurocognitively heterogeneous; 65% displayed neurocognitive impairment and 84% experienced a decline relative to premorbid levels. Individuals with better

community functioning, regardless of neurocognitive ability, had better clinical presentations compared to those with functional impairments. A novel finding was that 30% of our sample was higher functioning despite significant neurocognitive impairment. Differentiating between subgroups based on neurocognitive and community functioning could help tailor interventions to improve outcomes. Individuals who have neurocognitive deficits but are higher functioning may have different treatment targets and require different interventions as compared to those whose functioning is more strongly tied to neurocognition.

S36. REWARD PROCESSING RELATED GAMMA OSCILLATIONS IN SCHIZOPHRENIA

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Background: Motivation is the process which drives the organism to act towards a desired outcome. It is known that motivational deficits and anhedonia are good predictors for social functioning in schizophrenia. (Schlosser et al., 2014). Monetary incentive delay (MID) task is run to evaluate the neural activity in reward processing (Knutson et al., 2000). Previous studies reported that when the MID task is given to the patients with schizophrenia, ventral striatum activity is reduced (Schlagenhauf et al., 2008). Specifically, earlier findings suggested that during cognitive tasks, patients with schizophrenia showed deficits in gamma activity which can be related with attention and preparatory phases of information processing (Basar et al., 2007). Therefore, the aim of this study was to address neurophysiological aspects of reward processing in schizophrenia. In our study, it was hypothesized that patient and healthy control groups would respond differently in terms of gamma oscillations in MID task.

Methods: Event-related oscillation (ERO) were recorded during the execution of the MID task in 21 patients (15 males) with schizophrenia (SCH) and sex-, education-, age-matched 22 healthy controls (HC). In the MID task, a total of 450 trials (150 trials for each control, punishment and reward condition) were completed with a total task duration of 90 minutes. Statistical analyses were carried out with IBM SPSS. The maximum peak-to-peak gamma amplitudes (30-48 Hz) were measured at the midline electrodes (Fz, FCz, Cz, CPz, Pz, Oz). Repeated measures ANOVA included 2-levels group [controls, schizophrenia] as a between subjects factor, and 3-levels condition [control, punishment, reward], 4-levels cue [incentive, non-incentive, target, feedback] and 6-levels area [frontal, fronto-central, central, centro-parietal, parietal, occipital] as within-subject factors.

Results: The mean age was 37.71 (±9.01) and duration of education was 11.14 (±3.26) years for the patients. PANSS sum score was 68.24 (±17.03) and BNSS sum score was 41.33 (±13.12). Repeated-measures ANOVA of gamma ERO revealed group and area interaction [$F_{5,205}=6.251$; $p=0.005$]. Compared with HC, lower peak-to-peak gamma amplitudes were shown in SCH at FCz electrode. Moreover, there was a group, area and cue interaction [$F_{15,615}=3.294$; $p=0.007$]. Post-hoc analysis indicated decreased gamma amplitudes in SCH at Fz electrode in response to incentive cue ($p=0.044$); and at Fz and FCz electrodes in response to target cue (respectively; $p=0.047$, $p=0.040$). In contrast, patients showed increased gamma amplitudes for the feedback cue at Oz electrode ($p=0.048$).

Discussion: The present study aimed to investigate gamma oscillation during the reward processing in schizophrenia. In our study, we found that patients showed significantly reduced

gamma activity on frontal area when presented with incentive and target cues. Reward consumption has been related with activity in ventromedial frontal cortex structures (Knutson et al., 2001), which can be measured from frontal electrodes. That is consistent with the findings which report deficits in cognitive processing in schizophrenia (Eroglu-Basar et al., 2007). In addition, patients showed increased gamma activity for the feedback cue on occipital area. It is known that top-down attention processes (Hermann, 2001) and enhanced arousal can be shown in gamma oscillations (Engel, 2001). Therefore, it can be speculated that patients are more sensitive to feedbacks reporting money gains and losses. Further research is needed in order to understand motivational impairments in schizophrenia.
O. A. and E. F. contributed equally to this work.

S37. 'THEY' ARE NOT ALWAYS FRIENDS: SOCIAL (DE-)CONNECTEDNESS IN NARRATIVES, SOCIAL CONTACTS AND LONELINESS AND ITS LONGITUDINAL IMPACT ON SCHIZOTYPAL TRAITS DURING THE COVID-19 PANDEMIC

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Background: Being-with-others is an essential dimension of human existence. Its loss often precedes the development of schizophrenia-spectrum symptoms. While causal directions are undeniably dynamic, the absence of social relationships ('objective' social isolation) and loneliness ('subjective' social isolation) have both been linked to positive and negative symptoms. However, objective social isolation is often only weakly associated with loneliness and their predictive potentials have seldom been examined in context with an implicit marker such as the linguistic domain, where feelings and psychopathologies interact. In language we refer to people with pronouns, e.g. 'we' indicating intimacy and 'they' distant others. During the COVID-19 pandemic, that inevitably restricted all our social contacts, we conducted a longitudinal study on schizotypy and its relation to three dimensions of social isolation: objective (number of contacts), subjective (loneliness) and implicit (personal pronoun use).
Methods: Data were obtained from an ongoing longitudinal online-survey on the impact of COVID-19 assessed in spring (n = 371, age = 18 - 76), summer (n = 161) and winter (n = 133) 2020, with the last survey still being collected at time of analysis. At each survey, participants completed the Schizotypal Personality Questionnaire (SPQ), the UCLA Loneliness scale for subjective isolation, the Social Network Index (SNI) for objective isolation and wrote narratives about their everyday experience, thoughts and feelings. To provide the frequency of personal pronouns, narratives were subjected to Linguistic Inquiry and Word Count (LIWC), an automated language analysis tool. After identifying personal pronouns and dimensions of social isolation related to SPQ in correlational analysis, we ran a linear mixed model with random intercepts to investigate their longitudinal effect on SPQ scores.
Results: Loneliness, the number of high contact roles and 3rd person plural pronouns ('they') predicted increased schizotypy. There was a significant interaction between 'they' and loneliness on high contact roles each, in that the relation between 'they' and loneliness to schizotypal traits was reduced with increased number of high contact roles. Specific relevance for different SPQ subscales were shown, with 'they' being mostly predictive for disorganized, as well as high contact roles and loneliness for positive and negative schizotypy.
Discussion: Integrating three measures of social relatedness, we replicated findings of cross-sectional studies in a longitudinal sample. Putting linguistic markers and perceived social

isolation into context of the number of close relationships, we further elucidated their interrelations and effects on specific schizotypal traits. The more participants interacted with close relationships on a weekly basis, the less were the effects of loneliness on schizotypy – highlighting their potential for early detection of and interventions with people being at high risk for schizophrenia. As schizotypal individuals are often rejected for their odd behavior, an increased use of 'they' might reflect this perceived social exclusion. But the relation between 'they' and high schizotypal traits decreased with increased number of close relationships, stressing the relevance of combining different markers in predictive research. With more social contacts, the pronoun 'they' might shift its referent: from distrusted to trusted others.

S38. PERCEPTIONS OF CORONAVIRUS DISEASE 2019(COVID-19) IN SCHIZOPHRENIA

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Background: For prevention and containment of the spread of the coronavirus infectious disease 2019(COVID-19), it is important to follow the rules along with an accurate understanding of the disease.
The aim of this study was to investigated the impact of COVID-19 on activities of daily living for schizophrenic patients. This study also determined knowledge and perceptions of COVID-19 in patients with schizophrenia.

Methods: Participants were 161 inpatients and 117 outpatients with schizophrenia and 40 normal controls. Subjects completed the self-report questionnaires measuring changes in daily life, perceptions of the current status of COVID-19 and basic knowledge about it. The fear of COVID-19 scale was administered.
Results: 51.6% of inpatients with schizophrenia, 65.5% of outpatients, and 85.0% of normal groups reported that there was a change in daily life due to COVID-19. 82.9% of the outpatient group answered that the infection route of COVID-19 is transmitted by 'Droplets of saliva', while 41.6% of the inpatients selected the correct answer. Cough and fever were selected as the main symptoms of COVID-19 in 80% of outpatients. In the case of inpatients, more than 20% choose other symptoms such as skin rash, constipation, and urination disorder in addition to cough and fever. More than 90% of each group accurately recognized the question which is 'The most effective way to prevent COVID-19 is to wear a mask and wash hands.' Compared to the normal group, the patients with schizophrenia underestimated the cumulative number of COVID-19 confirmed cases and overestimated the mortality rate of COVID-19. The patients with schizophrenia showed higher subjective fear score for COVID-19 than normal group.
Discussion: It shows that the patients with schizophrenia, especially inpatients are not well aware of COVID-19.

S39. THERAPEUTIC MANAGEMENT OF MOOD DISORDERS DURING ACUTE SCHIZOPHRENIA

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Background: Mood symptoms represent an important component in many patients diagnosed with schizophrenia, both during acute episodes and inter-episodic intervals. A trial about comorbid depression rate in schizophrenia reported values of 50%, while other studies

mentioned values of up to 61% [1,2]. Depressive symptoms may further increase the risk for addictive disorders and decrease the treatment adherence, quality of life, and worsen these patients' prognosis [3]. The correlation between the severity of depressive and positive symptoms was reported in the literature, and more depressive symptoms have been detected in older patients with schizophrenia [4]. Isolated symptoms of depression, depressive syndrome, post-psychotic depression, and major depressive episodes may occur in patients with schizophrenia and a complete evaluation of the mood dimension in these patients is of major importance due to its therapeutic and prognosis implications.

Methods: A number of 4 patients diagnosed with schizophrenia, multiple episodes, currently in an acute episode, according to the DSM-5 criteria, who presented a Calgary Depression Scale for Schizophrenia (CDSS) score higher than 6, were monitored using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression- Severity (CGI-S), Global Assessment of Functioning (GAF), CDSS, and EuroQoL (EQ-5D-5L). These scales were administered at baseline (during the first 7 days of their hospitalization) and every 4 weeks for 6 months. All patients received as maintenance treatment flexible-dose of atypical antipsychotic (either oral, n=3, or long-acting, injectable, n=1) and selective serotonin reuptake inhibitor (sertraline, n=2, fluoxetine, n=1, escitalopram, n=1). Short-acting benzodiazepines (lorazepam, midazolam) were allowed for administration during the 6-month of active monitoring, but not more than 4 consecutive weeks.

Results: After 24 weeks, the mean PANSS score corresponded to a significant improvement compared to baseline (-26.5%, $p<0.001$), and the CDSS score also improved (-4.6, $p<0.01$). CGI-S reflected the overall improvement of the clinical status (-2.1, $p<0.01$), and the GAF scores also improved significantly ($p<0.01$). EuroQoL- Visual analogic scale (VAS) score increased with 22 points at week 24 ($p<0.01$). The most important improvement in EuroQoL was on anxiety/depression dimension and usual activities. No significant differences between patients' evolution related to the type of antidepressant administered were reported in any of the monitored variables. Improvements in the CDSS scores correlated with the highest scores on EuroQoL-VAS values. The overall tolerability of the treatment was good, with no serious adverse event being reported during the 24-week period.

Discussion: Treatment of the mood symptoms during an acute psychotic episode should be monitored using specific scales throughout the entire duration of the antidepressant administration. Antidepressant may be added to atypical antipsychotics without significant impact over the treatment tolerability. Antidepressants may improve the quality of life by decreasing the severity of depression in patients with schizophrenia.

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S40. WEIGHT GAIN AND METABOLIC ADVERSE EFFECTS OF OFF-LABEL SECOND-GENERATION ANTIPSYCHOTIC USE IN THE ADULT POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Prescription rates of second-generation antipsychotics (SGAs) are increasing rapidly in off-label populations. In on-label indications, SGAs are associated with significant metabolic adverse effects (MAEs), including weight gain, glucose dysregulation, and dyslipidemia. Currently, there is a limited body of literature assessing the MAEs of SGAs in off-label indications. As such, the objective of this systematic review and meta-analysis is to evaluate the MAEs of SGA use for off-label management of psychiatric illnesses in the adult population.

Methods: We conducted a comprehensive search in MEDLINE, EMBASE, Cochrane CENTRAL, PsycINFO, and CINAHL databases, as well a grey literature search on ClinicalTrials.gov and the ICTRP Search Portal. Inclusion criteria included all randomized controlled trials (RCTs) that reported on weight and other metabolic outcomes with the off-label use of SGAs among adults between the ages of 18 and 65. We reliably selected, quality assessed, and extracted data from all studies. Meta-analyses of reported weight gain were completed based on prescribed SGA, and subgroup analyses were conducted based on individual psychiatric diagnoses.

Results: Twenty-three RCTs were included in the meta-analysis, with a total of 4903 patients across a variety of psychiatric diagnoses, including post traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), borderline personality disorder (BPD), trichotillomania, and substance use disorders. Mean follow-up period was 10 weeks (range 8 to 24 weeks). Both olanzapine and quetiapine were associated with significantly greater weight gain across all disorders (Olanzapine: 3.40 kg, [2.56, 4.24], $p<0.001$, $I2=70\%$, n=9; Quetiapine: 0.96kg, [0.03, 1.90], p=0.04, $I2=96\%$, n=8). No significant differences were found between risperidone and placebo. A meta-regression analysis revealed a positive dose response association between average dose of olanzapine and weight gain (regression coefficient: 0.39 [0.17, 0.60], p-value = 0.04, $I2 = 62.8\%$), as well as between average dose of quetiapine and weight gain (regression coefficient: 0.0053 [0.00034, 0.0103], p= 0.038, $I2 = 90.40\%$).

Discussion: This review demonstrates that off-label use of SGAs, and particularly olanzapine and quetiapine, is associated with significant weight gain among adult patients across a variety of psychiatric diagnoses. SGA use in on-label patients irrefutably contributes to their significantly higher risks of type 2 diabetes, metabolic syndrome, and cardiovascular disease; therefore, similar attention should be given to these risks in off-label populations as well. Further studies are required to better understand the effects of off-label SGA use on other metabolic parameters.

S41. A SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION OF WEIGHT GAIN IN PEOPLE WITH SCHIZOPHRENIA: 2020 UPDATE

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Background: Antipsychotic medications induce concerning weight gain in patients with schizophrenia. The objective of this review is to determine the effects of adjunctive pharmacological interventions aimed at preventing weight gain in schizophrenia.
Methods: We searched the Cochrane Schizophrenia Group's Trials Register for all randomized controlled trials examining any adjunctive pharmacological intervention for prevention of weight gain in patients with schizophrenia or schizophrenia-like illnesses. As endpoint and change data were combined in the analysis, mean differences (MD) of the change from baseline were calculated using RevMan 5.3.
Results: Fifteen randomized controlled trials met the inclusion criteria for review (pooled n = 767) with fourteen being synthesized in a quantitative meta-analysis. Metformin may be effective in preventing weight gain (Weight: MD -4.03, 95% CI -5.78 to -2.28; participants = 131; studies = 4; BMI: MD -1.63 kg, 95% CI -2.96 to -0.29; participants = 227; studies = 5). Other agents that may be somewhat effective in preventing weight gain include histamine (H2) antagonists (Weight: MD = -1.32, 95% CI -2.09 to -0.56; participants = 248; studies = 3), as well as monoamine modulators (Weight: MD = -2.04, 95% CI -3.07 to -1.01; participants = 135; studies = 4).
Discussion: This review highlights the possibility of using adjunctive metformin pharmacotherapy for the prevention of antipsychotic induced weight gain. Interpretation for other agents is limited by the small number of studies, small sample size, and short study duration. Future studies that are adequately powered, with longer treatment duration, are required to inform recommendations for pharmacological interventions to prevent antipsychotic-induced weight gain.

S42. SHARED GENETIC EFFECTS BETWEEN SCHIZOPHRENIA AND SUBSTANCE ABUSE: A MULTIPLEX EXTENDED PEDIGREE STUDY

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Background: Substance abuse is a serious public health issue and is increased among those with schizophrenia (28-47% versus 14.6% in the general population). However, the reasons for this comorbidity are still unclear.
Methods: The current study used a multiplex extended pedigree (1st to 4th degree relatives) sample ascertained by schizophrenia probands with at least one other first degree relative with schizophrenia (total sample N=1306, with N=789 relatives and N=517 unrelated controls) to examine the degree to which genetic effects influence shared liability for schizophrenia (N=123) and three different categorizations of DSM-IV substance use diagnoses: any substance dependence or abuse diagnosis (N=251), cannabis dependence or abuse (N=105) and alcohol dependence or abuse (N=178). We also assessed shared genetic effects between schizophrenia and binary "ever smoked cigarettes daily" status (total available N=1082; smokers N=531).

Results: The univariate heritabilities of any substance dependence/abuse diagnosis (h2=0.601, p=2.087e-8), cannabis dependence/abuse (h2=0.926, p=2.091e-9), alcohol dependence/abuse (h2=0.434, p=1.00e-4), and smoking status (h2=0.487, p=2.00e-7) were all significant. The genetic correlations between schizophrenia and any substance dependence/abuse (Rg=0.303, p=0.039), and between schizophrenia and alcohol dependence/abuse (Rg=0.389, p=0.024) were significant; however, the genetic relationship between schizophrenia and cannabis dependence/abuse (Rg=0.195, p=0.104) and schizophrenia and smoker status (Rg=0.154, p=0.280) were not significant. Environmental correlations were all non-significant.
Discussion: Results indicate that genetic effects play a significant role in the comorbidity between schizophrenia and some measures of substance abuse. Future research will evaluate the genetic mediating effects of MRI brain structure volumes between schizophrenia and substance abuse.

S43. COMPARISON OF METHAMPHETAMINE INDUCED PSYCHOSIS AND PRIMARY PSYCHOTIC DISORDER: A SCOPING REVIEW OF SOCIAL COGNITION

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Background: Methamphetamine users risk developing several problems, with as many as 43% experiencing psychotic symptoms. Of these, 30% will see their diagnosis changed to a primary psychotic disorder. The current state of the literature does not currently allow us to determine who, of those who present in a psychotic state following methamphetamine abuse, will develop a primary psychotic disorder. Some studies have looked at distinguishing profiles of psychotic symptoms and of neurocognitive deficits, with limited, albeit promising results.Social cognition could also help predict distinct profiles.
Methods: Articles were recovered from PsychINFO, Medline and Web of science and were retained if they met the following inclusion criteria: (a) original research or meta-analyses, (b) complete or partial sample with a psychotic disorder diagnosis (i.e., schizophrenia, first-episode psychosis, schizoaffective disorder, schizophreniform disorder) with comorbid methamphetamine use, or MIPD, (c) studies focusing on the difference between a methamphetamine-induced psychosis and a psychotic disorder, and (d) studies focusing on social cognition in psychotic or methamphetamine using population.
Results: A total of 17 articles were identified, with none directly aiming at distinguishing MIPD and primary psychotic disorder using social cognition. Studies suggest deficits in emotion recognition and in theory of mind in both MIPD and primary psychotic disorders with substance misuse.
Discussion: Future studies on social cognition are needed in order to determine differences in the severity of deficits between the two profiles. More domains of social cognition also need to be assessed in the hope to better differentiate MIPD from a primary psychotic disorder.

S44. REMIND, A SMARTPHONE APPLICATION FOR RELAPSE PREDICTION IN PSYCHOSIS

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Background: Severe mental illnesses such as psychosis place huge burden on the infected individuals as well as the society alike. Relapse is one critical obstacle facing remitted patients, and hence a better understanding of potential predictors bears important implications. Apart from medication non-adherence, some psychosocial factors such as high expressed emotion and cognitive impairments have been found to be predictive of relapse. Given clinical consultations do not always allow for timely detection of these relapse precursors, "ReMind" – a smartphone application, is therefore developed to explore these potential relapse predictors in patients with psychosis.
Methods: In this one-year prospective follow-up study, 176 remitted Chinese patients with psychosis will be recruited. Monthly predictor assessments are to be conducted via "ReMind" throughout the one-year study duration. These assessments include neurocognitive tasks on visual patterns test and letter number span, medication adherence, and other psychosocial questionnaires such as expressed emotion and resilience.
Results: Preliminary user experience survey in using the "ReMind" has been conducted in 15 patients. 93% of patients (n=14) reported an overall positive experience with the app. A majority of them thought that the tests have clear instructions (100%, n=15), user-friendly interface (100%, n=15), and engaging content (73%, n=11). Up to 80% of patients (n=12) reported a preference in using the app based assessments compared to face-to-face ones. The 1-year follow-up study is still ongoing, and preliminary findings regarding the exploration of relapse predictors will be presented.
Discussion: While past research mainly focused on clinical and psychosocial predictors of relapse, there is growing evidence that suggests the promising role of cognitive factors. "ReMind" provides a step forward to the identification of relapse predictors in schizophrenia.

S45. ECOLOGICAL MOMENTARY ASSESSMENT OF BURDENSOMENESS AND BELONGINGNESS IN INDIVIDUALS WITH PSYCHOSIS

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Background: People with psychotic disorders are at an increased risk of suicide compared to the general population. However, there is still little understanding of suicidal ideation (SI) in people who experience psychotic symptoms. The Interpersonal Psychological Theory of Suicide posits that burdensomeness and belonginess converge to contribute to SI. There are no studies using ecological momentary assessment (EMA) to assess both perceived burdensomeness and thwarted belongingness in a sample of individuals with serious mental illness (SMI). The aim of this study is to examine variability of burdensomeness and belongingness in a sample of individuals with SMI and investigate whether burdensomeness and belongingness related to SI and EMA-measured psychotic symptoms.
Methods: Participants (N=97) with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or major depressive disorder with psychotic features completed in-lab assessments of symptoms and current SI (Columbia-Suicide Severity Rating Scale; Modified Scale for Suicidal Ideation). They were then given a smartphone and completed EMA assessments 3 times daily for 10 days at stratified random intervals. EMA

surveys included questions about burdensomeness, belonginess, affect (happiness, sadness), and psychotic symptoms (mistrust of others, hearing voices). Mean squared successive difference (MSSD) was calculated to quantify variability. Linear mixed models investigating real-time influences on burdensomeness and belongingness included a random effect for participant, and fixed effects of a participant's mean EMA value over time and a participant's deviation from the mean at each EMA survey.
Results: EMA burdensomeness (MSSD = 1.8) significantly varied less than EMA belongingness (MSSD = 2.7, t(95)=-3.74, p=< .001). Participants with SI had lower EMA mean belongingness scores than those without current SI (t(94) = 3.98, p < .001). Participants with SI had higher EMA mean burdensomeness scores than those without current SI (t(94) = -2.95, p < .001). Linear mixed models (all holding affect constant) revealed that greater mean mistrust was related to more burdensomeness only for people with SI (B=.20, p<.001), and greater deviation in mistrust was related to more burdensomeness only for people without SI (B=-.19, p<.001). Further, mean mistrust and deviation in mistrust were both related to belongingness for the entire sample, but in opposite directions based on SI (Mean- SI: B=.07, p=.023; No SI: B=-.17, p<.001). More EMA-measured mean voices and deviation in voices were related to more burdensomeness for the entire sample (Mean- SI: B=.33, p<.001; No SI: B=.24, p<.001). However, more deviation in voices related to less belongingness for people with SI (B=.13, p=.007), but not for those without SI.
Discussion: This is the first study to examine real-time influences on burdensomeness and belongingness in a sample of individuals experiencing psychotic symptoms. Belongingness varied more than EMA burdensomeness, suggesting that burdensomeness is a more stable construct. EMA burdensomeness and belongingness differed based on SI. Hearing voices and mistrust of others are related to increases in interpersonal suicide-related risk factors for people with SMI, and these symptoms have a differential influence on these factors for people with or without SI.

S46. AN SMS TEXT MESSAGING INTERVENTION TO IMPROVE CLINICAL ENGAGEMENT IN EARLY PSYCHOSIS: A PILOT RANDOMIZED-CONTROLLED TRIAL

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Background: Clinical disengagement of youth in early psychosis clinics continues to be a significant barrier to recovery as evidenced by high rates of premature drop-out from clinical service. Previous studies SMS text messaging as a means to boost engagement with promising early findings for individuals experiencing psychotic disorders, although with limited investigations in the context of early psychosis populations. To address this, we conducted a 9-month longitudinal randomized control trial to evaluate the efficacy of a weekly SMS intervention to improve clinical engagement for individuals in early psychosis services (ClinicalTrials.gov registration No. NCT04379349). Primary outcomes were appointment attendance rates and clinician-rated engagement, which we hypothesized would improve in the active group compared to the sham, with secondary hypothesized gains in clinical symptoms and functioning. We also explored subscale scores on included assessments to investigate potential areas of intervention responsiveness.
Methods: Participants between the ages of 16 and 29 presenting to early psychosis intervention services were randomized to either an active or sham SMS intervention, delivered weekly for nine months, in addition to their usual early psychosis care. Participants were blinded to group

assignment, and underwent assessments to evaluate clinical engagement, psychopathology, neurocognition, and community functioning at baseline, months 1, 3, 6, and 9. Intent-to-treat and pre-specified per-protocol analyses were conducted using linear mixed models to evaluate changes in our primary (clinical engagement) and secondary (clinical, neurocognition, functioning) outcomes over time between intervention groups.
Results: 61 participants (Active SMS n=32; Sham SMS n=29) were recruited and enrolled in this trial. Our primary outcome of attendance actually showed a significantly reduced clinic attendance rate over time in the active compared to the sham group (β = -0.21, p=0.007), with no significant group differences in overall engagement. Paradoxically, in examining subscale scores, we found a significant improvement over time in clinician-perceived availability (β = -2.12, p=0.02), in the active group compared to the sham. In terms of secondary outcomes, participants in the active SMS group exhibited a significant improvement over time in attitude towards medication (β = 2.88, p=0.044) compared to the sham group. In clinical symptoms, despite finding no overall differences in psychopathology ratings, the active SMS group exhibited reductions over time in positive symptoms (β = -2.33, p=0.022) and avolition-apathy (β = -3.67, p=0.046), although the sham group exhibited a significant improvement in social functioning compared to the active SMS group (β = -14.65, p=0.031). Notably, clinic attendance rate was inversely correlated with change in social functioning specifically in the active SMS group (r = -0.74, p=0.01). Per-protocol analyses revealed findings consistent with the intent-to-treat analyses.
Discussion: Overall, these findings suggest that SMS text messaging may help support at least some aspects of clinical engagement (i.e., attitude toward medication) and may suggest a potential pattern of engagement whereby those in the active group who reported feeling well (e.g., improved positive symptoms, avolition, and social functioning) may be attending less and inadvertently replacing in-person visits with the intervention check-in. These findings build on existing literature to support the investigation of asynchronous digital interventions and inform refinements for future clinical trials.

S47. IMPACT OF SCHIZOPHRENIA SPECTRUM DIAGNOSIS ON ACCEPTABILITY AND USABILITY OF TWO MOBILE APPS FOR SMOKING CESSATION AMONG A SAMPLE OF YOUNG ADULTS IN COMMUNITY MENTAL HEALTH CARE

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Background: Young adults with schizophrenia spectrum disorders (hereafter referred to as schizophrenia for concision) and other serious mental illnesses are over twice as likely to smoke cigarettes than the general population, but little research has evaluated the efficacy of interventions for this group. While smartphone apps are a promising tool to address this need, their usability and appeal should be evaluated among young adults with schizophrenia, whose mental illness-related cognitive impairments may be a barrier to app use.
Methods: We conducted app usability and acceptability testing involving 17 young adult smokers with serious mental illness (age range 18-35 years old) between May 2019 and February 2020. Participants were randomized to use one of two free smoking cessation apps created by the National Cancer Institute (QuitGuide or quitSTART) on their smartphone. App usability was evaluated at baseline and following two weeks of independent use via a video-recorded task-completion protocol, which was qualitatively analyzed using observational methods. Participant perceptions of usability at each time point were assessed via the 10-item

System Usability Scale (SUS), as well as by semi-structured interviews. Participant's app usage data between visits was obtained from the National Cancer Institute. All quantitative data were analyzed using descriptive statistics, comparing usability and appeal among participants with schizophrenia to those with other serious mental illness diagnoses.
Results: Participants were 17 daily smokers with a mean age of 29 years old (SD=4), of whom 7 (41%) self-identified as female, 16 (94%) self-identified as White, and 7 (41%) were diagnosed with schizophrenia spectrum disorders. At least 90% of participants in each diagnosis group reported using smartphone apps on a daily basis. Participants in in both groups assigned to QuitGuide had high objective task completion rates at both visits. quitSTART users with schizophrenia had lower objective task completion rates at Visit 1 compared to those without schizophrenia, but completion rates were similar at Visit 2. Mean SUS scores for QuitGuide at both visits were higher for participants with schizophrenia (76±1 and 74±8, respectively) compared to participants without schizophrenia (59±19 and 63±21, respectively). Mean SUS scores for quitSTART at Visit 1 and Visit 2 were similar between groups, and increased after two weeks among participants with schizophrenia (Schizophrenia: 53±29 and 68±22, respectively; No schizophrenia: 58±10 and 61±7, respectively). Participants in both groups opened QuitGuide less than once per day on average over the trial period. In contrast, quitSTART use was similar for both groups during the first week of the trial, but diverged during the second week: participants with schizophrenia opened quitSTART fewer times per day during the second week of the trial compared to participants without schizophrenia (1.9±1.5 vs 3.9±2.4). Qualitative comments indicated greater enthusiasm for quitSTART, and were similar for participants with and without schizophrenia. While quitting was not required for this study, 2 participants had biochemically confirmed abstinence at the follow up visit: both were quitSTART users, one with and one without a schizophrenia spectrum disorder.
Discussion: National Cancer Institute cessation apps were usable and appealing among young adult smokers with serious mental illness, but participants interacted more with quitSTART. Smokers with schizophrenia initially experienced difficulty using quitSTART, which resolved with use. Technical support may be required to engage young adult smokers with schizophrenia spectrum disorders to use appealing apps for cessation.

S48. LINGUISTIC MARKERS TO DISTINGUISH PATIENTS WITH PSYCHOSIS FROM THOSE WITH DEPRESSION

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Background: Although, clinical interviews and screening tests as primary and accessible approaches [1, 2, 3] can distinguish patients with different types of mental health problems with reasonable accuracy, several works suggested that systematic ex- amination of language content can reliably and accurately discriminate patients into relevant distinguishing classes. For example, in [4], an automated linguistic method was proposed to discriminate against patients with depression from patients with other types of mental illnesses. Another study suggested that lexical fea- tures such as lexical diversity and readability score could discriminate between patients with depression from patients with schizophrenia. In other words, patients with schizophrenia employed significantly less diverse lexicon in their languages [5] or have got a lower readability score [5] from their languages. Another work, [6] noted that syntactic and semantic aspects of patients' language cloud reveal that language impairments are associated with psychosis.
Another study showed that [7], deficit in semantic coherence and lower density in semantic could be associated with psychosis. It has also stated that that patients with psychosis had

employed higher volumes of first-person pro- nouns, biological process words, and negative emotion words. The above studies emphasize that psychosis and depression can be determined by examining the language of patients.

Methods: The following steps describe our methodology:
1) Extracting semantic-based features;

2) Defining metrics to measure incoherence and tangential speech;

3) Training binary machine learning (ML) classifiers such as support vector machines (SVMs) and Extra Trees (ETs) by calculated metris.

4) Employing the trained ML to distinguish patients with psychosis from depression.

In more details, we calculate the three incoherence metrics based on the cosine similarity between sentence embeddings provided by 1) simple average (SA); 2) smooth inverse frequency (SIF) embeddings; 3) term frequency-inverse document frequency (tf-IDF).

We also calculated the tangential metric employing latent dirichlet allocation or (LDA).

Results: We found that the incoherence metric that is calculated using SIF sentence embeddings has a higher value in psychosis language than depression language. It can be used as a discriminative marker to correctly group individuals with depression or psychosis.
Discussion: Our studies showed that semantic-based markers identified as specific language changes in depression and psychosis are probably markers of illness in general.

S49. IDIOGRAPHIC MODELING AND DATA VISUALIZATION OF SLEEP, AFFECT, AND PSYCHOTIC SYMPTOMS: THREE CASE EXAMPLES OF INDIVIDUALS WITH OR AT RISK OF A PSYCHOTIC DISORDER

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Background: Psychotic disorders are a heterogeneous array of disorders characterized by five key features: delusions, hallucinations, disorganization, abnormal motor behavior, and negative symptoms. Under the current classification system, researchers rely on nomothetic or between-individual analyses to explain heterogeneity both within and across disorder classification. While current nomothetic approaches have furthered understanding of psychotic disorders and mechanisms underlying symptom processes, ideographic analyses may represent an under-utilized approach to assess individuals' symptom experiences and to address within disorder heterogeneity.
Methods: Using an experience sampling methodology (ESM), 46 individuals aged 15-25 diagnosed as at clinical high risk for psychosis (CHR) or early psychosis (EP) provided information on affect, psychotic symptoms, and sleep using a smartphone application, MetricWire. Diagnoses were established using the Structured Clinical Interview of DSM-5 and the Structured Interview of Prodromal Syndromes. Using MetricWire, participants responded to 6 prompts per day within an individualized 12-hour window for a 21-day data collection period. For each prompt, participants rated multi-item scales of positive affect, negative affect, and psychotic symptoms on a 7-point Likert scale. For the first daily prompt, participants recorded sleep onset and offset times to allow for calculation of sleep duration and midpoint. An additional 21-day window of ESM data was obtained at either 6 or 12-months for a small subset (n=9) of participants. Data visualization methods characterized moment-level data for

affect and psychotic symptoms and day-level data for sleep measures. We employed group iterative multiple model estimation (GIMME) to model lagged and contemporaneous effects on a group, subgroup, and individual level. GIMME plots and symptom graphs shed light on unique intra-individual relationships between negative affect, positive affect, psychotic symptoms, sleep duration, and midpoint of sleep.
Results: Symptom graphs and GIMME plots for three individuals are used to illustrate the potential of ideographic approaches to understanding symptom dynamics. Of the two participants who met criteria for CHR at baseline, one converted to EP within the year, while the other saw symptoms remit. The third participant was diagnosed with EP. Graphs depict variability in momentary affect and psychotic symptoms and daily sleep metrics for each case example. GIMME plots depict unique temporal and bidirectional relationships between positive affect, negative affect, psychotic symptoms, sleep duration, and midpoint of sleep for each case example. Comparison of baseline and 12-month follow-up GIMME plots within each case demonstrates the degree to which temporal relationships emerged or remained stable over time.
Discussion: While nomothetic analyses predominate psychopathology research, findings demonstrate that ideographic analysis of ESM data can identify important dynamic relationships for individuals with CHR or EP. Ideographic approaches illustrate the unique temporal and bidirectional relationships between symptoms for individuals while showing that these relationships may vary according to the temporal frame of measurement and/or analysis. Results suggest ideographic approaches may address the weaknesses of nomothetic approaches and diagnosis-driven treatment by identifying potential therapeutic targets for individuals. Ideographic analyses promote the potential of individualized, hypothesis-driven assessment and selection of treatment priorities that may improve the understanding of mental health challenges and the delivery of mental healthcare.

S50. AVOLITION IN SCHIZOPHRENIA AND BIPOLAR DISORDER: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

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Background: Disability and dysthymia are prevalent in severe mental illness. We used ecological momentary assessment to examine daily activities in people with bipolar disorder and schizophrenia. We classified activities as productive, unproductive, or passive recreation in relation to the momentary experience of sadness, locations, and social context.
Methods: 102 people with schizophrenia were compared to 71 people with bipolar disorder. After a baseline assessment, participants were sampled 3 times per day for 30 days with a smartphone-based survey, asking where they were, with whom they were, what they were doing, and if they were sad.
Results: People with schizophrenia were more likely to be home and alone. There were no differences in the prevalence of the activity types across samples. People with bipolar disorder were less likely to report only one activity since the prior survey, but the majority of surveys reported only one. For both samples, sadness since the last survey was associated with less productive activity and more passive recreation. Being home and alone were also associated with more of these two activities.

Discussion: Both groups reported high levels of unproductive and passive activities, with momentary sadness found to be associated with these activities. These activity patterns are consistent with clinical descriptions of avolition and they minimally differentiate people with bipolar disorder and schizophrenia.

S51. NEGATIVE SYMPTOM HETEROGENEITY: FACTORS OF DIMENSIONS AND CLASSES OF SUBGROUPS

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Background: Recent research has established that negative symptoms are multidimensional comprising two second-order dimensions—Motivation and Pleasure (MAP) and Emotional Expression (EXP) that influence as many five first-order domains—anhedonia, asociality, avolition, affective flattening, and alogia. Studies also suggest that two or three subgroups may unpin negative symptom heterogeneity. The recent multidimensional models have yet to be examined in relation to theoretically and empirically-established negative symptom subgroups. The current study used latent variable modeling to compare purely dimensional, categorical, and hybrid dimensional-categorical models of negative symptoms.

Methods: The study used three independent samples (total N = 720) of outpatients with schizophrenia. In Sample 1, the Schedule for the Assessment of Negative Symptoms (SANS) served to rate negative symptoms. In Sample 2 the Brief Negative Symptom Scale (BNSS), and in Sample 3, the Clinical Assessment Interview for Negative Symptoms (CAINS) served to rate negative symptoms. Each study administered measures of external variables including cognition, function, psychopathology, defeatist beliefs, and trait emotional experience. In each sample, we fitted three purely dimensional models—two-factor, five-factor, and a hierarchical model with MAP/EXP as first-order factors and the five consensus domains as second-order factors. We also tested purely categorical models fitting up to four classes to each dataset. Finally, we tested factor-mixture models by fitting 2 to 4 classes on each dimensional model. We estimated each model in Mplus5 using Maximum Likelihood Estimation with robust standard errors. Goodness-of-fit statistics included Akaike (AIC), Bayesian (BIC), and Sample-size Adjusted (SSA-BIC) Information Criteria; Lo-Mendell-Rubin Test (LMR); and Bootstrap Likelihood Ratio test (BLRT).

Results: In the pure categorical models, the goodness-of-fit statistics tended to favor models with a larger number of classes. Of the purely dimensional models, the five-factor model produced the lowest information criteria estimates suggesting a preference for this model. In each independent sample, purely dimensional (factor) models of negative symptoms were preferred over categorical (class) models. Of the hybrid dimensional-categorical models, the goodness-of-fit indices produced the best support for the five-factor/two-class model and the hierarchical/two-class model. Across all latent variable models tested, the hybrid five-factor/two-class model produced the best fit to negative symptoms data in all three samples. Using Bayes posterior probabilities, we classified cases into subgroups identified fitting factor mixture models to the negative symptoms data. Each sample revealed a subgroup with relatively higher negative symptom severity. Posthoc comparison of the unveiled subgroups

showed greater impairments in cognition and function but not general psychopathology in the high negative symptoms group.
Discussion: Our findings suggest that a hybrid dimensional-categorical model best describe negative symptom heterogeneity in people with schizophrenia. Ratings scales should not only assess the five negative symptom dimensions but endeavor to identify meaningful subgroups. These results have implications for the delegation of clinical trial end-points and subgroup moderators of treatment effects.

S52. AUTOMATED CODING OF DISORGANIZED SPEECH TO DETECT DISORDERED THINKING

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Background: Automated speech analysis has shown to be highly beneficial for predicting transition to first episode psychosis (FEP) and diagnosing psychotic disorders (Argolo et al., 2020; MacKinley et al., 2020; Gupta et al., 2017; Rosenberg, 1979). Simultaneously, little research has compared its utility to other standardized measures of disordered thinking (Minor et al., 2019). The Rorschach Performance Assessment System (R-PAS) provides a structured procedure for gathering a speech sample to Rorschach inkblots and meta-analytically supported reliable (Schneider et al., 2020) and valid (Mihura et al., 2013) measure of disordered thinking. In addition, a more recently developed dimensional measure of disordered thinking –the Scales of Problematic Communication and Thinking (SPCT)—is also used to code speech samples collected using the Rorschach. Although various Rorschach methods have been suggested to assess negative symptoms, no formal scores currently exist. Therefore, first, we plan to investigate whether automated speech analysis provides incremental validity over R-PAS and SPCT scores of disordered thinking in predicting disorganized thinking ratings on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Second, we will investigate whether an automated coding of syntactic complexity will present clinician ratings of negative symptoms.
Methods: Patients (N = 90) were recruited from a maximum-security inpatient forensic hospital, ranging in age from 19 to 80 years-old (M = 40) and predominantly male (89%). R-PAS protocols were coded for thought disturbance using the R-PAS language and reasoning cognitive codes and the SPCT. The patient's primary clinician and psychiatrist provided PANSS ratings. The automated speech analysis software, Coh-Metrix, will be used to code the protocols using the indices such as syntactical complexity, semantic cohesion, and syntactical simplicity. Hierarchical regression analyses will be used to assess whether the Coh-Metrix cohesion indices provide incremental validity over the R-PAS scores of disordered thinking and the SPCT ratings in predicting PANSS ratings. Correlational analyses will be used to assess whether Coh-Metrix syntactical complexity and syntactical simplicity target PANSS negative symptoms.
Results: Rater agreement was excellent for the SPCT ratings was excellent (ICC = 0.97) and good for the PANSS ratings (ICC = 0.71). R-PAS Severe Cognitive Codes (SevCog) and the SPCT ratings were significantly correlated with PANSS Conceptual Disorganization ratings (r = 0.36, r = 0.38). SPCT ratings provided incremental validity over the R-PAS WSumCog score but not the hypothesized SevCog score. The last incremental validity step is to test whether Rorschach protocols coded by the chosen Coh-Metrix indices provide incremental validity over the SevCog score and SPCT ratings in predicting PANSS Conceptual Disorganization. Finally, we will test the correlation between Coh-Metrix syntactic complexity and PANSS negative symptoms. Initial hypotheses include syntactical complexity negatively correlating with

PANNS negative symptoms and syntactical simplicity positively correlating with PANNS negative symptoms.
Discussion: Our findings hope to provide clinicians with a more efficient and objective alternative to hand-scoring Rorschach protocols for disordered thinking as well as discover an automatic coding that targets negative symptoms. In all, we hope to contribute to the creation of an overarching framework for the use of automated speech analysis in the clinical assessment of emerging psychosis.

S53. 18-MONTH TRAJECTORIES OF DELUSIONAL DIMENSIONS AND RELATIONSHIPS WITH COGNITIVE-AFFECTIVE PROCESSES

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Background: Delusions manifest in a milder form in the general population, and consist of multiple dimensions, namely conviction, distress and preoccupation. It has been suggested that reasoning biases may be more strongly associated with delusional conviction, whereas anxiety-related processes such as worry and meta-worry may be more strongly associated with delusional distress and preoccupation. This study aimed to identify the trajectories of delusional conviction, distress, and preoccupation separately over 18 months, and to determine whether reasoning biases and worry at baseline differentiate the trajectories in a non-clinical sample.
Methods: A representative sample of 2596 young adults (age 18-35) were recruited from Hong Kong communities. Exclusion criteria: having a current psychiatric disorder (self-reported and then confirmed by diagnostic interview); severe brain injury or organic brain disorder; or intellectual disability. Participants were screened using the Peters et al Delusions Inventory (PDI; Peters et al, 2004); only participants who endorsed at least one delusional ideation were followed up longitudinally. Participants completed online surveys on delusional ideation, generalised anxiety, depression and level of functioning at baseline, 6 months, 12 months, and 18 months. Jumping to conclusions (JTC), bias against disconfirmatory evidence, trait worry and meta-worry were measured at baseline. Latent class growth modelling with non-normal distributions was used to identify the best-fitted number of trajectory classes for each delusional dimension (conviction, distress, preoccupation) through model comparison. MANOVA was then used to compare cognitive and affective processes between classes for each dimension.
Results: A total of 356 participants (238 females, age = 24.65 ± 3.32, estimated intelligence = 102.34 ± 8.36) were included in the longitudinal analysis. Sample sizes at 6, 12, and 18 months were 341, 339, and 336 respectively.
LCGA with skewed-t distribution showed that a three-group linear model was optimal for conviction (AIC = 2487.74, adjusted BIC = 2500.03, entropy = 0.62), distress (AIC = 2420.21, adjusted BIC = 2432.50, entropy = 0.69), and preoccupation (AIC = 2319.70, adjusted BIC = 2331.98, entropy = 0.63), compared to two- and four-group models as well as three-group quadratic or cubic models. The high-, moderate-, and low-intercept class sizes for each dimension were as follows: 38, 199, 111 for conviction, 85, 145, 117 for distress, and 154, 120, 74 for preoccupation, respectively. There was no significant change over time for seven out of nine classes (ps > .05).

MANOVA showed significant group differences across conviction classes and across distress classes on trait-worry at baseline ($F(1, 346) = 12.65$, $p < .001$, and $F(1, 346) = 90.34$, $p < .001$, respectively) and meta-worry at baseline ($F(1, 346) = 12.88$, $p < .001$, and $F(1, 346) = 80.75$, $p < .001$, respectively). Post-hoc multiple pairwise comparisons suggested that across conviction classes and across distress classes there was a significant graded difference on trait worry, with the highest level in the high-intercept class (ps < .001). There was a graded difference in meta-worry across distress classes (ps < .001). The difference across conviction classes on the 60-40 beads task approached significance ($F(1, 346) = 3.22$, $p = .07$). The preoccupation classes did not differ on all the baseline variables (ps > .05).

Discussion: Heterogeneous developmental trajectories of delusional dimensions were identified. Trait worry and meta-worry predicted distinct longitudinal development of delusional conviction and distress, whereas JTC was associated with delusional conviction.

S54. THE INFLUENCE OF SEX ON THE RELATIONSHIP BETWEEN EARLY LIFE TRAUMA, SCHIZOTYPY AND MOOD SYMPTOMS

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Background: Early life trauma has a negative impact on the developing brain and has been identified as a risk factor for a wide range of mental illnesses later in life, including psychosis and mood disorders. Not only has childhood trauma been shown to increase the risk of developing schizophrenia, it has also been shown to influence sub-clinical characteristics of psychosis. These sub-clinical 'schizotypy' characteristics are present in the general population to a milder degree. Sex differences are reported in the experience of trauma, schizophrenia and mood symptoms, and there is some emerging evidence suggesting sex also influences schizotypy. The relationship between childhood trauma and psychosis to be differentially affected by sex, with some research showing childhood trauma having a stronger effect on women with schizophrenia then in men. As this has not been thoroughly explored in schizotypy, this study aimed to investigate the sex differences in the relationship between childhood trauma, schizotypy and mood symptoms.

Methods: Sixty-one non-clinical participants (33 males and 28 females) aged between 18 and 45 completed the Childhood Trauma Questionnaire-short form (CTQ-DF) as a measure of early life trauma, the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) questionnaire as a measure of schizotypy and the Depression, Anxiety and Stress Scale (DASS) as a measure of mood symptoms. Mann-Whitney U tests were conducted to compare schizotypy factors, mood syptoms and trauma scores between males and females. Spearman Rank Correlation was conducted in males and females separately to observe sex differences in the relationship between schizotypy, mood symptoms and trauma. Bonferroni corrections were made to account for multiple comparisons, with significance set at $p = 0.004$.

Results: There were no sex differences for any trauma types, schizotypy factors or mood symptoms. When looking at the relationship between trauma and schizotypy in males, physical neglect correlated with stress (rho = 0.490). Emotional abuse, physical abuse, sexual abuse and emotional neglect did not correlate with any schizotypy traits or mood symptoms ($p > 0.005$). In females, physical neglect was correlated with disorganised schizotypy (rho = 0.615), depression (rho = 0.721), anxiety (rho = 0.541) and stress (rho = 0.551). Sexual abuse correlated with disorganised schizotypy (rho = 0.558) and anxiety (rho = 0.554). Emotional abuse was correlated with depression (rho = 0.652) and stress (rho = 0.635).

Discussion: Regarding the relationship between trauma, schizotypy traits and mood symptoms, our findings suggest that history of childhood trauma is related to disorganised schizotypy and mood symptoms in women but not in men. Schizotypy traits and mood symptoms in women do not appear to be associated with one specific type of trauma. Together, our findings indicate that there is a difference in vulnerability to the influence of childhood trauma between women and men. This suggests that the biological mechanisms affected by early life adversities may differ between the sexes and may result in different trajectories towards schizotypy traits and mood symptoms.

S55. INDIVIDUAL DIFFERENCES IN EFFORT-BASED DECISION-MAKING: A DIMENSIONAL INVESTIGATION IN SCHIZOPHRENIA AND MAJOR DEPRESSIVE DISORDER

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Background: Motivation deficits are prominent symptoms in schizophrenia (SZ) and major depressive disorder (MDD). One critical facet of motivation is effort-based decision-making, which refers to the mental processes involved in computing how much effort one is willing to expend for a desired reward. There are important individual differences associated with these computations, and motivation impairments can arise if any of the relevant cost-benefit information is not properly computed, appraised, or integrated. In order to advance our understanding of how individuals with SZ and MDD utilize different sources of cost-benefit information to guide choice behaviour, the present study utilized a dimensional approach to characterize the mechanistic processes underlying effort-based decision-making.

Methods: The sample consisted of 145 participants (n=51 SZ, n=43 MDD, n=51 healthy controls (HC)). Participants were administered a battery of clinical and cognitive assessments, as well as the Effort Expenditure for Rewards Task (EEfRT) as a measure of effort-based decision-making. Generalized linear mixed modelling (GLMM) was performed to estimate the subject-specific effects of reward, probability, and cost on choice behaviour, where cost was modelled based on cumulative physical exertion throughout the task. Bivariate correlations were conducted between each of the GLMM-derived coefficients with clinical and cognitive measures, and cluster analysis was applied to test for the presence of subgroups with different decision-making profiles.

Results: Correlational analyses revealed a significant association between the utilization of reward information with global cognition ($r = 0.46$, $p < 0.001$) and depressive symptoms ($r = -0.17$, $p = 0.04$), as well as a significant relationship between probability utilization and cognition ($r = 0.4$, $p < 0.001$). Further, k-means cluster analysis revealed an optimal 2-cluster solution, comprised of 76 participants in cluster 1 and 61 participants in cluster 2. Relative to cluster 1, cluster 2 is characterized by a significantly greater utilization of reward ($t(135) = -13.6$, $p < 0.001$) probability ($t(135) = -11.7$, $p < 0.001$), and cost information ($t(135) = 8.5$, $p < 0.001$) in guiding their decision-making. Participants in cluster 1 were significantly older ($t(135) = 1.8$, $p < 0.03$), more cognitively impaired ($t(134) = -3.3$, $p = 0.001$), and had lower levels of parental SES ($t(135) = -2.3$, $p = 0.03$). Within cluster 1, the utilization of reward, probability, and cost are all correlated with less severe clinical amotivation and depressive

symptoms, and greater cognitive functioning. Importantly, there were no significant differences in the distribution of diagnostic groups across clusters.
Discussion: Across diagnostic groups, we found that individuals use a range of reward and cost information in making effort-based decisions, to varying degrees. To this end, our findings revealed meaningful individual differences amongst SZ, MDD, and HC participants in their utilization of cost-benefit information in guiding effort-based decision-making. Further, two clusters of individuals were identified with distinct behavioural profiles of cost-benefit information utilization and differential clinical correlates, irrespective of diagnostic status. With elevated levels of clinical amotivation present in both clusters, it is possible that these distinct cost-benefit decision-making patterns represent different underlying motivational impairments. By parsing individuals into clinically meaningful subgroups based on similar effort-based decision-making profiles, this work may allow for greater opportunities to develop more individualized treatments for motivation deficits.

S56. HUMILIATION AND STATE ANXIETY AS PREDICTORS OF ATTENUATED PSYCHOSIS IN A COMMUNITY SAMPLE

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Background: Existing literature suggests that humiliation experiences, coupled with a negative family context, significantly predicted persecutory ideation in non-clinical participants. Whether this may also be linked to attenuated psychotic experiences is unknown. The current study aimed to assess whether familial adversity and humiliation may be related to hallucination-like experiences (HLEs) and other psychotic symptoms, and if state anxiety significant contributed to these relationships.
Methods: This cross-sectional study recruited a community sample of 93 adults (38% male; mean age=27.3 years, standard deviation=10.8 years), who completed measures of maladaptive familial environments, past and anticipated humiliation experiences, state anxiety and attenuated psychotic symptoms. Correlations and hierarchical regressions tested for direct and indirect relationships amongst study variables.
Results: A maladaptive family context, and humiliation (past and anticipated) were positively correlated with HLEs, and facets of attenuated psychotic symptoms. Anxiety uniquely predicted audio-visual and multisensory HLEs. Past humiliation and anxiety jointly predicted cognitive-perceptual disturbance and disorganisation, whereas fear of humiliation and anxiety jointly predicted interpersonal difficulty.
Discussion: Elevated state anxiety, coupled with humiliation, may increase attenuated psychotic symptoms in adulthood. Future research is needed to ascertain if these relationships hold true in clinical cohorts to examine the clinical significance of these data.

S57. CHARACTERIZING THE RELATIONSHIP BETWEEN PREMORBID ADJUSTMENT TRAJECTORIES AND EMOTION PROCESSING ABILITIES IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Individuals with schizophrenia demonstrate substantial heterogeneity in emotion processing abilities which may culminate from divergent trajectories of adjustment to various social contexts early on in development, as predicted by neurodevelopmental models of schizophrenia. However, few studies to date have investigated whether patterns of social adjustment from childhood through late adolescence may predict emotion processing abilities after the emergence of schizophrenia in late adolescence and early adulthood. We therefore examined the extent to which pre-onset adjustment trajectories are associated with post-onset emotion processing abilities in schizophrenia.

Methods: 112 outpatient participants who had recently experienced a first episode of schizophrenia underwent clinical evaluation for premorbid adjustment using the Cannon-Spoor Premorbid Adjustment Scale. Adjustment scores were averaged across four contexts (sociability and withdrawal, peer relationships, scholastic performance, and adaptation to school) during childhood, early adolescence, and late adolescence. Participants also completed the Mayer-Salovey-Caruso Emotional Intelligence Test, a task-based, problem-solving assessment of emotion processing which comprises four domains: identifying emotions, facilitating emotions, understanding emotions, and managing emotions. To classify premorbid adjustment trajectories, we compared the fits of a series of growth mixture models for mean adjustment scores across domains at each developmental period. We then examined whether premorbid adjustment trajectories from the best-fitting model predicted emotion processing domain scores.

Results: Participants were classified into three trajectories of premorbid adjustment: stable-poor adjustment (N=53, 47.3%), stable-good adjustment (N=50, 44.6%), and declining adjustment (N=9, 8.0%). In contrast to participants with stable-poor adjustment or stable-good adjustment, who showed no significant changes in adjustment across developmental periods, participants with declining adjustment demonstrated similar levels of adjustment to those with stable-good adjustment during childhood and early adolescence but showed a significant decrease in adjustment from early adolescence to late adolescence. Across the three trajectories, participants demonstrated similar performance for identifying emotions, facilitating emotions, and managing emotions. However, participants with stable-poor adjustment demonstrated significantly worse performance for understanding emotions (mean standard score = 82.2, s.d. = 14.6) compared to participants with stable-good adjustment (mean = 89.5, s.d. = 12.4) or participants with declining adjustment (mean = 87.4, s.d. = 12.8), ($F(2,109)=3.886$, $p=0.023$).

Discussion: As far as we are aware, this is the first study to elucidate associations between premorbid adjustment trajectories from childhood through late adolescence and emotion processing after onset of schizophrenia. In particular, our findings suggest that individuals who experienced low levels of functioning from childhood onwards are more likely to show difficulties with understanding emotions compared to individuals who had experienced relatively high functioning in childhood that endured or declined thereafter. In light of recent efforts towards identifying and remediating emotion processing skills in schizophrenia, our work highlights the utility of considering that the understanding of emotions may be rooted in earlier developmental periods than other aspects of processing emotional content.

S58. MOLECULAR VALIDATION OF SCHIZOPHRENIA SPECTRUM DIAGNOSES IN THE VA ELECTRONIC HEALTH RECORD

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Background: Schizophrenia (SCZ) is a common and heterogeneous disorder, with combined societal costs of treatment and loss of productivity exceeding $155 billion in 2013. Recognizing the major impact of serious mental illnesses (SMI) on the psychosocial function of affected veterans, the VA funded recruitment, assessment, and genotyping of 8,785 veterans with SCZ or bipolar disorder (BPD) as part of Cooperative Studies Program (CSP) #572, Genetics of Functional Disability in Schizophrenia and Bipolar Illness.
Methods: Leveraging the VA's extensive electronic health record (EHR) and available SCID-based diagnoses in CSP #572, we evaluated the sensitivity and specificity of automated clinical characterizations based on "phecodes." For consensus definitions of SCZ and related disorders, we identified putative cases and screened controls among ~700,000 Million Veteran Program (MVP) enrollees. We attempted to validate automated phenotyping assignments using polygenic risk score profiles (PRS) constructed from published genome-wide association study (GWAS) results.
Results: Among 3,953 SCZ and 5,425 BPD cases in CSP #572, 95.4% and 25.2% received ≥2 ICD-9/10 codes for SCZ; and 75.3% and 15.6% received an inpatient diagnosis. Similarly, 25% of SCZ cases and 95.7% of BPD cases received ≥2 codes for BPD; and 20.3% and 69.9% received an inpatient diagnosis. Among 697,921 MVP participants, 17,979 (2.6%) and 53,775 (7.7%) received ≥2 codes for SCZ or BPD, respectively. Encouragingly, PRS performed best for SCID-diagnosed cases, followed by participants with ≥2 ICD-9/10 codes for SCZ (R2~0.04 and 0.02; P<10-78). Subsequent PheWAS highlighted significant associations between SCZ PRS and suicidality, mood and anxiety disorders, post-traumatic stress disorders, and substance-use disorders, as well as hepatitis C infections and dental problems.
Discussion: The validity of the clinical assessments in CSP #572 represent a "gold standard" for the curation of SMI cases and controls in the VA population. We evaluate an automated phenotyping approach based on ICD codes using PRS, and highlight the challenges of differential diagnosis. We demonstrate that published genetic findings for SCZ and BPD are largely transferable to the VA's diverse patient population.

S59. ETHNIC DISPARITIES IN PSYCHOSIS PRONENESS AND MENTAL HEALTH RISK FACTORS DURING THE COVID-19 PANDEMIC

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Background: While the COVID-19 pandemic has worsened mental health in the general population, certain communities have been disproportionately impacted by the virus. In order

to determine which communities are especially at risk for developing psychosis, we examined the risk factors among individuals who identified as non-Hispanic/Latinx white, Hispanic/Latinx, and Black, Indigenous, or People of Color (BIPOC).
Methods: 430 respondents completed an anonymous, online survey evaluating mental, social, and physical wellbeing. Respondents completed a series of questions on demographics, physical health, history of hallucinations and past trauma. Participants had the option to identify their racial and/or ethnic background by selecting from a list of white, Black, Native Hawaiian, Asian, Native American, Hispanic/Latinx, or other. Mental health was assessed by the Depression, Anxiety, and Stress Scale (DASS); the UCLA Loneliness Scale; and the Prodromal Questionnaire-16 (PQ-16). Social isolation was assessed by the Social Network Index (SNI).
Results: Non-Hispanic white persons made up 36.51% of the total respondents. Hispanic/Latinx people accounted for 35.06% of the sample. The remaining 28.42% of the participants were designated to the BIPOC group. Hispanic/Latinx respondents reported significantly worse financial and general health than the BIPOC ($p<0.001$) and white respondents ($p<0.0001$). Hispanic/Latinx respondents reported significantly greater concern for COVID-19; traumatic events ($p<0.001$); DASS Depression ($p<0.001$), Anxiety, and Stress; PQ items; PQ Distress; and UCLA Loneliness compared to the white and BIPOC groups. Additionally, they had significantly reduced social network size compared to the other groups. White respondents reported significantly more negative attitudes about mask wearing when compared to Latinx/Hispanic and BIPOC respondents. BIPOC respondents had the greatest social network index compared to the other groups.
Discussion: Participants who identified as Hispanic/Latinx appear to be at the greatest risk for psychosis and overall poor mental health. It is necessary to provide comprehensive, culturally-competent mental health care throughout the pandemic in order to care for this community. Limitations of this study include combining multiple ethnicities into one BIPOC group due to small sample sizes; future research should aim to recruit more BIPOC respondents in order to determine the unique and critically important mental health care needs of each community.

S60. CUMULATIVE INCIDENCE OF ADOLESCENT ONSET SCHIZOPHRENIA SPECTRUM CONDITIONS IN BRITISH COLUMBIA, CANADA

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Background: Early identification and treatment of adolescent-onset schizophrenia spectrum conditions is associated with improved prognosis. Estimates of incidence and distribution of risk in the population are essential for health service and education planning. In the current study, we estimate cumulative incidence of schizophrenia spectrum conditions between the ages 13-19, and examine associations with sex, neighbourhood income quintile, family migration background, and birth year in British Columbia (B.C.), Canada.
Methods: Linked administrative health data was used to construct a cohort of individuals born between 1990-98 and residing in B.C. for all or part of the study period (N=191,846). Cases were identified by either one hospitalization or two outpatient physician visits within two years with a primary diagnosis of a schizophrenia spectrum condition (ICD-10: F20-29, ICD-9: 295, 297, 298). Survival analysis and cox proportional hazards regression were used to estimate cumulative incidence between age 13-19 and associations between risk and demographic factors.

Results: We found that 757 [95% CI: 718-797] per 100,000 in the population, 641 [95% CI: 590-695] per 100,000 females and 866 [95% CI: 909-927] per 100,000 males were diagnosed with a schizophrenia spectrum condition between ages 13-19 (male compared to female HR = 1.35 [95% CI: 1.29,1.40]). Risk was elevated among those in lower income neighborhoods (lowest compared to highest HR = 1.68 [95% CI: 1.59, 1.76]) and among those born in later years (birth cohorts 1996-98 compared to birth cohorts 1990-92 HR = 1.37 [95% CI: 1.30, 1.44]). Children of immigrants (HR = 0.66 [95% CI: .59, .73]), and to a lesser extent, children of refugees (HR = 0.83 [95% CI: .68, .98]), exhibited lower risk of schizophrenia spectrum conditions compared to children of non-migrants.
Discussion: Findings from this study will provide important information for the planning of early psychosis intervention services and the development of social and education policy in British Columbia. Future work should examine whether lower incidence among children of migrants and increasing incidence among later birth years is driven by differences in health service use or diagnostic patterns.

S61. WORDS MATTER: TRACKING STIGMA THROUGH SCHIZOPHRENIA RESEARCH – THE "SCHIZOPHRENIC" TERM CASE

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Background: Despite extensive efforts to reduce schizophrenia stigma in the general media and among healthcare professionals, we lack investigations on the stigma that may arise in the research literature. We aimed to evaluate how scientific articles refer to people with schizophrenia, specifically whether the "person-first" was used (e. g., a person with schizophrenia) or if the condition is described first (e. g., schizophrenic person). Thus, we verified whether the use of the term "schizophrenic," which is now widely recognized for conveying prejudice has changed over the years.
Methods: We conducted the following electronic-based search on Pubmed, from inception to August 6th, 2020: (schizophrenia[MeSH Terms]) AND (Schizophrenia[Title]). We randomly selected 50 articles among all retrieved records that were written in the English language, without type or time restriction. For each included article, two independent researchers extracted the year of publication, whether it was published in a schizophrenia specialized journal and how people with schizophrenia were referred to. Studies containing the term "schizophrenic" (i.e., schizophrenic, schizophrenic patient) were classified as stigmatizing and categorized into: 1) use of "schizophrenic" at least once in its corpus, and 2) "schizophrenic" employed as the primary term to designate people with schizophrenia. A third investigator resolved any extraction conflicts. We gathered this information by counting the frequency of each term used according to the context.
Results: Our search resulted in 48,317 reports, after excluding duplicates. Among the 50 articles selected at random, 30 (60%) described patients as "schizophrenic" at least once, and 17 (34%) adopted the term as the main word to refer to people with schizophrenia. Regarding the year of publication, 16 of the 30 articles using the term "schizophrenic" at least once (53,3%) were written before the year 2000, 10 (33,3%) between 2000 and 2010, and 4 (13,3%) between 2012 and 2019. Among the articles that adopted "schizophrenic" as the main word, 13 of the 17 articles (76%) were written before 2000, 3 until 2010, and none after. Twelve (40%) of the 50 studies were published in journals specialized in schizophrenia, of which 7 (58%) were among the articles that used the term "schizophrenic" at least once.

Discussion: We hypothesized that older articles would be the most stigmatizing, which was confirmed since 76% of the articles that used “schizophrenic" as the main term were published between 1959 and 1999. This result seems to follow the emergence of the Recovery movement and anti-stigma campaigns in the last decades. However, a considerable part of the papers written after 2000 still employed it to some degree, even in schizophrenia specialized journals, that need to keep alert to this topic. Overall, stigma is still present in schizophrenia research, although declining, indicating the need to maintain efforts and campaigns to reduce stigma. Further investigation of indicators and consequences of stigma among researchers deserves more attention in the literature.

S62. NEUROLOGICAL SOFT SIGNS (NSS) IN CENSUS BASED, DECADE-ADJUSTED HEALTHY ADULTS, 20 TO 80 YEARS OF AGE

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Background: Neurological Soft Signs (NSS) represent minor neurological features and have been widely studied in psychiatric disease. The assessment is easily performed. Quantity and quality may provide useful information concerning the disease course. Mostly, NSS scores differ significantly between patients and controls. However, literature does not give reference values.
Methods: We recruited 120 healthy women and men to build a representative, cross-sectional, census based sample of healthy individuals, ages 20 to >70 years, subdivided in 10-year blocks for a close approach to the human lifeline. Testing for NSS and neurocognitive functioning was performed following the exclusion of mental and severe physical illness.
Results1. NSS scores increased with age in this sample of 120 healthy subjects, independently of gender, intelligence, education, and handedness. Not only did NSS increase with age, but there was a period when most pronounced change occurred, namely between the 5th and 6th decade of life. 2. Worsening of motor function yielded the most important share of overall NSS increase. 3. The cognitive domains processing speed, visual search function, and concentration worsened in parallel with NSS. None of the remaining cognitive functions explained NSS increase with age.
Discussion: To our knowledge, this is the first study which systematically assessed age-related changes of NSS in healthy subjects on the basis of census data including age and education. The sample encompasses a well-characterized group of adults with similar cell sizes per decade (20 to > 70 years of age). We hypothesize that this worsening of NSS functionally reflects brain volume loss, which comes about at age 50 and increases thereafter.
Although the number of individuals is small, study results may lay a foundation for further validation of NSS in healthy individuals as reference values.

S63. LEVELS OF GLUTAMATERGIC NEUROMETABOLITES IN PATIENTS WITH SEVERE TREATMENT-RESISTANT SCHIZOPHRENIA: A PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY

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Background: Approximately 30% of patients with schizophrenia do not respond to antipsychotics and are thus considered to have treatmentresistant schizophrenia (TRS). To date, only four studies have examined glutamatergic neurometabolite levels using proton magnetic resonance spectroscopy (1H-MRS) in patients with TRS, collectively suggesting that glutamatergic dysfunction may be implicated in the pathophysiology of TRS. Notably, the TRS patient population in these studies had mild-to-moderate illness severity, which is not entirely reflective of what is observed in clinical practice.
Methods: In this present work, we compared glutamate + glutamine (Glx) levels in the dorsal anterior cingulate cortex (dACC) and caudate among patients with TRS, patients with non-TRS, and healthy controls (HCs), using 3T 1H-MRS (PRESS, TE = 35 ms). TRS criteria were defined by severe positive symptoms (i.e., ≥5 on 2 Positive and Negative Syndrome Scale (PANSS)-positive symptom items or ≥4 on 3 PANSS-positive symptom items), despite standard antipsychotic treatment.
Results: A total of 95 participants were included (29 TRS patients [PANSS = 111.2 ± 20.4], 33 non-TRS patients [PANSS = 49.8 ± 13.7], and 33 HCs). dACC Glx levels were higher in the TRS group vs. HCs (group effect: $F[2,75] = 4.74$, $p = 0.011$; TRS vs. HCs: $p = 0.012$). No group differences were identified in the caudate. There were no associations between Glx levels and clinical severity in either patient group.
Discussion: Our results are suggestive of greater heterogeneity in TRS relative to non-TRS with respect to dACC Glx levels, necessitating further research to determine biological subtypes of TRS.

S64. ATTENTION TO SOUND MODULATES GAMMA OSCILLATION: TOWARDS NEUROFEEDBACK TRAINING

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Background: Recent advances in computational neurophysiology have renewed attention in neurofeedback (NFB), a method in which brain activity is modulated via self-regulation to reduce symptoms such as auditory verbal hallucinations (AVH) in patients with schizophrenia (SZ). The gamma-band oscillation (GBO), which relates to cognitive function, has received much attention as a robust neurophysiological index in NFB. Moreover, current findings suggest that regulating GBO abnormality during the auditory tasks in SZ may reduce cognitive impairments or symptoms such as AVH. Thus, to determine whether attention to sound stimuli modulates GBO and increases synchronization to the stimulation, we measured EEG during an auditory attention task and examined its correlation with task performance in healthy subjects.
Methods: Twenty-five healthy subjects participated in the experiment. During EEG recording, subjects were presented with a 40 Hz and a 42 Hz click train in a 9:1 ratio, and were asked to 1) passively listen to the stimuli (passive task) and 2) respond to whether the same stimuli were presented, or whether there was a mixture of several different stimuli (attention task). The EEG data were analyzed for phase-locking factor (PLF) and evoked power for 40 Hz stimuli, and the differences between passive listening and auditory attention sessions were examined in relation to task performance.

Results: Compared with the passive listening sessions, both PLF (synchronicity to stimulus) and evoked power for 40 Hz stimuli were significantly increased ($p<0.05$) during the active attention tasks.
Discussion: Our results provide evidence that actively directing attention to sound stimuli modulates GBO and increases synchronization to the stimulation in healthy subjects. Thus, we may argue that this auditory attention task would be a useful paradigm for NFB training in clinical populations such as SZ, which may lead to reduce auditory cognitive impairments or symptoms such as AVH.

S65. SOCIAL BRAIN RESPONSIVITY DURING A TEAM-BASED GAME IN PATIENTS WITH PSYCHOSIS SPECTRUM DISORDERS: AN FMRI STUDY

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Background: Affiliative tendencies in humans reflect a powerful internal motivation to seek out and maintain interpersonal attachments. These attachments are among the most important sources of life satisfaction and mental and physical wellbeing. However, for individuals with psychosis spectrum disorders (PSD; e.g., schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features), developing and maintaining close relationships is often difficult. These difficulties may be driven by abnormalities in both the social approach and social avoidance motivation systems. The social approach system promotes engagement and attachment, and primarily involves the ventral striatum (VS) and orbital frontal cortex (OFC). The social avoidance system promotes avoidance of rejection and discord, and primarily involves the anterior insula (AI), anterior cingulate cortex (ACC), and amygdala. The aim of the current study was to investigate potential abnormalities in social approach and social avoidance motivation systems in individuals with PSD.
Methods: 72 individuals with PSD and 37 healthy controls completed an fMRI task in which participants performed a simple dot counting task in a social game context. The participant's goal in the task was to win as many trials as possible for his/her own team. After each trial, participants received verbal feedback on the outcome of their task performance paired with the expressive face of teammate or opponent team member. The faces of teammates were happy for win and angry for loss outcomes (i.e., congruent with outcome), whereas the faces of opponent team members were angry for win and happy for loss outcomes (i.e., incongruent with outcome). Thus, the task design allowed for a 2 x 2 analysis by group: outcome (Win vs. Lose) x team (same vs. other). Beta values were extracted from the five key regions of interest (ROIs) described above during performance feedback receipt and repeated measures ANOVA was used to compare within- and between-group activation across the task conditions.
Results: Across patient and control groups, social approach ROIs responded differentially to win vs. loss feedback (significant main effect of outcome). That is, VS and OFC both showed significantly greater activation during win trials versus lose trials, regardless of whether the feedback was from same or other team members. In contrast, across groups, only one of the social avoidance ROIs, the ACC, was sensitive to task manipulations. Specifically, both groups showed significantly greater deactivation for loss versus win trials, particularly when the feedback was from same team members (significant outcome by team interaction). There were no significant main or interaction effects involving group.

Discussion: Patients with psychosis spectrum disorders showed a pattern of activation in a priori ROIs that was similar to healthy controls during a novel team-based game playing paradigm. Notably, key social brain regions showed differential sensitivity to different types of feedback during this paradigm. Social approach system regions were uniformly sensitive to rewarding performance outcome feedback (wins) regardless of whether the feedback was delivered by a teammate or opponent. Only one social avoidance system region was sensitive to task conditions, reflecting a more complex interaction of outcome and team status. In this case, greater deactivation was observed in response to punishing performance outcome feedback (losses) delivered by a teammate. These findings suggest that intact neural activation previously found in those with PSDs during some relatively simple social cognitive tasks may extend to tasks that involve more complex social feedback processing.

S66. WHITE MATTER NEUROMETABOLIC SIGNATURES SUPPORT THE DEFICIT AND NON-DEFICIT DISTINCTION IN ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

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Background: The deficit syndrome (DS) is thought to be a subtype of schizophrenia characterized by more pronounced negative symptoms and is associated with treatment resistance, poorer quality of life, and worse outcomes. Postmortem and imaging studies have shown white matter (WM) differences between DS and non-deficit (nonDS) groups. It is hypothesized that non-DS WM abnormalities reflect myelin injury due to aberrant glutamatergic signaling, while DS abnormalities are due to early developmental processes.
Methods: We used single voxel magnetic resonance spectroscopy (PRESS; TE: 30ms) to measure left frontal white matter neurometabolites levels in 61 antipsychotic-naïve first episode psychosis patients (39 nonDS, 22 DS, assessed with the Schedule for the Deficit Syndrome) and 59 healthy controls. Partial volume correction was accomplished using the methods described by Gasparovic and colleagues. Metabolite levels were quantified with the LCModel. We used a multivariate analysis of co-variance (MANCOVA) to determine neurometabolite differences between groups.
Results: There were significant group differences when all metabolites were included in the model ($F(10, 208)= 2.16$; $p= 0.02$). Glutamate levels were higher in nonDS patients than DS and controls ($F(2, 108)= 3.10$, $p= 0.049$). NonDS patients had higher myo-inositol levels than controls ($F(2, 108)= 4.73$, $p= 0.01$)and DS trending higher than controls.
Discussion: Our results provide support for the hypothesis that deficit syndrome has a pathophysiology distinct from other forms of schizophrenia, and that this is already evident in antipsychotic medication-naive first episode psychosis patients. Future studies could potentially benefit from stratifying patients accordingly when investigating target engagement and efficacy of novel pharmacotherapies.

S67. REAL-TIME FMRI NEUROFEEDBACK FROM THE SUPERIOR TEMPORAL GYRUS MODULATES SELF-REFERENTIAL PROCESSES IN SCHIZOPHRENIA

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Background: Disturbances of self-referential processes are thought to contribute to the symptomatology of schizophrenia (SZ; Frith 1992). The medial prefrontal cortex (mPFC) and the superior temporal gyrus (STG) are core regions of the self-reference network both in healthy controls (HC; Philippi 2012; Jenkins & Mitchell 2011; Kelly 2002) and in SZ (Brent 2014; Lariviere 2017). Several studies have shown that lower activation of the self-reference network is associated with positive symptoms in SZ (Brent 2014; Lariviere 2017; Holt 2011). In particular, Holt (2011) showed that SZ is characterized by a hypoactivation of the mPFC selective to self-reflection during a self-reference task. Aberrant activation patterns to self-referential processes have been found also in the STG, in both SZ (Qin 2016) and in unaffected relatives (Brent 2014). Taken together, these results suggest that the mPFC and the STG are key components of the self-reference network and that they show aberrant activation patterns in SZ. Since mPFC and STG form a network, we propose that training SZ patients to modulate STG activity would impact the mPFC. In particular, we hypothesized that STG modulation will increase self-reflection sensitive activation in the mPFC during a self-reference task. In order to modulate STG activity, we trained patients to pay attention to sentences spoken in their own voices, which increases STG activation, and ignore sentences spoken in another person's voice, which decreases STG activation. Real-time neurofeedback (NF) in the form of a thermometer depicting STG activation levels was visually presented to subjects in the scanner while they performed the NF task.

Methods: SZ patients underwent a self-reference task on two separate occasions: before (pre-NF) and after neurofeedback directed at the STG (post-NF). The self-reference task was similar to that used in Holt (2011) in which patients listened to adjectives pre-recorded with a stranger's voice and judged whether the adjective referred to themselves (self) or had a positive or negative valence (semantic). No two adjectives were presented twice. We measured STG activation by extracting the activation pattern from patient-specific STG, which we identified using a localizer task that asked subjects to passively listen to sentences recorded in one's own vs. a stranger's voice (Okano 2020). Activation analysis of the self-reference task was performed with FSL v6.00, and motion outliers were identified with Artifact Detection Tools (Whitfield-Gabrieli, 2009) and censored. To test our hypothesis, we defined an a priori ROI in the mPFC (25mm radius) centered on the results from Holt (2011) and performed mPFC-masked analysis. The main contrast of interest was self > semantic during the Self-Reference task for post-NF vs pre-NF visits.

Results: Fourteen SZ patients underwent NF and completed the self-reference tasks (78% male, 71% Caucasian, mean age 35 ± 9). Activation analysis within the mPFC-ROI revealed significant activation increase after NF (pre-NF < post-NF) in three regions: the frontal medial cortex (peak MNI -12, 46, -6), para/cingulate gyrus (MNI 4, 46, 4), and frontal pole (MNI 32, 44, -8). All results were cluster uncorrected with a voxel threshold of $P<0.001$.

Discussion: Our results suggest that real-time fMRI NF directed at modulating the STG leads to activation increase in the mPFC selective for self-reflection in SZ patients. These results support our hypothesis that modulating one brain region belonging to the self-referential network, here the STG, brings about changes in other regions of the network such as the mPFC, even if not directly targeted with NF.

S68. REVIEW OF ANTIPSYCHOTIC EFFECTS OF CANNABIDIOL ON CRAVING IN SCHIZOPHRENIA PATIENTS

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Background: The burden of Schizophrenia (SZ) affects 20 million people worldwide. Addiction comorbidity affects nearly half of all patients with a SZ diagnosis. Cannabidiol therapy lightens this burden through its anti-psychotic effects and decreases craving in addiction. SZ patients are a group of people most vulnerable to addiction and using CBD to decrease craving helps break addictive habits. CBD can be used to decrease cognitive impairments and THC-induced psychotic symptoms. Research shows CBD alters brain activity in people with psychosis during memory tasks, making it similar to activation observed in people without psychosis during the same task.
Methods: In this review, 24 articles were examined and 14 were selected. Literature was reviewed for CBD effects at dosages of 600-1200 mg in clinically at-risk youth, patients with a SZ diagnosis, and patients with treatment resistant SZ.
Results: From the literature, we found CBD can (1) reverse effects of psychosis and (2) break the addictive craving cycle in subjects, particularly SZ patients most vulnerable to addiction. The optimal CBD dosage is 600mg or less for young individuals at clinically-high-risk for psychosis, 800-1000mg for standard treatment of SZ, and above 1000mg only for use in patients with a treatment-resistant SZ diagnosis. As confirmed by fMRI, CBD neutralizes areas of the brain showing unusual activity in people with psychosis, particularly SZ.
Discussion: SZ patients often use drugs and alcohol to temporarily decrease psychosis, and an addiction is formed. All current medications used in clinical practice to decrease psychosis have adverse effects. CBD can decrease psychosis and reduce craving in addiction. Cannabidiol therapy has potential to be the future of psychiatric treatment and improve quality of life for SZ and at high-risk SZ dimensions.

S69. EFFECTS OF 30-MINUTE SINGLE SESSIONS OF YOGA AND PILATES ON FRAILTY IN PATIENTS WITH PSYCHIATRIC DISORDERS: A PILOT RANDOMIZED CONTROLLED TRIAL

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Background: Frailty and subsequent falls are grave concerns, especially in patients with chronic psychiatric disorders in light of less exercise, insufficient nutrition, and negative effects of medications. We aimed to evaluate the effects and the clinical utility of a 30-minute single session of yoga and Pilates each on frailty in patients with chronic psychiatric disorders. Moreover, we tested whether the immediate effects of the session would be sustainable or transient.
Methods: In this open-label randomized controlled trial (University Medical Information Network Clinical Trial Registry: 000028835), participants aged 40 or above with any psychiatric diagnoses and no changes in antipsychotic treatment over the last eight weeks were randomly assigned to a single session of yoga, Pilates, or group therapy between August 2017 and June 2018 at the Minami-Hanno Hospital in Japan. Participants in each group received a 30-minute session of Hatha yoga, floor-based Pilates, or group therapy focusing on a healthy lifestyle with tips on fall prevention (1:1:1) in addition to their ongoing psychopharmacological treatments. We measured postural stability using the clinical stabilometric platform, salivary alpha-amylase (SAA) activity, anteflexion, handgrip, the Fatigue Visual Analogue Scale, and

the Subjective Happiness Scale before and after each session and at the one-week follow-up. Analysis of covariance (ANCOVA) and repeated measures analysis of variance were used to compare the session's effects with baseline values as covariates. Post-hoc analyses were performed with Bonferroni corrections for multiple comparisons as per requirement. Statistical analyses were performed using the IBM SPSS Statistics Version 24.
Results: Thirty-one patients participated in this study (19 men; mean±SD age, 52.6±9.5 years; schizophrenia, 80.7%; mean±SD duration of illness, 14.7±10.8 years). There were no significant differences in any demographic and clinical variables at baseline among the three groups. The ANCOVA demonstrated a significant difference in the range of trunk motion ($P<0.001$) and the SAA activity ($P=0.046$) among the three groups. Participants in the yoga (n=11) and the Pilates groups (n=10) showed significantly greater improvement in the range of trunk motion compared to those in the group therapy ($P=0.002$ and $P<0.001$, respectively). The yoga group participants also showed a decrease in the SAA activity relative to the Pilates group ($P=0.043$). We did not find any significant differences between any other variables, including anteflexion in sitting, handgrip, fatigue VAS, and SHS. In addition, clinical gains in the range of trunk motion and the SAA activity following a single session were not maintained in the 1-week follow-up.
Discussion: This preliminary study found beneficial but transient effects of a 30-minute single session of Hatha yoga and Pilates on postural stability in patients with chronic psychiatric disorders. Our findings represent the potential clinical utility of single yoga and Pilates sessions to reduce the risk of frailty among patients with schizophrenia. The transient clinical gains emphasize the need for further investigations on potential strategies to maintain such acute effects. However, this pilot study has several limitations, such as limited sample size (n=31), shorter session module, and uncontrol for the effects of medications considered while interpreting the findings. Therefore, future investigations on optimal frequency and intensity of the intervention are warranted to achieve sustained therapeutic effects of yoga and Pilates on the frailty among this population.

S70. CORTICOSTRIATAL CONNECTIVITY AND THE PREFRONTAL GLUTAMATE AND GLUTATHIONE PROFILE IN SCHIZOPHRENIA

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Background: Three major notions in the mechanistic pursuit of schizophrenia(SZ) are (1) striatal abnormality centered on dopamine (2) prefrontal abnormality centered on glutamate and (3) oxidative stress dysregulation, with most evidence focused on prefrontal cortex, especially the anterior cingulate cortex. We combined neuroimaging data on striatal structure, corticostriatal white matter connectivity and anterior cingulate glutamate and glutathione levels in patients at an early stage of schizophrenia (0 to 5 years of illness) to assess if a highly accurate identification of the diagnostic status is possible with this multimodal information
Methods: 7-Tesla diffusion and T1weighted MRI data of 81 subjects with SZ and 28 healthy control subjects were locally obtained along with proton magnetic resonance spectroscopy (37 slices, TR = 8000 ms, TE = 70 ms) from a 8 cm3 1H-MRS voxel on the bilateral dorsal ACC (dACC) to estimate glutamate (Glu) and glutathione (GSH) resonance. Probabilistic tractography from the seed (striatum) with winner-take-all voting was used to parcellate the striatum into 14 sub-regions (7 per hemisphere) according to its connectivity to 14 lobar regions

of the cortex. We parcellated the bilateral striatum into 14 sub-regions based on its structural connectivity profile in each individual. These parcellated sub-regions were then used to identify regionally selective corticostriatal fibers whose fractional anisotropy (FA) and mean diffusivity (MD) were estimated and averaged to derive singular FA and MD values for each of the 14 striatal subregions. The volume of each striatal subregion was also computed from T1 weighted structural images. A total of 44 features (2 metabolite values, 2 diffusion-based and 1 volume metric for 14 regions) were used in a random forest classifier. This was trained with 80% of the data using the above information as features to distinguish patients from healthy controls. The trained model was tested on the remaining 20% of the data. Area under the Precision-Recall curves (PRC) and F1-scores were used to evaluate the accuracies of the models. Feature importance was obtained to investigate which features are contributing most to the classifier

Results: The features extracted from the striatal sub-regions were able to distinguish patients with schizophrenia from the healthy controls with 80% of area under PRC along with a F1-score of 75%. Evaluation of feature ranking revealed that the anterior cingulate GSH and mean diffusivity of multiple corticostriatal tracts had the highest importance compared to volume or FA metrics in the classifier. We also noted that glutamate and glutathione levels were higher in healthy subjects with higher MD (specially along the connectivity between striatum and limbic, r=0.5, 0.39, respectively) but such a relationship was not seen among patients. Moreover, a group comparison using Welch's t-test was performed and it was found that the GSH values are significantly different ($p<0.03$) between the two groups (Schizophrenia>Healthy controls; but glutamate was not significantly different).

Discussion: Our results indicate that the combination of corticostrital connectivity, striatal subregional structural information and anterior cingulate glutamate and glutathione information provides incomplete diagnostic information on schizophrenia. The 80% accuracy level is modest and unlikely to be clinically meaningful. Nevertheless, this work highlights the importance of glutathione as well as corticostriatal white matter microstructure in schizophrenia. Further work on the interaction between glutathione and white matter connectivity is required to understand the downstream effects of oxidative stress in schizophrenia.

S71. RIGHT SIDED INFERIOR PARIETAL AND LATERAL OCCIPITAL HYPERGYRIA CHARACTERIZES CONVERTERS TO SYNDROMAL PSYCHOSIS IN A CLINICAL HIGH RISK COHORT

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Background: Clinical High Risk (CHR) includes that population who are at a prodromal phase of psychosis, a crucial period for early diagnosis, prognostication and intervention. Conventional brain morphometric measures (thickness, volume) are dynamic markers influenced by age, duration of illness, medications and other environmental factors in addition to the disorder itself. In contrast, cortical folding calculated by local gyrification index (lGI) is a static marker of in-utero neuronal development, is formed maximally by birth and remains relatively stable thereafter. This entity is least affected by adolescent neuromaturational processes and hence, is a useful marker to study the role of early abnormal neurodevelopmental processes in psychosis. We studied lGI patterns in a CHR cohort to know the differences between converters to psychosis and non-converters.

Methods: Seventy-two CHR subjects with attenuated positive symptom syndrome as defined by the Structured Interview for Psychosis-Risk Syndromes were followed up for 2 years. A standard analysis pipeline of vertex-based whole-brain lGI analysis was performed on the baseline T1-weighted MRI scans of all 72 subjects on Freesurfer version 6.0. The differences in baseline lGI were examined between subjects who converted to psychosis within the follow-up period (N=24) and non-converters (N=48), in a general linear model adjusted for age and gender. Thresholded ($p<0.001$) vertex-wise maps of both hemispheres obtained from the model were corrected for multiple comparisons by non-parametric cluster-wise permutation test. Clusters with corrected p-value (cwpcorr) < 0.05 were considered statistically significant.
Results: Increased lGI was observed in converters in a single cluster spanning the right sided inferior parietal and lateral occipital areas (cwpcorr=0.009), with a surface area of 1669.94mm2, with the vertex of maximum significance ($p<0.00001$) located in the right inferior parietal cortex (MNI coordinates: X=32.2, Y=-80.4, Z=14.3). There were no brain areas which demonstrated decreased lGI in converters compared to non-converters.
Discussion: Right sided inferior parietal and lateral occipital hypergyria represents a surface based morphometric vulnerability marker predisposing for conversion to syndromal psychosis in CHR. This finding may be a proxy marker for neurodevelopmental anomalies in parts of the brain that are earliest to develop in-utero (parietal and occipital) that might confer an increased risk of conversion to syndromal psychosis subsequently.

S72. CEREBRAL BLOOD FLOW ACROSS THE SPECTRUM OF PSYCHOSIS RISK: A PSEUDO-CONTINUOUS ARTERIAL SPIN LABELLING STUDY

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Background: The impact of primary indicated prevention of psychosis through the clinical high-risk state for psychosis (CHR-P) is dependent on the ability to accurately predict their outcomes. 22% of CHR-P individuals will transition to psychosis within two years but there are few options for refining these risk estimates. Currently, there is further refinement through the three CHR-P subgroups (attenuated psychosis syndrome [APS], brief limited intermittent psychotic symptoms [BLIPS] and genetic risk and deterioration [GRD]). BLIPS is a fairly uncommon subgroup (10% of all CHR-P individuals) and carries the highest level of psychosis risk (39% transition to psychosis within two years) compared to APS (85% of CHR-P individuals; 19% transition within two years) and GRD (5% of CHR-P individuals; 3% transition within two years). To better refine these risk estimates, it is key to supplement clinical assessments with further information, such as neuroimaging. Arterial spin labelling allows for direct measurement of cerebral blood flow (CBF), an indirect measure of neuronal function. Higher hippocampal and striatal CBF is seen in CHR-P individuals and elevated hippocampal CBF is also associated with a higher risk of transition. Due to this, we hypothesise that BLIPS

will have the highest global CBF, in addition to regional CBF in hippocampus and striatum, relative to APS, which will have higher global and regional CBF than healthy controls.
Methods: 20 CHR-P subjects meeting BLIPS criteria, 80 CHR-P subjects meeting APS criteria and 30 healthy control subjects were scanned using pseudo-continuous arterial spin labelling. All subjects were matched for age and gender. Global cerebral blood flow was examined in addition to a region-of-interest analysis to explore the differences in CBF in the striatum, hippocampus and hippocampal subregions (CA1 and subiculum). Group differences were assessed using ANOVA.
Results: No significant differences were found between healthy controls, APS and BLIPS in global CBF ($F = 2.124$, $p = 0.124$), striatum ($F = 0.459$, $p = 0.633$), hippocampus ($F = 0.625$, $p = 0.537$), CA1 ($F = 0.914$, $p = 0.403$) or subiculum ($F = 0.248$, $p = 0.781$).
Discussion: Groups with a contrasting inherent risk of developing a psychotic disorder do not appear to differ in terms of global, hippocampal or striatal CBF. Low statistical power, particularly in the BLIPS group, meant that we were unable to assess effects in transitions and limits our ability to detect small effect sizes. CBF may not be the best approach to refine estimates of psychosis risk, however, more highly powered research is needed to assess this further.

S73. CORTICAL PATTERNING OF ABNORMAL MORPHOMETRIC SIMILARITY IN PSYCHOSIS IS ASSOCIATED WITH BRAIN EXPRESSION OF SCHIZOPHRENIA-RELATED GENES

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Background: Schizophrenia has been conceived as a disorder of brain connectivity, however despite significant research, the biological mechanisms underlying schizophrenia are still unclear. The aims of this study were: 1) to assess whether there are reproducible case-control differences in structural brain connectivity in psychotic disorders, using a novel approach called morphometric similarity mapping; 2) to relate these differences to the underlying biological mechanisms using post-mortem gene expression data. We note that this study has been published (Morgan et al, PNAS 2019, https://doi.org/10.1073/pnas.1820754116).
Methods: We quantified structural brain differences in patients with psychotic disorders using morphometric similarity mapping, which measures the structural similarity between pairs of brain regions. Prior work has shown that morphometric similarity can be used as a marker of interareal cortical connectivity (Seidlitz et al, Neuron 2018). We therefore performed morphometric similarity analysis of MRI data in three prior case–control studies of psychotic disorders: in total, $n = 185$ cases with psychotic disorders and $n = 227$ healthy control subjects. We then used partial least squares (PLS) regression to test the hypothesis that this MRI network phenotype of psychotic disorders was correlated with anatomically patterned gene expression using data from the Allen Human Brain Atlas.
Results: Psychosis was associated with globally reduced morphometric similarity in all three case-control studies, in-line with the dysconnectivity hypothesis of schizophrenia. There was

also a replicable pattern of case–control differences in regional morphometric similarity, which was significantly reduced in patients in frontal and temporal cortical areas but increased in parietal cortex. Using prior brain-wide gene expression data from the Allen Human Brain Atlas, we found that the 1 2020 Congress of the Schizophrenia International Research Society cortical map of case–control differences in morphometric similarity was spatially correlated with cortical expression of a weighted combination of genes enriched for neurobiologically relevant ontology terms and pathways. In particular, a subset of these genes formed a dense, topologically clustered interaction network which included several genes previously linked to antipsychotic mechanisms of action. In addition, genes that were normally overexpressed in cortical areas with reduced morphometric similarity were significantly up-regulated in three prior post mortem studies of schizophrenia.

Discussion: Morphometric similarity mapping disclosed a robust and replicable cortical pattern of differences in psychosis patients. This pattern was consistent across three independent datasets with different samples, locations, scanners, and scanning parameters, suggesting that it is robust enough to be plausible as a candidate imaging biomarker in large-scale, multicenter studies of psychosis. The tight coupling we observed between MRI-derived transcriptional weights and gene transcription measured histologically was highly significant. Some of the genes identified may deserve additional attention as targets for antipsychotic interventions. Overall, we begin to see how combining genomics and imaging can give a more integrative understanding of schizophrenia, which might inform future treatments.

S74. RESTING STATE FUNCTIONAL CONNECTIVITY OF THE FRONTOPARIETAL NETWORK IN THE DEFICIT SYNDROME

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Background: It remains debated whether the deficit syndrome is a distinct disease or if it lies on the more severe end of the schizophrenia spectrum. Neuroimaging is an important tool that can help shed light on the underlying neurobiology and has potential implications in the diagnosis and treatment of patients with or without deficit syndrome.

Methods: Eighty-four medication-naïve, first-episode psychosis (FEP) patients were recruited from the emergency psychiatric department at The University of Alabama at Birmingham, along with 74 healthy controls. Of the patient sample, 27 people were diagnosed with deficit syndrome based on the Schedule for the Deficit Syndrome (SDS) and 57 were considered non-deficit. Images were obtained using a 3T whole-body Siemens MAGNETOM Prisma MRI scanner (Siemens AG, Erlangen, Germany). Structural images were acquired using a high-resolution T1-weighted scanner (magnetization prepared rapid acquisition gradient-echo: repetition time = 2400 ms; echo time = 2.22 ms; inversion time = 1000 ms; flip angle = 8 degrees; generalized autocalibrating partially parallel acquisitions (GRAPPA) factor = 2; voxel size = 0.8 mm^3). Resting state functional images were obtained by opposite phase encoding directions (anterior to posterior and posterior to anterior; repetition time = 1550 ms; echo time = 37.80 ms; flip angle = 71 degrees, field of view = 104 mm^2; multiband acceleration factor = 4; voxel size= 2 mm^3; 225 volumes, and 72 axial slices). Participants were asked to lie still and let their mind wander while keeping their eyes open. Preprocessing was performed using CONN toolbox (version 18a). Functional scans underwent functional alignment and unwarping, slice-timing correction, outlier identification, and smoothing. After removing poor quality scans, 80 patients and all 74 controls were included in final analyses. Resting state functional connectivity was analyzed using the frontoparietal network (FPN) as the region-of-

interest (ROI). Resting state functional connectivity was also analyzed based on the subnetworks of the FPN proposed by Patterson and Yeo.
Results:: Patients and healthy controls were matched on age and sex. FPN connectivity was decreased in patients compared to controls, but we found no differences between deficit and non-deficit patients in functional connectivity of the FPN. In addition, there was no difference between the patient groups in the FPN subnetworks.
Discussion: Few studies have examined the resting state functional connectivity in the FPN as a factor in comparing deficit syndrome to non-deficit schizophrenia. Our functional MRI data demonstrated that FPN connectivity did not differ between deficit and non-deficit patients suggesting that the resting state functional connectivity of the FPN may not be a reliable measure to differentiate these subgroups.

S75. ASSOCIATIONS OF NEUROLOGICAL SOFT SIGNS AND CEREBELLAR-CEREBRAL FUNCTIONAL CONNECTIVITY IN PATIENT WITH FIRST-EPISODE SCHIZOPHRENIA AND THEIR UNAFFECTED SIBLINGS

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Background: Neurological softs signs (NSS) are defined as subtle neurological abnormalities with manifestations of motor coordination, sensory integration and disinhibition. Evidence has suggested NSS as one of the promising endophenotypes for schizophrenia spectrum disorders. Moreover, accumulating evidence also suggests that NSS may be associated with specific functional connectivity. The present study aimed to examine the cerebellar-cerebral resting-state functional connectivity (rsFC) of NSS in patients with first-episode schizophrenia (FES) and their unaffected siblings (SB).
Methods: We administered the abridge version of the Cambridge Neurological Inventory (CNI) to 51 FES patients, 20 unaffected SB, and 50 healthy controls (HC) to assess the severity of NSS. All the participants also underwent a resting-state functional magnetic resonance imaging (MRI) scan. Ten regions of interest (ROIs) in the cerebellum were selected to represent cerebellar motor network (MN) and cerebellar executive control network (EN), which correspond to the "sensorimotor-cognitive" dichotomy of NSS. The rsFC between each ROI and the whole brain voxels were constructed, and the linear regression analysis was conducted to examine the cerebellar-cerebral rsFC patterns of NSS in each group.
Results: Regarding the cerebellar MN, there were positive correlations observed between the rsFC of the cerebellar MN with the default mode network (DMN) and NSS in FES patients group (CNI total score and the motor coordination subscale) and the SB group (CNI total score and the motor coordination and sensory integration subscales). The rsFC of the cerebellar MN and the sensorimotor network were significantly and positively correlated with NSS (CNI total score and the motor coordination and sensory integration subscales) in the SB group.
Regarding the cerebellar EN, we found that both the FES and the SB groups exhibited significantly negative correlations between NSS (CNI total score and the motor coordination subscale) and the rsFC of the cerebellar EN with the DMN. Moreover, the rsFC between the cerebellar EN and the sensorimotor network was positively correlated with NSS (CNI total score and the motor coordination and disinhibition subscales) in the SB group.

Discussion: We found inverse correlations between NSS and the rsFC of the cerebellar EN/MN and the DMN in both FES patients and their unaffected SB. These findings suggest that altered

cerebellar-cerebral rsFC between these networks is correlated with the NSS. The SB group also exhibited a unique correlational pattern that NSS were correlated with the cerebellar-sensorimotor network rsFC. These findings suggest that such a network connectivity may serve as a potential biomarker for schizophrenia.

S76. THE TRAJECTORY OF PUTATIVE ASTROGLIAL DYSFUNCTION IN FIRST EPISODE SCHIZOPHRENIA: A LONGITUDINAL 7-TESLA MRS STUDY

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Background: Astroglial pathology has been long suspected in schizophrenia. Myo-inositol, a metabolic marker that is particularly abundant in astroglia, is reduced in the anterior cingulate cortex of patients with schizophrenia. This has been taken to indicate a deficit in astroglial activation and recruitment; though the status of this putative astroglial pathology in untreated first episode schizophrenia and its subsequent trajectory are unknown to date.
Methods: We employed 7T magnetic resonance spectroscopy (1H-MRS) and quantified myo-inositol spectra at the dorsal anterior cingulate cortex in 31 participants; 21 patients with schizophrenia and a median lifetime antipsychotic exposure of less than 3 days, followed them up after 6 months of treatment, and 10 healthy subjects scanned twice over the same time period. We studied time by group interaction on myo-inositol after adjusting for gender and age.
Results: There was a significant time by group interaction in myo-inositol concentration ($\eta p2 = 0.19$, $p = 0.02$), with patients showing a significant reduction at the baseline ($\eta p2 = 0.47$, $p < 0.001$) but not at the 6-months follow-up ($\eta p2 = 0.02$, $p = 0.44$). Older age and female gender were associated with lower levels at both time points ($\eta p2 = 0.14\text{-}0.36$, $p = 0.06\text{-}0.001$). On average, patients with early psychosis receiving treatment showed an 8.9% increase, while healthy controls showed an 8.2% decrease in MRS myo-inositol levels over the follow-up period.
Discussion: We report a significant reduction in myo-inositol concentration in the anterior cingulate cortex in schizophrenia at an early, untreated state of acute illness that improves over time. This trajectory indicates that dynamic astroglial changes are likely to operate in the early stages of schizophrenia. MRS myo-inositol may be a critical marker of amelioration of active psychosis in early stages of schizophrenia.

S77. BASAL GANGLIA VOLUMES BEFORE AND AFTER EXERCISE INTERVENTION IN PEOPLE WITH CHRONICALLY TREATED SCHIZOPHRENIA

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Background: People with chronic schizophrenia may have basal ganglia expansion linked to movement disorders and psychomotor deficits. Increased basal ganglia volumes has been associated with antipsychotic medication and duration of illness. Exercise has been shown to modulate adverse metabolic effects of antipsychotics and induce neuroplastic changes in

people with treatment-resistant schizophrenia and may help address basal ganglia expansion and extrapyramidal symptom severity.
Methods: Sixteen treatment-resistant schizophrenia in-patients and ten age- and sex-matched healthy volunteers participated in a 12-week moderate-intensity aerobic and weight-bearing exercise program to examine the effects of exercise on basal ganglia volumes, cardiovascular health, and clinical symptoms. Structural neuroimaging, clinical, and physical health assessments were conducted at baseline and follow-up.
Results: At baseline, participants with schizophrenia had significantly increased caudate volume compared to healthy volunteers ($F(25) = 8.974$, $p = 0.006$, $\eta2 = 0.281$). Putamen and pallidal volumes were not significantly different at baseline. Participants with schizophrenia had significantly higher resting heart rate ($F(25) = 6.946$, $p = 0.014$, $\eta2 = 0.224$), BMI ($F(24) = 11.379$, $p = 0.003$, $\eta2 = 0.331$), triglyceride levels ($F(24) = 4.502$, $p = 0.045$, $\eta2 = 0.164$), and reduced VO2Max ($F(24) = 16.306$, $p = 0.001$, $\eta2 = 0.415$) compared to healthy volunteers and these measures were all significantly correlated with antipsychotic dose for participants with schizophrenia. No significant relationships were observed between antipsychotic dose and volumes of interest at baseline or between change in antipsychotic dose and change in volumes over the 12 weeks (all p-values > 0.10).
A significant reduction in putamen volume was observed at 12-weeks for the patient group ($F(14) = 6.226$, $p = 0.026$, $\eta2 = 0.308$). No significant change was seen in caudate or pallidal volume or putamen volume of healthy volunteers. A significant Group x Time interaction was observed for caudate volume ($F(23) = 5.617$, $p = 0.027$, $\eta2 = 0.196$), and putamen volume ($F(23) = 8.721$, $p = 0.007$, $\eta2 = 0.275$) indicating that the change in volume differed between the patient participant and healthy volunteer groups over the 12-weeks of the exercise intervention with a decrease in caudate and putamen volume for participants with schizophrenia only. Although a similar pattern was observed for pallidal volume, it was not statistically significant. Total psychosis symptom severity scores ($F(15) = 34.791$, $p < 0.001$, $\eta2 = 0.699$) and body mass index ($F(13) = 5.496$, $p = 0.036$, $\eta2 = 0.297$) were significantly decreased at follow-up. Decreased extrapyramidal symptom severity was associated with reduction in putamen volume ($ß = 0.649$, $t = 2.608$, $p = 0.022$).

Discussion: Regular exercise may reduce caudate and putamen volume for individuals with chronically treated schizophrenia and reductions in putamen volume may be associated with improvements in extrapyramidal symptoms. Regular exercise at a moderate level of intensity may be an effective nonpharmacological intervention even for treatment-resistant in-patients with significant burden of illness.

S78. RICH-CLUB CONNECTIVITY AND STRUCTURAL CONNECTOME ORGANIZATION IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS AND INDIVIDUALS WITH EARLY ILLNESS SCHIZOPHRENIA

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Background: Brain dysconnectivity has been posited to be a biological marker of schizophrenia, with alterations of brain network organization present in the early stages of schizophrenia. Emerging structural connectome research in psychosis has focused on rich-club regions, a selective collection of highly centralized and densely interconnected brain hubs that

is critical in global brain communication but is disproportionately vulnerable to dysconnectivity. These studies found rich-club connectivity and structural network organization abnormalities in schizophrenia; however, less is known about the extent to which these abnormalities are present in individuals at clinical high risk for psychosis (CHR), and how they compare with abnormalities early in the course of schizophrenia (ESZ).
Methods: Combining structural magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI), we created connectome maps and concurrently examined rich-club connectivity and structural network organization in CHR (n = 53) and ESZ (n = 70) relative to healthy controls (HC; n = 74) after accounting for the effects of normal aging. To further characterize rich-club regions, we examined the DWI white matter microstructure and MRI structural morphology of rich-club regions. Additionally, we examined associations with clinical symptoms, antipsychotic medication status, and in CHR specifically, conversion to psychosis.
Results: Using the HC data and selecting brain regions that shared the most connections with other regions (connections > 18), bilateral precuneus, superior frontal, superior temporal, superior parietal, and insula were identified as rich-club regions. Intact rich-club organization was found in all three groups. However, compared to HC and CHR, ESZ had significantly decreased connectivity between and among rich-club and non-rich club regions (ps < .026). ESZ also had decreased structural network organization, as evidenced by decreased network density and network strength (ps < .015) compared to HC and CHR, and increased modularity (i.e., measure of network segregation) compared to CHR (p = .009). Additionally, ESZ had white matter microstructural differences in the insula and decreased cortical thickness in all rich-club regions (ps < .021) compared to HC and CHR. Further, clinical general psychopathology symptoms, but not antipsychotic dosage, in ESZ were associated with multiple structural network organization metrics (ps < .012). In contrast, CHR did not have abnormalities in rich-club connectivity or structural network organization, and there were no significant differences between CHR converters to psychosis (n = 10) and CHR non-converters followed for at least 24 months (n = 25).
Discussion: Overall, we found decreased rich-club connectivity and characteristics as well as structural connectome disorganization were present early in schizophrenia. These abnormalities were not yet evident at initial ascertainment of CHR individuals, irrespective of whether they subsequently converted to psychosis. These suggest that decreased rich-club and network abnormalities may be an early feature of schizophrenia and may also be related to general psychopathology symptoms and widespread global deficits present in schizophrenia. Findings from the current study provide novel insights into the neurobiological mechanisms underlying schizophrenia and highlight the critical roles of rich-club connectivity and structural network disorganization early in schizophrenia.

S79. BASELINE STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING PREDICTS EARLY TREATMENT RESPONSE IN SCHIZOPHRENIA

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Background: Multimodal neuroimaging features provide opportunities for accurate classification and personalized treatment options in the psychiatric domain. This study aimed to investigate whether brain structural and functional features predict responses to the overall treatment of schizophrenia at the end of the first or a single hospitalization.
Methods: Structural and functional magnetic resonance imaging (MRI) data from two independent samples (N = 85 and 63, separately) of schizophrenia patients at baseline were

included. After treatment, patients were classified as responders and non-responders. Radiomics features of gray matter morphology and functional connectivity were extracted using Least Absolute Shrinkage and Selection Operator. Support vector machine was used to explore the predictive performance. Prediction models were based on structural features (cortical thickness, surface area, gray matter regional volume, mean curvature, metric distortion, and sulcal depth), functional features (functional connectivity), and combined features.
Results: There were 12 features after dimensionality reduction. The structural features involved the right precuneus, cuneus, and inferior parietal lobule. The functional features predominately included inter-hemispheric connectivity. We observed a prediction accuracy of 80.38% (sensitivity: 87.28%; specificity 82.47%) for the model using functional features, and 69.68% (sensitivity: 83.96%; specificity: 72.41%) for the model using structural features. Our model combining both structural and functional features achieved a higher accuracy of 85.03%, with 92.04% responder and 80.23% non-responders to the overall treatment to be correctly predicted.
Discussion: These results highlight the power of structural and functional MRI-derived radiomics features to predict early response to treatment in schizophrenia. Prediction models of the very early treatment response in schizophrenia could augment effective therapeutic strategies.

S80. Abstract not included

S81. USING STATISTICAL GENETICS AND GENOME EDITING TO IDENTIFY FUNCTIONAL VARIATIONS OF SCHIZOPHRENIA ASSOCIATED EQTLS

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Background: Schizophrenia and related psychotic disorders are among the world's most debilitating brain diseases. Despite having a significant heritability, the syndrome's complexity and polygenic architecture has made genetic association challenging. While large GWAS provide strong clues to the location of genetically significant variation affecting the regulation of gene expression in schizophrenia, we now need to complete the picture at the biological level and convert the genetic inference to biochemical mechanisms. The problem is that we often cannot functionally segregate all the correlated variants transmitted together into individual genes, as the causal SNPs are obscured by linkage disequilibrium. This study aims to identify the non-coding causal variation within eQTLs and characterize their biological influence in schizophrenia using RNA-guided genome editing (CRISPR).
Methods: Summary statistics from schizophrenia working group (PGC2) GWAS were integrated with brain eQTL data from the GTEx database using MAGMA, Sherlock and FUSION. The candidate variants were then ranked to priorities biological validation by RNA-guided genome editing. In each case synthetic guide RNAs were synthesised before complexation with recombinant Cas9 protein. The Cas9-guide RNA ribonucleoprotein complexes were then transfected or electroporated into HEK293 or SH-SY5Y cells with a donor repair template to facilitate homology directed genome (HDR) editing. Transfected cell populations were then screened for edited cells using the TOPO-TA cloning and/or sanger sequencing before isogenic cell.

Results: Our bioinformatic analysis revealed 16 genes among undifferentiated loci with high likelihood of being causal variants contributing risk for schizophrenia. Candidate SNPs considered most likely to modulate eQTLs were then prioritized for in vitro analysis through CRISPR/Cas9 genome editing. The most significant genes including PCCB, SF3B1, SNX19, PITPNM2 and ITHI4 as they showed greater association with schizophrenia compared to others in the same locus. We are currently analysing allelic of isogenic cell lines clones to confirm their allelic variation and epression.
Discussion: This analysis suggests there are several gene candidates among undifferentiated loci with high likelihood of functional variants contributing risk for schizophrenia. To further validate these candidates, we are implementing RNA-guided genome editing to generate isogenic cell lines for and allelic expression analysis in vitro. This study is paving a way to an improving our understanding of the components that contribute to the pathogenesis of schizophrenia and has clinical significance for the development of new treatment strategies for the disorder.

S82. THE EFFECT OF NRN1 GENE ON CORTICAL THICKNESS IN HEALTHY SUBJECTS AND SUBJECTS WITH SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is considered a neurodevelopmental disorder with associated neuroanatomical and synaptic plasticity alterations (Berdenis et al., 2020; Keshavan et al., 2020). Such alterations have been associated with CT reductions (Watsky et al., 2016). Recent GWAS data have shown the involvement of neurodevelopment and plasticity-related genes in SZ (Pardiñas et al., 2019), and cortical thinning has been associated with the presence of risk-factor genes of SZ (Ball et al., 2020; Rimol et al., 2010). Neuritin1 gene (NRN1) plays a key role in neurodevelopment and synaptic plasticity (Zhou and Zhou, 2014) and has been associated with SZ risk (Fatjó-Vilas et al., 2016). Therefore, we aimed to conduct a neuroimaging-genetics study in order to: i) determine the association of NRN1 sequence variants with CT variability both within patients and healthy subjects; ii) to compare the impact of NRN1 on CT measures between patients and controls.
Methods: We conducted a neuroimaging-genetic study in a sample of 47 subjects with SZ and 47 healthy subjects (matched by sex, age and premorbid IQ). CT measures obtained from MRI scans for five lobes per hemisphere plus the insula cortex according to Desikan-Killiany atlas (FreeSurfer). Eleven Single Nucleotide Polymorphisms (SNPs) at NRN1 were genotyped. The SNPs were dichotomised (carriers of the minor allele versus homozygous for the major allele).

Linear regression analyses were performed as implemented in PLINK. Multiple testing corrections were applied.
Results: Within healthy subjects (HS), the minor alleles of rs9379002 and rs1475157 were associated with higher CT scores of the temporal lobe and the left hemisphere. Within subjects with SZ the results were more spread: i) the minor allele of rs9405890 was associated with greater CT values of the parietal lobe of the right hemisphere; ii) the minor allele of rs2208870 was associated with lower CT values of the occipital lobe of the left hemisphere, while the minor alleles of rs4960155 and rs9405890 were associated with higher values in this same lobe; iii) the minor allele of rs1475157 was associated with inferior CT values of the left insula. We also describe the interaction NRN1xdiagnosis for rs1475157 and rs2208870. The minor alleles of both polymorphisms were associated with cortical thinning in subjects with SZ and increased CT in HS in the left temporal and occipital lobes respectively.
Discussion: Our results suggest an effect of NRN1 on CT on different brain areas within HS and subjects with SZ, being its effect more widespread in subjects with SSD than in HS. We also detected an interaction NRN1xdiagnosis effect in CT, suggesting that NRN1 is involved in neurodevelopmental processes altered in SZ, in particular those reflected as cortical thickness reductions. These results are in line with previous work describing strong genetic underpinnings and high heritability of CT and specifically add evidence on the role of NRN1 gene (Ball et al., 2020; Goldman et al., 2009; Rimol et al., 2010). Also, our results converge with evidence showing that temporal and occipital lobes are some of the brain regions where CT is more affected by the genetic risk for SCZ, specifically in the left hemisphere (Hedman et al., 2016; Yan et al., 2019).
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S83. POLYGENIC RISK SCORES FOR LATE SMOKING INITIATION ASSOCIATED WITH THE RISK OF SCHIZOPHRENIA

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Background: Patients with schizophrenia display characteristic smoking-related behaviors, and genetic correlations between smoking behaviors and schizophrenia have been identified in European individuals. However, the genetic etiology of the association remains to be clarified. The present study investigated transethnic genetic overlaps between European-based smoking behaviors and the risk of Japanese schizophrenia by conducting polygenic risk score (PRS) analyses.
Methods: Large-scale European genome-wide association study (GWAS) datasets (n=24,114—74,035) related to four smoking-related intermediate phenotypes [(i) smoking initiation, (ii) age at smoking initiation, (iii) smoking quantity, and (iv) smoking cessation] were utilized as discovery samples. PRSs derived from these discovery GWASs were calculated for 332 Japanese subjects [schizophrenia patients, their unaffected first-degree relatives (FRs) and healthy controls (HCs)] as a target sample. Based on GWASs of European

smoking phenotypes, we investigated the effects of PRSs on smoking phenotypes as well as the risk of schizophrenia in the Japanese population.
Results: Of the four smoking-related behaviors, the PRSs for age at smoking initiation in Europeans significantly predicted the age at smoking initiation (R2=0.049, p=0.026), and the PRSs for smoking cessation significantly predicted the smoking cessation (R2=0.092, p=0.027) in Japanese ever smokers. Furthermore, the PRSs related to age at smoking initiation in Europeans were higher in Japanese schizophrenia patients than in the HCs, and those of the FRs were intermediate between those of patients with schizophrenia and those of the HCs (R2=0.015, p=0.015). In our target subjects, patients with schizophrenia had a higher mean age at smoking initiation (p=0.018) and rate of daily smoking initiation after age 20 (p=0.023) compared with the HCs. A total of 60.6% of the patients started to smoke before the onset of schizophrenia.
Discussion: These findings suggest that genetic factors affecting late smoking initiation are associated with the risk of schizophrenia.

S84. CLOZAPINE, BUT NOT HALOPERIDOL, PARTIALLY ATTENUATES MK-801-INDUCED PROTEOME CHANGES IN HUMAN BRAIN SLICES: IMPLICATIONS FOR SCHIZOPHRENIA TREATMENT

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Background: The N-methyl-D-aspartate receptor (NMDAr) presents a profile of hypofunction in schizophrenia and plays a central role in its pathophysiology. Preclinical and postmortem studies have already attempted to decipher the molecular pathways involved with NMDAr dysfunction. In this study, an ex vivo culture of human brain samples was used to visualize the proteomic changes related to NMDAr hypofunction and how antipsychotics modulate these changes.
Methods: Cortical tissue was obtained from adult patients (n=10) who underwent amygdalohippocampectomy for the treatment of refractory temporal lobe epilepsy (HCRP #17578/15). Lateral temporal cortex samples were sliced at 200 μm in a VT1000s vibratome (Leica). Free-floating slices were kept in culture for two days. First, the concentration of MK-801 that reduces the downstream intracellular cascade triggered by NMDAr activation in human brain slices was determined. Slices (n=4-6) were treated with vehicle, MK-801 (100 μM), or the combination of MK-801 plus haloperidol (100 μM) or clozapine (100 μM or 300 μM) for proteomic analysis. After eight hours, slices were collected for proteome extraction and digestion. Peptides were injected into an ACQUITY UPLC M-Class (Waters, Co) coupled to a Synapt G2-Si mass spectrometer (Waters, Co). Raw data processing, protein identification, and protein quantitation were performed using Progenesis QI for Proteomics 4.0. Proteins differentially regulated (ANOVA<0.05) were used to perform the in silico analyses.
Results: We identified and quantified 1074 proteins, and MK-801 was found to differentially regulate 198 proteins compared to vehicle. The ANOVA test revealed that cotreatment of slices with MK-801 and haloperidol, low- or high-dose clozapine compared with MK-801, regulated 50, 50, and 299 proteins, respectively. MK-801 regulated proteins and pathways previously associated with the pathophysiology of schizophrenia such as actin, integrin, ephrin, melatonin, Rho family GTPases, sirtuin, endocannabinoid, and dopamine DARPP32 signaling pathways.

Haloperidol had no significant effect on biological pathways and clozapine (low-dose) partially modulated the changes induced by MK-801. High-dose clozapine attenuated the activation induced by MK-801 on signaling pathways. Lastly, we investigated potential targets behind the MK-801-induced proteome changes, leading us to suggest potential targets to treat NMDAr hypofunction in schizophrenia.
Discussion: Since studies have shown that the antipsychotics used here exhibit effects on schizophrenia-like behavior induced by NMDAr antagonists, we thought that MK-801-induced changes in brain slices could be reversed by both antipsychotics. However, only a high dose of clozapine was able to attenuate the alterations induced by MK-801. Thus, our data contribute to understanding how clozapine, at the correct dose, is more effective in the clinic compared to haloperidol and other antipsychotics for some patients. Furthermore, MK-801-induced changes did not fully overlap with antipsychotics, suggesting that proteins and pathways found in our work should be further investigated in terms of potential treatment targets for NMDAr hypofunction in schizophrenia.

S85. FACIAL MOTOR ABNORMALITIES IN INDIVIDUALS AT RISK FOR PSYCHOTIC ONSET

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Background: Earlier studies have indicated that individuals at risk for psychotic onset have facial motor abnormalities. Moreover, more severe facial motor abnormalities predict a higher probability of subsequent transition to full-blown psychotic diseases in at-risk individuals. It is of clinical value to explore existence of other motor abnormalities in at-risk individuals because results will greatly benefit future studies identifying reliable risk factors of psychotic onset. In drug-naïve first-episode schizophrenia patients, bradykinesia and dyskinesia are common motor abnormalities. However, earlier studies examining facial motor abnormalities in at-risk individuals mainly focused on dyskinesia. Little has been known about whether both facial bradykinesia and facial dyskinesia exist in at-risk individuals. Therefore, this study was to examine whether at-risk individuals had facial bradykinesia and facial dyskinesia. Measuring facial motor abnormalities in at-risk individuals is challenging because their facial motor impairments are subtle and easily missed if observation-based measures are used. In order to overcome this measuring challenge and be able to sensitively and objectively measure facial bradykinesia and dyskinesia in at-risk individuals, this study used motion analysis technology.
Methods: A total of 13 at-risk individuals and 13 healthy controls were recruited in this study. A score of or larger than 17 in Schizotypal Personality Questionnaire-Brief was used to identify at-risk individuals from the community. The VICON motion capture system was used to capture three-dimensional trajectory data of the reflective marker attached to the medial side of the left eyebrow of the participant when s/he showed facial expression of surprise to the maximal level. On the basis of captured data, the normalized movement time (nMT) and the normalized number of movement units (nNMU) were calculated to reflect bradykinesia and dyskinesia respectively. The independent sample t test was used to compare nMT and nNMU between at-risk individuals and healthy controls.
Results: At-risk individuals (age: 20.46±3.09 years; 5 men and 8 women) and healthy controls (age: 20.06±1.80 years; 5 men and 8 women) were matched by age (t=-.41, p=.687) and sex. Significant differences between at-risk individuals and healthy controls were found in nMT (.08±.05 and .05±.02 respectively; t=-2.08, p=.049) and nNMU (.34±.19 and .20±.10 respectively; t=-2.21, p=.040).

Discussion: Individuals at risk for psychotic onset have both facial bradykinesia and facial dyskinesia. Results of this study and earlier research show that both bradykinesia and dyskinesia in the face exist across different stages of schizophrenia, including the at-risk stage, the drug-naïve first-episode stage, and the chronic stage. These results reflect that facial bradykinesia and facial dyskinesia are core manifestations of the schizophrenia disease. Future studies further examining whether facial bradykinesia, like facial dyskinesia, is a predictor of the imminent onset of psychotic diseases in at-risk individuals are warranted.

S86. EVIDENCE-BASED PSYCHOSOCIAL INTERVENTIONS FOR YOUNG PATIENTS DIAGNOSED WITH SCHIZOPHRENIA

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Background: Lack of response to antipsychotics is an important aspect of clinical practice in patients diagnosed with schizophrenia, and up to 30% of these patients are considered treatment-resistant [1]. Multiple augmentation strategies for the pharmacologic treatment have been suggested, but the need for psychosocial interventions targeting key symptoms of schizophrenia cannot be overemphasized [2]. Psychotherapy associated with schizophrenia spectrum disorders with minimal or no antipsychotic treatment was associated with results similar to the control group (antipsychotics/treatment as usual) in a systematic review, although the included studies' quality was low [3]. Psychosocial interventions should be integrated into a comprehensive management program especially for young patients, if multiple variables, like the quality of life, daily functioning, and treatment adherence are considered major therapeutic objectives [4].
Methods: This review included papers published between January 2000 and August 2020 in the main electronic databases (PubMed, Cochrane, EMBASE, CINAHL). The search paradigm used was "schizophrenia" OR "chronic schizophrenia" OR "acute schizophrenia" AND "psychotherapy" OR "psychosocial intervention". Trials including co-morbid psychiatric disorders and non-structured methods of monitoring were excluded.
Results: Cognitive-behavioral therapy (CBT) plus standard of care (SOC) versus SOC showed improvement for the active group in the global clinical status and treatment satisfaction, but its efficacy over the relapse prevention and social functioning was not distinguishable from the control condition (n=24 clinical trials). CBT-oriented family interventions were associated with moderate efficacy over positive and negative symptoms of psychosis, when compared to treatment as usual (TAU), and may be useful in relapse prevention, reducing hospitalization duration, and increasing treatment adherence (n=4 clinical trials). Cognitive remediation was associated with significant improvement of the cognitive performances, and moderate effect over social functioning and psychotic symptoms in schizophrenia |(n=12 clinical trials). Social skills training demonstrated in a large number of trials (n=17) an efficacy similar to the CBT approaches for positive symptoms, and superior to TAU for negative symptoms and general psychopathology. Assertive community training reduced hospitalizations and increased overall functionality, with possible positive effects over the quality of life (n=11 clinical trials). Family psychoeducation may decrease the risk of relapse in the short term, but not when longer intervals were taken into consideration (n=4 clinical trials).
Discussion: Psychosocial interventions for young patients diagnosed with SSD can be efficient augmentative strategies to the pharmacological treatment because they may reduce key symptoms of psychosis and may prevent the rate of relapse, although attention should be paid to individual factors.

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S87. BASELINE PREDICTORS OF ATTRITION DURING A MULTI-SITE RANDOMIZED TRIAL OF COGNITIVE ENHANCEMENT THERAPY FOR EARLY COURSE SCHIZOPHRENIA

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Background: Treatment engagement in the early phase of schizophrenia is critical for reducing long-term disability. However, high attrition rates are common among psychosocial treatment trials in early schizophrenia. The factors associated with treatment dropout are not well understood in this population. Identifying predictors of attrition has important implications for developing strategies to increase treatment engagement. As such, this research sought to identify predictors of attrition among a large sample (N = 102) of outpatients with early course schizophrenia participating in a multi-site (Pittsburgh: n = 53; Boston: n = 49) randomized trial of two interventions, Cognitive Enhancement Therapy (CET; n = 58) compared to Enriched Supportive Therapy (EST; n = 44).

Methods: The study attrition rate was high at 48%, with 53 (52%) treatment completers and 49 (48%) non-completers. Exploratory binary logistic regression analyses were utilized to examine potential baseline predictors of attrition, including demographics (age, sex, race, IQ, education, employment, illness length, and substance abuse history), antipsychotic medication characteristics (dose and adherence), study site, and performance on main outcome cognitive and behavioral composite indexes. First, univariate analyses were conducted to identify which of the above variables were significant predictors of attrition. Next, any significant predictors of attrition were entered into a multivariate logistic regression analysis. Finally, post-hoc interactions with treatment assignment were conducted to examine differences in the multivariate predictors of attrition between CET and EST.

Results: The significant univariate predictors of attrition included age (b = .11, z = 2.40, p = .016), illness duration (b = .29, z = 2.82, p = .005), antipsychotic dose (b = .00, z = 2.26, p = .024), and history of substance abuse (b = -.79, z = -1.96, p = .050), along with a trending association with IQ (b = .04, z = 1.84, p = .066). Of these predictors, IQ (b = .05, z = 2.08, p = .038) and history of substance abuse (b = -.98, z = -2.09, p = .036) were significant in the

multivariate model, such that the probability of completing treatment increased by an odds ratio of 1.05 (95% CI: 1.00 – 1.10) for participants with higher IQs. The probability of completing treatment decreased for participants with a substance abuse history by an odds of 0.38 (95% CI: 0.15 – 0.92). No interactions with treatment assignment were significant for IQ (p = .939) or substance abuse history (p = .596).

Discussion: Although attrition was a limitation of the parent study, it also provided an important opportunity to contribute to the understanding of factors associated with treatment dropout among people with early course schizophrenia. The findings indicated that individuals who have lower IQs and histories of substance abuse may require more support to remain engaged in psychosocial treatment during the early phases of this condition. Furthermore, the implications of this research are vital to future clinical trials of CET and EST for early course schizophrenia in order to address attrition challenges.

S88. ASSOCIATIONS BETWEEN CLINICAL IMPROVEMENT, LENGTH OF STAY, AND REHOSPITALIZATION FOLLOWING INPATIENT EARLY INTERVENTION

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Background: The majority of individuals with serious mental illness (SMI) are rehospitalized within a few years of initial hospitalization, resulting in negative outcomes for patients and health care systems. Early interventions for psychosis aim to improve long-term outcomes for individuals early in the course of illness and have demonstrated some effectiveness in improving clinical outcomes and reducing rehospitalization rates. Investigations have identified preliminary predictors of rehospitalization, but few have examined the association between treatment effects and rehospitalization following early intervention programming.

Methods: A total of 36 patients completed an inpatient early intervention program within a large academic medical center, designed to provide cost-free services to uninsured individuals recently diagnosed with a schizophrenia spectrum disorder or major mood disorder with significant psychotic features. Funding covers up to 90 days of inpatient multidisciplinary early intervention treatment aimed to facilitate clinical improvement and reduce rehospitalizations. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) pre- and post-treatment. Length of stay (LOS) and rehospitalization counts at 1- and 2-year follow-up were tabulated. Associations were determined using chi-square goodness of fit tests and Pearson product-moment correlations.

Results: Primary diagnoses included schizophrenia (30.6%), schizoaffective disorder (33.3%), or major mood disorder with psychotic features (36.1%). Mean LOS was 81.28 days (SD = 9.9). Age (M = 21.5 years), gender (58.3% male), and ethnicity (28% White, 28% Black, 44% Hispanic) were not associated with any variables. Length of stay was significantly associated with PANSS pre-treatment scores of negative symptoms [r(34) = .50, p = .002], general psychopathology [r(34) = .439, p = .008], and total PANSS scores [r(34) = .50, p = .002]. Length of stay was negatively correlated with change in PANSS positive symptoms [r(34) = .36, p = .034) and total PANSS score [r(34) = -.379, p = .023]. The majority of patients (86.1%) made significant clinical improvement per PANSS scores at discharge.

A third (33.3%) of patients were readmitted within 1 year and 55.5% within 2 years. Rehospitalization at 1-year significantly differed by diagnosis [$\chi 2(2, N= 36) = 6.323$, p = .042]. Patients with schizophrenia were least likely to be rehospitalized (9.1%), followed by patients with mood disorder with psychotic features (33.3%), and patients with schizoaffective disorder

(58.3%); significance did not persist at 2-year follow-up. PANSS scores (pre-treatment, post-treatment, or change) were not significantly associated with rehospitalization at either time point.

Discussion: Consistent with prior literature, the present study indicates that multidisciplinary early interventions are effective in significantly reducing clinical symptomatology in patients with SMI. Lengths of stay vary by symptom severity and clinical improvement; more severe baseline negative and general symptoms appear to necessitate longer stays, while improvement in positive symptoms and overall symptomatology are associated with earlier discharges. Interestingly, patients with schizophrenia appear least likely to be rehospitalized within the first year post-treatment while patients with schizoaffective disorder are most likely to be rehospitalized, though differences do not persist at 2-year follow-up. Surprisingly, symptom severity and change in symptoms were not associated with rehospitalization, suggesting these measures may not be as useful for long-term prognostication as previously suggested.

S89. ENHANCING ENGAGEMENT AND ADHERENCE TO COGNITIVE REMEDIATION

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Background: There is also ample evidence of significant cognitive impairments in schizophrenia, and these cognitive impairments directly relate to poorer functional outcomes. An increasing number of reviews and meta-analyses provide support for the efficacy of cognitive remediation in schizophrenia, and cognitive remediation services are proliferating across the nation. However, in individuals with schizophrenia, the (real-world) effectiveness of this and other psychosocial treatments is diminished by lack of motivation for treatment, leading to poor treatment engagement and/or dropout. Motivational interviewing is a brief, clinically-feasible approach that has been successfully used to increase adherence to and efficacy of various treatments, and our prior data suggest that it may also be effective in improving adherence to cognitive remediation. Our primary objective was to evaluate whether motivational enhancement can improve adherence to cognitive remediation in participants with schizophrenia spectrum disorders. Additional objectives were to examine potential mechanisms of action (mediators) and predictors of treatment effects (moderators) associated with providing motivational enhancement for cognitive rehabilitation.

Methods: One hundred fourteen participants with schizophrenia spectrum diagnoses were randomized to receive either brief motivational interviewing (MI) or a sham control interview (CI), both of which were followed by a 4-month active phase during which participants could attend up to 50 unpaid computerized cognitive training sessions. Booster MI or CI sessions were administered monthly over the course of the active phase remediation. Comprehensive assessments were conducted at baseline and end of cognitive remediation.

Results: In intent to treat analyses, there was a small effect of condition on total number of sessions attended over the course of the 4-month cognitive remediation phase, with those in the MI condition attending more sessions (7.70 vs 4.98, respectively), thought this difference was not significant. On average, rate of session attendance was low, with fewer sessions attended over each successive month of the remediation. Twenty nine percent of participants did not attend any sessions, and there was no difference in the likelihood of non-attendance between the MI and CI conditions (OR = .081, p = .62). When number of sessions attended

was compared for the 71% of participants who attended at least one session, there was a significant between group difference in favor of the MI condition (estimated mean number of sessions 10.51 vs. 7.22, respectively, p<.0001). Additional data will be presented on pre-post interview change in motivation for the MI and CI conditions, along with the relationship between change in motivation and number of sessions attended. We will also present data on the relationships between motivation change, number of sessions attended, and cognitive improvements, as well as on potential moderators of change in motivation.
Discussion: There is a need to improve the efficacy of psychosocial interventions for people with psychosis, as well as to identify variables that might impact treatment effects. The current project explores the links between motivational enhancement, motivation change, treatment adherence, and treatment efficacy, along with moderators that may impact these relationships. This line of research is focused on personalizing treatments and enhancing their efficacy, with the overarching goal of improving real-world functional outcomes for people with psychosis.

S90. THE INTERPLAY BETWEEN STRESS, SELF-ESTEEM, AND NEGATIVE MOOD IN EARLY PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

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Background: Influential psychological models of psychosis have highlighted that the impact of putative casual factors on positive symptoms might be explained partly through affective disturbances. We explored whether stress was associated with paranoia and positive psychotic-like symptoms through specific negative mental states of sadness, anxiety, and low self-esteem. We also investigated whether low self-esteem would be associated with paranoia through anxiety and sadness.
Methods: Using experience sampling methodology 113 participants (74 ARMS and 39 FEP) were assessed for levels of momentary stress, self-esteem, anxiety, sadness, psychotic-like symptoms and paranoia. Multilevel mediation models were performed to examine indirect effects of these pathways individually. In light of evidence of mediation, each indirect pathway was combined in a single model in order to explore its relative contribution.
Results: Anxiety, sadness, and self-esteem mediated the pathway from stress to psychotic-like symptoms and paranoia when they were examined separately. Subsequent multilevel meditational analyses combining the significant indirect effects of each pathway in a single model showed that indirect effects of stress on psychotic-like symptoms through anxiety, sadness and self-esteem remained all statistically significant. The relative contribution of each indirect effect was statistically similar. However, in the pathway from stress to paranoia anxiety lost its mediating effect when it was combined in the same model with sadness and self-esteem. Regarding pathways from self-esteem to psychotic-like symptoms and paranoia, both anxiety and sadness mediated these pathways when they were examined separately. Subsequent analyses combining both mediators in the same model revealed that the two indirect effects remained significant for the pathway from self-esteem to psychotic-like symptoms as well as for the pathway from self-esteem to paranoia. However, the relative contribution of sadness was larger than the contribution of anxiety for both pathways.
Discussion: This study lends support to psychological models of psychosis that highlight the relevance of affective disturbances in the onset stages of psychosis. Furthermore, specific

influences of different negative emotional states were unveiled, which should contribute to refine the design of psychological treatments.

S91. CAN EXTERNAL EVENTS TRIGGER IDEAS OF REFERENCE? OBSERVATIONS FROM A LARGE-SCALE POPULATION SURVEY FOLLOWING SOCIAL UNREST AND COVID-19 PANDEMIC

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Background: Ideas of reference (IOR) are key symptoms that could inform the prediction of psychosis onset. In addition to being frequently observed in clinical samples, IOR have also been reported in a proportion of the general population. Previous studies have suggested the role of genetics, social, psychological, and cognitive factors in the manifestation of psychotic and psychotic-like symptoms. In the emergence of IOR, its relationship with external events has not been extensively investigated. Importantly, it can be challenging to investigate whether external events play a causal role in triggering IOR. Population-level stressors present an opportunity to investigate this problem.

Methods: We collected data from 9,873 community-dwelling individuals using a large-scale online survey amidst social unrest and virus pandemic in Hong Kong. In this context, IOR were defined as threatening experiences related to the social unrest, such as feelings of being watched, being followed, being monitored, getting doxxed, and being liquidated. More specifically, we distinguished between two spectra of IOR with the degree to which participants consider the threatening experience to be exclusively directed at them, namely attenuated IOR (IOR-A), which was defined as the feeling of being particularly but non-exclusively referred to, and exclusive IOR (IOR-E), which was defined as the feeling of being exclusively referred to in a group. Multivariate logistic regression (adjusted odds ratio [aOR] and 95%CI) was used to examine the external and individual factors associated with IOR-A and IOR-E.

Results: The regression model revealed that social unrest-related traumatic events (TEs), including being attacked or having experienced sexual violence (aOR=3.62, CI=1.82–7.21), being arrested (aOR=3.87, CI=1.84–8.11), and having experience verbal abuse (aOR=2.26, CI=1.17–4.37) contributed to IOR-A in a dose-response manner. Other factors associated with IOR-A included rumination induced by external population-level events (event-based rumination; aOR=1.07, CI=1.03–1.10), personal stressful life events (SLEs; aOR=1.14, CI=1.06–1.23), as well as symptoms of post-traumatic stress disorder (aOR=1.11, CI=1.08–1.14) and depression (aOR=1.01, CI=1.00–1.02). In contrast, TEs were not related to IOR-E. Meanwhile, education level (aOR=0.72, CI=0.52–0.99), SLEs (aOR=1.33, CI=1.16–1.53), and event-based rumination (aOR=1.09, CI=1.02–1.16) were significant associates of IOR-E. Other background factors, including younger age and past adversity were associated with both spectra of IOR.

Discussion: IOR can be differentiated into the two spectra of IOR-A and IOR-E in community samples to determine the nature of referential thoughts. IOR-A, but not IOR-E, showed a dose-response relationship to severe external stress. The findings suggest IOR may be triggered via two processes, such that TEs may act as an external trigger for attenuated referential symptoms, while individual cognitive capacity may act more on more severe referential symptoms. The final IOR outcome will likely be the result of the interaction of both such processes. Event-based rumination presented as a potential shared mechanism underlying both IOR-A and IOR-E and may be a potential future intervention target for IOR and other psychotic symptoms.

S92. NETWORK ANALYSIS OF SYMPTOM COMORBIDITY IN SCHIZOPHRENIA: RELATIONSHIP TO ILLNESS COURSE AND BRAIN WHITE MATTER MICROSTRUCTURE

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Background: Recent network-based analyses suggest that schizophrenia symptoms are intricately connected and interdependent, such that central symptoms can activate adjacent symptoms and increase global symptom burden. Here, we sought to identify key clinical and neurobiological factors that relate to symptom organization in established schizophrenia.
Methods: A symptom comorbidity network was mapped for a broad constellation of symptoms measured in 642 individuals with a schizophrenia-spectrum disorder. Centrality analyses were used to identify hub symptoms. The extent to which each patient's symptoms formed clusters in the comorbidity network was quantified with cluster analysis and used to predict i) clinical features, including illness duration and psychosis (positive symptom) severity and ii) brain white matter microstructure, indexed by the fractional anisotropy (FA), in a subset (n=296) of individuals with diffusion-weighted imaging (DWI) data.
Results: Global functioning, substance use and blunted affect were the most central symptoms within the symptom comorbidity network. Symptom profiles for some patients formed highly interconnected clusters, whereas other patients displayed unrelated and disconnected symptoms. Stronger clustering among an individual's symptoms was significantly associated with shorter illness duration ($t=2.7$; $p=0.0074$), greater psychosis severity (i.e., positive symptoms expression) ($t=-5.5$; $p<0.0001$) and lower fractional anisotropy in fibers traversing the cortico-cerebellar-thalamic-cortical circuit ($r=0.59$, $p<0.05$).
Discussion: Symptom network structure varies over the course of schizophrenia: symptom interactions weaken with increasing illness duration and strengthen during periods of high positive symptom expression. Reduced white matter coherence relates to stronger symptom clustering, and thus, may underlie symptom cascades and global symptomatic burden in individuals with schizophrenia.

S93. EFFECTIVENESS OF INJECTABLE PALIPERIDONE PALMITATE ON TREATMENT ADHERENCE AND RELAPSE IN THE ADULT SCHIZOPHRENIA POPULATION OF COLOMBIA: A MIRROR-IMAGE SINGLE CENTER STUDY

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Background: Long-acting injectable (LAI) antipsychotics were shown to enhance treatment adherence, improve some outcomes and, lower health care costs. Data are however scarce in the Latin American region. This study aimed at evaluating the effectiveness of paliperidone palmitate once monthly (PP1M) in the adult schizophrenia population, in a government-funded mental health care facility with a broad geographical coverage in Bello, Antioquia, Colombia.

Methods: A single-arm, non-interventional pre-post comparison study was conducted using the electronic medical records of the Hospital Mental de Antioquia. Adult schizophrenia patients (age ≥18 years) treated with oral antipsychotics (OAPs) who subsequently initiated PP1M and received at least two injections between 1st Jan. 2015 and 31st Oct. 2018 were included. Study consisted of two retrospective phases: 12 months prior to 1st PP1M injection (pre-phase) and 12 months after (post-phase, with last follow-up until 31st Oct. 2019). Those who used other LAIs in pre-phase or did not have 12 months of follow-up were excluded. Outcomes were treatment adherence (proportion of days covered ≥80%), relapse leading to hospitalization or emergency department visit, number of relapse episodes, and non-hospitalized relapse symptoms. Effect of initiating PP1M on study outcomes was assessed using a relative risk (RR) obtained through multivariable conditional Poisson regression. Illicit substance use and number of psychosocial interventions varied between the phases and were thus included as adjustment variables in multivariable models.
Results: Out of 372 patients who initiated PP1M, 123 (33.1%) were eligible (mean age 30.3 years, 79.7% male, mean 7.9 years since diagnosis). Half of patients initiated PP1M due to adherence issues with OAPs, followed by lack of efficacy of OAPs (n=44, 35.8%); 37 (30.1%) patients initiated PP1M as inpatient. Overall, 23.6% of patients were adherent to any OAP treatment in pre-phase, increasing to 89.4% in post-phase (RR=3.77; 95% CI: 2.75-5.17). Proportion of patients with at least one hospitalized relapse decreased from 46.3% in pre-phase to 35.0% in post-phase (RR=0.76; 95% CI: 0.59-0.99). Mean number of relapse episodes also decreased (0.89 vs 0.54; RR=0.61; 95% CI: 0.45-0.83). There were 48 (39.0%) patients who discontinued PP1M during follow-up, with 29 (23.6%) who switched back to OAPs only and 10 (8.1%) to another LAI (pipotiazine palmitate or risperidone). Characteristics of patients who continued PP1M and of those who dropped out were similar. Effectiveness was greater in patients who continued PP1M (decrease in hospitalized relapse from 44.0% to 28.0%; RR=0.64; 95% CI: 0.42-0.98) than in dropouts (decrease from 50.0% to 45.8%; RR=0.91; 95% CI: 0.65-1.25). Number of hospitalized relapse decreased from 0.7 to 0.4 (RR=0.52; 95% CI: 0.33-0.83) in patients who continued PP1M and from 1.2 to 0.8 (RR=0.67; 95% CI: 0.44-1.03) in dropouts. Analyses stratified by reason for PP1M initiation yielded similar findings. Proportion of patients with non-hospitalized relapse symptoms increased from 6.5% to 18.7% (adjusting for number of outpatient visits, RR=2.27; 95% CI: 1.11-4.64).
Discussion: PP1M initiation led to a dramatic improvement in treatment adherence as well as a decrease in the occurrence and number of hospitalized relapse episodes. Effectiveness was higher in patients who continued PP1M treatment than in those who discontinued. PP1M initiation was also associated with an increase in the management of relapse symptoms in the outpatient setting, which could be explained by a decrease in relapse severity after PP1M initiation. Generalizability of results is limited to the population treated at this facility.

S94. CLOZAPINE AUGMENTATION WITH LONG ACTING ANTIPSYCHOTICS: DOES IT ADD VALUE?

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Background: A majority of individuals diagnosed with schizophrenia experience multiple relapses. Although research on the comparative effectiveness of antipsychotic treatments for relapse prevention has been extensive, many patients continue to relapse due to non-adherence. As such, clinicians have been augmenting oral antipsychotics upon hospital discharge with long-acting intramuscular compounds (LAI) in order to prolong relapse-free community

intervals. There is little data on the advantage of such combinations, particularly not for clozapine and LAIs for patients with treatment resistant schizophrenia. This study uses a cohort of patients with schizophrenia who were discharged from an inpatient psychiatric center after stabilization with clozapine and followed in the community for two years. The aims of this study were to compare the community survival time (time to relapse) of two cohorts of patients: (1) clozapine monotherapy, (2) clozapine plus long acting injectables (LAI).
Methods: This is a retrospective study evaluating the one- and two-year community outcome of 71 subjects after receiving antipsychotic and rehabilitative interventions at a tertiary care inpatient psychiatric facility (Manhattan Psychiatric Center, New York, NY). Subjects were enrolled and were evaluated at baseline as inpatients prior to discharge into the community and were seen at the Manhattan Psychiatric Center (MPC) outpatient facility.100.0% met the National Institute for Health and Clinical Excellence (NICE) criteria for Treatment Resistant Schizophrenia (TRS) and were placed on stable dosages of clozapine with plasma level monitoring. Patients were followed in once per month outpatient visits with a comprehensive mental health team. Relapse was defined as (1) psychiatric readmission; (2) visit to an emergency room for psychiatric reasons; (3) incarceration; (4) Increased outpatient treatment intensity. A regression analysis and Kaplan Meier curves were used to analyze the data.
Results: The mean PANSS Total at baseline was 78.22 (12.13) for the clozapine group and 77.89 (12.03) for the clozapine + LAI group. There were no significant differences noted at baseline for baseline characteristics (including age, chronicity of illness, years of substance use, length of prior inpatient hospitalization, PANSS subscale scores). Relapse rates were 52.11% (n=37 of 71) by Year 1, and 60.56% (n=43 of 71) by end of Year 2 for the total group. The estimated times to relapse in number of months for each group were: Clozapine only group (13.06 months), clozapine plus LAI group (15.47 months). The time to relapse between the clozapine only group and the clozapine plus LAI was not statistically different ($p = 0.207$). Relapses occurred due to psychiatric rehospitalization (81.36%), increase in level of psychiatric services (80.22%), and discontinuation of antipsychotic medications (81.23%). 58,54% of patients on clozapine relapsed compared to 63.33% of patients on clozapine + LAI. Moderators of time to relapse included age (younger age, less likely to relapse for clozapine and clozapine + LAI group) and number of previous hospitalizations (fewer hospitalizations, less likely to relapse for all three groups).
Discussion: Although individuals on clozapine + LAI remained in the community for 2.01 months longer than individuals treated with clozapine alone, there was no significant differences between the two groups. There was a lesser percentage of individuals on clozapine who relapsed (i.e., 58.54%) compared to individuals on LAIs. Larger prospective studies will be required to confirm the results

S95. CLOZAPINE COMBINATION WITH LONG-ACTING INJECTABLE ANTIPSYCHOTICS AND COMPLIANCE ENHANCING FORMULATIONS IN TREATMENT-RESISTANT SCHIZOPHRENIA: A LITERATURE REVIEW AND A CASE SERIES

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Background: Clozapine has a unique clinical efficacy for patients with treatment-resistant schizophrenia, but compliance might be a challenging issue. The most common reasons for discontinuation are side-effects, noncompliance and lack of efficacy. Clinicians may prefer adding a long-acting injectable antipsychotic (LAI) to overcome adverse effects of

noncompliance to clozapine such as psychotic relapse or hospitalization. Another way to increase compliance and enhance tolerability is using different pharmaceutical formulations of clozapine such as oral-dissolving tablets (ODT), liquid formulations or intramuscular injections (IM). We aimed to conduct a literature review of clozapine-LAI combination (C+LAI) use and different clozapine formulations, in addition to describe a case series on C+LAI.

Methods: We conducted a literature review of Pubmed with no date restriction using following terms: "clozapine AND long-acting", "clozapine AND depot", "clozapine AND formulation", "clozapine AND oral disintegrating", "clozapine AND oral dissolving", "clozapine AND intramuscular". We selected articles written in English and the studies which reported clinical data. In addition, seven schizophrenia patients using C+LAI from a community mental health center were presented.

Results: We extracted four case reports and six open trials including four retrospective, mirror-image studies, one cross-sectional comparison and one cohort study describing the use of C+LAI. The mirror-image studies showed a significant reduction in the number of hospitalizations, length of hospital stays, number of visits to emergency department on C+LAI with no major adverse events. One study also reported decreased side effects and increased total score in functioning. Patients on C+LAI had lower symptom severity, higher global functioning compared to clozapine monotherapy. Within-individual analysis of a nation-wide cohort showed that the risk of psychiatric rehospitalization decreased 50% on C+LAI compared to no treatment. But risk of rehospitalization was similar compared to "clozapine monotherapy".

We included 11 articles for clozapine formulations. Five of them were bioequivalence safety and tolerability studies. There was no clinical trial of a long-acting formulation of clozapine, an expected result considering the fatal side effects which require immediate discontinuation. An open-label study showed significant improvement on psychopathology measurements after twelve weeks of ODT. Two case reports and three retrospective studies were identified for acute acting IM formulation of clozapine, which was often well-tolerated despite quick sedation and resulted in an increased acceptance of oral clozapine in the acute phase of illness.

Case Series: Mean age, duration of illness and number of previous hospitalization were 46±9 years, 23.6±7.7 years and 2.4 respectively. The reason of adding LAI was lack of efficacy in all patients. Mean duration on combination was 4±3 years and clozapine dose was 293±73 mg. Only two patients were hospitalized during C+LAI treatment, and one of them had discontinued the combination. No serious adverse effect was observed.

Discussion: Clozapine-LAI combination may improve both symptom severity and long-term outcomes by reducing the risk of relapse and hospitalization. It may also function as a safety valve against adverse effects of noncompliance of clozapine. Different clozapine formulations may bring an alternative approach to increase compliance. However, they are often preferred to "save the day" and there are very few clinical data on their efficacy. These results suggest that there is an urgent need for well-designed, controlled studies of C+LAI.

S96. EFFECTS OF SEP-363856, A NOVEL TAAR1 AGONIST, ON NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: RESULTS ACROSS AN INITIAL DOUBLE-BLIND ACUTE STUDY AND A 6-MONTH, OPEN-LABEL EXTENSION STUDY

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Background: SEP-363856 is a novel trace amine receptor 1 (TAAR1) agonist with serotonin 5-HT1A activity that has demonstrated efficacy in animal models of psychosis. In a double-blind, placebo-controlled study, SEP-363856 was efficacious in the treatment of patients with an acute exacerbation of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score at Week 4 with a safety and tolerability profile similar to placebo. The current analyses examined the effects of SEP-363856 on negative symptoms in the initial double-blind study, followed by the subsequent 6-month open-label extension study.
Methods: Patients with an acute exacerbation of schizophrenia were randomized, double-blind, to 4 weeks of flexible-dose treatment with SEP-363856 (50 or 75 mg; n=120) or placebo (n=125). Four-week study completers continued into an open-label extension study which involved 26 weeks of treatment with flexible doses (25/50/75 mg/d) of SEP-363856. Prespecified measures evaluating negative symptoms included the Brief Negative Symptom Scale (BNSS) total and factor scores (blunted affect, alogia, avolition, anhedonia, asociality, distress), PANSS negative subscale score, Marder PANSS negative symptom factor, and the Uncorrelated PANSS Score Matrix (UPSM) transformation of the PANSS scale comprising UPSM-PANSS negative-apathy/avolition (UPSM-NAA) and negative-deficit of expression (UPSM-NDE) factors.
Results: In the initial 4-week double-blind study, treatment with SEP-363856 (vs. placebo) showed significant week 4 improvement in negative symptoms as assessed by the BNSS total score (effect size [ES], 0.48), and BNSS subscale scores for blunted affect (ES, 0.51), avolition (ES, 0.42), anhedonia (ES, 0.39), asociality (ES, 0.47), alogia (ES, 0.32), and distress (ES, 0.13); as well as on the Marder PANSS negative symptom factor (ES, 0.46), and the UPSM-DE (ES, 0.32) and UPSM-NAA (ES, 0.32) factors. In the open-label extension study, treatment with SEP-363856 was associated with additional mean improvement, from open-label baseline to Week 26 (observed/LOCF), on the BNSS total score (-11.3/-8.0); the PANSS negative subscale score (-5.2/-3.5); the Marder PANSS negative symptom factor (-5.3/-3.5); and the UPSM-DE (-0.5/-0.3) and UPSM-NAA (-0.4/-0.3) factors.
Discussion: Short-term treatment with SEP-363856 was associated with significant and robust improvement relative to placebo in negative symptoms of schizophrenia as assessed by multiple measures. Continued improvement in negative symptoms was observed during 26 weeks of additional open-label treatment with SEP-363856. These suggest that agonism at the TAAR1 receptor by SEP-363856 can treat both positive and negative symptoms in schizophrenia without incurring adverse effects on movement, prolactin, weight, and metabolic parameters associated with first and second generation antipsychotic drugs. These findings will need to be confirmed in future controlled studies.
ClinicalTrials.gov Identifier: NCT02969382, NCT02970929

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S97. CO-OCCURRING AUTISTIC AND POSITIVE SYMPTOMS IN SCHIZOPHRENIA: A COMPENSATION MECHANISM LEADING TO FUNCTIONAL BENEFITS

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Background: Disruption of daily functioning is a hallmark of both schizophrenia and autism spectrum disorder (ASD), affecting educational attainment, employment, independent living, and peer relationships. Recent evidence suggested that a subsample of patients with schizophrenia shows autistic traits (ATs; i.e., autistic-like symptoms that do not reach diagnostic levels), leading to the hypothesis that their co-occurrence would be associated with a 'double dose' of deficit. However, a growing body of research examining this hypothesis by looking at the joint effect of autistic and positive symptoms yielded contrasting results ranging from benefits to adverse effects. We examined the concurrent effect of ATs and positive symptom severity on daily functioning in a large sample of patients with schizophrenia. We hypothesized that the influence of co-occurring autistic and positive symptoms on functioning may depend on patients' different levels of symptom severity.
Methods: 170 patients with schizophrenia were enrolled and assessed for the severity of positive symptoms (Positive and Negative Syndrome Scale for Schizophrenia, PANSS Positive subscale) and ATs (PANSS Autism Severity Score, PAUSS), intellectual level (Wechsler Adult Intelligence Scale–Revised, WAIS-R), and daily functioning (Quality of Life Scale, QLS). Two-step cluster analysis identified two groups with different levels of ATs and positive symptom severity (Cluster 1 = patients with less severe symptoms; Cluster 2 = patients with more severe symptoms). Several general linear models (GLMs) were conducted, examining the interactions of Clusters, ATs and positive symptoms on functioning.
Results: For the entire sample, the PANSS Positive*PAUSS*Cluster interaction was significantly associated with QLS Total score ($p<.001$) and each of its subscales: QLS Interpersonal Relations ($p=.003$), QLS Instrumental Role ($p=.001$), QLS Personal Autonomy ($p=.007$). Separate GLMs in each Cluster revealed a significant positive effect of the interaction between PANSS Positive*PAUSS on QLS Total score ($p=.006$), QLS Interpersonal Relations ($p=.06$), QLS Instrumental Role ($p=.03$), and QLS Personal Autonomy ($p=.02$), only in Cluster 1 (the less severe patients). In contrast, PANSS Positive and PAUSS were independently associated with worse functioning (in all QLS scores) in Cluster 2 (the more severe patients). These associations were observed above and beyond the effects of I.Q. and illness duration.
Discussion: Our findings show that co-occurring ATs and positive symptoms can confer functional benefits in schizophrenia, but this may be delimited by symptom severity. These results are consistent with the Diametric Model, which posits that social dysfunction in ASD and schizophrenia might be precipitated by contrasting mechanisms, promoting the hypothesis that a balancing act between ATs and positive symptoms and underlying mechanisms can confer attenuated functional disruption. ATs may protect against the deleterious effects of positive psychotic symptoms on functioning only in patients that are not too ill to benefit from such compensation. Our findings may help to reconcile the seemingly contrasting results from previous studies, and to understand the heterogeneity of behavior and functional outcomes in schizophrenia.

S98. INFLUENCES ON SELF-ASSESSMENT OF EVERYDAY FUNCTIONING IN PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR DISORDER: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

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Background: People with schizophrenia (SCZ) and bipolar illness (BPI) often generate self-reports of their activities and work that diverge from objective information. It is suggested that these participants may not base their reports on their daily experiences; our prior studies have shown that this disconnect exists for self-reports of cognitive and social functioning as well. We used ecological momentary assessment (EMA) to sample socially relevant daily activities in SCZ and BPI and determined whether EMA responses were associated with self-reported and observer-reported work skills and everyday activities (as measured by Specific Level of Functioning Scale- SLOF subscales).
Methods: We included 38 people with BPI and 66 people with SCZ in this study. Participants were sampled 3 times per day for 30 days with a smartphone-based survey. Each survey asked where they were, with whom they were, what they were doing, and if they were sad, happy, anxious, or experiencing active psychotic symptoms since the last check-in. Participants and observers were asked to complete the SLOF scale at the end of 30 days. The activity and work subscales were used as our outcomes of interest. Generalized linear modeling with repeated measures was used to determine associations.
Results: There was an association between being home or alone and self-reports of productive functioning in everyday activities and work skills. Patients with significant paranoid ideation self-reported that their everyday activities as considerably better than those without paranoia even when controlling for other predictors. However, they also overestimated their functioning in activities and work skills when compared to observer reports. Patients who heard voices at least once during the 30-day EMA analysis were more likely to overestimate their work abilities compared to observers; this relationship also held true for patients who reported more delusions. Those who reported significant levels of sadness or depression were more likely to underestimate their functioning. When compared to those subjects who underestimated functioning, subjects who overestimated their everyday activities functioning had a higher mean paranoid score during their 30-day EMA assessment.
Discussion: Both SCZ and BPI were marked by a disconnect between momentary experiences and self-reports. Positive schizophrenia symptoms such as paranoia are associated with competence in overestimating activities but not work skills. Greater accuracy in self-reported work activities compared to previous findings regarding cognition and social outcomes may be due to the more concrete nature of work activities.

S99. THE ROLE OF EDUCATION LEVEL AND KNOWLEDGE OF PSYCHOSIS ON CHANGES IN PUBLIC STIGMA TOWARDS PSYCHOSIS IN HONG KONG – COMPARISON BETWEEN POPULATION SURVEYS ACROSS THREE TIME POINTS, 2009, 2014 AND 2018

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Background: Public stigma towards psychosis plays a large role in affecting the recovery of individuals with psychosis. Therefore, insights on changes in public stigma across time and identification of associated factors would help with development of effective interventions in reducing stigma in the general population. This study aimed to examine the changes in public stigma towards psychosis between 2009, 2014, and 2018 in the Hong Kong Chinese population, and the roles of education level and knowledge of psychosis on public stigma.
Methods: Telephone survey was conducted in 2009, 2014, and 2018. Similar study protocol was used in all time points to ensure comparability. Cantonese speaking Hong Kong Chinese

residents aged 18 years or above were included. Surveys were administered by experienced interviewers using the Web-based Computer-Assisted Telephone interview system. Sociodemographic details including age, gender and education level were collected. Respondents were split into three education groups, primary and below, secondary, and tertiary and above. Stigma towards psychosis was assessed using the revised Link's Perceived Discrimination-Devaluation Scale (LPDDS). Knowledge about psychosis was assessed using a binary variable on whether people with psychosis require medication to control their symptoms. The sample was weighted for age, gender and education level using the rim-weighting method. Kruskal-Wallis H test was used to compare LPDDS between the 2009, 2014 and 2018 cohorts. Univariate general linear model (GLM) was used to examine the role of education and knowledge of psychosis and their interactions with cohort years separately on public stigma. LPDDS scores across cohorts between the three education groups were further compared using the Kruskal-Wallis H test.

Results: The number of completed interviews were 1016, 1018, and 1514 in 2009, 2014, and 2018 respectively. The mean age was 45.18 (SD = 16.28), 45.84 (SD = 17.04), and 48.98 (SD = 18.15); and approximately half were males (45.4 – 47.5%) in all time points. Gender was not significantly different across the cohorts. However, age and education level were significantly different across cohorts. The 2018 group had older respondents and more respondents with secondary level education. Significantly more respondents in 2018 responded "no" on the knowledge question (19.2% compared to 15.7% and 10.9%). LPDDS was significantly different between the three cohorts, $\chi 2=6.78$, $p<.05$ (2.63 (SD=0.49), 2.67 (SD=0.47), and 2.65 (SD=0.32)). Education level, knowledge of psychosis, and interaction between cohort and education level were associated with LPDDS in the GLM analysis (all $p<.01$). Comparison of LPDDS of education groups across the three cohorts found that significant differences in LPDDS across cohorts was only observed between the primary and below group and tertiary and above group (all $p<.05$).

Discussion: Public stigma towards psychosis in the Hong Kong Chinese population was observed to be different between 2009, 2014 and 2018. Knowledge about psychosis on the need for medication to control symptoms was found to be associated with LPDDS. While cohort was not significantly associated with LPDDS after taking into account all other variables, an interaction effect was observed between cohort and education. Specifically, LPDDS was found to be higher in 2018 in respondents with primary level education and below, and lower in 2018 in those with tertiary education and above compared to 2009 and 2014. Those with secondary level education had similar level of LPDDS at all time points. This suggests that different interventions targeted at individuals with different education levels are needed in public campaigns on reducing stigma.

S100. MENTAL TIME TRAVEL IN FOR SELF AND OTHERS INDIVIDUALS WITH SCHIZOTYPY

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Background: Mental time travel (MTT) is the ability of re-experiencing the past events and pre-experiencing future events. One of the essential components of MTT is the protagonist of the events, including self-related and other-related events. Empirical findings suggest that self-related MTT showed better performance than other-related MTT. Although patients with schizophrenia and individuals with schizotypy are associated with impairment in discriminating self and others, the pattern of self- and other-related MTT are not clear in these individuals. The present study aimed to examine this issue in individuals with schizotypy.

Methods: Individuals with schizotypy (n=40) and non-schizotypy (n=21) completed a MTT task with four conditions [2 (condition: self vs. other) x 2 (time orientation: remember vs. imagine)]. They were required to recall past events happened to themselves or a non-intimate other, imagine possible future events that might happen to themselves or a non-intimate other. Each condition was provided a cue word list for recall or imagine. Outcome measures included specificity, vividness, sense of experience, emotional valence, emotional intensity, proportion of first-person visual perspective, and difficulty in MTT.
Results: A 2 (group: schizotypy vs. non-schizotypy) x 2 (condition: self vs. other) x 2 (time orientation: remember vs. imagine) mixed ANOVA was conducted on each index. Our results showed that individuals with schizotypy reported lower positive emotion than individuals without schizotypy. Self-related MTT showed more specific events, more vividness, more sense of experience, higher emotional intensity, less first-person visual perspective, and less difficulty than other-related MTT. Compared with remembering past events, participants generated fewer specific events, had less vividness, less sense of experience, and more difficulty in future thinking. Moreover, the condition x time orientation interaction was significant in vividness, sense of experience, and percentage of first-person visual perspective. Subsequent analysis further indicated that self-related MTT showed more vividness and sense of experience than other-related MTT, and this difference was more prominent in remembering than future thinking. In addition, less first-person visual perspective was adopted in self-related MTT than other-related MTT, this difference was more prominent in future thinking.
Discussion: These findings suggest that individuals with schizotypy did not exhibit significant deficits in MTT. Self-related MTT showed better performance than other-related MTT, and individuals with schizotypy showed a similar pattern with non-schizotypy.

S101. ASSESSING COGNITIVE MOTIVATION IN EARLY EPISODE PSYCHOSIS: DEVELOPMENT AND PSYCHOMETRIC VALIDATION OF A NOVEL SELF-REPORT INSTRUMENT

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Background: In psychotic illness, deficits in cognition and motivation are reliable predictors of poor functional outcomes. Patients demonstrate lower motivation to exert effort in rewarding and cognitively challenging experimental tasks. However, the performance-based measures of cognitive motivation inconsistently correlate with functioning. We hypothesize that there may be aspects of cognitive motivation that are important for daily functioning but are not captured by experimental tasks. Given that motivation is a multidimensional construct, we endeavored to develop and validate a self-report questionnaire to assess motivation processes associated with engagement in cognitively demanding activities in general adult samples (Studies 1-3) and in an early psychosis sample (Study 4).
Methods: Using the construct validation approach to scale development, items were written to reflect the contemporary understanding of the multiple processes underlying motivated behavior: reward responsiveness, volition, drive, and inhibition. The dimensionality and construct validity of the Cognitive Motivation (CM) scale was examined in three independent general adult samples using exploratory factor analysis (n1 = 205; n2 = 235) and confirmatory factor analysis (n3 = 181). Preliminary analyses for the internal reliability and construct validity of the CM scale in an early psychosis sample are presented herein (n4 = 20, projected n4 = 60).
Results: Studies 1 to 3 confirmed two internally consistent factors of the CM scale: Cognitive Approach and Cognitive Withdrawal. The CM scale outperformed traditional motivation scales in construct validity; higher ratings on the Cognitive Withdrawal subscale were strongly

associated with greater self-reported cognitive difficulties, depressive mood, and functional impairments. In Study 4, the Cognitive Approach (Cronbach's $\alpha = .92$) and Cognitive Withdrawal (Cronbach's $\alpha = .82$) subscales showed excellent internal consistency in a psychosis sample. Lower Cognitive Approach was associated with more severe anhedonia ($r = -.59$, $p < .01$) and asociality ($r = -.50$, $p < .05$). Both Cognitive Approach and Inhibition subscales did not significantly correlate with positive symptoms, $r = .21$ and $r = -.36$, respectively (p's $< .05$). Higher Cognitive Approach significantly correlated with better life functioning ($r = .55$, $p < .05$), while Cognitive Withdrawal did not emerge as a significant functional correlate ($r = -.11$, $p < .65$).

Discussion: The CM scale is a valid, internally consistent, bidimensional self-report measure of cognitive motivation with demonstrated applicability to indicators of psychosocial well-being in general adults and potentially in psychotic patients. The CM subscales measured two distinct dimensions of cognitive motivation. In the general population, individual differences in Cognitive Withdrawal (aversion and negative emotional response to cognitive challenges) is an aspect of cognitive motivation that is associated with well-being and functioning. In psychosis, Cognitive Approach is implicated in functioning; the more one seeks, initiates, and enjoys cognitive challenges, the better the life functioning. These unique associations highlight the clinical utility of the CM scale in identifying and monitoring impaired motivation processes that may hinder treatment engagement and functional recovery.

S102. BODILY DISTURBANCES AND SENSITIVITY TO THE RUBBER HAND ILLUSION IN THE SCHIZOTYPY SPECTRUM

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Background: In line with early conceptualizations, contemporary empirical evidence indicates that bodily self-disturbances are central to schizophrenia. For instance, studies using the Rubber Hand Illusion (RHI; Botvinik & Cohen, 1998) have consistently documented an increased sensitivity to the illusion in individuals with schizophrenia, suggesting body ownership disturbances in this population. Sensitivity of the RHI has also been associated with the cognitive/perceptual factor of schizotypy in healthy individuals, which implicates the role of bodily self-disturbances in psychosis-proneness. However, positive schizotypy is a composite construct consisting of suspiciousness, ideas of reference, magical thinking, and unusual perceptions, and the relationship between bodily self-disturbance and subscales of positive schizotypy has not been determined. Additionally, the link between self-reported bodily self-disturbances and sensitivity to the RHI has yet to be explored.

Methods: We recruited 98 healthy young adults. The RHI task was administered to assess body ownership. The RHI uses conflicting visual and tactile information (i.e., seeing a fake hand being brushed while simultaneously feeling one's own hand being brushed) to create a sense of body ownership over a foreign object (i.e., a rubber hand). RHI sensitivity was measured both objectively (i.e., proprioceptive drift) and subjectively (i.e., self-report questionnaire). Schizotypy was measured using the Schizotypal Personality Questionnaire (SPQ), and self-reported bodily disturbances were measured using the Perceptual Aberration Scale (PAS), and the Bodily Sensations and Sensed Presence subscales of the Multi-Modality Unusual Sensory Experiences Questionnaire (MUSEQ). The relationship between schizotypy, bodily disturbances, and RHI sensitivity was assessed using multiple linear regressions. Different path models will be examined to explore the relationship between subscales of schizotypy, self-reported bodily disturbances, and RHI sensitivity.

Results: Consistent with previous studies, we found a link between positive schizotypy and RHI sensitivity. More specifically, odd beliefs/magical thinking predicted the subjective experience of the illusion. Self-reported bodily disturbances also predicted the magnitude of the proprioceptive drift.
Discussion: Our results suggest that odd beliefs/magical ideation and self-reported bodily disturbances predict sensitivity to the RHI. Focusing on bodily self-disturbances in the context of early intervention may provide further insight into the onset of psychosis. Furthermore, assessment of bodily self-disturbances using both empirical and self-report measures could enhance the power to identify individuals at risk for transitioning to psychosis.

S103. TREATING SOCIAL ANXIETY IN SCHIZOPHRENIA: A PILOT STUDY USING A COGNITIVE BIAS MODIFICATION TRAINING

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Background: Schizophrenia is associated with multiple comorbid disorders, namely anxiety disorders, and more specifically social anxiety. Several studies have demonstrated that not only does social anxiety worsen the prognosis of schizophrenia, but it also impedes with the overall social recovery of the person. The objective of this pilot study is to investigate the efficacy of Cognitive Bias Modification Training (CBMT) for the treatment of social anxiety in schizophrenia.
Methods: A total of 17 individuals (21 to 36 years old, 47% women) presenting with both schizophrenia and social anxiety participated in the study. The participants were recruited from different early psychosis intervention clinics in Montreal (Canada). Participants were evaluated before and after the treatment, using different measures of social anxiety, cognitive biases, and quality of life. The Cognitive Bias Modification Training (CBMT) consists of 8 weekly sessions of 50 minutes on average, during which participants receive an assisted computerized training. This training can help participants recognize neutral and positive emotions more effectively, and react in a more balanced way to negative emotions (modification of emotion/attentional biases).
Results: Following treatment, participants experienced a reduction in social anxiety and cognitive biases, as well as an improvement in the level of quality of life. The results will be presented in more details and compared with the literature.
Discussion: Cognitive Bias Modification Training (CBMT) is an intervention that seems to be promising for the treatment of social anxiety, however further research is needed to study the impact and relevance of the CBMT in people with schizophrenia and social anxiety.

S104. THE STRUCTURE OF SOCIAL SKILLS: DIVERGENCE BETWEEN SOCIAL COMPETENCE AND SOCIAL INAPPROPRIATENESS

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Background: Performance-based assessments of social skills have detected differences between people with severe mental illness and are correlated with clinical ratings of social outcome in people with schizophrenia and bipolar disorder. The most commonly used of these

assessments, The Social Skills performance Assessment (SSPA) measures both social competence and inappropriate communications. As real-world measures of social competence and social disruptiveness appear to have different correlates, we hypothesized that SSPA items measuring social competence and social inappropriateness would be differentially correlated with each other and with performance-based measures such as neurocognition and functional capacity.

Methods: We aggregated data from 378 healthy controls, 557 people with schizophrenia, and 106 with bipolar disorder who were recruited from studies conducted at four different research sites. All participants were assessed with both SSPA scenarios, a social interaction and an instrumental interaction. Each SSPA scenario included a single item measuring socially inappropriate communication and either 5 or 6 other items measuring social competence. All participants were also assessed with performance-based measures of processing speed, working memory, verbal fluency, and functional capacity. Clinicians rating the interviews were blind to participant diagnoses and supervised by a single central rater.

Results: Participants with bipolar disorder and schizophrenia performed more poorly on every item of the SSPA as compared to healthy controls. In the sample as a whole and in each of the subgroups, socially inappropriate communication correlated across scenarios, as did the elements of socially competent communication. However, inappropriate communication was not correlated with indices of social competence. The items measuring socially competent communication, but not social inappropriateness, were correlated with the other performance-based measures. Finally, individuals who were living in unsupported housing and those who were financially responsible performed better on the social competence items, with no differences on the inappropriateness items.

Discussion: Social competence and social appropriateness are distinct elements of performance-based social skills. Social competence has wide ranging functional correlates that appear different from those associated with inappropriate behavior. Much like real-world assessments of social outcomes, social competence and inappropriateness can be differentiated and measured.

S105. ECOLOGICAL MOMENTARY ASSESSMENT OF SAD MOODS IN PEOPLE WITH SCHIZOPHRENIA: NEVER BEING SAD IS ASSOCIATED WITH OVERESTIMATION OF SOCIAL FUNCTIONING

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Background: Research on depression in patients with schizophrenia (SCZ) suggests that insight and self-reported depression have an inverse relationship; patients who report extremely low levels of depression often generate excessively positive self-reports of their functioning. Those with more insight tend to report depression and produce more realistic self-assessments as indexed by informant ratings. Although these findings have been consistent, they are all based on cross-sectional data. We cannot determine whether these apparently biased reports of mood symptoms or functioning are based on true momentary experiences or if they reflect a single day sampling bias and a tendency to make global judgments on the basis of a momentary mood or experience. To address this issue more systematically, we examined daily reports of mood over a 30-day period, compared these reports to a comparison sample with

bipolar illness (BPI), and related these reports of sadness to self-reports of functioning and ratings of functioning generated by observers.
Methods: Three times a day for 30 days, participants with SCZ (n=102) and a comparison sample of participants with BPI (n=71) completed smartphone surveys assessing sadness, in addition to reporting their location and who they were with. Participants also self-reported their everyday social functioning, with observer ratings of social functioning also collected. We defined the absence of sadness as a survey response of 0 (none) or 1 (very minimal).
Results: Patients with SCZ reported a complete absence of sad moods across surveys at a higher prevalence than patients with bipolar disorder (57% of returned surveys versus 43%, p<.001). Patients with SCZ were more likely than patients with BPI to report an absence of any sad mood on any survey (46% vs. 36%; p<.001). When never reporting any sadness was related to self-assessment of social functioning with HLM analyses, it was found that these participants with SCZ who never reported sadness on any survey overestimated their everyday functioning by 18% compared to observer ratings (P<.001), in marked contrast to those who reported being sad on at least some surveys (0%). This relationship was not found in BPI, with a 2% difference compared to observers for participants who never reported sad moods on any survey, p=.24.
Discussion: Our results are consistent with previous findings that patients with SCZ commonly report the complete absence of sadness. They are more likely than people with BPI to say that they never were sad at any time. However, consistent with previous cross-sectional studies, the complete absence of sadness in participants with SCZ was associated with overestimation of social functioning compared to observer ratings. Participants with BPI who reported no sadness self-reported their everyday functioning as being congruent with the judgments of observers. These data indicate that the complete absence of sad moods may be an indicator predicting biased self-reports of functioning in participants with SCZ with some evidence of diagnostic specificity.

S106. ALTERED ATTENTIVE BIAS TOWARD INFORMATION OF INTERPERSONAL COMMUNICATION ACROSS PHASES OF SCHIZOPHRENIA: AN EYE-TRACKING STUDY

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Background: Interpersonal communication is a specific scenario for which patients with psychiatric symptoms may manifest different behavioral pattern connecting to psychopathology. This was a pilot study by eye-tracking technology to investigate attentive bias towards information of interpersonal communication across different clinical phases in schizophrenia.
Methods: We included 74 healthy controls, and 78 high risk, 68 first episode, and 39 chronic patients from the Shanghai High Risk Psychosis project (SHARP cohort) conducted in Shanghai Mental Health Center. The experiment was an unguided-viewing task composed of 24 trials with three types of pictures varying in degree of communication shown. We used two measures: 1) initial fixation duration, 2) total fixation duration.
Results: There was no significant difference in age or educational levels, but a gender difference was found (p=0.033). Ratio of initial fixation duration of pictures with communicating people against pictures with non-communicating individuals was lowest in chronic patients (0.13±0.34), compared to controls (0.31±0.36), first episode patients (0.31±0.46) and high risk patients (0.36±0.42). The ANCOVA analysis revealed a significant group difference between subjects (p=0.022). For overall attentive engagement, no group difference was found (p=0.101). Ratio of initial fixation duration on non-communicating

individuals against no-person scenes negatively correlated with SIPS (rho=-0.35, p=0.002) in high risk group. Ratio of initial fixation duration on communicating people against no-person scenes was associated with PANSS negative symptoms in chronic patients (rho=-0.33, p=0.037), not in first episode (rho=-0.14, p=0.266).

Discussion: The current study refined the grouping by collecting four groups in order to observe the difference across clinical phases, and used eye tracking to detect the attentive processing toward interpersonal visual stimuli. A pattern of "late attentive orienting and fewer attentive engagement" was found in this study.

Several limitations need to be acknowledged. Social cognitive function is an important influencial factor for interpersonal interaction. However, we did not find significant correlations between these outcomes and variables, presumably due to high variability between individuals with respect to experiences and background Finally, some subjects of chronic inpatient group and first-episode and CHR group were taking antipsychotics, however, the impact of medication on eye movement is controversial.

In conclusion, the results: suggest altered attentive bias towards pictures of intense interpersonal communicational information across different clinical phases of schizophrenia. The ratio of initial attentive orienting was found to be associated with negative symptoms, indicating that this pattern may be influenced by psychiatric symptom.

S107. EXAMINING FACTORS THAT IMPACT THE RELATION BETWEEN DEFEATIST PERFORMANCE BELIEFS, NEGATIVE SYMPTOMS, AND FUNCTIONING

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Background: Defeatist performance beliefs, overgeneralized negative thoughts about the degree to which one can perform a goal-directed behavior successfully (Campellone et al., 2016), are commonly experienced by people with psychosis (Campellone et al., 2016; Clay et al., 2020; Grant & Beck, 2009). Although research has indicated that greater defeatist performance beliefs are associated with greater severity of negative symptoms (Campellone et al., 2016; Clay et al., 2020; Grant & Beck, 2009), most studies have not assessed if these beliefs are differentially related to the two major facets of negative symptoms involving motivation and pleasure or expressivity (Blanchard et al., 2017; Kring et al., 2013). In addition, studies that examined if depression impacts the relation between defeatist performance beliefs and negative symptoms have shown mixed results (Couture et al., 2011; Edwards et al., 2019; Grant & Beck, 2009). Past research has also indicated that defeatist performance beliefs are related to poor functioning (e.g., social functioning, quality of life; Campellone et al., 2016; Horan et al., 2010). Importantly, most studies have not investigated if gender impacts the association between defeatist performance beliefs and functioning (Campellone et al., 2016). This is a notable limitation because a meta-analysis found that the relation between defeatist performance beliefs and functioning was stronger in males in two studies (Campellone et al., 2016).

The current study addressed these gaps by examining the impact that depression has on defeatist performance beliefs (DPBs) and negative symptoms. We also assessed the association between DPBs, social and community functioning, and gender. We evaluated the following hypotheses: 1) greater DPBs would be associated with greater negative symptoms of

motivation and pleasure, but not diminished expressivity; 2) greater DPBs would be related to poorer social and community functioning; and 3) the relation between DPBs and poorer social and community functioning would be stronger in men than women.

Methods: Participants with a psychotic disorder and community controls (N = 119) completed several measures. We administered the Dysfunctional Performance Attitudes subscale (Weissman, 1979) to assess defeatist performance beliefs; clinical interviews to evaluate psychiatric symptomatology (i.e., depression-anxiety, Brief Psychiatric Rating Scale-Extended, Ventura et al., 1993) and negative symptoms (Clinical Assessment Interview for Negative Symptoms, Kring et al., 2013); and the Specific Levels of Functioning Scale (Schneider & Struening, 1983) to measure social and community functioning.

Results: Results indicated that DPBs were positively correlated with negative symptoms of motivation and pleasure ($r = .27$, $p = .003$) and expressivity ($r = .21$, $p = .02$). The associations between DPBs and negative symptoms of motivation and pleasure ($pr = .26$, $p = .01$) and expressivity ($pr = .19$, $p = .04$) were significant after controlling for depression-anxiety. Greater DPBs were correlated with poorer overall social functioning ($r = -.21$, $p = .02$), but not overall community functioning ($r = -.11$, $p = .26$). Multiple regression analysis showed that gender moderated the relation between DPBs and social functioning ($R2 = .11$, $F (3.00, 115.00) = 4.80$, $p = .003$). Specifically, DPBs were associated with poorer social functioning in women alone ($b = -.21$, $SE = .05$, $t = -3.68$, $p = .0004$).

Discussion: Defeatist performance beliefs and negative symptoms appear to be related independent of depression-anxiety. Defeatist performance beliefs may impact social functioning in women with psychosis, but this association is not evident in men. An in-depth discussion will be presented at the poster presentation.

S108. IMPAIRED SOCIAL COST-BENEFIT ANALYSIS IN SCHIZOPHRENIA

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Background: Amotivation is a key manifestation of negative symptoms in schizophrenia (SCZ), which can lead to profound effects on SCZ patients' social functioning. Altered effort-based decision making has been proposed as one of the potential explanations that contributes to the motivation deficits in SCZ patients. However, it still remains highly uncertain whether this motivation deficit could be further applied to social scenarios. The present study aimed to examine social effort decision making and its relation to amotivation symptoms in SCZ patients.

Methods: We recruited 31 SCZ patients and 41 healthy controls (HC) with well-matched age and gender. The Mock Job Interview Task required incrementally greater amounts of social effort (i.e., highly intense and challenging) to obtain social reward (i.e., job offer). Briefly, subjects were presented with a series of trials where they may choose to expend a greater amount of social effort for a larger social reward versus less social effort for a smaller reward. The proportion of higher social effort tasks they chose were observed and taken as an indicator which reflected the 'social cost-benefit analysis' process. A larger proportion representing a

greater willingness to make effort. Subjective ratings were applied to assess the participants' efforts during the interview, including their emotional valence and arousal after receiving the interview results. The Scale for the Assessment of Negative Symptoms was used to evaluate the amotivation symptoms.
Results: There was a significant interaction between Group and Reward points ($F(2,140) = 3.806$, $P = 0.025$). It was found that SCZ patients were less likely to choose the tasks requiring higher social effort during the job interviews than HC did, when the medium ($P = 0.03$) and high ($P < 0.01$) reward magnitude was provided. The proportion of higher social effort choice was negatively correlated with patients' amotivation symptoms ($r = -0.568$, $P < 0.01$), with severe symptoms of amotivation indicating less manifestation of higher social effort making. What's more, there was no significant interaction between Group and Interview results (Success vs. Fail) on emotional valence ($F(1,140) = 0.372$, $P = 0.543$) and arousal ($F(1,140) = 0.404$, $P = 0.526$). Interestingly, the main effect of group was significant ($P=0.012$), indicating that SCZ patients exhibited more aroused experiences than HC regardless of the type of interview results.
Discussion: In line with most previous studies investigating effort-based decision making under the influence of physical or cognitive functioning in SCZ patients, the present study again suggests that SCZ patients are impaired in their cost-benefit analysis regarding social rewards. This expands our understandings that impaired effort-based decision making in SCZ can be generalized from the monetary/non-social to a more ecologically social dimension, which might aid in the precise clinical diagnosis and treatment of negative symptoms in SCZ.

S109. THE MEDIATING ROLE OF CREATIVITY ON FUNCTIONAL OUTCOME AMONG PEOPLE WITH SCHIZOPHRENIA

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Background: In spite of the advances in the pharmacological treatment, functional impairment is still a major issue in schizophrenia treatment. Patients with schizophrenia experience difficulties in a variety of daily life functioning domains, which has an enormous impact on the quality of life of both patients and relatives or caregivers. In an attempt to develop effective interventions for this disability, studies have mainly focused on the negative aspects of the disease, such as clinical symptoms and cognitive impairment, as possible determinants of functional outcome. However, other factors like creativity, which is considered an essential adaptive capacity for coping with life's adversities and for real-life problem-solving, could have a positive impact on functional outcome. Therefore, the aim of this study was to analyze the predictive role of creativity on functional outcome in schizophrenia through a mediational model also including sociodemographic, clinical, neurocognitive, and social cognitive variables.
Methods: Ninety-six patients with schizophrenia from the Mental Health Network from Álava (Spain) underwent a comprehensive assessment of clinical symptoms, neurocognition, social cognition, verbal and figural creativity, and functional outcome. Spearman´s Rho, Pearson's r and point-biserial correlations were carried out using IBM SPSS version 26.0 (SPSS Inc., Chicago, USA). Path analysis with robust maximum likelihood method was carried out by LISREL 9.2. The goodness of fit of the model was evaluated by the Mean Square Error of Approximation Error (RMSEA), Comparative Fit Index (CFI), Non-Normed Fit Index (NNFI),

and Standard Residual Mean Square Root (SRMR). The significance of the mediational paths was examined via 5,000 bootstrapping samples.
Results: Path analysis revealed that figural creativity and social cognition significantly mediated the relationship between neurocognition and functional outcome (0.260; 95% confidence interval [0.256, 0.264]), and that figural creativity mediated between negative symptoms and functional outcome (-0.021; 95% confidence interval [-0.021, -0.020]). Additionally, neurocognition was directly associated with functional outcome. The fit of the model was very good, $\chi 2$ (20, N = 96) = 15.55, RMSEA = 0.00 (90% confidence interval: 0.00-0.07), CFI = 1.00, NNFI = 1.04, and SRMR = 0.06.
Discussion: Results suggest that creativity plays a mediatory role in the association between neurocognitive, social cognitive and functional outcome and in the relationship between negative symptoms and functional outcome in schizophrenia. The importance of these findings is based on the fact that understanding which factors influence functional outcome is relevant for the development of more efficient interventions. Specifically, these results suggest that functional outcome may be improved in this disease by including training on creative problem-solving skills. Furthermore, these findings open up a new field of research on additional positive personal resources as possible determinants of functional outcome in schizophrenia and other diseases.

S110. ABNORMAL BODILY SELF EXPERIENCES IN SCHIZOPHRENIA; A COMPARATIVE STUDY OF SOUTH KOREA AND USA

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Background: Bodily self-disturbances in schizophrenia are highly prominent and prevalent from the prodromal to chronic stage of schizophrenia but overlooked in the current DSM diagnostic system. With new methodological advances, it is now possible to empirically investigate the etiology and nature of self-disorders. Such efforts could lead to more effective treatments. However, cultural factors underlying bodily self-disturbances have not yet been examined systematically. Given the impact of culture on defining self-experiences, it is important to test whether bodily self-disturbances of schizophrenia are consistent across different cultures. To further elucidate the nature of self-disturbances, we compared empirical indices of self-disturbances in South Korea and the USA.
Methods: We investigated components of bodily self-disturbances in individuals with schizophrenia (SZ) and matched controls (CO) from South Korea and the USA in two experiments. A novel picture-based disturbance inventory (B-BODI; Benson et al., 2019) was administered to capture and assess the frequency, distress, and vividness of dissociative experiences. A computerized mapping task of emotion (emBODY; Nummenmaa et al., 2014) was used to generate visuospatial maps of bodily sensations that accompany 16 different emotion experiences. From all participants, we also collected data on positive/negative affect, and loneliness. We also assessed symptom severity in SZ and schizotypy in CO.
Results: Regardless of culture, SZ endorsed a greater number of bodily self-disturbances with increased frequency than CO. American participants, in general, reported increased distress and vividness compared with Korean participants. However, country-by-group interactions were not significant. Bodily self-disturbances were significantly associated with the severity of symptoms in schizophrenia and schizotypy in CO. In emotion mapping task, Korean SZ showed relatively weaker bodily sensations on high-arousal emotions such as anger and disgust. Moreover, bodily sensations of Korean SZ were starkly diminished or near absent for low-arousal emotions such as sadness, depression, loneliness, and lethargy compared to Korean

CO. Interesting cultural difference emerged in the embodiment of disgust, shame and sadness; bodily maps of these emotions were similar for SZ and CO in Korea but in the U.S., SZ and CO participants showed stark differences.
Discussion: Bodily self-disturbances were universally salient in SZ but there were potential culture-specific findings in bodily self-experiences that need to be further verified for future research.

S111. LITERATURE REVIEW AND CRITICAL ANALYSIS OF SHARED DECISION MAKING TOOLS FOR THE CHOICE OF ANTIPSYCHOTICS IN EARLY PSYCHOSIS

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Background: Shared decision making is an approach seldom used in psychiatry. A published survey in 2009 showed that only 51% of psychiatrists claimed to have implanted the shared decision in their clinical practice, a figure that is inflated as the claims were not objectively verified.
Several studies have demonstrated the usefulness of decision aid tools to support patients and clinicians in the choice of treatment. The purpose was to increase their active participation in decision making and to guide them towards recovery.

The objective was to review the literature for the existing shared decision tools for the choice of antipsychotics in early psychosis and to analyze their usability and limits.

Methods: A literature research was performed using MEDLINE, Embase and psycINFO electronic databases.
Studies were eligible for inclusion if they met the following criteria: (i) written in English or French, (ii) study population aged over 18 and (iii) discusses a shared decision-making tool or approach.

The initial literature search, after removing duplicates, yielded 535 articles. Full articles were then read and validated by two reviewers. After culling, 38 articles were included. The search was expanded by free search in the internet.

Results: We found 15 tools/approaches meeting our criteria.
Most of the tools were developed after semi-structured interviews and literature review.

Four tools had free access. Eleven tools/approaches were inaccessible of which 3 were chargeable.

SDM PLUS and SDM model program were approaches aimed at involving and empowering patients to be more active in their therapeutic decision-making.

The paper based decision support tool and the antipsychotic cards were tools based on informative cards about antipsychotic side effects.

Encounter decision aid, PAC index, Medication review tool and Decision support tool were tools to assess the efficacy and/or adverse effects of antipsychotics.

Several tools were used as support to initiate and promote discussion about medication between patient and caregiver.

Discussion: Few tools for shared decision making were found especially for mental health. No shared decision tool or approach exists for the choice of antipsychotics in early psychosis, in particular regarding the choice to continue or to stop treatment after sustaining a 1.5-year period of recovery. This is worrisome as patient empowerment can be a powerful tool to promote recovery in the early stages of mental health disorders.

Most of the tools found were designed to assess the decision already made rather than to support a shared decision making for the choice of antipsychotics between the patient and the mental health professional.

The main limit of these instruments was the scarcity of consideration of the additional challenge of non-recognition of the disease, which is common in psychotic disorders.

Shared decision aid should be a tool to improve the treatment-option understanding for the patient. The given informations should be clearly accessible for them while taking into consideration their preferences and concerns. The tool should be a support to collaborative decision between patient and healthworker.

A project is currently under development in our setting to develop a shared decision support tool for antipsychotics in early psychosis.

S112. PREDICTION OF QUALITY OF LIFE IN SCHIZOPHRENIA USING MACHINE LEARNING MODELS ON DATA FROM CLINICAL ANTIPSYCHOTIC TRIALS OF INTERVENTION EFFECTIVENESS (CATIE) SCHIZOPHRENIA TRIAL

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Background: Schizophrenia is a chronic and severe mental disorder. While research focus remains mainly on negative outcomes, it is questionable whether we are placing enough emphasis on improving their sense of well-being and functioning. This could be accessed through the study of the quality of life (QoL). To date, QoL prediction models mainly focused on neurocognition and psychotic symptoms, but their predictive power remained limited. Therefore, the aim of this study was to accurately predict the QoL within schizophrenia using unsupervised learning methods.

Methods: We computed variables from 952 patients from the CATIE study, Randomized, double-blind clinical trial of antipsychotic medications for schizophrenia treatment, conducted between 2000 and 2004. Findings from the screening and baseline visits, as well from the 6-month and 12-month follow-up visits were reported. QoL was measured using the Heinrichs-Carpenter Quality of Life Scale and potential predictors included all available variables: symptoms, neurocognition, medication adherence, insight, adverse effects, etc. By optimizing parameters to reach optimal models, three linear regressions were calculated: (1) baseline predictors of 12-month QoL, (2) 6-month predictors of 12-month QoL, and (3) baseline predictors of 6-month QoL. Adjustments were made to ensure that included variables were not collinear nor redundant with QoL.

Results: Calculated models had adjusted R-squared of 0.911, 0.916 and 0.915, respectively. Best predictors were sociodemographic characteristics, treatment attitudes, social inclusion, specific symptoms, neurocognition (processing speed) and many others. Physical health variables were also included, suggesting that they could have a significant impact on QoL in schizophrenia.
Discussion: Calculated models had adjusted R-squared of 0.911, 0.916 and 0.915, respectively. Best predictors were sociodemographic characteristics, treatment attitudes, social inclusion, specific symptoms, neurocognition (processing speed) and many others. Physical health variables were also included, suggesting that they could have a significant impact on QoL in schizophrenia.

S113. PROMOTING PRECISE PSYCHOSIS CARE BY FOCUSING ON DIFFERENCES IN CAUSAL BELIEFS TO PSYCHOSIS BETWEEN PATIENTS AND CLINICIANS

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Background: Disengagement from psychiatric care is highly prevalent among people with psychosis, including service disengagement and medication non-adherence. A central component of psychosis care is understanding the psychotic experience and specifically linking a person's history with their current experience in order to tailor a personalized treatment plan. Gaps in causal beliefs, the etiology and reasons attached to an illness, between clinicians and patients with psychosis may pose a barrier to psychosis care. Causal beliefs influence emotional responses and coping strategies, such as deciding whether and what kind of treatment people prefer. The purpose of the present study was to map casual beliefs among people with psychosis and clinicians and explore their degree of concordance.
Methods: We conducted a systematic literature search of Pubmed, Embase, Scopus, PsycInfo, ASSIA, and a grey literature search that included PsyArXiv and MedNar that yielded 11,821 eligible references.
Results: The final sample includes 42 articles indicating considerable gaps between patients and clinicians in casual beliefs. While clinicians tend to endorse biogenetic beliefs of the origin of psychosis, people with psychosis tend to endorse more psychosocial beliefs.
Discussion: Our findings suggest several implications for the treatment of psychosis. First, rethink the role of casual beliefs in treatment adherence and service engagement. Our findings indicate that clinicians' use of medicalizing language is related to their tendency to hold biogenetic causal beliefs and may be indirectly related to treatment non-adherence. Also, psychosocial interventions are often not offered to patients with psychosis. Fostering person-centered care and establishing an open and respectful ongoing dialogue can facilitate shared meaning, which in turn could improve effective use of treatment and services. Second, addressing patients' and clinicians' causal beliefs and raising clinicians' awareness to possible gaps in causal beliefs between them and the people they treat, can serve as important elements of psychosis care, as the process of understanding the psychotic experience occurs within this dyad and may also influence the therapeutic relationship. Thus it may have the potential to improve precise care and engagement among people with psychosis.

FACILITATING PATIENT AND FAMILY PARTICIPATION IN EARLY PSYCHOSIS RESEARCH: ASSESSING UPTAKE OF DIGITAL TOOLS

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Background: While research is critical to advancing assessment and treatment of psychosis, recruiting and retaining patients with psychosis and their families in research is a challenge. Study burden, illness severity, reluctance to accept diagnosis and treatment, low interest in participating among patients, and an unwillingness among care providers to refer patients to research have been identified as barriers in prior studies. With high rates of digital engagement among young people with psychosis, digital tools, such as online platforms, mobile apps and text messaging, have the potential to address barriers by facilitating remote recruitment and participation. However, there has been limited research on leveraging these technologies to engage people with psychosis and their families in research. We sought to assess the uptake of digital tools to engage patients with provisional psychosis and their families in research and their preferences for different research administration methods.

Methods: This study used Research Electronic Data Capture (REDCap), a secure web-based platform with built-in tools for data collection and storage, to send web-based consent forms and surveys to patients and family members referred to early psychosis intervention services between July 2018 and February 2020. Web-based surveys were sent automatically through REDCap, along with 2 automated reminders, 30 days after participants consented to the study. Some participants were also contacted by phone and reminded to complete the survey. If the survey was not completed remotely, participants attending clinic were approached in person to complete the survey using a tablet or pen and paper depending on their preferences. Those who completed the survey were given the option to select a $10 e-gift card or hard copy gift card from their choice of 3 major chain retailers. We used descriptive statistics to calculate completion rates and timing using remote and in-person administration methods and compensation preferences.

Results: A total of 447 patients with provisional psychosis and 187 of their family members agreed to receive the web-based consent form, and approximately half of patients (48.3%) and family members (58.3%) consented to participate in the survey. Most patients (79.5%) and to a lesser extent, family members (64.7%) who completed the consent form did so remotely. Of participants who consented, 77.3% of patients and 72.5% of family members completed the survey, most of them remotely (84.1%). Almost all patients (90.5%) and family members (91.6%) requested to receive the consent form and survey by email, and only 4.1% and 3.2% preferred text message. Just over half of patients (54.5%) and family members (53.2%) preferred to receive e-gift cards from a coffee shop as study compensation. Most surveys were completed weekdays between 12 and 6 pm.

Discussion: Our findings suggest that digital tools offer a feasible and acceptable way to conduct research with patients with psychosis and their families. When offered the choice, most participants with psychosis and their families chose remote methods. However, in-person engagement was still a useful strategy for reminding patients and family members about the research, explaining it, and providing technical support. Leveraging data on preferences and usage patterns to target use of a variety of digital and in-person research tools can help optimize study recruitment and retention, improving the quality and representativeness of psychosis research. This is particularly timely given the impact of the COVID-19 pandemic on clinical research across disorders, when evidence to guide the use of digital tools to conduct remote research is so critical.

UNIVERSITY COUNSELING CENTER STAFFS' CAPABILITY AND COMFORTABILITY WORKING WITH STUDENTS WITH SCHIZOPHRENIA

Delaney Collins*[1], Jennifer Muehlenkamp[1]

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Background: While there is sufficient research regarding psychosis in young adults, there is a lack regarding schizophrenia treatment in college counseling centers. University counseling centers are meant for short-term care, which does not align with treatment plans for those with schizophrenia (Francis & Abbrassi, 2010). College counseling centers claim 21% of students have severe mental health concerns, and three of 1000 students experience schizophrenia (Mistler et al., 2012; Psychosis and Your College Student, 2017). Universities can be a first-line contact to treat students who experience these symptoms, and college counseling centers must be capable, and staff comfortable, to work with students with such issues. Support may retain students and guide them throughout treatment process. The project's aim is to understand the capability and comfortability of university center counseling staff when working with students with schizophrenia.

Hypothesis: Participants that have higher scores of perceived knowledge for utilizing therapeutic techniques with students with schizophrenia, will score higher on comfortability to treat students with schizophrenia, and report lower stigma towards students with schizophrenia than those who report lower perceived knowledge.

Methods: Online surveys evaluated study constructs of perceived knowledge of treatment strategies for working with students who have schizophrenia, training experiences, attitudes, and comfortability in working with students with schizophrenia. Participants included 34 individuals (82% women; mean age of 39 years; 85% white; mean length of time working in a counseling center 10.9 SD= 8.9).

Results: Independent sample T-tests were run to observe differences between high/low categories of knowledge. High and low categories for knowledge were determined by a median split; with 39 and above being the high group, and 38.9 being the low group. Independent sample T-tests were run on comfort-treating and generalized stigma scales, with the grouping variable being the perceived knowledge scores.

Participants reporting higher levels of perceived knowledge also reported higher levels of comfort in treating students with schizophrenia ($M=19.28$, $SD= 1.78$) compared to those reporting lower levels of perceived knowledge ($M=14.94$, $SD= 3.22$), $t(32) = 4.8$, $p < .001$. There was no significant difference between knowledge groups on the measures of generalized stigma; $t(32)= .562$ ($p=.562$). In addition, there was no significant difference in the social stigma scores between the knowledge groups, $t(32) = 0.428$ $p =.780$.

Discussion: Findings indicate those reporting higher scores of perceived knowledge also report higher levels of comfort working with students who have schizophrenia; however, there were no meaningful differences regarding generalized stigma or social stigma.: Results suggest counselors who feel confident in their knowledge about students with schizophrenia feel more comfortable and prepared to work with such students. Current results suggest that knowledge does not relate to generalized or social stigma about individuals with schizophrenia. Further research should examine how/if stigma interferes with therapeutic relationships and client outcomes. While college counselors are not consistently exposed to students with schizophrenia, results indicate that many perceive themselves to be knowledgeable and comfortable in working with such students. These findings are promising as they suggest universities may be equipped and capable to work with students with schizophrenia. Further

research on counselor training and perception of students with schizophrenia is needed to promote equity, diversity and inclusivity in attending to the needs of these students.

Monday Poster Session

M1. THE SAFETY PROFILE OF THE TAAR1 AGONIST, SEP-363856, IS DISTINCT FROM ATYPICAL ANTIPSYCHOTICS

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Background: The past decade has seen increased utilization of data-mining Methods: as an adjunct to traditional approaches to pharmacovigilance. The availability of sensitive Methods: for detecting safety signals is especially important in the development of drugs with a novel mechanism of action. SEP-363856 does not act on dopamine D2 receptors but has agonist activity at trace amine–associated receptor 1 (TAAR1) and 5-hydroxytryptamine type 1A (5-HT1A) receptors. In a double-blind study, SEP-363856 demonstrated significant efficacy in the treatment of an acute exacerbation of schizophrenia. The aim of the current analysis was to identify the adverse event signals of this first agent in a novel drug class that differentiate it from the available class of atypical antipsychotics.

Methods: We performed a disproportionality analysis, calculated using the empirical Bayes geometric mean (EBGM) method, to identify and rank-order preferred terms associated with the 11 most recently approved antipsychotics from the FDA real-world adverse event reporting database (FAERS). We used the results of this analysis to evaluate the frequency and cumulative percentages of drug-associated adverse event (AE) signals in the currently available safety database of SEP-363856, consisting of one placebo-controlled 4 week study (SEP361-201; total N=245 patients) and one 6-month open-label safety study (SEP361-202; total N=157 patients). The results were also compared to the cumulative AE percentages for FAERS-identified, class-related preferred terms for the atypical antipsychotic lurasidone, based on 5 pooled studies (N=1795). A conservative threshold of 3-fold risk in FAERS was used as the criterion level to determine if a class-specific AE was occurring.

Results: In the SEP-363856 safety database, utilizing the 3-fold risk threshold, the cumulative rate of adverse events for preferred terms in FAERS was below 20% for antipsychotic class-specific risks. In contrast, in clinical trials of lurasidone, the cumulative rate of adverse events for preferred terms was approximately 50%, indicating about half of the adverse events reported in clinical trials of lurasidone were antipsychotic class-specific risks.

Discussion: SEP-363856 demonstrated markedly lower cumulative risk for antipsychotic class-related adverse events in comparison with similarly-designed acute schizophrenia trials of the atypical antipsychotic lurasidone. These results support characterization of SEP-363856 as a novel class for the treatment of schizophrenia. This database-driven approach represents a new way to summarize adverse events by cumulative burden of class-specific risks and will serve as a helpful tool to evaluate novel classes of drugs with otherwise uncharacterized safety profiles.

M2. PHYSICAL ACTIVITY AND CHILDHOOD TRAUMA EXPERIENCES IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDERS

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Background: Physical activity promotes resilience and reduces stress. Here we aimed to clarify the impact of physical activity and childhood trauma experiences on current mood and cognitive function in patients with schizophrenia (SZ) or bipolar disorders (BD).

Methods: Three-hundred-and-six patients with a DSM-IV schizophrenia (SZ) or bipolar disorder (BD) were included in the study. Diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Physical activity was measured as hours spent on any regular physical activity per week. All patients underwent a neuropsychological test battery. A history of Childhood trauma was assessed using the Childhood Trauma Questionnaire and mood symptoms were assessed with the Inventory of Depressive Symptoms.

Results: Patients with childhood trauma who were physically inactive (< 90 min. per week) had the most severe clinical profile, characterized by the highest depressive symptoms ($P<0.001$) and lowest performance on working memory tasks ($P<0.001$). Among patients with childhood trauma, those who were physically active (≥90 min. per week) had better working memory performance than physically inactive patients ($p=0.02$).

Discussion: A history of childhood trauma was associated with poorer working memory and more depressive symptoms only in patients who were physically inactive, suggesting a possible protective factor of physical activity in severe mental disorder.

M3. CLOZAPINE IS ASSOCIATED WITH DECREASES IN IMMUNOGLOBULINS LEVELS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Clozapine is the treatment of choice for patients with Treatment-Resistant Schizophrenia (TRS), but its use is limited due to life-threatening side effects involving the immune system, such as neutropenia. Recent cross-sectional evidence associated clozapine with immunoglobulin deficiency, however, findings were limited. This study aimed to replicate previous findings using a longitudinal design and to determine whether changes in immunoglobulin levels were associated with response to clozapine.

Methods: Blood samples were taken from 56 participants with treatment-resistant psychosis that were due to start clozapine. Their immunoglobulin A, M and G levels were measured in plasma using a sandwich immunoassay. They were determined before starting clozapine and at 6, 12 and 24 weeks after initiating treatment. Clinical instruments were measured over time.

Results: The three types of immunoglobulins decreased significantly over time. For IgA there was a significant effect of time on clozapine at 24 weeks (B – 32.7, 95% CI = -61.19, -4.21, z = - 2.25, p = 0.024), for IgM at 12 (B = - 21.73, 95% CI = -37.1, -6.35, z = - 2.77, p= 0.006) and 24 weeks (B = - 32.54, 95% CI = -48.89, -16.18, z = - 3.90, p < 0.001) and for IgG at 24 weeks (B – 55.94, 95% CI = -111.03, -0.844, z = -1.99, p = 0.047). Responders to clozapine had higher baseline IgG levels (B= - 402.49, 95% CI = -701.4314, -103.54, p = 0.011), but there were no differences in IgA or IgM nor differences in any immunoglobulin levels at 24 weeks.
Discussion: These results are in line with previous evidence and suggest that the effect of clozapine on antibody levels appears within the first six months of treatment. Antibody measurements are not included in the regular assessment of clozapine users and deficits might explain the increased risk of pneumonia seen in this vulnerable population.

M4. NEUROLOGICAL SOFT SIGNS IN PATIENTS WITH EARLY ONSET PSYCHOSIS, FIRST-DEGREE RELATIVES AND HEALTHY CONTROLS

Sofia Chávez[1], Igor Bombin[2], Elisa Rodríguez-Toscano[3], Arantzazu Zabala[4], Maria Mayoral[3], Josefina Castro-Fornieles[6], Elena de la Serna[7], Celso Arango[8], Marta Rapado-Castro[9], Sofia Chavez Mejia*[10]

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Background: Early-onset psychosis (EOP) is a debilitating condition generally associated with short- and long-term loss of psychosocial functionality [1]. It is thus important to identify key features that predate the onset of the illness. The evaluation of Neurological Soft Signs (NSS) in patients with EOP and their first-degree relatives may be of great relevance to understand the aetiology of the disorders. They can be present as a result of subtle developmental variations during neurodevelopment and predate the onset of psychotic illness [2]. Our study aims to examine a) the prevalence of NSS in patients with EOP, their first degree relatives and their corresponding paired control groups matched by age and sociodemographic factors; and b) to establish the severity of NSS in patients with EOP, their first degree relatives and their corresponding paired control groups.
Methods: The NSS were assessed using the Neurological Evaluation Scale (NES) in a sample of 87 patients with first episodes of EOP, 97 first-degree relatives, 87 healthy adolescent controls and 130 healthy adult controls. Individuals with EOP and healthy adolescent controls were recruited

from Hospital General Universitario Gregorio Marañón (HGUGM) and Hospital Clínico Universitario de Barcelona as part of The child and adolescent first-episode psychosis study (CAFEPS) [3], first degree relatives were recruited at the HGUGM and healthy adult controls were recruited at the HGUGM and Reintregra Centre in Oviedo. In order to examine the differences between groups, one-way analysis of variance (ANOVA) and covariance (ANCOVA, using age, years of education and socioeconomic status as covariates) were conducted (Bonferroni corrected).
Results: Patients with EOP presented with higher prevalence of NSS in the 4 subscales: Sensory integration, Motor coordination, sequencing of complex motor acts, and Others ($p = <0.001$), as well as in the global score and the positive signs ($p=<0.001$) with respect to their correspondent adolescent control group. No differences were observed between patients with EOP and their first-degree relatives, in any subscale, global score or the number of positive NSS signs. However, we found significant differences between first-degree relatives of patients with EOP and the adult control group in 3 subscales: Sensory integration, sequencing of complex motor acts, and Others ($p = <0.001$). There were no significant differences between first-degree relatives and the adult controls in the global score and the positive signs.
Discussion: Patients with EOP present a deficit in neurological signs, in all components of the scale. Patients with EOP have a higher prevalence of NSS compared to their correspondent adolescent control group. First-degree relatives have a higher prevalence of NSS compared to their adult controls. The plausible consideration of NSS as an intermediate phenotype was confirmed since the severity of NSS in first-degree relatives was in an intermediate range between EOP individuals and controls.

M5. PLASMA LEVELS OF METABOLITES DIFFERENTIATE FIRST EPISODE OF PSYCHOSIS IN SCHIZOPHRENIA AND BIPOLAR DISORDER PATIENTS

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Background: Schizophrenia (SCZ) and bipolar disorder (BD) are serious psychiatric disorders that affect young adults and lead to disability, psychosocial functioning impairment and premature death (Murray and Lopez, 1996). These disorders share several characteristics and symptoms (Dunayevich and Keck, 2000; Yatham et al., 2010) and the diagnosis yet is mainly clinical. It is known that the sooner they are identified, diagnosed and treated, the better the clinical prognosis. Therefore, the development of sensitive and accurate biomarkers is highly required. Lipids play an increasingly recognized role in the neuronal function and plasticity of the brain. The lipid composition of the brain substantially influences perception, mood and behavior. Glycerophospholipids and molecules-like comprise 60% of the non-aqueous portion of the brain and in an even greater proportion of the dendrites and synapses. They are the major constituents of neuronal and glial cell membranes, membranes of synaptic vesicles, nuclear endoplasmic reticulum, membranes of the mitochondria and the golgiense complex. However, the lipid bilayer is not exclusively composed of glycerophospholipids, but also the presence of cholesterol, proteins and other lipids, such as sphingolipids. In addition, other metabolites directly influence its functioning and remodeling, such as acylcarnitines. Since lipid metabolism is altered differently in neuropsychiatric

diseases, alterations in the lipid profile of the membrane can allow a discrimination between subjects in first episode psychosis, thus suggesting a specificity of the findings for this clinical state. Thus, our aim was to determine plasma levels of metabolites of subjects in first episode psychosis and healthy controls and find cutoff values that differentiate each group.

Methods: Plasma samples were analyzed for 55 drug-naïve patients (28 SCZ and 27 BD) and 30 healthy controls in this study. All participants were <60 years old. Determining the lipid profile was performed by mass spectrometry - Flow injection analysis, using AbsoluteIDQ p180 ® kit (Biocrates Life Sciences). Statistical analyzes were performed using a classification method - Classification And Regression Tree.

Results: We observed that there the combination of four metabolites are able to differentiate the diagnoses studied: PC aa C26:0, PC aa C38:4, PC aa C34:3 and C16-OH. The accuracy of the method is 87,1%.

Discussion: Our results suggest that the levels of some plasma metabolites differentiate subjects in first episode psychosis in SCZ, BD and healthy controls. The levels of these metabolites can be a potential biomarker for psychosis, as well as a diagnostic marker for SCZ and BD, aiding clinical practice. The findings from this study require further validation in BD and SCZ subjects, but suggest that the metabolome is a good tool to understand the pathophysiology of these disorders and presents potential diagnostic biomarkers for the diseases studied.

M6. AUTOANTIBODY PROFILES ASSOCIATED WITH CLINICAL FEATURES IN PSYCHOTIC DISORDERS

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Background: Autoimmune processes are suspected to play a role in the pathophysiology of psychotic disorders. Better understanding of the associations of auto-immunoglobulin G (IgG) repertoires with clinical features of mental illness could yield novel models of psychosis pathophysiology and markers for biological patient stratification.

Therefore, the objective of the present study was to undertake comprehensive global screening for auto-IgG expression in a large and well characterized cohort of people with psychotic disorders; to determine whether associations exist between autoantibody expression and clinical features.

Methods: We performed a cross-sectional detection and quantification of auto-IgGs in peripheral blood plasma of 461 people with established psychotic disorder diagnoses. For global screening, pooled samples of phenotypically representative patient groups were exposed to planar protein microarrays containing 42,000 human antigens. For targeted profiling, expression levels of 380 autoantibodies were quantified by suspension bead array (SBA) in each patient's plasma.

Results: Planar arrays detected 181 auto-IgGs across the pooled diagnostic groups. SBA profiling revealed highly individual autoantibody profiles with no evidence for co-expression patterns. People with the highest overall autoantibody counts (top 5%), compared to people with the lowest counts (bottom 5%) were more likely to be female and to have family histories of obesity and psychiatric disorders other than schizophrenia; people with the lowest overall counts were more likely to have experienced formal thought disorder, and there was a trend towards clozapine treatment in this group. We found 6 autoantibodies robustly associated with specific

psychopathology: anti-AP3B2, detected in 23 patients (5% of the cohort) of whom 100% had persecutory delusions; anti-TDO2, 5% of the cohort, 100% hallucinations); anti-CRYGN (4%, 86% initial insomnia); anti-APMAP (3%, 86% poor appetite); anti-OLFM1 (2.5%, 100% above median cognitive function); and anti-WHAMMP3 (2%, 90% anhedonia and dysphoria). Examination of the auto-IgG binding site on the TDO2 protein revealed a putative pathophysiological mechanism involving the kynurenine pathway.
Discussion: Certain common autoantibody profiles are associated with specific clinical features in people with psychotic disorders. Future studies should clarify whether associations reflect causal biological relationships, and whether autoantibodies could be used as clinical markers to inform diagnostic patient stratification and choice of treatment.

M7. THE IMPACT OF COMBINED CYP2D6, CYP2C19 AND CYP1A2 POLYMORPHIC VARIANTS ON SUICIDAL BEHAVIOR IN SCHIZOPHRENIA SPECTRUM DISORDERS

Rosa Catalan Campos*[1], Mireia Vazquez[2], Rafael Penadés[3], Alexandre Gonzalez[4], Barbara Arias[5], Marina Mitjans[6], Merce Brunet[7], Victoria Ruiz[8], Josefina Perez-Blanco[9], María Jesús Arranz[10]

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Background: Suicide is the leading cause of premature death among those with schizophrenia (Palmer, Pankratz, & Bostwick, 2005). A meta-analysis indicated that the suicide rate of those with schizophrenia is 12 times greater than that of the general population (Saha, Chant, & McGrath, 2007). Studies of risk factors predicting suicide consistently suggest that suicidal ideation and a history of suicide attempts are among the most salient risk factors for suicide (Nordström et al. 1995; Beck et al. 1999)
The aim of this study was to assess the propensity to suicidal behavior and its association with the metabolic capacity of antipsychotic drugs evaluated by the combined CYP2D6, CYP2C19 and CYP1A2 genotypes were associated with STBs as measured with suicidal behavior

Methods: Our sample consisted of two hundred and forty five patients with schizophrenia spectrum disorders in which 69 subjects attempted suicide. Mostly were outpatients (55% male, mean age 47,5 ± 13,77 years). Every subject received treatment with a variety of antipsychotic drugs (37% clozapine, 15% olanzapine, 11% paliperidone, 9% risperidone, 7% aripiprazole, 7% quetiapine, 14% others).
Measurements: The degree of STBs was measured using the standardized Columbia Suicide Severity Rating Scale (CSSRS) scale (Posner et al.,2011) at baseline and at 12-weeks of follow-up.

Genotyping techniques for polymorphisms were performed using iPlex® Gold chemistry and the MassARRAY platform.

Statistical analysis: Linear regression analyses were performed considering baseline CSSRS score as dependent variables; and age, sex, and antipsychotic drug taken as co-variables for each genetic polymorphism. Software used: SPSS (IBM, v. 23) and PLINK

Results: PM phenotypes of CYP2D6, CYP1A2 and CYP2C19 combined were associated with presence of suicide ideas (Wald Chi-Square = 5.166,df 1, p=0.023) ; wishes of being dead (Wald Chi-Square = 4.126,df 1, p= 0.042) ; For non-specific active suicidal thoughts (Wald Chi-Square = 3.219, df 1, p=0.073) and active suicidal ideation without specific plan(Wald Chi-Square =4.303,df 1, p=0.038).
-When only CYP1A2 was evaluated, no statistically significant differences were found.

-PM and IM phenotypes of CYP2C19 were significantly associated with non-specific suicidal ideation (Wald Chi-Square = 4.636, df 1, p=0.031)and wishes of being dead when current age, age at onset and patient gender were also considered (Wald Chi-Square = 8.160,df, p=0.004)

Discussion: Results support the utility of genotyping in the treatment of schizophrenia spectrum disorders and we propose to use combined CYP2D6, CYP2C19 and CYP1A2 polymorphic variants as possible biological predictors of suicidal behavior. More work is also needed to better understand the underlying mechanisms tied to suicidal ideation among individuals with schizophrenia

M8. LACK OF COVARIANCE OF HAIR CORTISOL WITH STRESS-RELATED MEASURES AND PHENOTYPES IN SCHIZOTYPY

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Background: There is robust evidence that psychosis-spectrum disorders are associated to childhood adversity, heightened stress-sensitivity, and elevated HPA activity, suggesting the HPA axis as a mediator of the effects of stress on psychotic symptoms. Hair cortisol concentrations (HCC) are considered a more accurate index of chronic stress compared to other cortisol measurements. Specifically, elevated HCC have been found in clinical samples of schizophrenia and bipolar disorder patients, First Episode of Psychosis (FEP) individuals and clinical at-risk populations for psychosis. However, its direct association with psychosocial stressors (i.e., childhood trauma, recent life events) and different stress-related measures (e.g., perceived stress, anxiety, depression) commonly related to a heightened risk to psychosis remains unclear. In addition, although some studies have examined the association of HCC with established psychosis and clinical high-risk groups, the association of HCC with the nonclinical manifestations of the extended psychosis phenotype, that is, schizotypy traits, is yet unknown. Therefore, we investigated the association between long-term cortisol levels with a wide range of distal and recent stress measures (including objective as well as subjective appraisals) and stress-related phenotypes in a sample of nonclinical young adults with psychometric risk for schizotypy.
Methods: The present sample comprised a subset of 132 nonclinical young adults recruited at college and technical schools (mean age=27.09, SD= 3.07) with high psychometric risk for schizotypy belonging to the ongoing Barcelona Longitudinal Investigation of Schizotypy Study

(BLISS). Participants had valid HCC data and were cross-sectionally assessed for 1) both questionnaire and interview measures of adversity, recent life-events, perceived stress, 2) stress-related phenotypes, including affective and psychosis spectrum features (i.e. depression, anxiety, neuroticism, suspiciousness, ideas of reference, schizotypy), 3) stress-regulation (i.e. attachment and self-esteem) as well as stress-buffering (i.e. social support) measures. Pearson correlations were used to test associations between HCC and the psychometric measures.
Results: One participant was excluded because of abnormally increased HCC (244.6 pg/mg). Mean cortisol levels of the final sample of 131 participants were 6.22 pg/mg (SD= 4.93). No differences between college and technical school students were found on HCC. Therefore, the two samples were combined. Correlational analyses showed no significant associations of HCC with any of the measures included in this study. Only suspiciousness showed a trend association with HCC with a small positive correlation of $r= 0.149$ ($p< 0.10$).
Discussion: This is the first study examining a very wide range of stress and transdiagnostic stress-related phenotypes in relation to HCC in a sample of young adults with high psychometric risk for schizotypy. No significant association was found with HCC despite the fact that measurement of stress and stress-related traits and subclinical symptoms was very comprehensive; it combined self-report and interview, subjective and objective measures, risk and protective factors, distal and recent stress measures and encompassed both affective and psychosis-spectrum features. The present results question the assumption of HCC as a "trait-like" marker by showing a lack of psychoendocrine covariance between stressors and cortisol levels and support previous evidence on the poor concordance between psychosocial stressors and cortisol found so far in established and clinical high-risk psychosis groups.

M9. GLOBAL FRACTIONAL ANISOTROPY PREDICTS CONVERSION TO PSYCHOSIS AFTER 12 MONTHS IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

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Research, CINS, Mental Health Centre Glostrup, University of Copenhagen AND University of Copenhagen, Faculty of Health and Medical Sciences, [8]Copenhagen Research Centre for Mental Health (CORE), Copenhagen University Hospital,Faculty of Health and Medical Sciences, University of Copenhagen

Background: Disorders in the psychosis spectrum are associated with cerebral changes, but the predictive accuracy of biomarkers are limited. Longitudinal neuroimaging studies of individuals at ultra-high risk of developing psychosis (UHR) offers a unique opportunity to examine the neurobiological underpinnings for psychosis development. Here, we examine white matter fractional anisotropy (FA) as a prognostic marker of conversion to psychosis in UHR-individuals.
Methods: 110 UHR-individuals underwent 3 Tesla diffusion weighted imaging at baseline, combined with clinical assessments at baseline and after 6 and 12 months. First, we examined if mean global FA at baseline could predict conversion to psychosis after 12 months using logistic regression. Secondly, we investigated if global FA at baseline could predict symptom level on functional status (SOFAS), positive UHR-symptoms (CAARMS), negative symptoms (SANS), and depressive symptoms (MADRS) at 6 and 12 months, using uni- and multivariate linear regression.
Results: 10 UHR-individuals had converted into psychosis after 12 months. Global FA at baseline predicted conversion to psychosis at 12 months in a univariate model ($\chi 2$=4.35, P=0.037, β=-44.16), as well as in a multivariate model ($\chi 2$=10.46, P=0.036, β=-50.65), including potential confounders to FA (motion in MRI-scanner, gender, age, antipsychotic medication, and activity level) as covariates. Furthermore, global FA predicted level of positive UHR-symptoms (P=0.016, R2=0.055, F=6.084) and functional level (P=0.036, R2= 0.040, F=4.57) at 6 months, but not at 12 months. Antipsychotic medication did not affect the results.
Discussion: Mean global FA at baseline appear to contribute with prognostic information on clinical outcome and symptom course of UHR-individuals. Predictive models may improve by integrating neuroimaging data on baseline white matter.

M10. NEUROMELANIN MRI AS BIOMARKER FOR TREATMENT RESISTANCE IN FIRST EPISODE SCHIZOPHRENIA PATIENTS

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Background: Treatment resistance (TR) in schizophrenia is a major clinical problem with 20-35% of psychotic patients showing non-response to standard antipsychotic treatment. A biomarker that could predict TR is needed to reduce the delay in effective treatment. A well-established finding in schizophrenia, is increased striatal dopamine synthesis, but interestingly TR patients do not show this altered synthesis. A novel neuromelanin-sensitive MRI sequence NM-MR, which indirectly measures striatal dopamine synthesis, has potential as biomarker for TR. NM-MRI indeed shows increased signal in schizophrenia patients, but has not yet been tested in TR. The current study assessed 1) NM-MRI as a biomarker for TR, and investigated if TR patients show lower NM-MRI signal than responders, and 2) the optimal analysis method, by comparing two different segmentation protocols of the NM-MRI data.

Methods: Twenty-three first episode schizophrenia patients underwent a NM-MRI scan. Treatment response was determined during a six months follow-up. The NM-MRI scan contained a T1-weighted gradient recalled echo (GRE) sequence with resonance magnetization transfer preparation pulses (8 slices; slice thickness=2.5mm; TR=260ms; TE=3.9ms; FOV=162x199x22mm; voxelsize=0.39x0.39mm) and was conducted on an 3 Tesla Ingenia MRI scanner equipped with a 32-channel sense head coil. NM levels in the Substantia Nigra (SN) were measured as contrast ratio (NMcr), with the Crus Cerebri (CC) as reference region. The signal intensities in the SN and the CC were determined by a manual segmentation and a standardized segmentation protocol. For the standardized segmentation, the NM-MRI scans were normalized into MNI standard brain space. Template masks for both the SN and CC were created by manual tracing on an average image of the 23 standardized NM-MRI scans. These masks were then placed on each individual standardized scan to obtain the signal intensity of the SN and CC of each patient.
Results: Eight patients were classified as TR and 15 patients as responders. The two groups did not significantly differ on demographics. However, the duration of medication use was longer in the TR patients, $t(21)= -1.873$ $p = 0.039$. The standardized and manual segmentation Methods: both demonstrated that mean NMcr of the TR patients was significantly lower than the mean NMcr of the responders, $t(21)= 2.318$, $p = 0.031$ and $t(21) = 3.043$, $p = 0.006$, respectively. A moderate correlation (ICC=0.66) was found between the NMcr-standardized and NMcr-manual measurements. No correlations were found between NMcr and duration of medication use in both TR and responders.
Discussion: Both segmentation methods showed significant lower NMcr levels in TR patients compared to responders. These findings are in line with the [18F]F-DOPA studies, showing lower dopamine synthesis in TR compared to responders. However, there was only a moderate correlation between the two segmentation protocols, which might be explained by the normalizing step in standardized protocol. Hence, normalization of the SN remains challenging and needs to be improved.
To conclude this study demonstrated the potential of NM-MRI as a biomarker for TR in schizophrenia. Further research is needed to optimize the measurements and to investigate the predictive value of NM-MRI.

M11. ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND METHYLATION OF NMDA RECEPTOR GENES IN FIRST-EPISODE SCHIZOPHRENIA, NON-AFFECTED SIBLINGS AND COMMUNITY-BASED CONTROLS

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Background: N-methyl-d-aspartate (NMDAR) plays a central role in neurodevelopment, stress response and cognitive function and its dysfunction underlie the core symptoms of schizophrenia. Childhood trauma may affect epigenetic mechanisms, such as DNA methylation, altering the expression of several candidate genes, which increase the risk of developing schizophrenia. As we previously found hypermethylation of the Grin1 and Grin2b promoter genes in the isolation reared

rats (Loureiro et al., 2020, Epigenomics, ahead of print); we investigated whether childhood trauma is related to our previously reported GRIN2B methylation changes observed in the first-episode schizophrenia patients (FESp) (Fachim et al., 2019, Epigenomics, 11(4):401-410). In more details, we explored associations between childhood trauma and peripheral blood DNA methylation of NMDAR genes (GRIN1, GRIN2A and GRIN2B), among FESp, age- and sex-matched controls and non-affected siblings.

Methods: This case-sibling-control study is part of the epidemiological investigation "Schizophrenia and Other Psychoses Translational Research: Environment and Molecular Biology", conducted in Ribeirão Preto catchment area, Brazil, between April 2012 and March 2015, which is included in the EU-GEI consortium. We selected 40 FESp, 23 unaffected siblings and 40 community-based controls. The history of childhood trauma was investigated using the Childhood Trauma Questionnaire. Genomic DNA was bisulfite converted from blood and pyrosequencing was employed to quantify DNA methylation. To investigate the interaction between diagnostic groups and a history of childhood trauma, we used the Generalized Linear Model with linear distribution with Bonferroni correction and Pearson's correlations.

Results: A history of childhood trauma was not associated with glutamatergic DNA methylation changes of GRIN1, GRIN2A and GRIN2B specific to FESp. Childhood trauma total score was correlated positively with GRIN1 hypermethylation at CpG1 in non-affected siblings of FES patients ($r=0.440$, $p=0.036$), and negatively with GRIN2B hypomethylation at CpG4 ($r=-0.363$, $p=0.021$) and CpG5 ($r=-0.384$, $p=0.014$) in controls.

Discussion: Our study did not identify associations between childhood trauma and DNA methylation of NMDAR genes that were specific to schizophrenia patients evaluated in the early stages of the disorder. DNA methylation changes in GRIN2B in patients may be related to other aspects of the disorder rather than the influence of an early-life environmental stressor, although this is contrary to our hypothesis based in part on findings in an animal model of such early life stress (Loureiro et al., 2020, Epigenomics, ahead of print). However, we found hypermethylation of GRIN1 to be associated with childhood trauma, and interactions with diagnostic groups indicating specific effects of childhood trauma on methylation in siblings and healthy controls, respectively. These opposite effects of childhood trauma on the glutamatergic methylation changes evaluated here might reflect biological mechanisms of vulnerability and resilience to early-life stress and its impact as a risk factor for schizophrenia. Our findings suggest that childhood trauma experiences may increase GRIN1 methylation, particularly on those biologically predisposed to psychosis, since non-affected siblings share a proportion of the genotype with FESp, and shared the same environment during childhood. Our data also may be related to Grin1 hypermethylation seen in post-weaning social isolation reared rats when compared to controls, as an alteration for susceptibility to psychiatric disorders arising through early life stressors.

M12. THE ROLE OF HEART RATE VARIABILITY (HRV) AND PSYCHOTIC-LIKE EXPERIENCES IN SOCIAL COGNITION AND FUNCTIONING

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Background: Understanding the mechanisms of poor psychosocial outcomes in those with schizophrenia (SZ) has been a major aim toward diagnostic classification and preventive treatment. Some evidence from behavioral tasks suggests that certain aspects of social cognition (SC) may

play a larger role in global functioning in SZ than non-social cognitive processes (Roncone et al., 2002). Moreover, one possible biomarker candidate, heart rate variability (HRV), a measure of Autonomic Nervous System (ANS) adaptability, may also play a crucial role in psychosocial outcomes (Kok & Fredrickson, 2010). Higher HRV in SZ populations has been associated with more successful role functioning – but paradoxically only in individuals with impaired social cognition; those with intact social cognition failed to demonstrate an HRV-psychosocial function relationship (Hamilton et al., 2014). As such, further study in individuals who may be at risk for developing SZ may clarify how social cognition and physiological adaptability may interact to predict which patients may be on a trajectory toward poor outcomes. This study aims to investigate the role of social cognition on psychosocial function in individuals who report Psychotic-Like Experiences (PLE) in the general population. ANS adaptability measured through HRV is examined as a potential mechanism that may underlie this relationship.

Methods: Participants ages 18-40 years were recruited from the community, and completed the Prodromal Questionnaire – Brief (PQ-B) through the online platform Qualtrics for group designation (At-risk=AR or Not at-risk=NAR). Participants met with the researcher virtually to measure social cognitive performance with the Penn Emotion Recognition Test (ER-40), and HRV was measured using the CameraHRV smartphone application. HRV was collected for a 5-minute baseline, during stress induction with the serial 7's task, and for the 5-minute recovery post-test. Task sequence was counterbalanced where the ER-40 was either completed prior to the serial 7's or after the 5 minute recovery. Finally, social and role functioning was assessed by self-report modified from the Global Function: Social and Role Scales.

Results: Preliminary results show that AR individuals (n=5) demonstrate a significantly different positive relationship ($z=2.4$, $p<.01$) between HRV and social functioning ($r=.883$, $p<.05$) relative to the trending negative relationship found in NAR individuals (n=16; $r=-.435$, $p=.092$). Furthermore, individuals with lower social cognitive scores based on a median split (n=12) of ER-40 performance demonstrated a trending positive relationship with HRV and social functioning, but this was not seen in higher social cognitive performers (n=10), replicating Hamilton et al. (2014).

In both AR and NAR groups, higher distress in response to psychotic-like experiences was marginally associated with higher social cognitive performance ($r=.862$, $p=.06$; $r=.472$, $p=.065$, respectively).

Discussion: Preliminary analyses suggest that high ANS adaptability, as demonstrated with higher HRV, divergently predicts social outcomes in AR versus NAR participants. Additionally, higher HRV may provide compensatory processes for the subset of individuals with lower social cognitive skills, but play a lesser role in social function in individuals with intact social cognition. Interestingly, distressing responses to psychotic-like experiences may worsen as one's social cognition is higher. Ongoing data collection seeks to continue to examine the role of HRV as a compensatory mechanism for social cognitive deficits as they relate to poor functioning, specifically in those at risk for the disorders that are among the most predictive of lifelong disability.

M13. MICRORNA SIGNATURE DURING CONVERSION TO PSYCHOSIS: A LONGITUDINAL MACHINE-LEARNING APPROACH

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Background: Psychosis occurs during adolescence in a third of subjects clinically diagnosed as ultra-high-risk (UHR). It results from progressive interactions between genetic and environmental risk factors that lead to high phenotypic variability. Epigenetic modifications, such as miRNAs, which regulate gene expression, have been postulated to be a plausible source of such phenotypic variability. Longitudinal studies in short time frames close to the point of conversion are required to detect miRNAs whose variation may be pathophysiologically relevant. However, progression into the disease is more likely to involve small changes in different highly interconnected miRNAs, as part of a co-regulatory network, rather than large variations of one isolated miRNA. Therefore, in this UHR longitudinal study, we present a machine-learning strategy, leveraging all variations in miRNA expression, to identify those whose combination could constitute a dynamic epigenetic signature of conversion to psychosis.

Methods: In this prospective multicentric longitudinal study, next-generation high-throughput miRNA sequencing was done in plasma at two time-points one year apart in 81 UHR subjects, before and after conversion to psychosis (35 converters and 46 non-converters). For each subject, a measure of miRNA variation across time (Δmirna) was computed as the difference between baseline and follow-up microRNA measures, divided by the subject's follow-up time. All measured Δmirna for all subjects were given as input to a supervised learning algorithm that we built to classify between converters and non-converters. The classifier was a logistic regression with a norm l2 penalty, adjusted for frequency of status, and applied within a 5-fold nested cross-validation. Harmonization for age and sex was done within each loop of the cross-validation to prevent any information leakage. Repeated analysis after random permutation of status labels allowed to compute the significance of the resulting area-under-the-curve (AUC). Bootstrapping was used to compute the 95% confidence intervals of each Δmirna's weight. Further pathway analysis was done with mirDIP and Metascape.

Results: We detected 2479 miRNAs in total. The classifier showed a cross-validated accuracy with an AUC of 65.6 %. The AUC's non-parametric p-value was significant ($p = 0.009$). There was no overfitting since the application of the same algorithm to randomly labeled subjects led to an average classification, under the null hypothesis, with an AUC of 50 %, no better than chance. We identified 212 Δmirna (~8% of all Δmirna) that could best distinguish converters and non-converters, as the 95 % confidence intervals of their weights were different from zero, either all positive or all negative. Their top gene targets were enriched for brain development and neuron differentiation ($p < 10^{-20}$) and gene-disease association analysis showed that the most significantly enriched diseases were autistic disorder and intellectual disability ($p < 10^{-10}$), and bipolar disorders ($p < 10^{-8}$).

Discussion: To our knowledge, this is the first longitudinal study in an UHR population that leveraged the variation of all miRNAs across time, for each individual, in order to classify between converters and non-converters to psychosis. While accounting for intra-individual variation, this design allowed to identify miRNAs whose longitudinal differential expression was most relevant to the emergence of psychosis. Its combination with other biological levels, in a multi-omic approach, might better grasp pathophysiological variance and improve performance. As it is, we suggest this method be combined with selection-based procedures as a strategy to increase confidence in miRNA analysis.

M14. ALTERED ASSOCIATIONS BETWEEN CORTICAL GLUTAMATE LEVELS AND HIPPOCAMPAL RESTING ACTIVITY IN HIGH SCHIZOTYPY

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Background: Previous research indicates that elevations in both cortical levels of glutamatergic metabolites and hippocampal regional cerebral blood flow (rCBF) are associated with the development of psychotic symptoms. This is consistent with preclinical data showing that hippocampal hyperactivity leads to the expression of psychotic-like phenotypes by dysregulating subcortical dopaminergic system function, and that this arises from an imbalance between the glutamate and GABA neurotransmitter systems. Schizotypy, which refers to the phenotypic expression of subclinical psychotic-like experiences in the general population, has been widely used as a valuable paradigm to examine neural correlates of psychosis-like traits in healthy individuals without potential confounds of antipsychotic medication exposure or psychiatric comorbidities. We recently reported that individuals with high schizotypy (HS) showed increased hippocampal rCBF compared to individuals with low schizotypy (LS). While we did not find evidence of altered glutamate levels in the anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC), in HS individuals ACC/mPFC glutamate levels were negatively associated with (1) increased striatal, medial prefrontal and amygdala fMRI response to emotion, and (2) increased grey matter volume in the ACC/mPFC compared to HC. Taken together, these findings implicate the glutamatergic system in the neuroanatomical and neurophysiological correlates of psychosis-like experiences. However, the relationship between cortical glutamatergic levels and hippocampal rCBF in context of schizotypy has not been explored. Based on previous animal models and schizotypy neuroimaging studies, we hypothesized that ACC/mPFC levels of glutamate and Glx would be negatively correlated with hippocampal rCBF in individuals with HS.

Methods: We recruited 21 healthy individuals with HS and 22 individuals with LS using the unusual experiences (UE) subscale of the Oxford and Liverpool Inventory of Feelings and Experiences. Associations between ACC/mPFC glutamate and Glx (glutamine + glutamate) levels were measured using proton magnetic resonance spectroscopy and rCBF using arterial spin labeling on a Discovery MR750 3T system (General Electric, Chicago, USA) at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. Between-group differences in correlations between ACC/mPFC metabolite levels and rCBF were considered significant after voxel-wise $p<0.05$ family-wise error (FWE) correction, within pre-defined regions of interest (hippocampus and ACC/mPFC).

Results: There was a significant group interaction between cortical glutamate levels and rCBF in the left hippocampus (xyz: -32, -32, -4; k=45; t=-3.64, pFWE=0.03), which was driven by a negative association between ACC/mPFC glutamate levels and hippocampal rCBF in HS (xyz: -32, -32, -4; k=82; t=-3.97, pFWE=0.02), which was absent in the LS group. A negative association between ACC/mPFC Glx and hippocampal rCBF was also found in the HS sample (pFWE=0.01).

Discussion: Overall, our findings of a direct link between cortical glutamatergic metabolite levels and hippocampal activity in schizotypy supports a role for these mechanisms in the expression of psychotic-like experiences. These findings cannot be explained by illness chronicity, exposure to antipsychotic medication or other psychiatric comorbidities, and have potential implications for

characterizing the mechanisms underlying hippocampal dysfunction across the extended psychosis phenotype.

M15. EXOMES ANALYSIS REVEALS MIRNA-646 AND MIRNA-4739 AS NOVEL SCHIZOPHRENIA BIOMARKERS

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Background: Schizophrenia is one of the most common psychiatric disorders associated with a high level of disability. Although there is growing evidence that genes are implicated in Schizophrenia etiology, the environmental and epigenetic factors remain one of the major players in modulating the disease. This complex pattern of inheritance rendered exploring other processes that may govern genes' actions and interactions as of prime importance. Recently the microRNA has emerged as a promising factor in understanding the mechanism behind many disorders, Schizophrenia is one example.
Methods: We aimed to study miRNAs variants implicated in the etiology of schizophrenia in exomes data from 2 Sudanese families highly loaded with schizophrenia. Three siblings were from family one (two of them were diagnosed with schizophrenia), and 2 siblings were from the second family (one of them is affected). Four interesting approaches and many bioinformatics tools were used to achieve this goal.
Results: One of the interesting findings is the SNP rs1700 in the 3 prime UTR region of FSTL1 gene, which was stated as Schizophrenia susceptibility variant, and a target for many miRNAs, was found to be heterozygous in the 2 controls siblings and absent in the 3 cases. The second one is the microRNAs (miRNA-646, and miRNA-4739) were detected in the three cases, and absence in the control siblings.
Discussion: The SNP (rs 1700) probably was in linkage disequilibrium LD with another SNP near to the miRNA when reported as a Schizophrenia-associated variant. The microRNAs (miRNA-646, and miRNA-4739) are a promising novel Schizophrenia biomarker based on significant interaction with three pathways reported by the pathway-association study as Schizophrenia-associated. Also, miRNA-646 belongs to a miRNA superfamily reported to have a recent evolutionary history and some of the family members were reported to be associated with schizophrenia.

M16. INVESTIGATION OF MOTOR ABNORMALITIES AS PREDICTORS OF PSYCHOTIC EXPERIENCES IN BRAZILIAN CHILDREN AND ADOLESCENTS

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Background: Psychotic experiences (PE) are subthreshold symptoms that indicate higher genetic liability to psychotic disorders. Indeed, evidence about the developmental course in children and

adolescents relates PE with premorbid signals typically associated with schizophrenia, such as lower IQ, attention and executive functioning impairments, social isolation, and motor abnormalities. Motor abnormalities in premorbid schizophrenia encompass the slow acquisition of fine motor skills and dyskinesia. How PE and motor abnormalities associate in community samples has been less studied. Thus, we aimed to investigate the association between changes in motor performance and the subsequent presentation of PE throughout development. We hypothesize that early motor performance abnormalities will predict later presence of psychotic experiences.
Methods: This study is part of the multicentric research (São Paulo and Porto Alegre, Brazil) performed by the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders. Our sample comprised 2211 individuals at baseline and 1827 at 3-years follow-up with a mean age of 11.66 (SD=2.51) and 14.71 (SD=2.52) years old respectively. All subjects included were assessed for motor performance at baseline using the following tasks: Fingertip Tapping Sequences (FTS) - dexterity and motor speed; Alternating Hands Test (AHT) - imitation and rhythmic movements - and Extended Palm Test (EPT) - alternating movements with both hands. The tasks generate a total score for motor performance and four specific scores for fluency, coordination, precision, and symmetry. Psychotic Experiences were assessed at baseline and follow up using a previous reported latent variable of Community Assessment of Psychic Experiences (CAPE). For the analysis, we performed a multivariate linear regression using all motor domains and the total motor score as predictors of PE adopting age and sex as covariates.
Results: The mean score for motor performance was 4.67 (SD=1.59) and for CAPE was 45.87 (SD=7.99) at baseline and 44.23(SD=7.21) at follow up. We did not find any association between precision, symmetry, coordination, or fluency and PE. However, we have found an association between total motor performance score and PE on baseline (p-value=0.001, β=-0.381, r^2=0.018). Lastly, we did not find any motor association with the 3-years follow-up PE evaluation.
Discussion: Our association between motor performance changes and the presence of PE throughout development follows previous studies. The low effect-size was expected hence the performance on the motor tasks was very high, reducing sensitivity to detect abnormalities. Further studies should investigate if motor abnormalities can be a marker to psychosis progression and how it associates with other cognitive and symptomatic features.

M17. PREDICTING THE PERSISTENCE OF PSYCHOTIC EXPERIENCES IN YOUNG ADOLESCENTS: A MACHINE LEARNING APPROACH

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Background: It is important to identify accurate markers of psychiatric illness to aid in early prediction of disease course. Subclinical psychotic experiences (PEs) are an important risk factor

for later mental ill-health and suicidal behaviour. This study investigated the underlying neuroanatomical, psychosocial and cognitive underpinnings of PEs in early adolescence and the neuroanatomical predictors of later psychiatric ill-health.

Methods: Machine learning was applied to T1-weighted and diffusion MRI data from adolescents age 11-13 years. The primary goal was to classify adolescents with psychotic experiences vs. controls across 3 timepoints (11-13 years, 14-16 years, 18-20 years). We also compared the performance of a multi-modal model – combining neuroimaging and psychosocial-cognition data – to the performance of individual models for predicting current PEs.

Results: Neuroimaging data classified adolescents age 11-13 years with current PEs vs. controls (AUC 0.62) significantly better than a null model, (p=1.73e-29). Neuroimaging data also classified those with PEs at 18-20 years (AUC=0.59; p=7.19e-10). Left hemisphere frontal regions were the top discriminant classifiers for current PEs. Those with future PEs were best distinguished from controls based on left frontal regions, and also the genu of the corpus callosum, right-hemisphere medial lemniscus, cingulum bundle and precuneus. Combining psychosocial-cognition data with the neuroimaging model improved prediction capacity for current PEs (AUC=0. 72, p=4.89e-52) compared to the neuroimaging model.

While this multi-modal model returned a similar level of prediction compared to the psychosocial-cognition model (AUC=0.74, p=2.52e-53), it highlighted top psychosocial discriminant classifiers, such as higher scores on ratings of bullying, conduct and overall emotional and behavioural ratings as well as left hemisphere language-related frontal regions.

Discussion: Psychotic experiences, especially persistent psychotic experiences, fit within a clinical staging model as markers of more severe and enduring psychopathology. Therefore, models for predicting PE and their persistence over time are valuable. This study identified underlying markers of the earliest clinical stages of emerging mental disorders, thereby contributing to preventative and personalised psychiatry. Clinical staging requires widespread investment in novel systems of care to provide early access to large cohorts of help-seeking youths offering stepwise and evidence-informed care. Our results provide important new insights into early markers of PEs. The current research highlights that at pre-clinical stages of psychosis, machine learning can discriminate adolescents with PEs from controls based predominantly on left hemisphere frontal cortical morphology, right hemisphere motor-related white matter tracts and early social, behavioural and emotional problems such as bullying which may be early markers of psychotic experiences in young adolescents. These results emphasise the importance of multi-modal analysis for predicting PEs in adolescents.

M18. PREDICTORS OF SUSTAINED VERSUS TRANSIENT DISTRESSING PSYCHOTIC-LIKE EXPERIENCES IN SCHOOL-AGE CHILDREN

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Background: Psychotic-like experiences (PLEs), including nonclinical psychosis spectrum symptoms (e.g., perceptual abnormalities, mild delusional thoughts), are relatively common in

school-age children. A potential distinguishing factor between more benign and transient psychotic-like experiences versus PLEs that predict risk for psychiatric disorders is whether the PLEs are sustained and distressing (sustained dPLEs). However, it is unclear what factors differentiate sustained from transient dPLEs. The current study examined associations of both sustained and transient dPLEs with relevant risk factors (e.g., cognition), use of mental health services, and functional correlates (e.g., school performance) in school-age children.

Methods: The current study used data from the first three waves of the Adolescent Brain and Cognitive Development℠ study to create a sustained dPLEs group (n=272; >=97.5 percentile dPLEs for 2+ data waves), a transient dPLEs group (n=244; >=97.5 percentile dPLEs for 1 wave, <=50 percentile dPLEs on other waves), and a control group (n=272; <=50 percentile dPLEs on all waves and matched on sex, age, and race/ethnicity to the sustained dPLEs group). Hierarchical linear models examined whether these three groups differed in terms of baseline use of mental health services, functional correlates (i.e., school performance, social functioning), family history of mental disorders, other symptoms (e.g., parent-rated psychotic symptoms, internalizing, externalizing symptoms), environmental factors (e.g., adverse childhood events [ACEs], overall deprivation), cognitive functioning, developmental milestone delays, and both structural and resting state functional connectivity neuroimaging indices.

Results: At every time point the sustained group showed greater dPLEs than both the transient and control groups. Several factors were more strongly associated with sustained versus transient dPLEs, including use of mental health services (for sustained vs. controls: d=0.38), drop in grades (d=--.30), other symptoms (i.e., parent-rated psychotic, bipolar, internalizing, externalizing, suicidality; 0.33>ds<0.88), ACEs (d=.36), and lower fluid and executive functioning cognitive scores (-0.31>ds<-0.41). For most risk factors, the sustained dPLEs group showed the greatest impairments, followed by the transient group, with the control group showing the least impairments.

Discussion: These results have implications for understanding the pathogenesis of dPLEs, whereby several factors may distinguish transient from persisting dPLEs in children, including higher psychiatric symptoms and ACEs, lower executive functioning scores, greater use of mental health services, and worsening school performance. These data are consistent with the idea that clinicians may consider using persistence of dPLEs as a marker of identifying individuals most in need of evaluation and intervention.

M19. ANATOMIC SUBSTRATES OF EXCESS DA RELEASE IN THE 'ASSOCIATIVE STRIATUM' IN PSYCHOSIS

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Background: Excessive dopamine (DA) transmission in the striatum plays a role in psychosis, and both are worsened by stress. Importantly, excess DA release in psychosis is specific to the central ('associative') striatum which is associated with cognitive and decision-making tasks. While all striatal domains are strongly innervated by the DA neurons, specific DA cell groups are responsible for DA release in different striatal 'functional' regions. Specific DA subpopulations not only have unique physiologic signatures, but are also afferently regulated by different inputs. Since psychotic symptoms are exacerbated by stress, we recently examined amygdalo-nigrostriatal circuits in Macaque as a way of understanding how salient stimuli can directly affect DA

regulation. Using bidirectional tracer injections in ventral midbrain, we found that DA subpopulations receiving amygdala input specifically target 'associative' regions of the striatum. Furthermore, amygdala neurons innervating this subcircuit contained the stress peptide, corticotropin releasing factor (CRF), known to enhance DA release when injected into the midbrain. Together, these findings suggest a mechanism whereby novel or aversive stimuli can regulate the DA cells specifically projecting to the 'associative' striatum. In the present study we examined the distribution and phenotypic features of DA cells that specifically target the associative striatum.

Methods: We placed injections of retrograde neuronal tracers into 'associative' striatal regions previously mapped in the amygdalo-nigro-striatal study. These sites included the rostral central caudate nucleus, rostral ventral putamen, ventral body of the caudate nucleus, and caudal ventromedial putamen. Control injections into 'non-associative' striatum were also done. The distribution of retrogradely labeled cells throughout the ventral midbrain system was analyzed in terms of specific DA subpopulation(s).

Results: The midbrain DA system is classically divided into ventral tegmental area (VTA, A10), the substantia nigra, pars compacta (SNc, A9), and the retrorubal field (A8). In primates, the VTA's laterally displaced parabrachial pigmented nucleus (PBP) is massively enlarged and sweeps laterally over the SNc A9 neurons. The A8 field, like the PBP, is also disproportionately enlarged. Dopamine neurons in the A10 and A8 subregions are distinguished by the calcium buffering protein, calbindin D28k. Conversely, they lack the G-protein-regulated inward- rectifier potassium channel 2 protein (Girk2) which marks DA neurons in the SNc A9. Each DA subpopulation also has a differential balance of local inhibition by interneurons.

All injections into the 'associative striatum' were innervated by the PBP (A10) and retrorubal field (A8), with a lesser contribution from the caudal VTA. There were few to no labeled cells in the midline VTA. The rostral injections in associative striatum resulted in higher concentrations of labeled cells in the PBP (A10), while the caudal injections had more labeled cells in the A8 neurons. Within the SNc (A9), there were labeled cells mainly in the dorsal, central SNc.

Discussion: There is continuous projection from the PBP to A8 in all cases. Within this continuum, the PBP projection is relatively stronger to the rostral associative striatum, and the A8 projection relatively stronger to the caudal associative striatum. Both DA subpopulations are phylogenetically expanded in human and nonhuman primates. The associative striatum receives inputs from cortical regions, not found in rodents, that mediate in set shifting, rule detection, and social learning. In primates, stress-modulated inputs uniquely project to expanded DA subpopulations that modulate this striatal domain.

M20. ENHANCING ASSERTIVE COMMUNITY TREATMENT WITH COGNITIVE BEHAVIORAL SOCIAL SKILLS TRAINING FOR SCHIZOPHRENIA: AN EFFECTIVENESS TRIAL

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Background: Schizophrenia leads to profound disability in everyday functioning. Psychosocial evidence-based practices (EBPs) improve functioning, but these EBPs are not available to most people with schizophrenia. To facilitate widespread implementation of EBPs in community settings, we must close the gap between research and service delivery by adapting EBPs for persons with schizophrenia. In this effectiveness trial, we examined whether an existing EBP, Cognitive Behavioral Social Skills Training (CBSST), modified to be implemented by Assertive Community Treatment (ACT) teams (commonly available to persons with schizophrenia), resulted in better functional outcomes for persons with schizophrenia compared to those received ACT alone.
Methods: Persons with schizophrenia (N = 178) were recruited from existing publicly-funded ACT teams operating in community settings; participants were randomized to receive ACT alone or ACT + Adapted CBSST. Functional outcomes were assessed every 18 weeks after baseline for 18 months, resulting in five total assessment points.
Results: No significant differences were found on primary measures between treatment conditions; however, treatment dose was significant, suggesting that participants who received more sessions of ACT + Adapted CBSST showed greater skill acquisition and greater improvement in functioning.
Discussion: Adapting CBSST to fit into the ACT service delivery context creates an opportunity to substantially increase the number of persons with schizophrenia who could have access to and benefit from EBPs. Greater exposure to Adapted CBSST significantly increased skill acquisition and improved functioning among persons with schizophrenia receiving ACT services. Future studies are needed to determine optimal approaches to delivering EBPs to persons with schizophrenia in their communities; participants and provider characteristics, as well as institutional support/barriers may be important influences to examine.

M21. AN EXPLORATORY ANALYSIS CONVERTING SCORES BETWEEN THE NSA-16 AND THE PSP

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Background: Negative symptoms represent a significant unmet medical need significantly impacting the patient's ability to adequately function in the community. We have previously identified a significant correlation between the patient's severity of negative symptoms measured by the NSA-16 scale and her/his level of functioning as measured by the PSP (Daniel & Kott, 2018; Kott & Daniel, 2018). The current analysis aimed to expand our prior findings by exploring equations that would be informative in understanding the relationship between the NSA-16 and the PSP. Such equations could potentially assist both the clinician and a clinical trialist in understanding the relationship between the severity of negative symptoms and their impact on the level of patient's functioning.
Methods: Data from 2,278 schizophrenia clinical trials subjects with both NSA-16 and PSP data available were used. Regression analyses predicting the NSA-16 total score with the PSP score were performed on data from all subjects. On a subset of 2,143 subjects with change from baseline data available we performed regression analysis predicting the NSA-16 score change with the PSP total change from baseline. To account for the fact that from each subject a number of score

readings was obtained we used mixed effect models to establish the relationship between the instruments.

Results: Significant correlations consistent with our previous findings were identified between the PSP and the NSA-16 total scores (rho = -.69) as well as change from baseline (rho = -0.60). Visual inspection of scatter plots as well post-regression diagnostics supported the linear relationship between the two instruments across the full spectrum of total scores. The following formula describes the relationship between the NSA-16 and the PSP total scores:

NSA-16 = 81.70 – 0.49 *PSP.

The following formula describes the relationship between the change from baseline in NSA-16 and the PSP:

NSA-16_change = -4.60 – 0.40*PSP_change.

Discussion: In our analysis we have replicated the strong correlation between the NSA-16 total score and the PSP as well as the strong correlation in change from baseline between these 2 instruments. The provided equations offer a useful tool allowing researchers and clinicians to easily convert the data between the symptomatic and the functional outcome in the population of subjects suffering from predominantly negative symptoms. Using equipercentile linking we have previously established a 10 point change in PSP to represent a minimal clinically meaningful change in this population (Kott and Daniel, 2019). Using the derived conversion formula the severity of symptoms measured by the NSA-16 would need to improve by about 9 points to achieve a minimal clinically meaningful change in the level of functioning. The relationship between the NSA and the PSP is not perfect as one would expect given the different focus of the instruments. Additionally, unlike the PSP, the NSA does not address areas such as disruptive or inappropriate behavior that could represent a source of noise and contribute to imprecision in the conversion between the two scales.

M22. LONG-TERM WEIGHT AND METABOLIC EFFECTS OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 3 STUDIES

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Background: In schizophrenia, efficacious agents may be avoided to circumvent safety issues; for olanzapine, this includes weight gain liability. A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia and bipolar I disorder to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. We report long-term weight and metabolic effects of OLZ/SAM in multiple phase 3 studies in patients with schizophrenia.

Methods: Results from 2 pivotal studies and their respective extension studies were integrated longitudinally into 2 groups. Group 1 included patients from ENLIGHTEN-1 (NCT02634346), a 4-week, randomized, double-blind study evaluating antipsychotic efficacy of OLZ/SAM, olanzapine and placebo in patients with an acute exacerbation of schizophrenia, who could enroll in a 52-week, single-arm, open-label safety extension (NCT02669758) and a 48-month follow-on study (NCT03201757, ongoing). Group 2 included patients from ENLIGHTEN-2

(NCT02694328), a 24-week, randomized, double-blind study evaluating mitigation of olanzapine-associated weight gain with OLZ/SAM in adult outpatients with schizophrenia, who could enroll in a 52-week, single-arm, open-label OLZ/SAM extension (NCT02873208, ongoing) and a 48-month follow-on study (NCT03201757, ongoing; this study also includes patients from group 1). Analyses included all patients exposed to OLZ/SAM with ≥1 postbaseline body weight and PANSS assessment. Changes from baseline (ie, relative to start of OLZ/SAM exposure) in body weight, waist circumference, metabolic parameters, and proportion of patients with ≥7% weight gain were summarized descriptively using observed data.
Results: Groups 1 and 2 included 281 and 381 patients, respectively. As of April 2019, mean OLZ/SAM exposure was 479.1 days in group 1; 64.1% received ≥52 weeks of OLZ/SAM. In group 2, mean OLZ/SAM exposure was 348.1 days; 42% were treated for ≥52 weeks. Baseline mean (SD) weight was 77.28 (16.56) kg in group 1 and 78.82 (14.38) kg in group 2. At week 6, mean (SD) respective absolute and percent weight increase was 2.01 (3.07) kg and 2.63 (3.93)% in group 1 and 1.81 (3.12) kg and 2.42 (4.20)% in group 2. At week 76, mean (SD) absolute and percent weight increase was 2.83 (6.45) kg and 4.43 (9.14)% in group 1. In group 2, week 76 mean (SD) absolute and percent weight increase was 1.76 (7.90) kg and 2.71 (10.35)%. 34.6% (46/133) and 26.7% (28/105) of patients in groups 1 and 2 had ≥7% weight gain at week 76. Absolute mean (SD) increase in waist circumference was 2.22 (6.93) cm in group 1 and 0.93 (8.20) cm in group 2 at week 76. On average, changes in fasting lipid and glycemic parameters were not clinically significant.
Discussion: After an initial 4 to 6 weeks of weight gain, weight stabilized with long-term OLZ/SAM treatment in patients with schizophrenia. Waist circumference and metabolic parameters exhibited long-term stability over 76 weeks in patients continuing treatment.

M23. DETECTING CARELESS RESPONSES ON THE PANSS USING AUDITING AND EXPERT CONSENSUS BASED METHODS

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Background: Previously published work has presented expert consensus consistency checks for PANSS (Positive and Negative Syndrome Scale) administrations (Rabinowitz et al, 2017). Those consistency checks were based primarily on flagging incompatibilities in scoring among items within and between PANSS administrations. The field of auditing checks, as applied to survey research to identify careless responses, provides yet another method for identifying irregularities in data.
Methods: Six methods for identifying careless responses were identified as potentially useful: underuse of values, overuse of values, disproportionate use of even or odd values, multivariate outliers (Mahalonobis distance), using the same response repeatedly ("long-string") and individual consistency (inter-item standard deviation). These were applied to see how frequently they occur in the NewMeds repository of 122,000 PANSS ratings and how these relate to previously published expert validated consistency flags. Recursive partitioning, a statistical procedure that identifies optimal groupings, was used to find those auditing irregularities that were associated with ratings that had serious inconsistencies based on applying expert derived consistency checks.
Results: Six percent of the PANSS administrations (n=7280/121,636) were multivariate outliers these cases were 6.3 times more likely to have a low flag, 2.7 times more likely to have a medium

flag and 1.5 times more likely to have a high flag. PANSS administrations that did not include any items rated with a score of 2 (5.2%, n=6300), 3 (3.3%, n=4001) or 4 (16%, n=19526), administrations that repeated the same rating score on 20 or more items (8.6%, n=10532), the same response on 7 or more consecutive items, administrations that used odd numbers for 25 or more item ratings (8.9%, n=10840) and those with an interitem standard deviation less than .69 (10.1%, n=12365) were 1.6 to 3 times more likely to also have at least one serious inconsistency based on expert derived checks.

Discussion: Auditing based inconsistency checks appear to be a useful adjunct to expert derived checks in the quest to identify problematic PANSS administrations. Application of auditing consistency checks to find potentially careless PANSS ratings have the potential to improve reliability and validity of clinical trials.

M24. CLOZAPINE PHARMACOKINETIC PROFILES OF PATIENTS WITH SCHIZOPHRENIA TREATED WITH CLOZAPINE IN A NATURALISTIC SETTING

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Background: Trough serum concentrations have been used to show differences in clozapine (CLZ) and N-desmethylclozapine (NCLZ) levels in smoking and nonsmoking patients. Naturalistic studies often comprise patients under varying dose regimens. Single trough concentrations might then not optimally reflect patients drug exposure.

Methods: Clozapine pharmacokinetic (PK) profiles were assessed in a naturalistic sample of smoking (n=11) and nonsmoking (n=7) patients with schizophrenia. Capillary whole blood and venous serum samples were simultaneously drawn just before drug administration (trough levels, 8:30am) at steady state conditions. Three additional whole blood samples were collected from each patient at 10:37am, 20:30pm and 22:37pm. Serum concentrations of CLZ, NCLZ were quantified using liquid-chromatography-mass spectrometry (LC-MS/MS). Whole blood concentrations of CLZ were quantified using a Point-of-Care (POC) immunoassay test (MyCare Insite). Dose-adjusted serum concentrations (ratio of the drug concentration and the applied daily dose, C/D, in [ng/mL]/[mg/day]) for CLZ, NCLZ, the metabolite-to-parent ratio (MPR; NCLZ/CLZ) and the fluctuation ratio for CLZ (FR; ratio of the highest and the lowest drug concentration measured by POC testing) were calculated. Two patients were excluded from analysis due to a confounding co-medication with a CYP1A2 inhibitor. Results were compared between both groups, smokers (S, n=10, age 41.7(8.4), male sex 80%, dose (mg/d) 522.5 (133.9)) and nonsmokers (NS, n=6, age 36.3(12.5), male sex 67%, dose (mg/d) 400 (190.9), using non-parametrical tests.

Within-subject variances were calculated between whole blood and serum concentration for 16 subjects. Two patients' samples were eliminated from the analysis due to results >1390 ng/ml on the MyCare Insite. Additional clinical measures were eligible for 13 patients comprising of PANSS total score, clinical global impression severity (CGI-S) and the evaluation of medication side effects (UKU).

Results: Smoking patients had lower CLZ and NCLZ concentrations (ng/mL) (CLZ S= 337 (176-1430); NCLZ S = 198 (116-930); MPR = 0.75 (0.36-1.1)) compared to nonsmoking patients (CLZ NS= 547 (312-854); NCLZ NS= 356 (178-412); MPR = 0.54 (0.42-0.76)). Significant differences were detected between the two groups for dose-adjusted serum concentrations of both, CLZ (p =

0.02; C/D S= 0.57 (0.35-1.97); C/D NS= 1.6 (1.2-1.8)) and NCLZ (p = 0.04; C/D S= 0.47 (0.20-1.28); C/D NS= 0.85 (0.59-1.19)). Our data indicates a decrease in peak-to-trough fluctuation in patients when treated with a multiple dose regimen (FR; 1/d = 3.34 (2.11-3.65) (n=3), 2/d = 2.51 (1.91-3.19) (n=9), 3/d = 1.63 (n=1), 4/d = 1.75 (1.72-1.79) (n=2)) despite increasing trough concentrations. Notably, once daily dose regimens have been exclusively observed in smokers, whose overall fluctuation ratios are slightly higher than those of nonsmokers (FR S= 2.52; n=6, FR NS = 1.94; n=9).
Mean PANSS total score (n=13) was 75.23 (21.81), mean CGI-S was 4.23 (0.97). Increased salivation was reported in all 13 patients. Increased fatigability, sleepiness/ sedation and increased duration of sleep were reported in 77%, 62% and 62% of patients.

Passing-Bablok regression marks a shift towards serum concentrations when compared to whole blood (R = 0.94, slope = 1.06, intercept = -67.3).

Discussion: The applied blood sampling schedule provides valuable insight in individual PKs of patients treated with multiple CLZ dose regimens. Our preliminary results from the first patients indicate that smoking might not have a large impact on peak-to-trough fluctuations in individuals. The effect of clinical measures, e.g. sleepiness/sedation, should be further explored in relation to individual PK profiles.

M25. NEURAL CHANGES FOLLOWING A BODY-ORIENTED RESILIENCE THERAPY WITH ELEMENTS OF KICKBOXING FOR INDIVIDUALS WITH A PSYCHOTIC DISORDER: A RANDOMIZED CONTROLLED TRIAL

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Background: Individuals with a psychotic disorder are at an increased risk of becoming the victim of a crime. A body-oriented resilience therapy with elements of kickboxing ('BEATVIC') aimed at preventing victimization by addressing putatively underlying factors was developed. One of these factors is social cognition, particularly facial affect processing. The current study investigated neural effects of BEATVIC using two face processing tasks.
Methods: Participants were randomized to either BEATVIC or a 'Befriending' control group consisting of social group meetings. Twenty-seven patients (BEATVIC n=14; Befriending n=13) completed an Emotional Faces task and the Wall of Faces task during fMRI, pre and post intervention. General linear model (GLM) analyses and Independent component analyses (ICA) were performed to define networks and investigate group*time effects.
Results: Voxelwise GLM analyses yielded no differences between groups over time. On a network level (ICA) we found overall increased activation of the salience network to angry and fearful faces in BEATVIC compared to Befriending. A trend towards significance (p=0.05) for increased activation of the (medial) visual network to (a group of predominantly) angry faces, and decreased deactivation (p=0.08) in the sensorimotor network in response to fearful faces in BEATVIC was observed.
Discussion: Increased activation of the salience network may suggest an increased alertness for potentially dangerous faces. Trend findings of the visual network and the sensorimotor network

which are formally statistically insignificant may be regarded as tentative and strongly warrant further investigation to allow for more definite conclusions. Increased activation of the visual network might suggest more elaborate processing of visual information. Decreased deactivation in the sensorimotor network might indicate a reduced tendency for "freezing" and enhanced action readiness in response to indirect threat.

M26. CLINICOPATHOLOGIC CORRELATIONS IN OLDER ADULTS WITH SCHIZOPHRENIA

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Background: Cognitive impairment is a pervasive and severe symptom domain in schizophrenia, affecting attention, learning and memory, working memory, and executive function. Cognitive impairment may present prior to the prodromal phase of schizophrenia and is established once the patient is diagnosed with this condition. The cognitive deficits have been shown to remain relatively stable over the course of illness but then accelerate with aging. This accelerated cognitive decline is not associated with increased incidence of neurodegenerative conditions, and it remains poorly understood. We sought to perform clinicopathological correlations between demographic variables, neurocognitive testing and neuropathological changes in a well-defined cohort of older adults with chronic schizophrenia to identify possible contributing factors to this age-related cognitive decline.

Methods: A unique cohort of 55 older adults with chronic schizophrenia were evaluated. All cases had extensive clinical assessment and neurocognitive testing including domains of attention, memory, and executive function, and detailed post-mortem neuropathological evaluation. Cases were grouped into mild executive dysfunction, moderate cognitive impairment or severe cognitive impairment based on neuropsychological evaluation. Similarly, the cases were dichotomised into ‘mild’ or ‘significant’ neuropathology based on the likelihood of the identified neuropathological changes to explain cognitive impairment during life. These groups were then evaluated in terms of their demographic, clinical and neuropathological characteristics.

Results: Demographic variables such as age at onset, disease duration, or age at death were not statistically different between groups, although those with significant cognitive impairment or neuropathological changes showed a trend towards longer disease duration and older age at death. Clinical rating scales such as PANSS, Global Assessment of Functioning and Clinical Global Impression were not statistically different between the groups with varying cognitive impairment or severity of neuropathological findings. Neurocognitive test scores clearly delineated groups with mild, moderate and severe cognitive impairment. However, they were not correlated with severity of neuropathological changes.

Discussion: These results suggest that the accelerated age-related cognitive impairments seen in chronic schizophrenia occur independent of neurodegenerative and other age-related pathological changes that commonly explain cognitive deficits in older adults. Future histological studies in this cohort will aim to provide further insights into alternative factors responsible for this phenomenon.

M27. A META-ANALYSIS OF COGNITION AND VOCATIONAL FUNCTIONING IN FIRST EPISODE PSYCHOSIS: RESEARCH AND CLINICAL GUIDELINES

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Background: Cognitive deficits are a core feature of psychosis associated with difficulties in vocational functioning. Several studies suggest that cognitive deficits are significantly associated with returning to school or work in first-episode psychosis (FEP). The aim of this meta-analysis is to document the magnitude of the associations between cognition and vocational functioning in people with FEP.
Methods: References were identified through several databases and screened by two independent evaluators. English or French studies providing a correlation between a cognitive score and a vocational measure in a FEP sample were included. Correlations were extracted from the retained studies, transformed into Zr effect sizes, and pooled as weighted means.
Results: Only four studies (Total N = 729) were included. Working memory, verbal learning, executive functions, global neurocognition, emotion processing, and attributional style were thus combined into a global cognition domain for analyses. A small to moderate association was found between global cognition and global vocational functioning (Zr = 0.21).
Discussion: The results of this meta-analysis suggest an association between cognition and vocational functioning in FEP, but also importantly highlight the lack of available data regarding the association of cognition with school and job tenure in FEP. Research guidelines will be discussed with regards to the concept of vocational functioning, key instruments, and methodological caveats. A model of the aspects of vocational functioning is proposed.

M28. LIKETREMOR, LIKE PSYCHOSIS, NEUROPROTECTION & MOTOR COORDINATION ENHANCED BY NIGELLA SATIVA FOLLOWING PHENOL ADMINISTRATION IN BALB/C MICE

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Background: Psychiatric symptoms and movement abnormalities are often comorbid and exacerbate each other, with treatment of one possibly evoking the other as seen with neuroleptics resulting in tardive dyskinesia when used in treating psychosis. Novel neuro-protective treatments to be associated to neuroleptic treatments are urgently needed. Using albino mice, this study evaluated the therapeutic roles of Nigella sativa oil (NS; a medicinal herb with therapeutic potentials in various neurological conditions) through neurobehavioral, neurochemical and histological assays on cerebellar phenotypes of phenol-induced essential tremor (ET). We hypothesized that NS will protect from the effects of phenol on cerebellar morphometry and function as neuroimaging studies have revealed that the cerebellum is implicated in cases of essential tremor and schizophrenia.

Methods: Seventy-five (75) adult male BALB/c mice weighing 25 ± 5g, were equally divided into 5 groups. They were administered either feed and water only (CONTROL); 100 mg/kgbw phenol (PHE); 100 mg/kg body weight (bw) phenol plus 1 ml/kgbw Nigella sativa oil (PNSC); 1ml/kgbw Nigella sativa oil followed by 100 mg/kg/bw phenol (NSP); or 1 ml/kgbw Nigella sativa oil only (NS) for a period of 16 days. Tremor response, body weight, temperature, motor coordination (using the parallel bars and static rods tests), relative brain weights, cerebellar glutamate, glutathione peroxidase (GPX) and histoarchitecture were assayed 24hours following last administration. Statistical analysis was carried out using one-way ANOVA at 95% CI.
Results: Histoarchitectural defects, unchanged weight, increased GPX and glutamate levels as well as poor motor coordination were exhibited by the PHE group, while the PNSC, NSP and NS mice decreased in weight while performing significantly better than the PHE-only group in motor tasks. Weight effects: The PNSC, NSP and NS weight decreased (-7%, -5% and -3%, respectively) corroborating the weight reducing effect of Nigella sativa oil. Motor Measures: Both the CTRL and NS animals demonstrated good motor coordination indicating no side effects of the NS treatment. In the absence of NS, the PHE-only mice exhibited significantly longer turning and transit time (average of 16.5secs and 24.3secs/ animal respectively) on the motor coordinative testing apparatus (the static rods) than PNSC and NSP mice groups (8secs and 9secs turning time per animal and 10.25secs and 3secs transit time). Histo-morphological examination: NS and PNSC animals exhibited better cerebellar histoarchitecture than PHE-only mice, as evidenced by increased neuronal sizes, densities and neuropiliary staining.
Discussion: Several forms of motor abnormalities such as impaired motor coordination, retarded movement as well as tremor and subtle eye motion abnormalities were observed in PHE-only mice. These symptoms were less pronounced in the PHE plus NS treated groups (NSC and NSP) compared to the PHE-only group. The above results indicate the motor coordinative, neuroprotective and neuro-regenerative effects of Nigella sativa oil in the modeled condition as the NS+PHE mice exhibited significantly better motor coordination, better histoarchitecture and better neurochemical phenotypes than the untreated PHE group ($P < 0.05$). The model and the results: obtained warrant further investigation as novel, neuro-protective compounds are urgently needed in the field of psychiatry.

M29. IS THERE A MEDIATING ROLE OF SOCIAL COGNITION FOR THE RELATIONSHIP BETWEEN VERBAL MEMORY AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA?

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Background: From the onset of schizophrenia, verbal memory (VM) deficits and negative symptoms are strongly associated and both additively predict functioning and quality of life. Social cognition, which encompasses emotion recognition (ER) and theory of mind (ToM; the ability to infer others' mental states) is also particularly affected in schizophrenia. Previous studies have revealed relationships between social cognition, negative symptoms, and verbal memory, but the organization of these associations remains unclear. We aimed to determine whether VM impairments and, in turn, social cognition impairments, pave the way for the emergence of

negative symptoms in schizophrenia. To this end, we used mediation analyses to question the process by which VM predicts social cognition, which in turn predicts negative symptoms.
Methods: One hundred and forty participants with a diagnosis of schizophrenia or schizoaffective disorder, according to the DSM-IV criteria, were recruited. VM was assessed with the CogState Schizophrenia Battery (International Shopping List). Two subdomains of social cognition were assessed: ER using the Ekman global score and ToM using the Hinting task. Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS). Spearman correlations were used to examine predicted associations between our variables of interest (SANS score, VM score, ER accuracy, and Hinting score). The mediating effect of social cognition between VM and negative symptoms was examined using the PROCESS macro which uses a regression-based model. Two models were tested: one with a single mediating variable (ER or ToM) and one with a serial multiple mediation (ER then ToM or ToM then ER).
Results: Variables of interest were significantly correlated, except for VM and ToM ($r = |.125|$ to $|.340|$). First, simple mediation models exploring if VM was influencing negative symptoms through a single variable (ER or ToM) were not significant (β =-.313, 95% CI = -.747 to .139 and β =-.398, 95% CI = -.991 to .015 respectively). Secondly, the serial multiple mediation model with 2 mediators (ER accuracy first and Hinting total score second) revealed a significant indirect effect of VM, mediated through ER and ToM, on negative symptoms (β =- .225, 95% CI= -.483 to -.041). Thus, both mediators had to be included in the model to explain a significant portion of VM's variance.
Discussion: The relationship between VM and negative symptoms can be partially attributed to ER through ToM. The association of ER and ToM is of particular interest as these two social cognitive subdomains are interrelated constructs; indeed, assessing others' intentions involves the appraisal of their emotional status. In general, this study illustrates the complexity of the relationship between cognitive deficits and negative symptoms and contributes to delineate the potential implication of different cognitive domains in negative symptoms' etiology. Additional relevant therapeutic targets for negative symptoms could then be tested. For example, cognitive remediation therapy focusing on ER and ToM might help to partially alleviate negative symptoms and ultimately improve functional outcomes. Future longitudinal studies would contribute to confirm our results and assess the predictive value of these potential interventions.

M30. CEREBRAL BLOOD FLOW IN INITIALLY ANTIPSYCHOTIC-NAïVE PATIENTS WITH PSYCHOSIS BEFORE AND AFTER ANTIPSYCHOTIC MONOTHERAPY - THE RELATION WITH CLINICAL OUTCOME AND COGNITION

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Background: Resting cerebral blood flow (rCBF) changes in putamen and thalamus have recently been related to schizophrenia spectrum disorders in twins. In medicated schizophrenia patients, increased rCBF has consistently been found in putamen, and thalamic rCBF alterations are reported as well. However, it is unclear if these changes reflect pathophysiological mechanisms or the effect of antipsychotics. Moreover, the association between longitudinal rCBF changes and symptom improvement is sparsely investigated. Last, decreased whole brain rCBF has been associated with impaired cognitive performance in neurodegenerative disorders, but this has not been studied in antipsychotic-naïve patients with psychosis.
Methods: We conducted a longitudinal study of initially antipsychotic-naïve patients with schizophrenia or psychosis and healthy controls matched on age, sex, and parental socioeconomic status. rCBF was estimated with the pseudo-Continuous Arterial Spin Labelling (pCASL) sequence in 49 patients and 50 healthy controls at baseline and in 32 patients and 53 healthy controls after 6 weeks of monotherapy with a partial dopamine agonist (aripiprazole, patients only). rCBF in putamen and thalamus was estimated with a region of interest approach and findings were corrected for age, sex, and whole brain rCBF (to eliminate global effects on specific regions). Psychopathology was evaluated with the positive and negative syndrome scale and cognitive performance using tests of attention, executive functions, and verbal memory.
Results: There was a differential rCBF change in patients compared with healthy controls with a significant group*time interaction in putamen ($p=0.002$) and thalamus ($p=0.021$). Post hoc tests revealed that rCBF in patients did not differ from healthy controls in the antipsychotic-naïve state at baseline, but rCBF increased significantly in patients after treatment in putamen ($p=0.01$) and at trend level in thalamus ($p=0.05$). PANSS positive score decreased after treatment ($p<0.001$), but the symptom improvement was not significantly related to rCBF changes. Cognitive performance in healthy controls was significantly associated with lower whole brain rCBF in tests of attention ($p=0.007$) and executive functions ($p=0.005$) at baseline, but similar associations were not found in antipsychotic-naïve patients.
Discussion: The findings support that rCBF alterations in putamen and thalamus are induced by treatment and that measurable rCBF alterations may not be due to the primary pathophysiology of psychosis. Symptom improvement was not related to rCBF changes in putamen or thalamus, which might reflect that the treatment effect is due to widespread changes in neural networks and not single anatomical structures. Decreased whole brain rCBF was associated with better cognitive performance in healthy controls, which is opposite of findings in neurodegenerative disorders. Therefore, both too high and too low rCBF may be related to impaired cognition, which suggests an optimal range of rCBF for cognitive performance. The association between whole brain rCBF and cognitive performance seems disturbed in patients and further clarification of the mechanisms behind this abnormality might pave the way for development of novel therapies.

M31. FACTORS AFFECTING COGNITIVE REMEDIATION OUTCOME IN SCHIZOPHRENIA: THE ROLE OF TREATMENT RESISTANCE

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Background: Treatment-resistant schizophrenia (TRS) represents a major clinical issue, characterized by worse psychopathological outcome, a more disrupted neurobiological substrate

and higher healthcare costs. Cognitive impairment is a core feature of schizophrenia and its severity has been strongly associated with global functional outcome and patient's quality of life. Different studies showed that TRS patients exhibit poorer neurocognitive performance on a broad range of cognitive functions, particularly on verbal domains. Given the lack of effective procognitive drugs, to date Cognitive Remediation Therapy (CRT) represents the best available tool for treating cognitive deficits in schizophrenia. However, CRT outcomes are highly heterogeneous and significant treatment predictors are still lacking. Based on these data, the aim of this study is to investigate possible differences of CRT outcome in a sample of patients with schizophrenia, stratified according to antipsychotic response (TRS patients treated with clozapine vs. first-line responders, FLRs). Given the differential neurocognitive profiles and neurobiological substrates, we hypothesized a diverse effect of CRT between the two treatment groups.
Methods: The sample included 150 patients with schizophrenia (DSM-V criteria, 95 FLRs, 55 TRSs) recruited at the Psychotic Disorders Unit of IRCCS San Raffaele Hospital (Milan, Italy). All patients were assessed for neurocognition with BACS and WCST at baseline and after CRT. To quantify the magnitude of cognitive changes, Cohen's d was used in order to estimate effect size (ES) of each cognitive domain (verbal memory, working memory, psychomotor speed and coordination, speed of processing, verbal fluency, executive functions and cognitive index). General Linear Models (GLMs) were performed to analyze possible differences between treatment groups in cognition before and after CRT intervention, and at CRT cognitive improvement (ES).
Results: At baseline, GLMs showed significant differences in Verbal Memory (F=4,66; p=0,03) and WCST–executive functions (F=5,59; p=0,02), both worse in the TRS group. ESs of CRT outcome resulted significantly different in domains of Verbal Memory (F=4,68; p=0,03) and WCST–executive functions (F=4,62; p=0,03), with greater improvements among TRS patients. No significant cognitive differences were observed between groups after CRT.
Discussion: This is the first study to indicate treatment-resistance as a possible predictor of CRT outcome in schizophrenia. Consistently with previous literature, TRS patients showed impaired basal cognitive functions in verbal memory and executive functions. However, we observed that CRT resulted able to fill the cognitive gap between treatment groups, reporting higher cognitive ESs among TRS subjects. Results of this study further highlight the importance of early cognitive interventions in order to reduce the neuropsychological and functional burden associated with the disease, especially for TRS patients.

M32. COGNITIVE PERFORMANCE AT FIRST EPISODE TREATMENT PREDICTS TREATMENT RESISTANCE: EVIDENCE FROM AN INTERNATIONAL PROSPECTIVE COHORT STUDY

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Background: Treatment resistant schizophrenia (TRS) affects about a third of individuals with a schizophrenia diagnosis, with recent research finding systematic biological differences between responders (NTRS) and non-responders. Likewise, cross-sectional and prospective cohort studies have identified significant impairments in TRS cases on tasks of executive function and verbal memory. Cognitive factors may be able to provide further insight into the neurodevelopmental factors associated with treatment resistance. With better predictors from first episode psychosis (FEP), this may aid in our prediction and early intervention in antipsychotic resistance.
Methods: Cognitive data from 1,300 participants was included in this study. Data collected originates from seven international cohorts of FEP with follow-up data to determine response group membership. Cognitive tasks were grouped into one of seven cognitive domains: executive function, attention, working memory and processing speed, IQ/general cognition, visual-spatial memory and learning, verbal intelligence and processing, verbal memory and learning and visual-spatial intelligence and processing.
Results: TRS cases had poorer cognitive performance across domains. Significant differences were observed between responders on tasks of executive function, attention, working memory and processing speed and verbal memory and learning. Multivariate logistic regressions adjusted for age and gender identified verbal memory and executive function performance to significantly predict response status. Postestimation statistics indicate this prediction model to show some ability to classify TRS and NTRS cases from cognitive performance.
Discussion: The results from this investigation, in line with the pre-existing literature, identified significant poorer performance between NTRS and TRS cases at first episode on measures of executive function and verbal memory and learning. With the aim to utilize baseline cognitive performance at first episode psychosis to predict future response status, this study identified significant multilevel prediction models for executive function and verbal memory and learning. Postestimation statistics indicated that cognitive domains were good specifiers of treatment responders and non-responders, promoting their use for predicting antipsychotic response at first episode.

M33. THE FLICKERING SPOTLIGHT OF VISUAL ATTENTION: CHARACTERIZING THE SPATIOTEMPORAL DYNAMICS OF VISUAL ATTENTION IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is associated with impaired visual attention, but these impairments have not been characterized comprehensively. Recent research in healthy populations has shown that sustained visual attention does not produce a constant-intensity “spotlight” focus. Rather, the intensity of the attentional focus naturally tends to ramp up and down about eight times per second. These attentional cycles lead to corresponding fluctuations in target-detection accuracy. Shifts in the location of the attentional focus are also tied to this rhythm. When multiple objects appear in the visual field, even when one is actively attended, the focus tends to alternate between the actively attended object and others. Thus, when two objects are present and one is cued, two opposite-phase 4Hz fluctuations in target-detection accuracy can be measured for the

cued and uncued objects, respectively. No study to date has investigated whether the rhythmic fluctuations of visual attention might be abnormal in SZ.

Methods: 30 outpatient adults with chronic SZ and 20 healthy control (HC) participants completed a behavioral task adapted from basic research. On each trial, two objects appeared and one was cued. After a delay of variable duration, a target appeared over either the cued or uncued object, except in 25% of trials (catch trials). Participants indicated after each trial whether or not a target appeared. Pre-task thresholding was performed to tailor target intensity to each participant's detection threshold. Critically, cue-target delay varied in 10ms increments over many pseudorandomized trials, yielding a response accuracy timecourse sampled at 100Hz.

We performed signal detection theory (SDT) and Fourier analyses on the accuracy timecourses. For SDT, we focused on A', which measures ability to distinguish a signal from noise. A' ranges from 0.5 – 1.0; 0.5 indicates total inability to discriminate signal from noise, and 1.0 indicates perfect discrimination. We considered scores below 0.6 to indicate invalid performance. We used Fourier analysis to characterize the amplitude and phase of attentional oscillations for each object at the primary frequency of interest (4Hz), as well as subharmonic (2Hz) and harmonic (e.g., 8Hz) frequencies.

Results: Fourteen SZ and 9 HC participants had A' scores under 0.6 and were excluded from further analysis. A' scores for remaining participants did not differ by group ($t(25)=0.56$, $p=0.58$; mean A'= 0.77).

We found a significant difference in the amplitude of 4Hz attentional oscillations between cued and uncued objects (condition main effect $F(1,22)=4.45$, $p=0.046$), but no group main effect or interaction. For phase, there was a weak trend toward a group main effect at 4Hz ($F(1,22)=2.83$, $p=0.11$), but no condition main effect or interaction. However, there was a significant group difference in phase at 2Hz ($F(1,22)=5.06$, $p=0.03$) and a weak trend toward a main effect of condition at that frequency ($F(1,22)=2.79$, $p=0.11$).

Discussion: Overall, the results suggest that oscillations in sustained visual attention can be measured in SZ, and differences in the spatiotemporal dynamics of the attentional spotlight may exist between SZ and HC. The lack of SZ-HC differences in oscillatory amplitude and the presence of phase differences suggest that to some degree abnormal attention in SZ may relate to differences in when attention is allocated (i.e., aberrant spatiotemporal dynamics), rather than how much attention is allocated. Further investigation is needed to understand precisely how and why the spatiotemporal dynamics of attention differ between SZ and HC (e.g., why significant group differences were found at 2Hz rather than 4Hz). Additional task optimization may help address these issues and improve A' scores.

M34. PROXY-BASED ASSIGNMENTS TO SCHIZOPHRENIA COGNITIVE TRAJECTORY SUBGROUPS CORRESPOND TO REPORTED CHILDHOOD AND TEENAGE COGNITIVE ISSUES

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Background: People with schizophrenia vary greatly in symptoms and progression, including the cognitive impairments associated with the illness. Previous work used adult cognitive test data as

a proxy to cluster patients into subgroups based on hypothesized cognitive development trajectories. The Wechsler Adult Intelligence Scale (WAIS) was used to estimate current cognitive ability (i.e., IQ), while the Wide Range Achievement Test (WRAT), which measures early-maturing and developmentally stable word-reading ability, was used to estimate pre-morbid cognitive ability. Using these data from the two assessments, three distinct cognitive trajectory subgroups emerged: 'cognitively stable' (high WRAT, high WAIS), 'adolescent decline' (high WRAT, low WAIS), and 'pre-adolescent impairment' (low WRAT, low WAIS). These resulting groups show distinct clinical, genetic, and cognitive characteristics. We sought evidence regarding the effectiveness of this proxy-assignment method. Did individuals in the subgroups actually show different patterns of childhood and teenage cognitive issues? What early-life issues were most predictive of trajectory patterns?

Methods: Data on childhood and teenage development were abstracted from parent-completed questionnaires for 347 schizophrenia cases with trajectory subgroup assignments from the earlier work. Questions targeted doctor referrals for math or reading difficulties, special education, speech difficulties, and other related academic, social and health issues. Responses were scored as cognitive, social-behavioral, or neuromotor issues. Issues were also identified as either pre-adolescent (before age 13) or adolescent-onset issues. We used logistic regression analyses to test the predictive associations, particularly of childhood and teenage cognitive issues with cognitive trajectory subgroup assignment. All analyses controlled for age, sex, and race.

Results: Those in the pre-adolescent impairment subgroup reported more childhood cognitive issues (before age 13) than those in the other subgroups (chi-sq[2] =20.99, p=2.8e-5). This overall effect was driven by the following items on the developmental history questionnaire: referral to a specialist for reading problems (p=3.0e-5), being held back in school (p=1.95e-4), participation in special education (p=9.5e-5), and needing extra help in school (p=0.001). Individuals assigned to the adolescent decline subgroup reported more teenage cognitive issues, overall, than those in the other subgroups (chi-sq[2] =8.501, p=0.014). This finding was driven by participation in special education (p=0.003) and needing extra help in school (p=0.051) that originated by or after age 13.

Discussion: Childhood cognitive issues – reading problems, being held back in school, special education referrals, and needing extra help in school – were common and statistically very robust in distinguishing the pre-adolescent impairment subgroup in our data. Teenage cognitive issues were rarer overall and less distinctive (most cognitive issues do not emerge in adolescence). This may reflect the variable and insidious emergence of the psychosis prodrome in some cases. Nevertheless, teenage issues were reported significantly more frequently in the adolescent decline subgroup, as hypothesized. Reports of actual childhood and teenage cognitive issues in our sample, documented by caregivers in developmental history questionnaires, were generally consistent with the cognitive trajectory subgroups framework and provided some support for the use of the WAIS/WRAT proxy to operationalize these subgroups.

M35. IMPAIRED AUDITORY CORTEX ATTENTIONAL GAIN MODULATION IN FIRST-EPISODE PSYCHOSIS

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Background: Selective attention is impaired at the first episode of psychosis (FEP). Selective attention can be measured with EEG and MEG during an auditory oddball task, as the event-related negativity present ~100ms post-stimulus (N100) amplitude increases with attention. We previously reported a reduced EEG-measured N100-enhancement in FEP. Here, we source-resolved the concurrently recorded MEG activity and examined source activity within auditory cortex as a function of attention to sounds.
Methods: MEG was recorded from 24 FEP and 30 matched healthy controls (HC) while individuals either ignored tones while watching a silent movie or attended tones by pressing a button to oddball tones. The HCP parcellation defined 3 bilateral auditory regions of interest: A1, lateral belt, and parabelt. MEG source activity was determined with minimum norm estimation, and averaged activity during the M100 (the MEG analogue of the EEG N100) within regions was compared between conditions and groups.
Results: At the MEG source level, FE had overall less source activity within the regions in both conditions ($p<0.01$). In addition, there was a significant interaction between group and attention ($F(1,51)=7.63$, $p<0.01$), where HC enhanced source activity with attention ($p=0.01$), while FEP did not ($p=0.32$).
Discussion: These results suggest deficits in both sensory and attentional modulation of the M100 in FEP. Future work will investigate functional connectivity with auditory-executive frontal cortex that may mediate this attentional modulation deficit. The M100 sensory reduction and failure to modulate with selective attention may serve as useful biomarkers early in disease course but also indicate local and systems-level pathophysiology proximal to disease onset that may be critical for etiology.

M36. PSYCHIATRIC SYMPTOMS ARE DIFFERENTIALLY ASSOCIATED WITH VERBAL FLUENCY PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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Background: Despite verbal fluency (VF) being a common task in psychiatric research, there is very little consensus on the nature of VF deficits in psychiatric populations and their implications for our knowledge about cognitive and specifically linguistic functioning in these populations. Previous studies have found that negative symptoms, including alogia, are associated with poorer overall VF production in patients with schizophrenia (SCH), while studies investigating positive symptoms, including formal thought disorder, have yielded mixed results. Because most studies didn't analyze additional VF measures such as clustering and lexical characteristics, it remains unclear whether the association between negative and positive symptoms and VF performance in patients with schizophrenia reflects abnormalities in linguistic and/or semantic processing or other aspects of cognition. Furthermore, it is uncertain whether these associations are specific to patients with schizophrenia, while the associations with manic and depressive symptoms are understudied.
Methods: We recruited 58 German-speaking inpatients diagnosed with either schizophrenia (N = 36), bipolar disorder (BD; N = 10), or major depression (DEP; N = 12). All patients were assessed on conventional symptom scales including the SANS/SAPS, HAMD, and YMRS, and were further administered the semantic (SF; animals) and letter (LF; P) fluency tasks (60 s). The following

dependent variables were analyzed: correct words, error rate, response latencies, switching rate, cluster size, idiosyncratic word production rate, and word frequency.
Results: BD produced significantly larger clusters and had significantly higher idiosyncratic word production rates on SF compared to both SCH and DEP, while overall word frequency on SF differentiated between all patient groups. Overall negative symptomatology and specifically alogia were negatively associated with overall performance and positively with between-cluster response latencies on SF. Alogia was not significantly associated with other VF variables. Cluster size and overall word frequency on SF were positively associated with depressive and negatively with manic symptoms, idiosyncratic word production rate on SF was positively associated with manic symptoms, while positive symptoms were only negatively associated with the frequency of the first three words on SF.
Discussion: Previous evidence for an association between negative and positive symptoms, and VF performance in SCH has been to some extent replicated in a diverse psychiatric sample. Because alogia was not significantly associated with VF variables other than overall productivity and between-cluster response latencies, we found no evidence that alogia is associated with deficient processing within the semantic memory or mental lexicon. Yet, its positive association with between-cluster response latencies possibly suggests that alogia reflects transdiagnostic dysfunctional connectivity between the prefrontal and temporal cortices and, thus, inefficient lexical access. Furthermore, clinical levels of mania were associated with normal cluster sizes, in line with one previous study. Intriguingly, cluster sizes did not differ between SCH and DEP, indicating a similar level of the semantic deficit with possibly different underlying mechanisms. Additionally, manic symptoms were associated with relatively unusual (but appropriate) word production, indicating aberrant saliency of words during lexical access in mania. Further research regarding word frequency is needed to adequately interpret those results. Finally, LF performance was diagnostically and symptomatically unremarkable.

M37. EFFECTS OF SCHEMAS, INTERNALIZED STIGMA, AND SYMPTOMS ON THE EXPERIENCE OF SOCIAL EXCLUSION IN PSYCHOSIS

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Background: Social exclusion has immediate negative effects on healthy individuals' sense of belonging, sense of control, self-esteem, and cognitive functioning. Individuals with psychosis are more likely to be ostracized than healthy individuals. Moreover, social exclusion plays a role in the development, maintenance, and severity of psychosis. However, social exclusion has rarely been experimentally examined, and to our knowledge, social exclusion has never been experimentally examined in psychosis. Internalized stigma is associated with numerous negative outcomes and may be associated with how individuals react to social exclusion. Schemas are cognitive constructs that provide a framework for understanding the world. It is likely that schemas of the self and others may affect how individuals respond to social exclusion. Furthermore, effects of these factors in relation to overinclusion in psychosis have not been studied. The goal of the current study was to examine the effects of schemas, internalized stigma, and symptoms on the experience of social exclusion and overinclusion for individuals with psychosis.
Methods: 27 participants diagnosed with schizophrenia, ages 18 to 65, completed a computerized Cyberball game in which they passed a ball with two other players. Participants were led to believe

that the two other players were in the lab with them and that they could meet the other players after the game. Participants completed three blocks of Cyberball; an exclusion, fairplay and overinclusion block. In the exclusion block, participants were tossed the ball a disproportionately low number of times (approximately one-fifth of the throws). In the overinclusion block, participants were tossed the ball a disproportionately large number of times (four-fifths of the throws). In the fairplay block, participants received the ball a proportionate amount of times (approximately one-third of throws). The Need Threat Questionnaire (NTQ) was used to measure the emotional impact of the manipulation. Schemas about the self and others were measured with the Brief Core Schema Scale, internalized stigma was measured with the Internalized Stigma of Mental Illness Scale, and symptoms were measured with the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms.

Results: Individuals with psychosis with greater negative self-schemas and lower positive self-schemas were more likely to experience greater need threat when socially excluded ($r= -0.488$, $p= .022$; $r= 0.440$, $p=.025$). However, other-schemas were not significantly correlated with need threat in the social exclusion condition. Neither self-schemas nor other-schemas were significantly associated with need threat in the overinclusion condition. Individuals who reported greater internalized stigma experienced greater need threat when socially excluded ($r= -0.561$, $p= .004$). Whereas, internalized stigma was not associated with need threat in the social overinclusion condition. Individuals with greater positive symptoms experienced more negative emotionality in response to social overinclusion ($r= -0.399$, $p= .044$). Individuals with greater negative symptoms experienced more negative emotionality in response to social exclusion ($r= -0.455$, $p= .02$). There were no significant associations between schemas, internalized stigma, or symptoms and need threat in fair play.

Discussion: The results suggest that therapies targeting self-esteem, internalized stigma, and negative symptoms may be beneficial in protecting against the negative consequences of social exclusion. Furthermore, overt social inclusion may be experienced negatively by individuals with psychosis with greater positive symptoms.

M38. DISPROPORTIONATE SPATIAL AND NON-SPATIAL FEATURE BINDING IMPAIRMENTS IN VISUAL WORKING MEMORY IN SCHIZOPHRENIA

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Background: Working memory impairment is a core cognitive deficit in schizophrenia and predicts psycho-social outcome in affected individuals. Animal lesion and patient studies, however, suggest that distinct neural circuits underpin different working memory processes,

raising the possibility that working memory impairments in schizophrenia may be material or process specific.
Methods: We recruited 24 schizophrenia patients and 24 age and gender matched controls. Participants were tested on a number of visual working memory tasks, including a delayed spatial recall task and an object-location task.
Results: Schizophrenia patients showed increased proportion of binding errors in the delayed spatial recall task [$F(1, 41) = 6.524$, $p = 0.014$, $\eta 2 = 0.137$]. In the object-location task, patients made disproportionately higher binding errors than controls [$F(1, 46) = 19.407$, $p < 0.001$, $\eta 2 = 0.297$]. Spatial recall precision showed no appreciable group difference [$F(1, 41) = 3.129$, $p = 0.084$, $\eta 2 = 0.071$].
Discussion: Our results suggest that visual working memory impairments in schizophrenia predominantly reflect spatial and non-spatial binding deficits, with largely preserved information about visual features. These binding deficits may reflect impaired effective connectivity between frontal and medial-temporal cortical regions.

M39. ACOUSTIC SPEECH MARKERS FOR SCHIZOPHRENIA-SPECTRUM DISORDERS: A DIAGNOSTIC AND SYMPTOM-RECOGNITION TOOL

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Background: Clinicians routinely use impressions of speech as an element of mental status examination. In schizophrenia-spectrum disorders, descriptions of speech are used to assess severity of both negative and positive symptoms. In the present study, we assessed the diagnostic value of acoustic speech parameters in schizophrenia-spectrum disorders, as well as its value in recognizing positive and negative symptoms.
Methods: Speech was obtained from 142 patients with a schizophrenia-spectrum disorder and 142 matched controls during a semi-structured interview on neutral topics. Patients were categorized as having predominantly positive or negative symptoms using the Positive and Negative Syndrome Scale (PANSS). Acoustic parameters were extracted with OpenSMILE, employing the extended Geneva Acoustic Minimalistic Parameter Set (eGeMAPS), which includes standardized analyses of pitch (F0), speech quality and pauses. Speech parameters were fed into a random forest algorithm with leave-ten-out cross-validation to assess their value for a schizophrenia-spectrum diagnosis, and PANSS subtype recognition.
Results: The machine-learning speech classifier reached an accuracy of 86.2% in classifying patients with a schizophrenia-spectrum disorder and controls on speech parameters alone. Patients with predominantly positive versus negative symptoms could be classified with an accuracy of 76.3%.
Discussion: Our results show that automatically extracted speech parameters can be used to accurately classify patients with a schizophrenia-spectrum disorder and healthy controls, as well as differentiate between patients with predominantly positive versus negatives symptoms. Thus, the field of speech technology has provided a powerful tool that has high potential for clinical application in diagnosis and differentiation, given its ease of acquirement, low costs and negligible patient burden.

M40. EXPLORING THE SOCIODEMOGRAPHIC, CLINICAL AND NEUROPSYCHOLOGICAL FACTORS ASSOCIATED WITH RELATIONAL MEMORY IN SCHIZOPHRENIA

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Background: Episodic memory impairments in schizophrenia, including its relational memory component, are associated with significant clinical and functional variables, such as employment status, social and occupational functioning, and early and long-term remission. The Transverse Patterning (TP) task, a computer task designed to detect impairment in relational memory performance, has been used as a measure of relational binding deficit in this population. Individuals with schizophrenia often fail to learn TP with standard training and more than a quarter of patients fail the task even when extensive training is provided. TP failure may reflect multiple cognitive deficits (i.e. executive functions, working memory and visual memory). Identifying the neuropsychological factors, awareness distinctions, and strategy use differences between TP learners and non-learners can improve our understanding of underlying mechanisms required for successful performance in TP and, consequently, improve cognitive interventions that are targeted to ameliorate relational memory performance. The present study investigated the sociodemographic, clinical, neuropsychological and task-specific (i.e. task awareness and strategy use) factors associated with TP learning and impairment in schizophrenia.

Methods: Sixty-nine participants with a diagnosis of schizophrenia or related psychosis were recruited for this study (66 completers). They completed two versions of the TP task (one semantically-rich and one relational-binding dependent) and answered a questionnaire to evaluate task awareness and strategy use in each condition and had sociodemographic and clinical data collected at screening.

Results: Twenty-six participants (38.8%) were unable to learn all the task rules after extensive training. In a subset of participants who underwent neurocognitive assessment (N = 29), learners had significantly superior verbal, visual and working memory, executive functions and overall cognitive functioning compared to non-learners. Group comparisons also suggested superior awareness of task rules and pairs relationships for learners compared to non-learners. Learners used cognitive strategies (such as memorizing how the objects interacted, naming the objects and qualifying their interactions with action verbs) more often than non-learners, and strategies seemed to be more elaborated for learners than for non-learners.

Discussion: This study confirmed previous findings that a subset of individuals with schizophrenia shows significant relational memory impairment assessed by the transverse-patterning paradigm which is not improved by stepwise TP training. It also brings new insight into factors associated with TP task performance, including neurocognitive markers that seem to contribute to TP learning. Finally, this study points to task awareness and strategy use components underlying successful TP learning. This knowledge could be useful for future interventions that are targeted to improve relational memory performance in schizophrenia when stepwise training is not sufficient.

M41. IMPROVEMENTS IN COGNITION FOLLOWING COGNITIVE TRAINING IN INDIVIDUALS AT RISK FOR PSYCHOSIS

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Background: Individuals at clinical high risk (CHR) for psychosis have neurocognitive deficits which are associated with functional disability and risk of transitioning to psychosis spectrum disorders, such as schizophrenia. Targeted cognitive training (TCT) aimed at engaging neuroplasticity in neural networks has been proposed as a therapeutic intervention for CHR individuals. However, while TCT has been shown to improve cognition and neural function in individuals with schizophrenia, there have been few randomized clinical trials evaluating these effects. This study investigated whether cognitive and social cognitive training in CHR participants would improve their overall cognitive functioning and their social cognitive functioning.
Methods: 102 CHR participants were compared to 29 healthy control (HC) participants at baseline to identify areas of cognitive, social cognitive and neural impairments. Participants completed a comprehensive cognitive battery including the MATRICS Consensus Cognitive Battery (MCCB) for identifying cognitive impairments in individuals with psychosis. CHR individuals then completed either 40 hours/8 weeks of computer-based, targeted cognitive and social-cognitive training (TCT) or an equivalent amount of a computer game control condition (CG). CHR individuals were randomly assigned to the TCT or CG condition. Training targeted speed of processing, attention, memory, cognitive-control, and facial emotion recognition. N=84 CHR individuals completed training. The cognitive battery was repeated midway through cognitive training, following completion of cognitive training and 9 months after completing training.
Results: CHR and HC did not significantly differ on age, gender or estimated IQ. However, CHR individuals were impaired on the MCCB. CHR participants performed significantly worse than HC on overall cognition ($t(28)= p<.001$). Specific impairment was found in processing speed ($t(28)=-2.92$, $p=.007$), visual learning ($t(20)=-2.76$, $p = .01$) and social cognition ($t(13)=-3.11$, $p = .008$) as well as a trend in reasoning and problem solving ($t(13)=-2.10$, $p = .05$).There were no group differences on attention/vigilance, working memory or verbal learning. CHR participants also demonstrated significantly lower global functioning (GAF; $t(30) = 10.64$, $p<.001$), lower role functioning ($t(39) = 3.75$, $p<.001$, and lower social functioning ($t(39) = 6.57$, $p<.001$).
Within the CHR sample, there were no significant differences between individuals randomized to TCT compared to individuals randomized to CG on the overall cognitive composite or on any subtests of the MCCB. There was a significant group by time relationship on the overall cognitive composite score such that individuals who received TCT improved over the course of the training compared to those who received CG ($p=.04$). Furthermore, these gains were enhanced at the 9-month follow up. The primary social cognition measure, the MSCEIT, also showed a significant group by time interaction with improved performance in the TCT group compared to the CG group over the course of training ($p=.002$).

Discussion: These results suggest that the TCT exercises were associated with improvements in overall cognition and that these improvements continued following the cessation of the training program, indicating that cognitive impairments in CHR individuals may be amenable to behavioral treatment like TCT. These findings support continued development of TCT for individuals at risk for psychosis as well as extension of these methods to address impairments in other psychiatric disorders.

M42. USING ONLINE RECRUITMENT TO EXAMINE THE ROLE OF SOCIAL COGNITION IN PSYCHOSOCIAL FUNCTIONING IN INDIVIDUALS AT-RISK FOR PSYCHOSIS

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Background: Schizophrenia is a debilitating psychosis disorder with neurocognitive, emotional, and psychosocial dysfunction, often preceded by a clinically distressing prodromal phase. It has been robustly demonstrated in previous research that the social cognitive impairments that precede the onset of florid psychosis are prognostic of social and role dysfunction. Individuals who are at-risk (AR) for developing a psychosis-spectrum disorder and are absent from treatment may transition to a full psychotic disorder as subthreshold, yet distressing, social cognitive impairments and related dysfunction continue to progress.

Methods: The current study examined those AR for psychosis by employing a psychometrically-based risk assessment tool in an online format to examine the role of social cognitive performance in psychosocial outcomes across the psychosis-spectrum. We subsequently examined how symptom severity, psychosocial functioning, and social cognition relate to attitudes and actions toward help-seeking. We recruited individuals identified as AR (n = 46) as well as a healthy comparison group (HC, n = 43) via the Prodromal Questionnaire-Brief (PQ-B). Participants were recruited and screened for inclusion and group identification on Amazon Mechanical Turk (MTurk), and completed symptom, cognitive, functioning, and help-seeking assessments online.

Results: Findings revealed that AR participants did not demonstrate significantly poorer social cognition than HC ($p=.14$), while social and role functioning were significantly impaired in AR relative to the HC group ($F(1,87)=14.995$, $p<.001$, $d=.83$; $F(1,85)=11.769$, $p=.001$, $d=.75$ respectively). Social cognition was significantly inversely related to social, but not role, functioning ($r=.475$, $p<.01$), and positively related to attitudes toward help-seeking within the AR group ($r=.331$, $p<.05$). While there were no differences between AR and HC in help-seeking attitudes ($M=20.20$, $SD=4.71$; $M=19.47$, $SD=6.96$), the AR group reported more help-seeking actions ($M=2.26$, $SD=.25$; $M=1.51$, $SD=.23$). Symptom severity and psychosocial functioning did not impact help-seeking attitudes and actions in either group.

Discussion: The present study utilized a multi-method online psychosis risk screening to reach an AR sample with a range of attitudes and recent actions toward help-seeking. The finding that social cognition, but not psychological or psychosocial dysfunction, is associated with more positive attitudes toward help seeking contributes to a better understanding of those AR for psychosis in the general population and highlights the potential utility of social cognitive assessment in future wide-reaching screening and early intervention efforts.

M43. BETA-FREQUENCY ELECTROPHYSIOLOGICAL ACTIVITY IN RESPONSE TO ERRORS: RELATIONSHIPS WITH SCHIZOTYPY AND DISORGANISATION

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Background: During movement there is a reduction of beta waves, called Event-Related Beta Desynchronisation (ERBD), followed by a peak at above baseline levels, called Post-Movement Beta Rebound (PMBR). Research demonstrates PMBR levels are attenuated in schizophrenia and schizotypy. Previous studies show that PMBR is negatively correlated to the Schizotypal Personality Questionnaire, but beta has shown to peak at higher levels for incorrect responses. Research suggests higher PMBR reflects an update to, or confidence in, the brain's predictive model for motor responses, but relationships between PMBR and SPQ have only been investigated for motor responses classified as 'correct'; relationships with PMBR when errors are made have not been examined.
Methods: Data from a previous study was re-analysed. Forty participants completed the Erikson Flanker task while a 128-channel electroencephalography recorded electrophysiological changes. Cleaned data from all participants were combined and a group independent component analysis identified consistent sources of beta activity across participants. Beta-frequency bursts were identified in activity time courses for each participant and component. Beta burst rate was calculated in sliding time windows relative to times of motor responses.
Results: PMBR was present within the sample. Incorrect responses produced greater peak post-movement beta burst rates than correct responses but there was no correlation between correct response beta attenuation and higher SPQ-B and disorganisation scores. However, higher SPQ-B and disorganisation scores predicted a greater peak post-movement burst for incorrect responses. Difference in peak post-movement bursts between correct and incorrect responses had stronger, more significant correlations.
Discussion: Investigating peak post-movement beta burst rate is a valid measure. It suggests incorrect responses require more model space to update the predictive model and proposes higher SPQ-B and disorganisation scores indicate inefficient processing during updates, resulting in larger peak PMBR. It suggests beta could contribute to the core deficit of schizophrenia, manifesting as disorganisation.

M44. SOMATIC COMORBIDITY IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS- A RETROSPECTIVE ANALYSIS

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Background: A high degree of co-morbidity has been reported in the literature in patients diagnosed with schizophrenia spectrum disorders (SSD), and this is an important factor that may decrease these patients' quality of life, overall functionality, and life expectancy [1]. Beside primary somatic diseases, several illnesses are secondary to the antipsychotic treatment (e.g., metabolic syndrome, obesity), while others may be consequences of psychiatric comorbidity (e.g., hepatic cirrhosis secondary to coexisting alcohol use disorder) [2]. Men diagnosed with schizophrenia died 15 years earlier, and women 12 years earlier, than the rest of the population, a phenomenon not accounted for by unnatural deaths, with ischemic heart disease or cancer diagnoses being the lead causes [3]. Due to communicational dysfunctions frequently detected in patients with schizophrenia spectrum disorders (SSD) the latency period until a correct diagnosis of a somatic disease is formulated may be longer than in the general population, and executive

dysfunctions and low level of insight may be responsible for the discontinuation of the appropriate treatment [4].

Methods: A retrospective analysis of 35 charts of patients diagnosed with SSD (schizophrenia, n=27, schizoaffective disorder, n=5, delusional disorder, n=3, according to the DSM-5 criteria), admitted in our Psychiatry Department, was conducted in order to detect the most frequently organic co-morbidities. All patients aged 18 to 65 with a primary diagnosis of SSD have been included in this analysis, regardless of their evolution specifiers or duration of their disorder. The mean age of these patients was 52.6 years, and male: female ratio was 3:4.

Results: A number of 15 patients (representing 42.8%) presented at least one organic comorbidity. Obesity was the most frequently diagnosed organic disease (n=12, standing for 34% of the total patients' number), followed by high blood pressure (n=8, 22.8%), and diabetes mellitus (n=7, 20%). Other diagnoses were chronic obstructive pulmonary disease (11.4%), liver alcoholic disease (11.4%), and chronic gastritis (8.5%). The mean number of medications administered for these patients was 7.2, psychotropic medication included. The mean duration of their organic illnesses, determined by documents or by self-report, when medical documentation was not available, was 10.2 years.

Discussion: Patients diagnosed with schizophrenia have high rates of organic co-morbidity, long-duration spent dealing with these diseases, and multiple drugs being administered for these indications. A complex evaluation involving a multidisciplinary team should be recommended both during the initial examination and during the monitoring visits in patients diagnosed with schizophrenia.

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M45. TOBACCO SMOKING AND CLINICAL HIGH RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EVIDENCE

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Background: There is converging evidence that youths at clinical high risk (CHR) are not only likely to develop a first episode of psychosis but also to develop poor physical outcomes. Some

physical health risk factors - such as smoking - have been shown to increase the probability of a frank onset of psychosis in those at risk. A meta-analysis conducted in psychotic patients confirmed that daily tobacco use is associated with increased risk of psychosis. A significant association between any attenuated psychotic symptoms (that characterize CHR state) and cigarette smoking has been recently shown in a study conducted in South London.
Nowadays, it is not completely clear how these findings would translate to CHR population but a better understanding on how physical health parameters could affect psychopathological outcomes could be beneficial for these vulnerable clinical populations. To shed light on the percentage of smokers in CHR populations, an updated systematic review and meta-analysis of the literature has been carried out. Our main aim was to test whether the probability of being a smoker was higher in the CHR subjects or in the control group.

Methods: The literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We systematically scrutinized from literature inception to 2019 the following on-line databases: Web of Science Core Collection, BIOSIS Citation Index, KCL-Korean Journal Database, MEDLINE, Russian Science Citation Index, SCiELO Citation Index.
We have considered all the relevant studies reporting the smoking status in CHR subjects and in control groups.

We used the odds ratio as effect size measure and data were pooled using a random effect approach.

Results: Preliminary data show that CHR individuals were more likely to use tobacco that matched healthy controls. Specifically, the overall OR of 2.016 ($p<.001$ 95%CI=1.476-2.749) indicated a higher likelihood that CHR individuals would use tobacco compared to controls. Heterogeneity was not significant ($I2=30.193$ $p=0.11$). The visual inspection of funnel plots did not reveal a clear suggestion for publication bias and the Egger's test was non-significant ($p=0.10$).
Discussion: Our systematic review and meta-analysis suggest that is crucial to investigate physical health outcomes such as tobacco use as part of clinical practice in CHR services. Unfortunately, current CHR assessment tools are entirely based on the measurement of psychopathological features and do not always include an assessment of these parameters on a regular basis.

M46. PERIPHERAL EXPRESSION OF HEME OXYGENASE 1 AND FREE WATER LEVELS IN THE SUPERIOR TEMPORAL GYRUS ARE ASSOCIATED WITH EXECUTIVE FUNCTION DEFICITS, AND CANNABIS USE IN FIRST EPISODE PSYCHOTIC PATIENTS

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Marta Barrera-Conde

Background: Evidence for a redox imbalance has been found in post-mortem brains and plasmatic samples from psychotic patients. Moreover, epidemiological studies report that cannabinoids modulate cellular oxidative state, and cannabis consumption increases the risk for psychosis. A central protein in redox response is Heme oxygenase 1 (HO-1). Its expression exerts a neuroprotective action in homeostatic conditions, but it has been associated with neuronal damage in neurodegenerative disease models. In addition, HO1 overactivation induces a psychotic-like phenotype in rodents. Therefore, in this study, we evaluated the impact of psychosis and cannabis use on the peripheral expression of HO1, and on extracellular free water (FW) in the brain.
Methods: Healthy control subjects (HC/nc), first-psychotic episode patients without a history of cannabis use (FEP/nc), and first-psychotic episode patients with a reported history of cannabis use (FEP/c) underwent diffusion weighted MRI scanning, complete neuropsychological evaluation and a blood extraction. FW was quantified using the extracellular FW elimination model. FW mean values were calculated in total grey matter, white matter, superior temporal gyrus and middle frontal gyrus using free-surfer segmentations. mRNA was extracted from white blood cells and HO1 expression was quantified by RT-qPCR using Quantity 12K (Applied Byosistems). For mRNA expression quantification, fold change was calculated using GAPDH as a control and a one-way ANOVA followed by an LSD post-hoc test was performed. To evaluate the interactions between cannabis use, FW and HO1 a spearman correlation matrix was designed.
Results: mRNA levels of HO1 in white blood cells were significantly increased in FEP/nc as compared to HC/nc ($p<0.05$), but not in FEP/c. The correlation matrix revealed a negative relationship between HO1 expression and inhibitory control in the STROOP test ($R=-0.59$, $p<0.05$). Similarly, FW levels in the right superior temporal gyrus ($R=0.52$, $p<0.05$) positively correlated with inhibitory control. Additionally, FW in the right superior temporal gyrus positively correlated with the reported amount of cannabis use per week in the last twelve months ($R=0.84$, $p<0.05$).
Discussion: Increased peripheral expression of HO1 and/or lower FW in the right superior temporal gyrus were associated with executive function deficits in a population including psychotic patients. In addition, cannabis use modulates both the expression HO1 and the levels of FW in FEP.

M47. REAL-WORLD EFFECTIVENESS OF ANTIPSYCHOTIC TREATMENTS IN SCHIZOPHRENIA WITH COMORBID SUBSTANCE USE DISORDER

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Background: Schizophrenia is highly comorbid with substance use disorders (SUDs), which have a detrimental impact on the course of illness. However, large studies exploring the best lines of treatment for this co-morbidity are lacking.
Methods: We compared the effectiveness of specific antipsychotics in preventing the development of SUD among patients with schizophrenia and, among patients already suffering from an SUD, in preventing hospitalizations and mortality. Two independent national cohort registries were used to study the generalizability of the results. Participants were followed during 22 (1996–2017,

Finland) and 11 years (2006–2016, Sweden) by using specialized inpatient and outpatient healthcare and social insurance agency registers. All persons treated for schizophrenia, aged <46 years at cohort entry were included. Adjusted Hazard ratios (aHRs) of psychiatric hospitalization and developing SUDs when using vs. not using antipsychotics, were analyzed with Cox regression models. The risks of developing SUD and mortality were calculated with between-individual models, and the risk of hospitalization with within-individual model.
Results: A total of 45,476 patients with schizophrenia were identified (30,860 in Finland; 14,616 in Sweden). The results for specific treatments (clozapine, olanzapine, risperidone, quetiapine, other oral, any long-acting injection, antipsychotic polypharmacy) were highly consistent between Finland and Sweden ($r = 0.83$, $p = 0.013$). For patients without SUDs, clozapine (aHR 0.09, 95% CI 0.05–0.16, $p<0.0001$ in Finland; 0.35, 0.24–0.50, $p<0.0001$ in Sweden) and antipsychotic polytherapy (aHR 0.26, 0.20–0.35, $p<0.0001$ in Finland; 0.54, 0.44–0.66, $p<0.0001$ in Sweden) were associated with the lowest risks of developing an initial SUD in both countries. Among patients already suffering from an SUD, clozapine use was associated with a substantially better outcome when compared with the second best monotherapy, olanzapine (aHR 0.23, 0.12–0.47, $p<0.0001$ in Finland, 0.52, 0.35–0.76, $p=0.0008$ in Sweden). Their risk of psychiatric hospitalization was lowest with clozapine, polytherapy, and long-acting injectables. Antipsychotic polypharmacy was associated with lowest mortality in both Finland and Sweden. Sensitivity analyses confirmed all results.
Discussion: Clozapine should be considered the treatment of choice in patients with schizophrenia at risk of developing SUDs or already suffering from one.

M48. COCAINE-INDUCED PSYCHOSIS

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Background: Cocaine is an illicit substance extracted from the leaf of Erythroxylon coca.
The consumption of cocaine is increasing in Europe, and in the world these last years.

In the space of 5 years, it has become the second most commonly used illicit drug in the world after cannabis. Taking cocaine causes a transient psychotic state: a Cocaine-Induced Psychosis, that usually resolves by stopping consumption.

Methods: We conducted a narrative literature review on electronic databases Medline, EMBASE, PsycINFO, and Google Scholar, describing cases of cocaine use that caused psychotic episodes and studying the particularities of these episodes.
Results: Acute psychotic disorders generally begin a few hours after taking cocaine and are corrected twenty-four hours after consumption. However, repeated catches may promote the development of chronic psychotic disorders.
The characteristics of Cocaine-Induced Psychosis are :

-paranoid elements: mistrust, persecution, fear of being discovered during cocaine use, being followed or injured by police, unknown enemies or bandits

- visual hallucinations: shadows, flashes of light

- tactile hallucinations: Formications, also called "cocaine bugs", defined by a sensation similar to insects crawling on the skin.

-delusion parasitosis or Ekbom syndrome: delusional disorder manifested by the feeling of being infested by insects or internal parasites, favored by the formications. We then find itching, burning, tingling, leading to obstinate scratching and tenacious.

The therapeutic management of the acute psychotic episode consists of hospitalization, sedation if the subject is agitated, and treatment by a second-generation antipsychotic.

But the main treatment consists in stopping the consumption of cocaine, with first weaning by symptomatic treatment, and secondly the maintenance of abstinence which will be pharmacological, psychotherapeutic and sociotherapeutic.

Finally, we must not forget to treat comorbidities such as depressive episodes, co-addictions, attention deficit hyperactivity disorder, and the management of suicidal behavior.

Discussion: In conclusion, the consumption of cocaine causes psychiatric side effects, more specifically a Cocaine- Induced Psychosis, which has specific semiological characteristics.

M49. REMINDCARE APP FOR EARLY PSYCHOSIS: REAL-WORLD INTERVENTION DURING THE COVID-19 OUTBREAK

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Background: Since the COVID-19 crisis started, many authors have expressed their concerns about the negative effects of this unprecedent situation on mental health. Recent studies found higher rates of anxiety, depression and stress in general population, and some studies have claimed that this risk of psychological decompensating is increased for those with severe mental illness. Since telemedicine has shown its potential benefits to increase the quality of mental health interventions, the development of this digital interventions has surged as the access to health services was restricted. In this regard, ReMindCare is a smartphone application (Bonet et al. 2020a) whose development was based on two previous studies (Bonet et al. 2017-2018). This app showed its positive clinical outcomes after 19 months of implementation in a First Episode of Psychosis Program (FEPP) for patients with early psychosis (EP) (Bonet et al. 2020b). The objective of this study was to analyze the clinical impact of the COVID-19 outbreak in the group of patients followed in a FEPP and the impact of the use of ReMindCare app during this period.
Methods: Rates of incidence, relapse and hospitalizations were analyzed from patients in the FEPP at the Clinic Hospital of Valencia from the 1st of March to 31st of October of 2019 and 2020. The impact of the use of the app during the COVID-19 outbreak (March-October 2020) was also analyzed.

Results: The number of patients included in the FEPP during COVID-19 outbreak increased 21.6% (X2= 6.28, p=0.012) and the incidence during this period increased 78.6% (X2= 4.08, p=0.04) when we compared to data from the same period in 2019. However, no differences were found in terms of number of relapses (X2= 0.09, p=0.76) and hospitalizations (X2= 0.28, p=0.59) in both periods. 52 patients used the app during the COVID-19 outbreak and only 5.8% had a relapse during this period, compared to the 23.5% of the 81 patients who did not use the app (X2= 7.18, p=0.007). Moreover, no patient using the app had a hospitalization during this period while 8.6% of patients who did not use the app had (X2= 4.74, p=0.029). In addition, in regards of the use of the app during the months of March to October 2020, mean rate of engagement with the app was 86.5 (SD=15.9) and mean of moths using the app were 16.9 (SD=8.9).
Discussion: The use of ReMindCare app during the COVID-19 outbreak was correlated to fewer relapses and hospitalizations. In addition, we found an increase in the number of the EP patients in our FEPP when we compare data from March to October from 2019 to 2020. These data highlight the relevance of developing digital interventions to prevent the negatives effects of the pandemic crisis and the social isolation. To the best of our knowledge, ReMindCare app was the first e-Health intervention which was daily being used since the beginning of the COVID-19 outbreak and the first app for patients with psychosis that has obtained positive clinical outcomes during this period.

M50. DEVELOPMENT AND VALIDATION OF A RISK CALCULATOR OF FUNCTIONAL, SYMPTOMATIC AND PERSONAL OUTCOME FOR PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: The disease presentation and outcome of first episode psychosis (FEP) patients are heterogeneous, resulting in a demand for a practical clinical tool that can estimate an individual's disease outcome early on in the disease. Such risk calculators can aid in stratifying FEP patients according to predicted outcome risk, thereby aiding in the development of more personalized treatment plans. Furthermore, risk calculators support clinicians in informing patients about their disease outcome risk and present a start for shared-decision making. This study aims to develop and validate, both internally and externally, 6 prognostic multivariable prediction models that objectively determine the risk of poor functional, symptomatic and personal outcome at 2 and 5 years after the first presentation of an individual FEP patient.
Methods: We will include FEP patients who are enrolled in both the 'Psychosis Recent Onset GRoningen survey' (PROGRs) and the 'Pharmacotherapy Outcome and Monitoring Survey' (PHAMOUS). These naturalistic prospective Dutch cohort studies will provide socio-demographic, premorbid, diagnostic, clinical, cognitive and medication baseline characteristics collected between 1998 and 2020 (PROGRs) and follow-up measurements collected between 2007 and 2020 (PHAMOUS). We already conducted a pilot study with a subsample of 408 FEP patients aiming to identify potential predictors of poor symptomatic and/or functional outcome after an FEP. Associations between potential predictors and poor symptomatic and functional outcome between baseline and 5 years (short/medium-term) and between 5 and 17 years (long-term) after inclusion were investigated with uni- and multivariable logistic regression analyses.

In the main study, ensemble machine learning methods: will be used to investigate associations between the candidate predictor variables and functional, symptomatic and personal outcome. For each outcome and each follow-up period (2 and 5 years), a separate multivariable prediction model will be developed. The predictive performance of the model will be evaluated using calibration and discrimination. The model will be internally validated using 1000 bootstrapping samples and externally validated in the Danish OPUS cohort.

Results: In the pilot study, 184 patients were included in the short/medium-term analyses and 239 patients in the long-term analyses. More negative symptoms were associated with poor short/medium-term symptomatic (Odds Ratio [OR]=1.16, 95% Confidence Interval [CI]=1.01-1.33) and functional outcome (OR=1.32, 95%CI=1.11-1.57). Poor overall role functioning (OR=1.18, 95%CI=1.04-1.35), less usage of reassuring thoughts as coping style (OR=0.75, 95%CI=0.60-0.95), poor recognition memory (OR=0.72, 95%CI=0.54-0.96) and poor global functioning (OR=0.96, 95%CI=0.92-1.00) predicted poor long-term symptomatic outcome. More negative symptoms (OR=1.08, 95%CI=1.00-1.16) and having repeated a grade (OR=0.96, 95%CI=0.92-1.00) were associated with poor long-term functional outcome. Explained variances ranged between 9.2 and 34.3 percent. Full results of the main study will be presented at the congress.

Discussion: The pilot study corroborated more negative symptoms and lower global functioning as predictors of outcome after an FEP. Also, new predictors were discovered: less usage of reassuring thoughts, poor recognition memory, poor overall role functioning and having repeated a grade. In the main study, a prediction model that calculates the risk of poor functional, symptomatic and personal outcome in FEP patients will be developed. This tool will contribute to improving personalized treatment of FEP patients.

M51. THE VARIETIES OF INDIVIDUAL VOICE-EXPERIENCES SCALE (VOICES): A NOVEL QUESTIONNAIRE FOR HEALTHY VOICE-HEARERS

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Background: Recent decades have seen a surge of research interest in the phenomenon of healthy individuals who experience auditory verbal hallucinations yet do no exhibit distress or need for care. A consistent finding is that clinical voice-hearers experience predominantly negative voice content, whereas healthy voice-hearers typically report neutral or positive voice content (Baumeister et al., 2017; Johns et al., 2014). The literature has highlighted the potential for auditory verbal hallucinations in healthy voice-hearers to be experienced as beneficial and life-enriching. However, most currently available measures aiming to capture the experiences of voice-hearers have been developed in a clinical context, where positive or neutral characteristics of voices have been largely ignored. We have developed a novel scale that attempts to cover the full spectrum and variety of voice-experiences, and report preliminary findings in healthy voice-hearers.

Methods: 22 healthy voice-hearers were recruited from a variety of sources, including psychics, mediums and spiritualists. Some of them worked in a professional or quasi-professional capacity as mediums or channelers. They were administered the VOICES scale, which consists of 50 questions covering dimensions of voices that have been identified to be central to the experience

of hearing voices in both clinical and non-clinical populations The structure of the scale follows three themes, namely phenomenology of voices, beliefs and relationship with voices, and emotional and behavioural impact. Items were derived from existing scales and focus-groups help with experts by experience (both clinical and non-clinical voice-hearers), as well as consultations with academic and clinical experts. Items were worded using language that was acceptable and understandable to healthy voice-hearers, as well as a clinical population.
Results: Despite in many cases hearing voices daily, the sample reported remarkably little distress and generally found them to be pleasant. Overall they could usually control the onset and offset of their voices; they received positive and helpful guidance from the voices that usually spoke clearly and mostly comprehensibly with the same loudness as their own voices; believed that the voices have good intentions towards them, have trusting and supportive relationships with the voices that get better over time; and they lacked paranoid and threatening appraisals (i.e., the voices giving orders, insulting or putting down the voice hearers, trying to cause problems, making the person feel ashamed, stressed or threatened). Although there was some variety in their experience of voice-hearing, generally they considered hearing voices as part of normal human experience. Most interpreted their voices as spirits, and spoke of learning to understand, to manage, and even to train their experience of communicating with spirits in a manner that was productive for them.
Discussion: The VOICES scale was found to be a useful tool in assessing the different characteristics of voice-hearing in a non-clinical population. We hope its use will further our understanding of voice-hearing in a wide range of populations, ultimately to enable us to refine psychological interventions for people whose voices are distressing.

M52. COMPARISON OF FORMAL THOUGHT DISORDER IN ACUTE EPISODE OF SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

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Background: The aim of the study was to compare formal thought disorder (FTD) in an acute episode of schizophrenia and bipolar affective disorder (BP), and to detect FTD domains related with BP.
Methods: Patients with schizophrenia (n=34) who did not meet the standardized remission criteria, and patients with BP manic episode (n=20) were included in this cross-sectional study. The Positive and Negative Syndrome Scale, the Clinical Global Impression Scale, the Young Mania Rating Scale, and for FTD, the Thought and Language Disorder Scale (TALD) were applied. The association between FTD and diagnosis was analyzed by a logistic regression model which included TALD factors and diagnostic groups.
Results: The schizophrenia and BP groups were similar in terms of demographic characteristics, global illness severity and the objective positive factor score of TALD. But the schizophrenia group had higher scores in the objective negative and subjective negative factors ($p < 0.001$, $p < 0.001$, respectively). The BP group had a higher score in the subjective positive factor ($p = 0.028$). The subjective positive factor was associated with BP diagnosis, and both subjective and objective negative factors were associated with schizophrenia in the regression analysis. In the BP group, the severity of manic episode was positively correlated with TALD score, and illness duration was negatively correlated with the subjective negative and subjective positive factors.

Discussion: Our findings suggest that objective positive FTD is shared in the acute episode of both schizophrenia and BP, but subjective positive FTD and negative FTD may be helpful to differentiate schizophrenia from BP.

M53. THE ROLE OF GENDER AND DEPRESSIVE SYMPTOMS ON DIFFERENTIATING PEOPLE WITH PSYCHOSIS OR DEPRESSION ON DIMENSIONS OF PERSONAL IDENTITY

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Background: People that suffer psychotic or depressive disorders have been reported to experience disturbances on self-personal identity. However, it remains unclear whether personal identity disruptions affect psychosis and depression in the same way, whether there are disorder-specific alterations, or the specific impact that depressive symptomatology may have on the personal identity of patients with psychosis. Moreover, to our knowledge, it is not known how gender affects the dynamics of personal identity in psychosis and depression.
Methods: Eighty-five adults who met the criteria for a psychotic spectrum disorder were matched by age with 85 adults with a diagnosis of major depression and 85 non-clinical adults as a control group. Dimensions of personal identity were assessed in all groups using the Repertory Grid Technique. Data was collected also on depressive symptoms (all groups), general functioning (clinical groups) and psychotic symptoms (psychosis group). The groups were compared using a multivariate factorial analysis of variance, with the personal identity dimensions as the dependent variables, and group and gender as the between-subject factors. A regression analysis was used to explore the specific impact of depression and functioning in each group.
Results: Our findings evidenced that discrepancies of self were higher in psychosis and depression than in controls, and were associated with having more depressive symptoms. Interpersonal dichotoous thinking was more common in women in both clinical groups. Women with psychosis showed higher ideal-others discrepancy. In contrast, men with psychosis had a poorer and simpler structure of personal identity than their female counterparts.
Discussion: Interventions focusing on self-discrepancies could be applied transdiagnostically to psychosis and depression. Women with psychosis might be the group most affected by feelings of resentment. Women with psychosis or depression may benefit from working therapeutically with the use of more modulated ‘‘shades of grey’’ in evaluations of self and others. Men with psychosis have a greater need for the development of the differentiation of representations of self and others and on incorporating more meaningful dimensions.

M54. THE CHARACTERISTICS OF SOCIAL ANXIETY, STIGMA, SHAME AND SAFETY (DEFENCE) BEHAVIOURS IN ASSOCIATION WITH PARANOIA AMONGST PEOPLE WITH A DIAGNOSIS OF SCHIZOPHRENIA

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Background: Although social anxiety disorder (SAD) is a common comorbidity in schizophrenia, but there is no current advice on the use of psychological interventions in treating SAD. Understanding mechanisms underlying both social anxiety and paranoia could help improve effective treatments. This study aimed to investigate mediators of the relationship between social anxiety and paranoia in people with schizophrenia. We asked whether negative social appraisals: stigma or shame (hypothesis1); and safety behaviours: social avoidance or in situ defence behaviours (hypothesis2) are mediators of the social anxiety and paranoia process.

Methods: A cross-sectional study was conducted at the outpatient department of a tertiary hospital in Thailand (January–April 2020). Demographic data including social anxiety, paranoia, depression, shame, stigma, social avoidance and in situ defence behaviours were collected. Associations of social anxiety in predicting paranoia were investigated using linear regression. Mediation analysis was used to test indirect effects of mediators. 10,000 bias-corrected bootstrap samples were performed to estimate 95% confidence intervals of the indirect effect.

Results: 113 (59.3% male) participants with mean age 44.2 (SD 13.1) years old were eligible. The expected linear relationship between social anxiety and paranoia was found. Controlling for age, gender and depression, shame (B -0.75, p=0.031) and stigma (B 0.88, p=0.022) as well as in situ defence behaviours (B 0.47, p=0.002) were significantly associated with predicting paranoia. As for the multiple mediation analyses co-varying for depression, higher social anxiety was significantly related to higher paranoia through in situ defence behaviours (indirect effects (ab)=0.11, 95%CI 0.0395 to 0.1959; a=0.21, p<0.001; b=0.50, p<0.05; c'=-0.04, p=0.55; and c=0.10, p=0.14) (hypothesis2). Stigma and shame (hypothesis1) did not show significant indirect effects.

Discussion: In people with schizophrenia, paranoid symptoms were significantly associated with social anxiety, and could be predicted by negative social appraisals (shame and stigma) as well as safety behaviours (in situ defence behaviours). Only safety behaviours, particularly the in situ defence behaviours, mediated the social anxiety and paranoia relationship. Targeted psychological intervention focusing on modifying safety behaviours could help reduce social anxiety and paranoia in people with psychosis. To demonstrate this promise, further interventionist-causal trials or treatment trials are needed.

M55. VOLATILITY ESTIMATES IN PEOPLE WITH SUBCLINICAL AND CLINICAL DELUSIONS

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Background: Current research indicates impaired probabilistic reward learning in individuals on the schizophreniform spectrum, particularly under conditions of high environmental uncertainty.

Recent accounts report increased estimates of environmental volatility in a sample at high risk for psychosis (Cole et al. 2020) and in individuals diagnosed with schizophrenia (Deserno et al. 2020). Yet, it remains unclear, whether deficits link to specific symptom dimensions or rather to an overarching predisposition for schizophreniform disorders. We aim to dissociate how the presence of a disorder versus delusional ideation impact learning under uncertainty. To this end, we adopted the computational modelling approach from Cole et al. (2020) and re-analyzed behavioral data during a probabilistic learning fMRI from individuals with and without subclinical and clinical delusions. This allowed us to differentiate whether alterations in learning behavior relate to the disorder in general or specifically to delusional ideation.

Methods: This study was preregistered in 07/2020 (https://aspredicted.org/8j4u7.pdf) and is a reanalysis of previously published data (Boehme et al., 2015; Deserno et al. 2020) using a novel computational modelling analytic approach introduced by Cole et al. 2020. Our sample (n=86, 29.2 ± 8.9 y, 32 females) comprised healthy participants (HC) with high (n=23) and without delusional ideation (n=24), participants with diagnosed schizophrenia (SZ) with (n=18) and without delusions (n=21). Delusional ideation was determined with Peters Delusion Inventory (Peters et al., 2004) in HC and with the P1 item of the Positive and Negative Syndrome Scale (Kay et al., 1987) in SZ. Participants performed a reversal-learning task with stable and volatile task phases (Boehme et al., 2015; Deserno et al. 2020). Behavioral choice data was fitted within the prespecified model space of Cole et al. 2020. Using Bayesian Model Selection, we evaluated six learning models and focused on the best fitting model, which was a 3-level Hierarchical Gaussian Filter (HGF). This model formalizes learning as a multi-level process and considers different types of uncertainty about the environment. Additionally, the model included an equilibrium parameter that attracts volatility estimates towards a subject specific constant. We compared the free parameters from the best fitting model between groups using a 2x2 MANOVA with the factors "delusion" and "disorder".

Results: The 3-level HGF with the equilibrium parameter provided best fit as indicated by a protected exceedance probability of 90.46%. There were no parameter differences between participants with and without delusion and no delusion by disorder interaction. We found a significant effect of disorder ($F(7,76) = 2,80$, $p = .012$) and post-hoc tests revealed lower estimates for (β) inverse decision temperature ($F=4.62$, $p=.034$) in SZ versus HC. We observed a statistical trend that the (m3) equilibrium parameter was higher ($F=3.62$, $p=.061$) in SZ. Lastly, we observed a trend for lower (ϑ) meta-volatility estimates ($F=3.48$, $p = .066$; determines the tonic update of beliefs about the environmental volatility) in SZ.

Discussion: Our result: suggest that computational parameters to formalize probabilistic learning are related to the general presence of a manifest schizophrenia disorder. We observed no parameter differences between individuals with versus without delusional ideation. However, computational parameters that indicate increased choice stochasticity and estimated environmental volatility were greater in the patient group, no matter if they experienced delusional ideation. We will examine task-related fMRI data in future analyses to evaluate associated neural activity.

M56. HETEROGENEITY OF SOCIAL - COGNITIVE IMPAIRMENTS ACROSS SCHIZOPHRENIA AND AUTISM

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Background: Autism spectrum disorders (ASD) and schizophrenia are both conceptualized as neurodevelopmental disorders with different times of onset but with extensive overlap in psychopathology, neurobiology, genetics, and various risk factors. In both conditions, impairment in social - cognitive abilities is considered among the hallmark symptoms of disorder. Previous studies found similar magnitudes of deficit in social - cognitive abilities in both clinical groups; however, it remains unclear whether social cognitive impairments are evenly distributed across these populations or if subgroups with different levels of impairment may exist within these conditions.

Methods: The sample consisted of 72 patients with schizophrenia and 94 with ASD. A social cognitive battery spanning the domains of theory of mind, emotion recognition, social perception, and attributional styles was administered. Raw data in clinical groups were transformed into Z - scores based on normative values. A Latent Profile Analysis (LPA) on standardized values was then carried out in order to identify homogeneous subgroups (participants with similar response patterns across tasks) in the combined sample of patients with ASD and SCZ. Subgroups were then compared in functional capacity, neurocogniton, and IQ.

Results: Based on the LPA, we identified four distinct subgroups. Two groups showed normal/intact (58 and 37 participants) performance across the majority of social cognitive tasks. The only difference between these intact groups was that the smaller one had significantly higher Hostility bias and Blame scores. Participants with ASD more often had overall intact performance (46.8% of all ASD). In contrast, more intact SCZ patients were in the group with the increased hostility and blaming bias (36.1% of all SCZ). The group with moderate impairment across tasks consisted of 46 participants, (20 SCZ and 26 ASD) and the group with severe impairment had 25 (12 SCZ and 13 ASD) participants. Based on our results, approx. 43% of the whole sample showed moderate to severe SC impairment, and the prevalence of moderate and severe impairment was comparable across clinical groups. Overall, the moderate and severe groups showed larger neurocognitive deficits, lower IQ, and lower functional capacity.

Discussion: Our results support previous studies which found similar magnitudes of social cognitive deficits across ASD and SCZ. An important distinction between intact groups was elevated levels of social cognitive biases, which were more typical for patients with SCZ. This pattern might be due to higher levels of paranoia in the SCZ sample. Participants with moderate to severe impairment also showed lower functional capacity. Deficits in social cognition were robustly tied lower IQ scores and cognitive impairment.

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M57. PREDICTION MODEL FOR PSYCHOSIS TRANSITION AMONG CHINESE INDIVIDUALS WITH AT-RISK MENTAL STATE IN HONG KONG

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Background: The prodromal stage of psychosis represents a critical window for pre-emptive intervention to mitigate the risk of illness progression and functional deterioration. Yet, research has suggested that diagnostic manuals for at-risk mental state (ARMS) only demonstrated acceptable prognostic accuracy. Identifying specific factors associated with the imminent onset of psychotic episodes among the ARMS population, therefore, may allow better detection of psychosis risk and optimize patients' clinical outcomes.

Methods: One hundred and thirty-two help-seeking individuals aged 15 to 40 years with ARMS ascertained using Comprehensive Assessment of At-Risk Mental State (CAARMS) criteria were recruited from a specialized early psychosis service in Hong Kong. Assessments entailing clinical symptoms, psychosocial functioning, and a brief cognitive battery were conducted at baseline. Transition to psychosis was verified through diagnostic interview and medical record review within the follow-up period. A machine-learning approach using the Least Absolute Shrinkage and Selection Operator (LASSO) for Cox proportional hazards model was adopted in the development and validation of the prediction model.

Results: At 30 months, the overall transition rate was 18.9%. The final model predicted transition to psychosis with an area under the receiver operating curve (AUC) of 0.790 (95% CI: 0.688, 0.891), and Harrel concordance index of 0.703. Positive predictors of psychosis transition included age and CAARMS positive symptom severity, and negative predictors included psychosocial functioning and the presence of comorbid psychiatric conditions. Internal validation of the predictive model was performed using 100 bootstrap resamples. The calibration slope obtained was 1.008, which did not differ significantly from 1 (95% CI: 0.975, 1.04), indicating good calibration. The prognostic index generated from the model stratified the sample into three risk classes with significantly different Kaplan-Meier survival curves, with the high-risk class demonstrating a significantly higher transition rate (54.5%) than the intermediate (13.0%) and low (5.6%) risk class at 30 months.

Discussion: The integration of baseline clinical and demographic characteristics provides an enriched assessment for psychosis transition risk. The subsequent stratification of ARMS service-users into distinct risk categories may facilitate future development of individualized intervention strategies to ameliorate or even prevent progression to psychosis among at-risk populations. Further large-scale Chinese ARMS sample is required to externally validate the our preliminary-derived prediction model for psychosis transition.

M58. THE COURSE AND CONCOMITANTS OF DEPRESSION IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS: A 24-MONTH LONGITUDINAL STUDY

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Background: Depressive symptoms are common in schizophrenia and have been associated with both favourable and unfavourable outcomes. We studied the longitudinal course of depressive symptoms and explored their temporal relationships with other manifestations of the illness and its treatment.
Methods: This longitudinal cohort study included 126 minimally treated patients with first-episode schizophrenia spectrum disorders treated with a long-acting antipsychotic over 24 months. Depressive symptoms were assessed at three monthly intervals using the Calgary Depression Scale for Schizophrenia and changes over time were assessed using linear mixed-effect models for continuous repeated measures.
Results: Depressive symptoms were most prominent at baseline with highly significant reductions during the first three months of treatment and maintenance of improvement thereafter. Most improvement occurred with antipsychotic treatment alone, with few patients requiring additional antidepressants. We also found that depressive symptoms were associated with positive symptoms, better insight and poorer quality of life, but not with negative symptoms, extrapyramidal symptoms, substance use or cumulative antipsychotic dose.
Discussion: During the early phase of illness, depressive symptoms respond well to antipsychotic medication. There were few differences between patients who met criteria for a depressive disorder during the acute phase of treatment and those in the post-acute phase.

M59. PRELIMINARY ANALYSIS ON THE PREVALENCE OF SUBCLINICAL PSYCHOTIC SYMPTOMS AND PSYCHOTIC DISORDERS AMONG CHINESE YOUTH IN HONG KONG: HONG KONG YOUTH EPIDEMIOLOGY STUDY (HKYES) OF MENTAL HEALTH

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Background: Subclinical psychotic symptoms (PS) are common in youths and are associated with functional impairment, lower quality of life and comorbid psychopathology. Notably, subclinical PS may be associated with an increased risk for psychotic disorders, which includes but not limited to schizophrenia, constituting one of the highest disease burdens in the world. However, the prevalence of subclinical PS among adolescents and young adults has not been well studied. This study aims to estimate the lifetime and period (12-month) prevalence of subclinical PS and lifetime prevalence of psychotic disorders among community youths in Hong Kong.
Methods: Hong Kong Youth Epidemiology Study of Mental Health (HKYES) is an ongoing territory-wide, population-based study examining mental health condition of 4500 Chinese youths aged 15-24 years in Hong Kong. Around 1500 participants have been recruited until now. The presence of subclinical PS was assessed by the Psychosis Module of WHO Composite International Diagnostic Interview (CIDI 3.0). The Psychosis Module of CIDI accesses several types of psychotic symptoms, including visual hallucination, auditory hallucination, mind control, thought insertion or withdrawal, persecutory beliefs and ideas of reference. The Chinese version of Psychosis Module was used in the study. Participants with lifetime diagnosis of psychotic or bipolar disorder, previous history of antipsychotic, or family history of psychotic or bipolar disorder, were excluded. Participants who endorsed one or more of the CIDI 3.0 Psychosis Module

items are invited for phase II interviewed-based diagnostic ascertainment based on DSM-5 criteria to verify diagnosis of psychotic disorder.
Results: Among 1500 youths, the lifetime prevalence of subclinical PS was 13.2% (n=199), while the 12-month prevalence was almost half of the lifetime prevalence (6%, n=90). Among participants with subclinical PS in 12-month, 20% (n=18) of them endorsed at least two symptoms. When focusing on individual type of psychotic symptoms, 73.3% (n=66) of participants with subclinical PS displayed symptom of auditory hallucination, 23.3% (n=21) with visual hallucination, 13.3% (n=12) with thought insertion or withdrawal beliefs, 10% (n=9) with mind control beliefs, 10% (n=9) with persecutory beliefs and 3.3% (n=3) with idea of reference. The lifetime prevalence of any psychotic disorder in the recruited sample was 1.3% (n=20).
Discussion: Our lifetime prevalence of subclinical PS is in the higher end of those reported in earlier studies. Discrepancies between lifetime and 12-month estimates of subclinical PS indicate that this subclinical status fluctuates over time, with subsequent remission in at least half of the subclinical PS sample. Ongoing data collection of HKYES will help verify our preliminary findings regarding prevalence of subclinical PS and psychotic disorders. Further investigation is warranted to identify factors predictive of persistence of subclinical PS over time.

M60. SOCIODEMOGRAPHIC AND CLINICAL PREDICTORS OF DELAY TO EARLY INTERVENTION FOR PSYCHOSIS SERVICE

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Background: Adults with a first episode of psychosis are recommended to start treatment in early intervention in psychosis services (EIS) within 2 weeks of referral (NICE 2015). We investigated the influence of sociodemographic and clinical characteristics on delay to reaching EIS and the length of stay (LOS) with EIS.
Methods: We used incidence data linked to the Clinical Record Interactive Search - First Episode Psychosis (CRIS-FEP) study, of 558 people presenting to the South London & Maudsley NHS Trust. We followed the patients from May 2010 to March 2016. At the time of our study, people aged 18-35 years old were eligible to receive an EIS. We performed multivariable Cox regression to estimate hazard ratios of delay to and LOS with EIS by sociodemographic and clinical characteristics, controlling for confounders.
Results: Of the 558 incident cases, 343 were eligible for receiving an EIS. Of these 229 patients received an EIS and 21 % did not. Overall, the median delay to EIS was 120 days (interquartile range (IQR); 15-1668) days; and median length of stay with an EIS was 385 days (IQR: 124 – 863). The adjusted hazard ratio (95%CI) showed that gender (women: 0.58; (0.42-0.78)) and ethnicity (Asian: 0.55; (0.28-1.08)), ('Other': 0.47; (0.23-0.98)) were associated with increased delay to EIS. However, university education 1.91 (1.20-3.04) and living with friends/family 1.62 (1.11-2.37) were associated with reduced delay to EIS. Previous service use was both associated with increased delay to EIS 0.46 (0.30-0.69) and prolonged LOS with EIS 0.79 (0.56-1.12).
Discussion: Initiatives that ameliorate indicators of social disadvantages are needed to reduce delay to EIS.

M61. OPEN BOARD

M62. ASSOCIATION OF AIR POLLUTION EXPOSURE WITH MENTAL HEALTH SERVICE-USE AMONG INDIVIDUALS WITH FIRST EPISODES OF PSYCHOTIC AND MOOD DISORDERS: A RETROSPECTIVE COHORT STUDY

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Background: Ambient air pollution is estimated to cause 482,000 premature deaths a year in the World Health Organization's (WHO) European region alone, at a cost of $1.575 trillion. These estimates are based on impacts on cardiorespiratory diseases, but emerging evidence suggests that air pollution can also adversely affect the brain and increase risk for psychiatric disorders such as schizophrenia and depression. However, the longitudinal role of air pollution exposure in mental health service-use (an indicator of illness severity and relapse) among individuals with first episodes of psychotic and mood disorders is unknown.

Methods: We conducted a retrospective cohort study in London, UK, using electronic clinical records from a large secondary mental healthcare provider: South London and Maudsley NHS Foundation Trust (SLaM). Service-users aged ≥15 years who had first contact with SLaM for psychotic (F20-F29) and mood (F30-F39) disorders in 2008-2012 and resided within the four-borough catchment area (Southwark, Lambeth, Lewisham, Croydon) were included (N=13,887). High-resolution (20x20 metre) estimates of nitrogen dioxide (NO2), nitrogen oxide (NOx), and particulate matter (PM2.5 and PM10) were linked to residential addresses of service-users. Inpatient days and community mental health service (CMHS) events were recorded over 1-year and 7-year follow-up periods. Associations between air pollutants and mental health service-use were examined using negative binomial regression models. We controlled for numerous potential confounds including season, year, gender, ethnicity, age, marital status, population density, deprivation, social fragmentation, and ethnic density. We also conducted multiple imputations to handle missing covariate data, and calculated E-values to evaluate unmeasured confounding.

Results: After full covariate adjustment, there was strong evidence that interquartile range increases in NO2, NOx, and PM2.5 were associated, respectively, with 18% (95% CI=4%–34%), 18% (95% CI=4%–34%), and 11% (95% CI=3%–19%) increased risk for inpatient days after 1 year. Similarly, interquartile range increases in NO2, NOx, PM2.5 and PM10 were associated, respectively, with 32% (95% CI=25%–38%), 31% (95% CI=24%–37%), 7% (95% CI=4%–11%), and 9% (95% CI=5%–14%) increased risk for CMHS events after 1 year. There was evidence of dose-response associations, whereby risk increased incrementally across quartiles of exposure. For instance, service-users in the second, third, and fourth quartiles (versus first quartile) of NO2 exposure had a 16% (95% CI=10%–23%), 32% (95% CI=22%–42%) and 48% (95% CI=36%–62%) increased risk for CMHS events, respectively, after 1 year. These associations persisted at 7 years follow-up. We conducted specificity analyses according to diagnosis (psychotic versus mood disorders) and exposure period (quarterly versus annualized pollution levels).

Discussion: Higher residential air pollution exposure is associated with increased mental health service-use among people recently diagnosed with psychotic and mood disorders. Assuming

causality, interventions to reduce air pollution exposure could improve mental health prognoses and reduce mental healthcare costs.

M63. IDENTIFYING DATA-DRIVEN, MULTIVARIATE RELATIONSHIPS BETWEEN FUNCTIONAL CONNECTIVITY AND SOCIAL COGNITIVE PERFORMANCE ACROSS SCHIZOPHRENIA SPECTRUM DISORDERS AND HEALTHY CONTROLS

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Background: Individuals with schizophrenia spectrum disorders (SSDs) often exhibit social cognitive deficits, with meta-analytic results showing a stronger relationship between community functioning and social cognition than non-social cognition. Social cognition can be divided into lower- and higher-level processes, subserved by partially dissociable neural networks. Abnormal neural activation in these networks during social tasks and atypical functional connectivity have been observed in people with SSDs. However, recent work suggests that neural activation patterns during social processing may relate to cognitive performance rather than diagnosis across SSDs and healthy controls. Our objective was to identify relationships between functional neural connectivity during a social processing task and social and non-social cognitive performance across a large group of individuals with SSDs and healthy controls using a data-driven, multivariate approach. We hypothesized that functional connectivity in relevant regions would covary with specific behavioral domains, perhaps reflecting the delineation of lower- and higher-level social cognitive and non-social cognitive constructs.

Methods: Data come from the Social Processes Initiative in the Neurobiology of the Schizophrenia(s) (SPINS) study. Across three sites, 204 people with SSDs and 159 healthy controls completed the Empathic Accuracy task during functional magnetic resonance imaging, a naturalistic social processing task. Participants also completed measures of lower- and higher-level social cognition and non-social cognition outside the scanner. Partial least squares correlation (PLSC) was used to identify latent variables capturing multivariate brain-behavior relationships with maximal covariance from a 'brain set' of functional connectivity metrics (between 360 cortical regions of interest) and a 'behavior set' of cognitive performance measures (9 social cognitive and 6 non-social cognitive metrics). Permutation testing (1000 iterations) and bootstrap resampling (1000 iterations) were used to evaluate the significance of identified latent variables, and the reliability of contributing brain and behavior measures, respectively.

Results: PLSC followed by permutation testing identified two significant latent variables ($p < .05$), explaining 73.3% and 11.9% of the variance, respectively. The first latent variable was characterized by an association between connectivity across much of the brain, including frontal, occipital, temporal, and parietal regions, and better performance across both lower- and higher-level social and non-social cognitive measures. The second latent variable was characterized by an association between frontal-parietal and temporal-parietal connectivity, among other regions, and worse social cognitive performance on a subset of lower-level social cognitive measures.

Discussion: Our results suggest that patterns of functional connectivity during social processing are associated with both social and non-social cognitive performance across people with SSDs and healthy controls. In particular, a general pattern of increased connectivity may be related to better

overall cognitive performance across groups. Interestingly, lower-level social cognitive performance also appeared to be negatively associated with increased connectivity in a subset of regions, indicative of functional connectivity patterns that may delineate this aspect of social cognitive processing. The data-driven delineation of social cognitive constructs is of particular interest given its relationship with functioning and the need to identify treatment targets in SSDs.

M64. QUANTIFIED WORD CONNECTEDNESS IN SCHIZOPHRENIA USING WORD2VEC

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Background: Language abnormalities are a core symptom of schizophrenia-spectrum disorders and may serve as a potential marker for diagnosis. Advances in natural language processing enable the quantitative assessment of connectedness of language. In spoken language of people with schizophrenia-spectrum disorders, connections in meaning between words may be lower. Here, we investigate connectedness of spontaneous speech in schizophrenia-spectrum patients using a semantic space model and compare them to healthy controls.
Methods: 50 patients with a schizophrenia-spectrum disorder and 50 healthy controls were included at the University Medical Center Utrecht, the Netherlands. Participants (mean age 30.2, mean duration of illness 2.6 years) were adult native Dutch speakers. Using a semi-structured interview, spontaneous speech was recorded and transcribed. Language connectedness in a word2vec model was calculated using word similarity over consecutive words, using moving windows of increasing sizes (2 to 20 words). Mean, minimal and variance of similarity were calculated per window size and used in a random forest classifier to distinguish patients and healthy controls.
Results: Classification of patients and healthy controls based on connectedness was possible with 85% cross-validated accuracy, with 84% specificity and 86% sensitivity. Feature importance was determined using classifier Gini score to examine word connectedness over window sizes and showed significant effect of word variance and minimum coherence. This signal was present both in word-to-word as well as sentence-level connectedness. The features that best discriminated patients from controls were variance of similarity at window sizes between 5 and 10.
Discussion: We show robust findings of impaired connectedness in spontaneous language of patients with schizophrenia-spectrum disorder in word2vec models, applicable for classification. The effects were most prominent at the level of sentence connectedness. New approaches in the fast-developing field of natural language processing enable real-time analysis of large-scale, subtle aspects of language. The high sensitivity and specificity of this method together with high tolerability argue for the use of automatic language analysis as a digital assistant in diagnosing schizophrenia-spectrum disorders.

M65. ASSESSING ABERRANT BRAIN STATE DYNAMICS IN HALLUCINATION PRONE INDIVIDUALS WITH HIDDEN SEMI-MARKOV MODELS

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Background: Auditory verbal hallucinations (AVH) are reported in clinical (i.e. Schizophrenia, SZ) and non-clinical populations, indicating that they lie on a continuum ranging from healthy to pathological, captured by hallucination proneness (HP). In both populations, AVH links to aberrant temporal dynamics in cortical networks during rest. These temporal dynamics can be captured using Hidden Semi-Markov Models (HSMM), which re-expresses continuous time-series data as a set of recurring discrete hidden brain states. Each state captures a distinct brain activity pattern, thus providing insight into underlying dynamic network interactions. Currently, we lack insight into brain state dynamics in hallucination-prone individuals using an HSMM. Thus, the present study used this approach to examine how HP relates to brain dynamics in resting-state EEG.
Methods: Ten minutes of resting-state EEG (5 minutes eyes-open and eyes-closed respectively) data were recorded in healthy participants varying in HP (e.g.Launay Slade Hallucination Scale). Modeling was based on the Brain State Dynamics (BSD) toolbox implemented in MATLAB, which is developed for dynamic brain state allocation of multivariate time-series data (e.g. EEG) into a finite set of discrete hidden states, each representing a characteristic quasi-stable pattern of functional connectivity. The HSMM was applied to concatenated, cleaned, and preprocessed EEG amplitude envelopes, resulting in six shared hidden brain states. We focused on two HSMM parameters i) fractional occupancy (i.e amount of time that is occupied by a state) and ii) state occurrence (i.e the total number of times a brain state is active). Both parameters were analyzed as a function of HP (i.e. total LSHS score) using Spearman's rank correlation coefficient.
Results: Preliminary correlational analyses of 10 participants (8 females; mean age = 22.2; age range = 20-27) revealed a trend towards a positive relationship between HP and state 2 parameters. More specifically, the mean occurrence of state 2 was positively correlated with HP ($\rho(9) = 0.750$, $p = 0.012$), whereas the correlation between HP and state 2 mean fractional occupancy showed a trend towards a positive correlation ($\rho(9) = 0.622$, $p = 0.055$). Correlations between the model parameters of the remaining 5 states and HP were not significant.
Discussion: The current pilot results (considering all limitations) provide preliminary novel evidence on the neural mechanisms underlying AVH. In particular, a positive correlation between HP and state 2 parameters point towards the fact that HP may alter temporal dynamics of the brain, perhaps resulting from impaired connectivity within/between resting-state networks. However, given the small sample size and recording times, we aim at replicating the findings using a larger data set (in progress). This research is the first to assess brain state dynamics linked to HP in a non-clinical sample using an HSMM to generate a predictive model for potential risk markers.

M66. SMALL WORDS THAT MATTER: LINGUISTIC STYLE AND CONCEPTUAL DISORGANISATION IN UNTREATED FIRST EPISODE SCHIZOPHRENIA

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Background: This study aimed to shed light on the linguistic style affecting the communication-discourse in First Episode Schizophrenia (FES) by investigating the analytical thinking index in relation to clinical scores of conceptual and thought disorganization (Positive and Negative Syndrome Scale, PANSS-P2 and Thought and Language Index, TLI).
Methods: Bayesian modeling.
Results: We report three major findings: (1) FES subjects showed reduced analytical thinking, exhibiting a more narrative linguistic style than healthy control (HC) subjects (Bayes factor, BF10 > 1000), despite using the same proportion of function and content words as HCs; (2) the lower the analytic thinking score, the higher the symptoms scores of conceptual disorganization (PANSS-P2, BF = 22.66) and global disorganization of thinking (TLI, BF10 = 112.73); (3) The linguistic style is a better predictor of conceptual disorganization than the cognitive measure of processing speed in schizophrenia.
Discussion: These findings, on the one hand, provide an objectively detectable linguistic style in schizophrenia that requires no clinical judgment; on the other hand, they provide a crucial insight into the primacy of linguistic structural disruption in clinically ascertained disorganised thinking in schizophrenia. Furthermore, PANSS-P2 and TLI disorganisation scores are notably influenced by this linguistic style, rather than cognitive deficits such as processing speed reduction. Our work contributes to an emergent body of literature on the linguistic basis of the psychopathology of schizophrenia. At an utilitarian level, this has implications for improving social and educational outcomes in this illness.

M67. NEURAL ACTIVATION TO EMOTION AT FIRST PSYCHOSIS EPISODE AND CLINICAL HIGH RISK FOR PSYCHOSIS – AN IMAGE-BASED META-ANALYSIS OF FMRI STUDIES

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Background: A consistent finding in patients with schizophrenia is that brain activation to emotional stimuli compared to neutral stimuli is lower than that in healthy controls. It is currently unclear when this abnormality develops. While several studies reported similar findings in patients with a first episode of psychosis (FEP), a recent systematic review and meta-analysis of this evidence is warranted. Furthermore, it remains unclear whether abnormal brain response to emotion is present in people at clinical high risk for psychosis (CHRp). The present study aimed to synthesise the existing functional magnetic resonance imaging (fMRI) studies of emotion processing in FEP and CHRp populations via an image-based meta-analysis, supported by a systematic review.
Methods: The MEDLINE database was searched for published articles employing an emotion processing task during a functional neuroimaging scan, in either people at CHRp or with an FEP compared to healthy controls until 3 July 2019. Whole-brain, unthresholded group comparison images (t-maps) provided by study authors were used for meta-analysis with Seed-based d Mapping v6.21. An initial uncorrected threshold of $p<0.005$ was applied, and subsequently family-

wise error correction was applied with a threshold-free cluster enhancement (TFCE) $p<0.05$. Region of effect and the p-value reported in the original article were extracted and summarised in a systematic review.

Results: The database search returned 4,189 articles. Of these, 19 relevant fMRI papers were found, and their references were screened. Twelve articles were eligible for meta-analysis (2 of which included both a FEP and a CHRp sample), and 16 were included in the systematic review. The FEP meta-analysis was performed on 4 studies, with a total of 48 patients and 73 healthy controls. The CHRp meta-analysis included 4 studies, with a total of 45 individuals at CHRp and 48 healthy volunteers. The FEP meta-analysis returned an extensive cluster of hypoactivation to emotional compared to neutral stimuli compared to healthy controls, including the left amygdala ($Z=-4.027$, $pTFCE<0.001$) and anterior cingulate cortex ($Z=-3.611$, $pTFCE<0.001$). These findings were complemented by the systematic review, which found convergent hypoactivation in these regions. No differences in neural activation were returned in the CHRp meta-analysis after family-wise error correction. Similarly, the systematic review found evidence of only one convergent result of increased neural activation in the posterior cingulate cortex, reported by two studies.

Discussion: The finding of decreased activation in a large cluster including the amygdala and anterior cingulate cortex to emotional compared to neutral stimuli in FEP patients relative to healthy controls was consistent with studies in chronic schizophrenia. This suggests that abnormalities in functional brain response to emotion observed in schizophrenia are already present at the first episode of psychosis. A lack of effects returned by the CHRp meta-analysis was mirrored by the paucity of convergent results reported by individual articles. Future studies into the putative effects of the heterogeneity of the CHRp population on neuroimaging Results: may elucidate the nature of emotional abnormalities in psychosis risk.

M68. FMRI-BASED CLOSED-LOOP NEUROFEEDBACK TO RELIEVE DRUG-RESISTANT HALLUCINATIONS IN SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is a severe psychiatric condition, primarily treated with antipsychotics. However more than 25% of SCZ patients do not respond to medication. Refractory symptoms negatively impact autonomy and social functioning, leading the medical and scientific community to search for alternative non-pharmacological therapies. Among these approaches, neurofeedback (NF) has risen as a promising option for individuals struggling with hallucinations (HA). NF allows for voluntary/self-directed control over neural activity and when the average fMRI signal calculated over (a) target brain area(s) is fed back to subjects in real time, it can be used to self-regulate neuronal response or cognitive strategies. In this context, however, identifying the brain network to modulate, remains very challenging, since HA are transient events which cannot be easily detected using conventional fMRI approaches. Here, we propose to rely on a multivariate decoder to address this issue. This approach will be tested in the future in a randomized control trial (RCT).

Methods: The first step of the project was to validate the decoder. Using a capture method previously described (Jardri et al, 2013 ; Leroy et al, 2017), we labelled the fMRI time-course of

60 participants who hallucinated during fMRI acquisition, from the onset of the episode (TRANS period), to the hallucinatory state (ON period) and its extinction (END). These data were split in a training-set and a test-set, and used to build a machine-learning algorithm able to detect hallucinatory-related periods. This algorithm was cross-validated on the independent test-set. The second step of the project will be to conduct a double-blind RCT to test the efficacy of our decoder-based NF vs sham to reduce HA severity (trial #20.11.20.57253). The target sample will consist of 70 drug-resistant SCZ patients, half of which will receive active NF (n=35), and the remaining half will receive random feedback (n=35). The outcome measures are HA severity and quality-of-life scores. We expect at least a 25% reduction in HA severity in the active group compared to sham.

Results: Our fMRI decoders were found to reliably detect the 'TRANS' period (dePierrefeu et al, 2018), as well as the 'ON' period for HA (Fovet et al, in prep), with good performances: 0.79 and 0.92 AUC respectively. These findings are the basis for setting up an automatic detection of HA during fMRI recordings, as the preliminary step towards fMRI-based NF of HA. Recruitment for the RCT is still on-going.

Discussion: Using advanced fMRI capture methods, we determined that HA are associated with subtle and brain-wide patterns. The novel fMRI capture technology findings we present and describe here have two critical therapeutic implications: (i) they confirm that the network dynamics underlying HA can be captured with our novel multivariate machine-learning algorithm, and (ii) that we can provide appropriate coping feedback to the participants based on this online detection to help them take over the experience. Based on these findings, we have launched a trial in which we test if SCZ patients suffering from severe and refractory HA can be trained to maintain the brain state associated with the no-hallucination condition. This trial is the first to test the efficacy of a closed-loop state- fMRI guided NF procedure to relieve drug-resistant HA on the basis of functional state markers.

M69. BETA-FREQUENCY ELECTROPHYSIOLOGICAL BURSTS: BOLD CORRELATES AND ASSOCIATIONS WITH PSYCHOTIC ILLNESS

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Background: There is growing evidence for abnormal beta (13-30 Hz) oscillations in psychosis. In particular, the size of the increase in average beta power observed following a movement (post movement beta rebound, PMBR), recorded with imaging methods such as electroencephalography (EEG), is reduced in patients with schizophrenia and is inversely correlated with illness severity. Therefore, beta-band activity may reflect a fundamental neural process whose disruption plays a key role in the pathophysiology of psychotic illness. Recent work has found that changes in average beta power reflect changes in the probability-of-occurrence of transient bursts of beta-frequency activity, rather than sustained changes in beta activity. We used this insight with concurrently-collected EEG and functional magnetic resonance imaging (fMRI) to identify the

blood oxygenation level dependent (BOLD) correlates of beta-frequency activity, and compare these correlates between healthy controls and patients with psychotic illness.
Methods: EEG data were recorded simultaneously with BOLD data measured with 3T fMRI, whilst participants performed an n-back working memory task. We included seventy-eight participants – 32 patients with schizophrenia, 16 with bipolar disorder and 30 healthy controls. Beta bursts were identified in the EEG data using a thresholding method and burst timings were used as markers in an event-related fMRI design convolved with a conventional haemodynamic response function. A region of interest analysis compared beta-event-related BOLD activity between patients and controls.
Results: PMBR, measured as increases in beta burst probability or rate in the EEG data, was smaller in patients than controls. In patients, smaller PMBR size was associated with poorer social, occupational and global functioning, poorer performance on a cognitive task, and greater persistence of symptoms of disorganisation. In the BOLD data, during task blocks and intervening rest periods, beta bursts phasically activated regions implicated in task relevant content, and suppressed regions that were currently tonically active. Despite their smaller PMBR, patients showed greater, more extensive, beta-burst-related BOLD activation than controls.
Discussion: The observed BOLD correlates of beta bursts support a model in which beta bursts serve to re-activate task-relevant latently-maintained sensorimotor representations. Our Results: suggest that this process is dysregulated and inefficient in psychosis. We propose that abnormalities in the mechanism by which beta bursts co-ordinate the reactivation of task-relevant content lead to inaccurate sensorimotor forward modelling, working memory deficits, and ultimately signs and symptoms of disorganisation, and thus may underlie a "core deficit" associated with impairment and persisting symptoms.

M70. THE PROCESSING OF ANGRY FACES IN SCHIZOPHRENIA PATIENTS WITH A HISTORY OF SUICIDE: AN FMRI STUDY EXAMINING BRAIN ACTIVITY AND CONNECTIVITY

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Background: The high rates of suicidal behaviors (SBs) in psychiatric populations remain an important preoccupation to address. The literature reveals emotional instability as an important risk factor for SBs. However, the neural mechanisms underpinning this risk factor have never been investigated in schizophrenia patients with SBs. The following study implemented a task-based emotional processing functional magnetic resonance imaging (fMRI) paradigm to evaluate the activation and connectivity differences exhibited by schizophrenia patients with a history of suicide attempt (SA).
Methods: A sample of 62 schizophrenia patients with and without SA and 22 controls completed an fMRI emotional processing task, which included the visualization of dynamic angry facial expressions. Task-based connectivity was assessed using generalized psychophysical interaction analyses.
Results: During the processing of angry faces, suicidal schizophrenia patients displayed increased activation of the left median cingulate gyrus, left middle frontal gyrus, and left precuneus when compared to nonsuicidal schizophrenia patients and healthy controls. Whole-brain connectivity

analyses yielded an increased coupling of the left amygdala and right superior frontal gyrus in suicidal schizophrenia patients. Schizophrenia patients' hostility scores on the Positive and Negative Symptom Scale (PANSS) were significantly and positively correlated with the activity of the left median cingulate gyrus.
Discussion: When exposed to angry faces, suicidal schizophrenia patients demonstrate elevated activation of brain regions associated to executive functioning and self-processing, as well as aberrant fronto-limbic connectivity involved in emotion regulation. Our results highlight the neglected role of anger when investigating the neural alterations underpinning SBs in schizophrenia.

M71. METABOLIC EVOLUTION AND LIFESTYLE OF A COHORT OF PATIENTS WITH SCHIZOPHRENIA UNDER CLOZAPINE TREATMENT

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Background: Patients suffering from schizophrenia are characterized by a 15-year mortality gap compared to the general population. The main cause of premature death are medical conditions such as metabolic syndrome, type 2 diabetes mellitus or other chronic diseases of cardiovascular origin. The use of antipsychotics such as clozapine is associated with a rapid increase in weight and the development of metabolic and lipid disorders in certain predisposed subjects. In this context, the use of non-pharmacological strategies for weight control have become a key element of secondary prevention in people with schizophrenia. The main objective of this study is to evaluate the cardio-metabolic risk factors and the effectiveness of an intervention program in physical health aimed at a cohort of patients with schizophrenia receiving clozapine treatment to improve the dietary pattern and avoid antipsychotic-induced weight gain.
Methods: 31 patients diagnosed with schizophrenia under clozapine treatment were enrolled in a longitudinal pre-post intervention study. Patients were attending an outpatient mental health care facility in Barcelona, Spain. Metabolic syndrome factors, physical activity, diet, smoking habit, and prescribed medication were evaluated by means of a face-to-face interview and medical team registration. Subsequently, they were exposed to an 8-week group program of therapeutic education in healthy lifestyle. Food craving inventory (FCI Spanish version), questionnaires of frequency of food consumption, Mediterranean diet test (based on the Predimet test), International Physical Activity Questionnaire (IPAQ), Scale of Subjective Perception of Health and a Likert-scale of satisfaction in the lifestyle intervention were evaluated. All the measures described were evaluated at baseline; post-intervention and 3 months after it.

Results: Different in cardiovascular risk factors, displayed a significant reduction after the intervention and three months after completion. For anthropometric measurements, weight ($p \leq 0.001$; $p. \leq 0.010$) Body Mass Index (BMI) ($p \leq 0.003$; $p \leq 0.030$) displayed significant differences after completion and three months later. Waist ($p \leq 0.030$), Hip ($p \leq 0.015$) after completion and waits to hip ratio (WHR) ($p \leq 0.017$) after 3 months. For metabolic parameters High density lipoprotein (HDL) ($p \leq 0.036$; $p \leq 0.050$). For questionnaires, Adherence Questionnaires_DIETMED ($p \leq 0.011$; $p \leq 0.017$) was significant at end and after three months while IPAQ ($p \leq 0.017$) was only significant at the end of the group lifestyle therapy.
Discussion: Cardiovascular risk factors were significantly reduced after the intervention, however few parameters remained 3 months after the completion of the program. Our results suggest the effectiveness of the lifestyle intervention in patients with schizophrenia receiving clozapine treatment. Strategies to prevent weight gain and metabolic decline will help prevent premature cardiometabolic disease in this vulnerable population.

M72. FIXEL-BASED ANALYSIS REVEALS CHANGES IN WHITE MATTER MORPHOLOGY AND CORRELATES WITH PSYCHOPATHOLOGY AND COGNITION IN ANTIPSYCHOTIC-NAïVE, FIRST-EPISODE SCHIZOPHRENIA

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Background: Deviations in cerebral white matter (WM) can be detected in schizophrenia patients from the earliest phases of the disease. Findings in first-episode psychotic patients have been subtle and can be confounded by medication status and recreational substance use and may be compromised by methodological limitations. A novel method called fixel-based analysis (FBA) uses higher-order diffusion models to extract structural measures such as fibre density (FD), fibre-bundle cross-section (FC), fibre density and cross-section (FDC) that correspond to a specific WM fibre-bundle. FBA uses constrained spherical deconvolution in order to resolve crossing fibres and partial volume effects of grey matter and cerebrospinal fluid, making fixel-based metrics more specific and sensitive to WM alterations than previous methods.
In the primary analyses of the current study, we applied FBA to investigate group differences and associations with psychopathology and cognition in antipsychotic-naïve, first-episode schizophrenia patients compared to healthy controls (HCs). In secondary analyses, we investigated recreational substance use as a confounder.

Methods: We included 86 antipsychotic-naïve patients with first-episode schizophrenia and 112 matched HCs. Subjects were recruited as part of two comparable, consecutive cohorts. Participants were examined using 3T magnetic resonance diffusion-weighted imaging. Images were processed using a pipeline for FBA in the Mrtrix3 software. Nuisance variables included age, gender, cohort, and intracranial volume.

The cognitive domain of executive functioning was assessed using the Stockings of Cambridge (SOC) and Intra-Extra Dimensional Set Shift (IED) tests. In patients, psychopathology was rated with the Positive And Negative Syndrome Scale (PANSS).

The 'substance-free' subsample (62 patients, 104 HCs) consisted of participants who, on a lifetime basis, had used cannabis, opioids, stimulants, hallucinogens, or other illicit drugs less than once per month. Participants in the 'substance-use' subsample (24 patients, 7 HCs) had had at least a monthly use of one of the substances.

All FBAs have been corrected for multiple comparisons using family-wise error correction and a significance threshold of $p < 0.05$.

Results: Preliminary results of the primary analyses revealed lower FD in patients in the trunk of corpus callosum and caudally in the left corticospinal tract. Correlations between FC in the splenium of corpus callosum and IED showed significant interaction between patients and controls. Controls showed positive correlation and patients showed negative correlation.
In preliminary results of the secondary analyses, we found lower FC in substance-free patients compared to substance-free HCs in the anterior thalamic radiation and corticospinal tract, both bilaterally. In substance-free patients, we identified negative correlations between FC in cingulum and positive symptoms (right side) and hallucinatory behaviour specifically (bilateral). We found positive correlations between negative symptoms and FC in cingulum and forceps minor as well as FDC in left anterior thalamic radiation, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and forceps major.

Discussion: This study presents novel insights in WM structure in first-episode schizophrenia. Alterations within the corpus callosum may play a central role in the early phase of illness and seem related to executive functioning. Furthermore, examining only substance-free subjects may uncover the relationship between WM morphology and psychopathology in antipsychotic-naïve patients.

M73. PSYCHOTIC-LIKE EXPERIENCES, POLYGENIC RISK SCORES FOR SCHIZOPHRENIA, AND STRUCTURAL PROPERTIES OF THE SALIENCE, DEFAULT MODE, AND CENTRAL-EXECUTIVE NETWORKS IN HEALTHY PARTICIPANTS FROM UK BIOBANK

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Background: Schizophrenia is a highly heritable disorder with considerable phenotypical heterogeneity. Hallmark psychotic symptoms exist on a continuum stretching from non-clinical to clinical populations. Assessing genetic risk and psychotic-like experiences (PLEs) in non-clinical

populations and their associated neurobiological underpinnings can offer valuable insights into disease mechanisms. In schizophrenia, psychotic symptoms have been associated with functional and structural abnormalities in distinct brain networks. The salience, default-mode (DMN) and central-executive (CEN) networks are among those commonly implicated in the disorder (Menon, 2011; Palaniyappan et al., 2011). However, much less is known about how these networks are linked to PLEs and polygenetic risk for schizophrenia (PRSSZ) in the general population. Leveraging a large population cohort (UKBiobank) comprising information on PLEs, PRSSZ and brain imaging, we computed morphometric (cortical thickness, volume) and diffusion (fractional anisotropy, FA) properties of the regions and pathways belonging to the salience, DMN and CEN.
Methods: We leveraged a large population-based cohort (UKBiobank) including information on PLEs, polygenic risk scores for schizophrenia (PRSSZ) and multi-modal brain imaging in combination with network neuroscience. Morphometric (cortical thickness, volume) and water diffusion (fractional anisotropy) properties of the regions and pathways belonging to the salience, default-mode and central-executive networks were computed. For each subject, two networks were constructed, the number of streamline network connecting each pair of the 85 node pairs from the Desikan-Killiany atlas (Desikan et al., 2006).
Associations between PRSSZ, PLEs and white matter tract FA values, cortical thickness (CT) and volume (GMV) were calculated using linear regression models. We then estimated a structural equation model (SEM) for FA values, cortical thickness and volume. Latent score models were used to assess associations of PRSSZ with MRI parameters. Three latent factors were derived: a cortical thickness, a volume and an FA factor derived from all pathways connecting bilateral nodes. We matched participants by age and sex using a propensity score method for the PLEs analysis.

Results: PRSSZ was associated with a latent measure of cortical thickness across the salience network ($r = -0.069$, $pFDR = 0.033$). Within the salience network, significant negative associations were found between the CT of the right and left insula and auditory hallucinations ($\beta = -0.114$ and $\beta = -0.083$, $pFDR < 0.045$). For the DMN, a significant negative association was found between the GMV of the right supramarginal gyrus and delusions of reference ($\beta = -0.195$, $pFDR = 0.022$) and between persecutory delusions and GMV of the left pars orbitalis ($\beta = 0.219$, $pFDR = 0.021$). For persecutory delusions, there was a positive association with the CT of the right supramarginal gyrus ($\beta = 0.177$, $pFDR = 0.003$). We found that the linear association between PRSSZ and auditory hallucinations was significantly mediated by CT of the right insula (from sigma = 0.023 to sigma' = 0.004, CI [0.020, 0.127] with the right insular cortex mediating 82.6% of the association between PRSSZ and auditory hallucinations).
Discussion: These results are consistent with the hypothesis that higher genetic liability for schizophrenia is related to subtle disruptions in brain structure and predisposes to PLEs even among healthy participants. In addition, our study suggests that networks engaged during auditory hallucinations show structural associations with PLEs in the general population.

M74. WHITE MATTER MICROSTRUCTURE AND STRUCTURAL NETWORKS IN TREATMENT-RESISTANT SCHIZOPHRENIA PATIENTS AFTER COMMENCING CLOZAPINE TREATMENT: A LONGITUDINAL DIFFUSION IMAGING STUDY

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Background: Clozapine has a superior clinical effect in refractory schizophrenia, however its potential impact on white matter microstructure and neural networks is unclear. This study investigates such changes after 6 months of switching to clozapine in schizophrenia patients compared to controls, and whether any changes are related to clinical variables.
Methods: T1 and diffusion-weighted MRI images were acquired at baseline before commencing clozapine and after 6 months of treatment for 22 patients with treatment-resistant schizophrenia and 23 controls. The Tract-based spatial statistics approach was used to compare changes over time between groups in fractional anisotropy (FA). Changes in structural network organisation and subnetwork connectivity weighted by FA and number of streamlines were assessed using graph theory and network-based statistics.
Results: Patients displayed a significant reduction of FA over time ($p<0.05$) compared to controls in the genu and body of the corpus callosum and bilaterally in the anterior and superior corona radiata. There was no correlation between FA change in patients and changes in clinical variables or serum level of clozapine. There was no significant overall interaction between time, group and structural network global ($F(7,280)= 2.80; p=0.187$) or local ($F(15,600)= 0.747$, $p=0.737$) measures. No subnetwork was identified when testing for time by group interaction.
Discussion: This longitudinal study demonstrated progressive focal FA abnormalities in key anterior tracts, such as corpus callosum and corona radiata, but preserved brain structural network organisation in patients. The FA reduction was independent of any clinical measures and may reflect progression of the underlying pathophysiology of this malignant form of schizophrenia illness.

M75. EFFECTIVE CONNECTIVITY OF FRONTO-STRIATO-THALAMIC CIRCUITRY AND DIMENSIONS OF PSYCHOSIS-LIKE EXPERIENCES

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Background: Psychosis-like experiences (PLEs) in the general community are continuously distributed with clinical symptoms of psychosis, and therefore provide an opportunity for understanding the pathogenesis of psychotic illnesses. Fronto-striato-thalamic (FST) circuits are central to the expression of psychosis symptoms along the severity continuum. Investigation of PLEs and FST connectivity have reported mixed findings, potentially due to varying self-reports used to assess PLEs, which yield coarse estimations of symptom dimensions. Furthermore,

correlational methods have mainly been used to investigate FST connectivity, which cannot disentangle inter-regional causal influences within a brain network. This study aimed to derive high resolution measures of distinct PLE dimensions and to investigate differential associations between PLEs and causal interactions (i.e., effective connectivity) within FST systems in a large non-clinical sample.

Methods: Item response theory (IRT) was used to obtain robust estimates of underlying latent dimensions of PLEs from a battery of measurements, comprising 12 subscales from four psychometrically valid questionnaires, that was administered to 726 healthy participants recruited from the general community. Effective connectivity of the FST system comprising the ventral and dorsal circuits was estimated using spectral dynamic causal modelling (DCM) on resting-state fMRI data for a subset of 352 participants who underwent neuroimaging (156 males; mean age [range] = 23.38 [18–50 years]). The model of the FST systems included 47 connections linking 8 regions that spanned across the dorsal and ventral circuits, including the dorsolateral and ventromedial prefrontal cortices, dorsal caudate, nucleus accumbens, anterior hippocampus, amygdala, thalamus, and the midbrain. Separate Bayesian general linear models were used to assess associations between FST effective connectivity and dimensions of positive and negative PLEs.

Results: IRT analysis yielded nine specific dimensions of PLEs with good fit, consisting of four positive dimensions (delusions, hallucinations, cognitive disorganization, and body image aberration) and five negative dimensions (anhedonia, asociality, avolition, blunted affect, and alogia). Positive PLEs comprising subthreshold delusions, cognitive disorganization, and body image aberration were associated with connectivity that were distributed across the ventral and dorsal FST circuits, and were consistently associated with bottom-up striatal influences on thalamus. Subthreshold hallucinations were associated with top-down connectivity of the thalamus on the nucleus accumbens. Negative PLEs, namely anhedonia, asociality, avolition, and alogia, were associated with connectivity restricted to the ventral circuit. Blunted affect was not associated with dorsal or ventral FST effective connectivity.

Discussion: Our high-resolution estimation of PLEs yielded nine dimensions that are continuously distributed with clinical symptoms. Consistent associations between positive PLE dimensions and striatothalamic pathways suggests the key role of information filtering by the striatum implicated in these symptom dimensions. Associations with negative PLEs, namely anhedonia, asociality, avolition, and alogia were restricted to the ventral circuit, indicating the potential contribution of emotional processing in this domain.

M76. A NEURODEVELOPMENTAL SIGNATURE OF PARKINSONISM IN SCHIZOPHRENIA

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Background: Sensorimotor abnormalities intrinsic to schizophrenia (SZ) have increasingly attracted scientific interest in the past years. However, very little is known about the neurodevelopmental significance of structural changes that underlie parkinsonism.
Methods: This multimodal magnetic resonance imaging (MRI) study examined healthy controls (HC, n=20) and SZ patients with and without parkinsonism, as defined by Simpson-Angus-Scale total score of ≥4 (SZ-P, n=38) or ≤1 (SZ-nonP, n=35). Using the Computational Anatomy Toolbox (CAT12), voxel- and surface-based morphometry were applied to investigate grey matter volume (GMV) and three cortical surface markers of distinct neurodevelopmental origin, i.e. cortical thickness (CTh), complexity of cortical folding (CCF) and sulcus length. In a subgroup of patients (SZ-nonP=29, SZ-P=25), resting-state fMRI data were analyzed using a regions-of-interest (ROI) approach based on fractional amplitude of low frequency fluctuations (fALFF).
Results: SZ-P patients showed increased CCF in the left supplementary motor cortex (SMC) and decreased left postcentral sulcus (PCS) length compared to SZ-nonP patients ($p<0.05$, FWE-corrected at the cluster level). SMC folding complexity was negatively associated with SMC activity, which also differed significantly between the patient groups as well as between patients and HC. In regression models, parkinsonism severity was negatively associated with left middle frontal CCF and left anterior cingulate CTh.
Discussion: These data provide novel insights into different trajectories of cortical development in SZ patients with parkinsonism. Cortical surface changes in these individuals distinctly involve the sensorimotor system, suggesting abnormal neurodevelopmental processes that could convey increased risk for sensorimotor abnormalities.

M77. ALTERED HESCHL'S GYRUS DUPLICATION PATTERN IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Reduced gray matter volume of the superior temporal gyrus and its subregions, such as Heschl's gyrus (HG) and planum temporale (PT), has been reported in schizophrenia (Sz). However, it remains largely unknown whether the patients exhibit altered gyrification pattern on the superior temporal plane.
Methods: This magnetic resonance imaging study examined the distribution of HG duplication pattern [i.e., single HG, common stem duplication (CSD), or complete posterior duplication (CPD)] as well as its relation to clinical variables and gray matter volume of the HG and PT in 64 first-episode (FE) patients with Sz and 64 healthy controls.
Results: We found significantly higher prevalence of duplicated HG patterns and smaller volume of the HG and PT for both hemispheres in the FESz patients than in healthy controls. Right CPD pattern in the FESz group was associated with less severe positive symptoms. For both FESz and control groups, CSD and CPD patterns were significantly associated with larger volumes for the HG and PT, respectively.
Discussion: The present Results: demonstrated an altered HG duplication pattern at earliest phase of Sz, which probably reflects early neurodevelopmental anomaly. However, reduced HG and PT volumes in the FESz could not be explained only by such gyrification pattern, supporting complicated superior temporal pathology of the illness.

M78. EVIDENCE OF EPISTATIC EFFECT INVOLVING NRN1, KCNH2 AND CACNA1C GENES ON THE RISK FOR SCHIZOPHRENIA-SPECTRUM DISORDERS AND ITS IMPACT ON PSYCHOPATHOLOGY

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Background: Genome-wide association studies have confirmed that schizophrenia (SZ) results from the aggregated effect of multiple genes of low impact and have also highlighted the involvement of biological pathways related to neuronal excitability mechanisms in the aetiology of SZ (Pardiñas et al. 2018; Ripke et al. 2014). These results have raised the interest in studying gene-gene interactions. Calcium and potassium voltage-gated channels, which are partially encoded by genes such as CANA1C and KCNH2, play a critical role in modulating action potentials rate and duration. It has been suggested that the Neuritin1 gene (NRN1) might participate in the cellular pathways related to the cell surface expression of both types of channels (Yao et al. 2012; Lu et al. 2017). Indeed, the three genes have been independently associated with SZ risk (Zhu et al. 2019; Fatjó-Vilas et al. 2017; Hashimoto et al. 2013). However, the impact of their interplay has not been studied on the pathogenesis of SZ. Consequently, we aimed to study whether these genes show epistatic effect i) on SSD risk and ii) on different clinical scales.

Methods: The sample comprised 388 healthy subjects (HS) and 342 subjects with SZ-spectrum disorder (SSD). Eleven SNPs at NRN1 were genotyped, as well as rs1006737 at CACNA1C gene and rs3800779 at KCNH2 gene. The genotypes were dichotomised and two-order epistasis models or three-order epistasis models were studied using the R package "mbmdr". Epistatic effects were tested comparing healthy subjects to subjects with SSD to find combinations associated with SSD risk (correcting by sex). The effects of significant epistasis models detected predicting the risk for SSD were tested on clinical measurements (PANSS, GAF and onset) within patients (adjusted by age and sex).

Results: The analyses of two-order epistatic effects on SSD risk showed that the NRN1-SNP7 TT/TC genotype was associated with a higher risk for SSD in combination with the CACNA1C GG (β=0.881; p=0.003) or with the KCNH2 AA/AC (β=0.869; p=0.005) genotypes. We also detected a three-order significant interaction associated with a higher risk for SSD including NRN1-SNP7 TT/TC x CACNA1C GG x KCNH2 AA/AC genotypes (β=1.019; p=0.015). The analyses of epistatic effects on clinical measurements showed that those SSD subjects carrying the three-order combination opposite to that associated with the SSD risk (NRN1-SNP7 CC x CACNA1C AA/AG x KCNH2 CC), had higher scores of GAF which are related to better functioning (β=15.364; p<0.001), and lower total PANSS scores which are associated with less severe symptomatology (β=-11.550; p=0.020).

Discussion: Our results suggest the epistatic effects of NRN1 with CACNA1C and KCHN2 genes, concretely, it seems that the NRN1 variability located at SNP7 in combination with CACNA1C or KCNH2 has an impact not only on SSD risk but also on GAF and total PANSS scores in subjects with SSD. In this sense, our results are in line with previous data linking these genes with SZ risk (Fatjó-Vilas et al. 2017; Zhu et al. 2019; Hashimoto et al. 2013). Therefore, although our results do not describe the precise mechanisms underlying the interaction of NRN1 with CACNA1C and KCHN2 genes on SSD risk or psychopathology, our data could be of value since it is in line to those studies derived from cellular and animal models describing their interplay (Yao et al. 2012; Lu et al. 2017).

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M79. THE INTERPLAY BETWEEN CANNABINOID RECEPTOR GENES AND CANNABIS USE: EFFECTS ON BRAIN ACTIVITY IN FIRST EPISODE PSYCHOSIS

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Background: Cannabis is a known risk factor for psychosis and it is associated with brain activity changes, possibly through its agonistic role in the endocannabinoid system, which in turn modulates dopamine levels in several brain regions. Genetic factors may explain the inter-individual differences in the psychosis-inducing effects of cannabis. We studied the impact of genetic variability at endocannabinoid receptor genes (CNR1 and CNR2) and cannabis use on brain activity (fMRI) in first-episode psychosis (FEP) patients.

Methods: The sample comprised 43 Caucasian FEP subjects: 21 cannabis users and 22 non-users. All performed a working memory N-back task (1-back and 2-back) during an fMRI protocol. Two SNPs were genotyped (CNR1-rs1049353-G/A, CNR2-rs2501431-A/G). Genotype and cannabis interaction was studied on whole-brain activity (FSL).

Results: CNR1 and cannabis use showed interaction (2-back vs 1-back contrast) in one cluster located within the right temporal and frontal and left cingulum (Zmax=4.35, p=1.08e-08). In the same contrast, CNR2 and cannabis interplay was detected in four clusters located within: 1, 2: vermis, cerebellum and left fusiform (Zmax=3.51, p=0.0177; Zmax=3.95, p=0.00593), 3: right temporal (Zmax=4.14, p=0.00096) and 4: left angular, temporal and occipital lobes (Zmax=3.85 p=0.00045). Genotype-related activation pattern was opposite for CNR1 and CNR2.

Discussion: Our results, although preliminary, suggest the putative modulating role of CNR1 and CNR2 in brain activity in FEP in regions that are related to the reward system, which is involved in addictions and also in psychosis.

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M80. POLYGENIC LIABILITY FOR ENVIRONMENTAL AND STRESS SENSITIVITY PATHWAYS, CHILDHOOD TRAUMA AND PSYCHOSIS-PRONENESS

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Background: Childhood trauma is a risk factor for developing psychosis. However, the effect of the interaction between childhood maltreatment and the underlying polygenic vulnerability on the expression of psychosis proneness is not well known. Our aim was to investigate the modulating role of Schizophrenia (SZ) Polygenic Risc Scores (PRS) and pathway-specific PRS on the association between childhood trauma and a measure of psychosis proneness.

Methods: The sample consisted of 252 non-clinical individuals evaluated in the Universitat Autònoma de Barcelona. All subjects completed the Spanish version of the Childhood Trauma Questionnaire (CTQ) providing a measure of the level of Abuse and Neglect suffered and were interviewed applying the Comprehensive Assessment of At-Risk Mental States (CAARMS) to assess their psychosis proneness.

PRS were derived based on the latest meta-analysis results from SZ GWAS. Apart from overall SZ PRS, pathway-specific PRS were also calculated for two biological pathways: environmental sensitivity and stress sensitivity. The PRS-CS method was used to compute the PRS.

Linear regression analyses were performed to test for interaction effects between the PRS and childhood trauma scores on the CAARMS subscales. Age, sex and the first two ancestry-based principal components were included as potential confounders. The False Discovery Rate (FDR) method was applied to correct for multiple testing.

Results: The linear regression analyses performed to test for interaction effects between the overall SZ PRS and childhood trauma on the CAARMS subscales showed no significant results for either Abuse or Neglect and for any of the CAARMS subscales. However, when we explored the modulating role of pathway-specific PRS on the association between childhood trauma and the CAARMS subscales we found statistically significant interaction effects with Neglect for: i) both environmental sensitivity and stress sensitivity PRS on the Positive Symptoms subscale of the CAARMS ($\beta = 8.86$, Adjusted R2 = 0.034, P = 0.004 and $\beta = -2.3$, Adjusted R2 = 0.028, P = 0.01,

respectively) and ii) stress sensitivity PRS on the Behavioural Change subscale of the CAARMS (β = -4.6, Adjusted R2 = 0.026, P = 0.02).
Discussion: Our results seem to suggest that the additive effect of genetic variants in biological pathways associated with environmental and stress sensitivity act making individuals more sensitive to childhood experiences, especially related to neglect.

M81. THE INTERPLAY BETWEEN TWO SCHIZOPHRENIA GWAS GENES ON FMRI WORKING MEMORY RESPONSE: EVIDENCE OF CACNA1C X ZNF804A EPISTATIC EFFECT ON BRAIN FUNCTION

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Background: CACNA1C and ZNF804A are among the most relevant GWAS associated loci with the susceptibility for schizophrenia (Ripke et al. 2013, Pardiñas et al. 2018). Their involvement in synaptic plasticity and neural excitability has derived in many studies inspecting their role on different cognitive phenotypes using fMRI (Zhang et al. 2019, Zhang et al. 2018, among others). Recent evidence has shown that the interaction between CACNA1C x ZNF804A (epistasis) and their interaction with diagnosis (three-way interaction) modulate the brain functional response while performing a verbal fluency task (Tecelao et al. 2019). Also, their interplay has been suggested at brain structural level (Mallas et al. 2017). To better understand how these genes might influence the risk for schizophrenia, we aimed to extend to working memory the previous fMRI findings and we studied the epitasis of both genes and their interaction with schizophrenia diagnosis in N-back functional response.
Methods: The sample consisted of 78 healthy subjects (HC) and 78 patients with schizophrenia (SZ), matched for age, sex and premorbid-IQ. All the individuals had available functional working memory data (N-back) obtained during an fMRI protocol (1.5-T scanner). Two polymorphic variants in the genes of interest were genotyped: the rs1006737 (A/G) in the CACNA1C gene and, the rs1344706 (A/C) in the ZNF804A gene. The effect of the genetic epistasis (CACNA1C x ZNF804A) and, the three-way interaction with diagnosis (CACNA1C x ZNF804A x diagnosis)

were tested on working memory functional response (2-back vs. 1-back contrast, whole-brain corrected) through a full factorial ANOVA (adjusted by age, sex, and premorbid-IQ with FSL software).
Results: The analyses revealed significant epistasis (CACNA1C x ZNF804A) on working memory functional response in regions that comprised the medial caudate, the left inferior frontal gyrus, the left temporal pole and the left dorsal-anterior insula and amygdala (718 voxels, peak activation at MNI [-2,6,-6], Zmax=4.15, p=0.015). Once mean activity values were extracted, it was seen that regardless of the diagnosis, individuals carrying the risk genotypes (CACNA1C-AA/AG and ZNF804A-AA) showed a lesser working memory-modulation response in these regions. The three-way interaction with diagnosis (CACNA1C x ZNF804A x diagnosis) showed no significant results.
Discussion: Our results suggest an interplay between CACNA1C and ZNF804A on the modulation of working memory functional response and add to previous data which evidenced also an epistatic effect of these two SZ risk genes on verbal fluency-associated brain activity (Tecelao et al. 2018). The regions where the epistasis was detected, have been previously associated with task-related deactivations and task-related diagnostic differences across HC and SZ patients (Pomarol-Clotet et al. 2010, Minzenberg et al. 2009). New research on the putative common pathway of these two genes should be encouraged to better comprehend the neurobiological mechanisms underlying their interplay. While further data and replication analyses in larger samples are needed, the converging pieces of evidence suggest the role of CACNA1C and ZNF804A in the altered functional mechanisms underlying the pathophysiology of schizophrenia.
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M82. HIPPOCAMPO-PROTECTIVE ROLES OF NIGELLA SATIVA IN SOCAILLY ISOLATED MICE MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia is a chronic debilitating mental disorder, modelled developmentally in animals by social isolation rearing (SIR). This study assessed the effects of Nigella sativa oil, a multi-therapeutic plant oil, on the hippocampal functions of socially isolated mice, while reappraising the validity of SIR in modeling schizophrenia.
Methods: Five groups (tagged CTRL, NS, SIR-NS, NS-SIR, and SIR) consisting of 12 BALB/c pups each were employed for the research. Weaned after 3 weeks, the pups were either reared socially on normal feed and saline (CTRL) or Nigella sativa oil (NS); or socially isolated and treated with either normal saline (SIR-NS) or Nigella sativa oil (SIR-NS); or had only been prenatally exposed to Nigella sativa (NS-SIR). Normal saline & Nigella sativa were orally administered at 10ml/kg and 1ml/kg respectively. Spatial memory was assayed using object location test, while neuro-istological assessments were also conducted on the hippocampal tissues.

Results: Nigella sativa increased object location index and relative brain weight in the NS-SIR mice following maternal exposure. The NS mice also showed the highest levels of hippocampal glutamate and GPX, while Nigella sativa also increased these parameters in the SIR-NS mice. No significant difference was however observed in the hippocampal neuroarchitecture across the groups. The socially isolated mice in addition exhibited body weight loss despite consuming the most feed daily, but such magnitude of weight loss was prevented and ameliorated by Nigella sativa exposure.
Discussion: This study suggests the prophylactic potentials of maternal Nigella sativa exposure prior to conception as modelled here. The schizotypic deficits recorded in the isolated mice weren't significant. We therefore recommend the use of total separation during isolation, as well as the use of Nissl and Dendritic markers in the histological evaluation of the hippocampus for further elucidation.

M83. DIFFERING LEVELS OF UBIQUITYLATED PROTEINS AND UBIQUITIN GENE EXPRESSION IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Ubiquitylation is a post-translational modification in which one or more ubiquitin molecules are covalently attached to lysine residues on the substrate protein. Ubiquitylation orchestrates targeted degradation of proteins as part of the ubiquitin-proteasome system (UPS), but can also exert proteasome-independent effects, including regulation of endocytosis, inflammation, signal transduction and DNA repair. As such, dysregulation of ubiquitylation is well placed to link the disparate cellular and molecular abnormalities previously reported in schizophrenia (SCZ). Evidence for the involvement of ubiquitin in SCZ comes in part from transcriptomic studies that have identified the UPS as one of the top canonical pathways associated with this disorder. Additional targeted investigation at the gene and protein levels may help elucidate the role of ubiquitylation in SCZ. In this study we quantified mRNA expression of genes that encode ubiquitin or polyubiquitin precursors, levels of free ubiquitin protein and presence of K48- (proteolytic) and K63- (non-proteolytic) linked polyubiquitin chains in postmortem brain tissue from SCZ, bipolar disorder (BD) and control subjects.
Methods: Postmortem dorsolateral prefrontal cortex from 104 subjects (35 control, 35 SCZ, 34 BD) was obtained from the Stanley Medical Research Institute. Levels of free ubiquitin and K48 and K63-linked ubiquitin chains were quantified by immunoblotting. Gene expression of the ubiquitin and polyubiquitin precursors UBA52, UBB and UBC was quantified by qPCR.
Results: UBC gene expression was significantly lower in both SCZ and BD, relative to controls. Immunoreactivity for two K48-linked bands was lower in the BD group. Sex by diagnosis effects were observed for several measures. Psychotropic medications did not significantly impact gene or protein levels.
Discussion: Our findings of lower UBC expression suggest that protein ubiquitinylation is dysregulated in both SCZ and BD. UBC contributes to maintenance of ubiquitin levels under cellular stress conditions. Further investigation of mechanisms underlying dysregulation of ubiquitylation and the UPS in SCZ may inform discovery of future therapeutic interventions in this disorder.

M84. AMELIORATION OF OLFACTORY DEFICITS AND OLFACTO-BULBAR GLUTAMATE AND GABA BY NIGELLA SATIVA OIL IN DEVELOPMENTALLY MODELLED SCHIZOPHRENIA IN BALB/C MICE

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Background: Olfactory deficit is an endophenotype of Schizophrenia as characterised by disruption in synaptic transmission in the olfactory apparatus. With our hypothesis of ameliorative tendencies, this study investigated the effects of Nigella sativa oil (NSO), a highly therapeutic and scientifically evidenced herbal medicine, on the olfactory parameters of social isolation rearing (SIR) models of developmental schizophrenia through neurobehavioural , neurochemical and histological assays on the olfactory bulb.
Methods: (60) BALB/c mice (3 weeks) were equally divided immediately post-weaning into 6 groups namely, CTRL (reared socially on normal chow only), SIR (socially isolated on normal chow only), NS (administered 1ml/kg NSO daily), SIR-NSC (socially isolated but concurrently administered 1ml/kg NSO daily), SIR-NS (socially isolated on normal chow before administration with 1ml/kg NSO for same duration as isolated), NS-SIR (dams pre-administered 1ml/kg NSO for 10 days prior to mating while their pups were commenced on isolation immediately post-weaning). Social isolation rearing was executed through individualised holding of each mouse in a separate cage (with adequate spacing and ventilation) devoid of all tactile and visual cues from all other mice. Isolation and NSO administration periods each lasted 8 weeks.
Results: Neurobehaviour: Olfactory sensitivity and discrimination was defective in SIR mice, but higher in all mice that were pre-, post or concurrently treated with NSO. Neurochemistry: Glutamate and GABA levels were higher in the olfactory bulb of mice that received NSO compared with untreated SIR mice. Weights: Brain-body ratio was also higher in all NSO-treated mice than the untreated ones. Histological data are still being completed.
Discussion: While olfactory deficits were re-affirmed in socially isolated mice as models of schizophrenia, Nigella sativa oil was shown to ameliorate and protect against the neurobehavioural and neurochemical olfacto-schizophrenic endophenotypes in BALB/c mice.

M85. IMPROVEMENTS OF NEGATIVE AND DISORGANIZED SYMPTOMS IN SCHIZOPHRENIA WITH BILATERAL PREFRONTAL TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS): PRELIMINARY RESULTS

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Background: Negative symptoms (NS) and Disorganized symptoms (DS) have been recognized as some of the core features of Schizophrenia. Moreover, these dimensions are predictors of poorer

psychosocial functioning and quality of life, posing significant burdens on people affected by Schizophrenia. However, the assessment and treatment of NS and DS is challenging in the clinical practice, because of the limited effectiveness of pharmacological and non-pharmacological treatments on these dimensions. Due to promising, although preliminary, Results: in reducing positive, negative and cognitive symptoms of Schizophrenia, transcranial Direct Current Stimulation (tDCS) is a novel neurostimulation approach aimed to improve NS and DS through modulation of the prefrontal cortex activity.

Methods: We designed a double-blind sham-controlled trial in which 18 patients with Schizophrenia were randomized 1:1 to receive 15 sessions (once daily for 3 weeks) of active-tDCS (2 mA, 20 min) versus a sham-tDCS as an add-on intervention to standard pharmacotherapy. Electrode montage used a bilateral bipolar-non-balanced setting: anode placed over the left DLPFC (F3); cathode over the right orbitofrontal cortex (FP2). Primary outcomes were: 1) change of the Negative subscale score and of the Composite Scale (obtained by subtracting the negative from the positive score) of the Positive and Negative Syndrome Scale (PANSS); 2) improvement of the Negative (Neg-PANSS) and of the Disorganized-concrete (DisC-PANSS) Factor of the PANSS according to the Wallwork five-factor model. Secondary outcomes were: 1) change in the total score, Positive and General psychopathology subscales of the PANSS; 2) variation of Positive (Pos-PANSS), Excited (Ex-PANSS) and Depressed (Dep-PANSS) factors of the PANSS Wallwork five-factor model. A within-subjects (clinical measurements at the baseline and after each week), and a between-subjects (active-tDCS versus sham-tDCS) repeated measures analyses of variance (rm-ANOVA) were performed.

Results: Only the active-tDCS group showed significant reductions of the PANSS Negative subscale score ($p = 0.004$, ES = 1.22), of the Composite Scale ($p = 0.005$, ES = 0.86), of the Neg-PANSS ($p = 0.01$, ES = 1.35), of the DisC-PANSS ($p = 0.003$, ES = 1.14), and of the PANSS total score ($p = 0.02$, ES = 0.50). The time x treatment interaction confirmed the differential effects of the active intervention compared to the sham condition for all these variables except for the PANSS total score ($p = 0.18$). Non-significant variations were detected in both groups for the other scales.

Discussion: tDCS is a promising non-invasive tool aimed to modulate core symptoms of Schizophrenia. Our results confirm and corroborate previous evidence regarding the effectiveness of tDCS in improving negative and disorganizative symptoms in patients with schizophrenia. These results should be confirmed also evaluating the impact of tDCS on subject real-world functioning and quality of life.

M86. GENDER DIFFERENCES IN PSYCHOLOGICAL TREATMENT FOR PEOPLE WITH PSYCHOSIS: A SYSTEMATIC REVIEW OF THE LITERATURE

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Background: Several gender differences have been found in different domains in people with schizophrenia or other psychosis (Ochoa et al., 2012; Riecher-Rössler et al, 2018). However, less is known about psychotherapeutic interventions.

The aim of the study is to review systematically the literature to explore the influence of gender in response to psychological treatments.

Methods: A PICOS criterion was used. Participants were patients with psychosis (schizophrenia, first-episodes, schizophreniform, delusional disorder, high risk, schizotypal, schizoid, and, paranoid). Interventions were based on psychosocial interventions with patients' outcomes related to psychological variables. Comparison variable was gender. The outcomes were psychosocial variables and the Study designs includes were clinical trials, quasi-experimental, pre-post designs, reviews, metaanalysis. The database reviewed were Pubmed, Psychoinfo, Psicodoc, scopus and google scholar (grey literature).

Results: A total of 1162 articles were identified. After review of title and abstract 191 articles were included. Finally, 43 articles were included in the final review.

Most of them used gender as a covariate in the analysis (N=12), 4 of them were systematic reviews or metaanalysis, 10 of them explore the effect of gender in drop-outs and adherence to treatment and only 17 of them assess gender differences in response to the main aims of their study. Men have higher taxes of dropouts or non-adherence. Regarding, six studies found that women improved more in familiar, CBT, MCT and work psychological interventions. The rest did not find gender differences and one found that men improved more in self-stigma than women.

Discussion: Our results suggest that a gender sensitive approach should be considered in the study of psychological interventions to people with psychosis in order to a better treatment personalization..

M87. AN EXERCISE MOTIVATION COACHING INTERVENTION ON IMPROVING EXERCISE ENGAGEMENT IN WOMEN WITH PSYCHOSIS: PRELIMINARY RESULTS OF AN OPEN LABEL RANDOMIZED CONTROLLED TRIAL STUDY

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Background: In most cases of psychotic disorder, there is a lack of motivation to exercise, which can lead to considerable physical health complications. Recent studies have shown that engaging in regular exercise habits such as aerobics and yoga can significantly improve health outcomes in women with psychosis. Interventions that can help patients establish an exercise habit are therefore becoming indispensable as a non-pharmacological treatment.

Methods: This is a two-arm parallel, open-label randomized controlled trial designed to evaluate the effectiveness of a 16-week exercise motivation coaching intervention for women with psychosis in Hong Kong. The effect of the intervention on participant's engagement in physical activity is measured primarily against psychoeducational intervention. The primary result is the change in the total metabolic equivalents (METS) of physical activity as measured by the Chinese version of the International Physical Activity Questionnaire (IPAQ). Prior to participating in any intervention programme, both groups would undergo a baseline assessment, which would include clinical, physical and functional assessments. The participants were followed immediately, 6 and 12 months after the intervention. In this abstract, the preliminary data between the baseline and the post-intervention period were presented.

This exercise motivation coaching intervention is an integration of aerobic exercise, yoga, mindfulness and exercise coaching. Exercise class and coaching will be provided weekly for the first 8 weeks. For the next 8 weeks, exercise class will be provided weekly while exercise coaching will be provided bi-weekly. The group of psychoeducation was similar to the group of movement-motivation coaching, while the coaching sessions were replaced by a psychoeducational sessions.

Results: From 1 August 2018 to 30 December 2019, 66 adult women psychosis patients (mean age = 35.45 years, SD = 12.29) were recruited from the outpatient psychiatric clinic in Kwai Chung Hospital and the community in Hong Kong. The participants were individually and randomly allocated to either exercise motivation group (n = 36) or psychoeducation group (n = 30). Compared with the exercise level at baseline, a significant increase was observed in the intervention group but not in the control group after intervention (Group x Time interaction: F1, 64 = 4.899, p = .03).

Discussion: There is no up-to-date study that has implemented a large-scale gender-specific intervention for women with psychosis in Hong Kong. The preliminary findings of the current study suggested that the 16-week exercise motivation coaching intervention should help women psychosis patients to establish exercise habit. The intervention deems adaptable in the community setting where patients can get access to easily and gain support from community members.

M88. IDENTIFICATION OF LINGUISTIC SUBTYPES IN AUDITORY VERBAL HALLUCINATIONS OF CLINICAL AND NON-CLINICAL VOICE HEARERS

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Background: In recent years, the appreciation of heterogeneous features in auditory verbal hallucinations (AVHs) has increased. While there are similarities in AVHs phenomenology between clinical and non-clinical voice-hearers, there are also differences between these groups. Distinguishing subtypes of AVHs can have important implications for both clinical practice and research. A potential source of heterogeneity that has scarcely been studied relates to the AVHs linguistic characteristics. In the present study we investigate how linguistic features can be used to distinguish subtypes of AVHs, and whether AVHs subtypes are associated with phenomenological aspects and voice-hearers' clinical status.

Methods: Both clinical (n=21) and non-clinical voice-hearers (n=19) took part in this study. Each participant was instructed to repeat verbatim of her/his AVHs just after experiencing them for a total of 3 minutes. These registrations were audio-recorded at the time AVHs were heard and later transcribed. The Auditory Hallucinations Rating Scale (AHRS) of the Psychotic Symptom Rating Scales (PSYRATS) was used to assess phenomenological features of the AVHs. Hierarchical clustering analyses without a priori dichotomization between groups were performed using quantitative measures of sixteen linguistic features in order to distinguish sets of AVHs. Follow-up comparisons using non-parametric tests were carried out to assess linguistic and phenomenological differences between sets of AVHs.

Results: The data-driven hierarchical clustering procedure showed that a two-cluster solution best partitioned the data. These clusters significantly differed in linguistic features ($p<.001$); hallucination phenomenology ($p<.001$); and distribution of clinical versus non-clinical voice-

hearers (p<.001). Cluster-one (expanded-AVHs) had more grammatical words and mainly included non-clinical voice hearers. Cluster-two (compact-AVHs) contained predominantly clinical voice-hearers, and was characterized by fewer grammatical words, shorter mean length of utterance (both p<.01), more negative content, and higher degree of negativity (both p<.05).
Discussion: Using a data-driven approach with linguistic features, two clusters of voice-speech could be recognized. Linguistically, these clusters mainly differed in their use of referential information and syntactic complexity, and phenomenologically, in the amount of negative content and degree of negativity. Our data suggest that clinical voice-hearers more often hear 'compact' rather than 'expanded' voices. This can inform neurocognitive models of AVHs, and also be useful in developing treatments for AVHs.

M89. COVID-19 EFFECTS ON AUDITORY HALLUCINATIONS IN HOSPITALIZED PATIENTS

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Background: The content of auditory hallucinations (AHs) is malleable and reflects the environment and culture experienced. For example, Texas hospital records detail how the content of AHs corresponded with periods of hostility (1980s) and religiosity (1930s; Mitchell & Vierkant, 1989). Further, perceptions of an individual's relationship with their voices mirrored their perception of and actual standing within society (Birchwood et al., 2000); these findings demonstrate the importance of perception and society when evaluating the content and impact of AHs.
Early evidence suggests that economic and social stress as well as viral exposure caused by the novel Coronavirus-19 (COVID-19) have triggered the onset of psychosis in patients (Brooks et al., 2020; Chandra et al. 2020). A rapid review found research has not yet determined how the phenomenology of AHs has changed since the COVID-19 outbreak (Brown et al., 2020).

Methods: Adult patients receiving care within an acute inpatient care setting in the Northeast U.S were recruited to participate in a mixed methods research study. They were asked to complete two short questionnaires (Varieties of Inner Speech Questionnaire Revised, R-VISPQ; Tellegen Absorption Scale, TAS) and an hour long Zoom qualitative interview regarding the phenomenology of their AHs. The intent of the interview was to understand the impact of COVID-19 on the participants' life; the modified interview protocol included topics regarding the frequency, duration, location, intensity, identity, realness, amount and degree of negative or positive content, and distress of the participant's AHs as well as the participants' control, agency, and perception (Luhrmann et al., 2015).
Results: A total of 9 participants have currently completed the study protocol and we aim to recruit an additional 11 participants. Demographic statistics indicate that the sample is middle-aged (M = 50.44, SD = 9.20) and they have been hearing voices for over a decade (M = 16.5, SD = 10.18). High levels of absorption (TAS; M = 21.83, SD = 5.11) and high levels of inner speech subfactors (R-VISPQ; Dialogic: M = 15.33, SD = 4.68; Condensed: M = 8.67, SD = 3.01; Evaluative / Critical: M = 22.00, SD = 4.19; Other people: M = 15.33, SD = 5.89; Positive / Regulatory: M = 9.33, SD = 7.45) were noted across the sample. Thematic analysis of interview data identified that COVID-19 was present in the content of AHs, shaped the paranoid ideation, and at least for some,

increased the frequency and loudness of the AHs. At least 33% of participants reported increased paranoia caused by COVID-19, particularly fear they would be blamed for spreading COVID-19. Two participants felt that the recent social isolation caused their AHs to be more distressing and more prominent. Additionally, 89% of participants indicated a dominant theme of violence and this theme was noted to generally cause distress.
Discussion: Our results show that COVID-19 influenced the content of AHs, but the impact of COVID-19 on AHs was not uniform across participants. The effect of social isolation, financial insecurity, and increased domestic violence caused by the COVID-19 pandemic are likely to negatively affect individuals with psychosis. Understanding how COVID-19 specifically has impacted AHs may provide insights into how societal and external factors may affect the pathology of distressing auditory hallucinations.

M90. THE STANDARD FOR CLINICIANS' INTERVIEW IN PSYCHIATRY (SCIP): A PERSONALIZED PRECISION MEDICINE ASSESSMENT TOOL FOR PSYCHIATRY

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Background: Personalized Precision Medicine in Psychiatry (PPMP) has four domains: life story, environmental factors, psychopathology assessment and translational neuroscience findings. These domains guide clinicians toward a person-centered diagnosis, person-centered prognosis, and person-centered therapeutics, all of which involve personalized selection and dosing of medications. There is a need for a comprehensive assessment tool that measures patients' symptoms and signs for use in conjunction with the other domains of PPMP.
Methods: The Standard for Clinicians' Interview in Psychiatry (SCIP) is a new assessment tool that measures symptoms and signs of psychopathology among adults. The SCIP was designed as a measurement-based care (MBC) tool for clinicians to use in assessment and decision-making. The SCIP measures psychopathology of most adult psychiatric disorders: anxiety, panic, phobias, obsessions, compulsions, posttraumatic stress, depression, mania, alcohol use, drug use, delusions, hallucinations, disorganized thoughts, disorganized behaviors, negative symptoms, eating disorders, attention deficit and hyperactivity. The SCIP measured Kappa for 30 screening items and 200 psychopathology items, providing the most comprehensive coverage of adult psychopathology. Among the 30 screening items: 19 items (63%) have good reliability (Kappa > 0.7) and 11 items (37%) have fair reliability (Kappa ranges from 0.5 to 0.7). Among the 200 psychopathology items, 7 items (3.5%) have poor reliability (Kappa < 0.5), 24 items (12%) have fair reliability (Kappa ranges from 0.5 to 0.7) and 169 items (84.5%) have good reliability (Kappa > 0.7). Each psychopathology item has a unique PPMP code.
Results: Descriptive Psychopathology Code (DPC) is a comprehensive psychological assessment (symptoms, signs and dimensions) of an individual at one point in time using the SCIP 230 items. Descriptive Psychopathology Map (DPM) is two or more descriptive psychopathology codes (DPCs) for the same patient obtained over time, as rated by either the same or different clinicians. Psychiatric evaluations and progress notes can be transformed into DPC and DPM. Example: a patient is a 40-year-old female with derailment (P_DIS102), paranoid delusions (P_DEL93), conspiracy delusions (P_DEL94) and her delusions are bizarre (P_DEL101). The DPC of the patient's episode is P_DIS102(2)P_DEL93(2)P_DEL94(2)P_DEL101(1). The number in

parenthesis reflects the severity of the symptom and sign as described in the SCIP instruction manual.
Discussion: The SCIP is a new assessment tool designed to be compatible with PPMP research.

M91. A RETROSPECTIVE CLINICAL CHART REVIEW OF LONG-ACTING INJECTABLE ARIPIPRAZOLE IN EARLY-PSYCHOSIS

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Background: Recommendation on long-acting injectable aripiprazole (LAIA) dosage based on phase II and phase III trials are that a 400mg dosage would be appropriate in 90% of patients and 300mg in 10%. Since these trials were performed in patients aged around 40, it is not known if they apply to first-episode psychosis (FEP), a population in which LAIA use may be particularly interesting given its relatively benign side-effects profile and findings of a more positive impact than long-acting palliperidone on quality of life in patients ≤35 years of age.
Methods: We systematically reviewed extensive medical charts of all 59 patients from a FEP program who have been exposed to LAI Aripiprazole (LAIA) and followed for 12 months in the context of an intensive inter-disciplinary team. Two trained psychiatry residents independently performed monthly ratings of efficacy (CGI-S) and tolerability (CGI-CB side effects subscale) and disagreements were reviewed to reach consensus and dosage was recorded. LAIA dosage used was generally based on the following rules: patients were first stabilized on oral Aripiprazole to assess an optimal dosage; based on the latter, the first injection was either 400 or 300mg; the LAIA dosage targeted at equilibrium was approximately 1mg oral for 20mg LAIA and was adjusted based on response. Response was defined a (CGI-S≤4, i.e., moderately ill at most) and full response according to a CGI-S≤3, at most mildly ill).
Results: Among the 56 subjects who had an initial response to LAIA (CGI-S≤4), 53 experienced a period of full response for ≥3 consecutive months and 45 for ≥6 consecutive months LAIA dose during their periods of remission was 281.6 (80.1) mg. The last dose received was ≤ 300 mg for 45 patients. Nine among the 56 initial responders experienced relapse that occurred on average 6.6 months after the onset of response. The average dose before relapsing was 326.6 (48.9) mg. Twenty-three out of the 56 initial-responders experienced clinically significant side-effects (CGI-CB side-effects subscale ≥2, i.e., side-effects having a significant impact on functioning), leading to treatment termination before the end of the observation period in 8 subjects. The most frequent recorded side effects were extrapyramidal symptoms (n=10), akathisia (n=5), drowsiness (n=4), weight gain (n=3) and impulse control disorder/pathological gambling (n=3). The average dose of occurrence for these significantly impairing side effects in this group was 306.1 (87.6) mg. Nineteen out of these 23 patients underwent a dosage decrease; 14 achieved a final CGI-CB of 2 or less, following an average reduction from a mean dosage of 312.1 (93.2) mg, to a mean dosage mg of 218.6 (112.2; mean decrease = 93.6 (SD) mg.
Discussion: These results of the current study suggest that it may be appropriate and/or needed to use LAI Aripiprazole dosage below 300mg in a significant proportion of FEP patients; hence, close monitoring of severity and tolerability may be required to “fine tune” LAI Aripiprazole dosage.

M92. ANTI-AGGRESSIVE EFFECTS OF CLOZAPINE IN INVOLUNTARILY COMMITTED BLACK PATIENTS WITH SEVERE MENTAL ILLNESS

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Background: Schizophrenia is a chronic mental illness characterized by hallucinations, delusions, and disorganized thought processes. Despite media exaggeration, data suggests that violent outbursts are more common in patients diagnosed with schizophrenia compared to the general population. A growing body of evidence suggests that the second-generation antipsychotic, clozapine, has a unique anti-aggressive effect in patients with treatment-resistant schizophrenia. Involuntarily committed Black patients with mental illness are underrepresented in these studies. The purpose of our study is to evaluate clozapine's effects on aggression in this population.
Methods: This analysis is a subgroup of involuntarily committed patients from a larger prospective 24-week open-label clozapine study. All patients were black and enrolled from two participating state psychiatric hospitals. The primary outcome measured was total use of as needed or stat medications for aggression. Secondary outcomes included changes in each individual as needed or stat medication, number and duration of seclusion and restraint episodes, and changes in Brief Psychiatric Rating Score (BPRS) total and hostility sub-scores.
Results: Sixty-nine patients were included in our analysis. Significant reductions were noted in as needed medication use over time ($\chi 2=6.90$; $p=0.008$) and the BPRS hostility subscore was reduced by 30% over the 24 weeks ($F=4.34$, $df=62$, $p=0.002$).
Discussion: Treatment with clozapine effectively reduced aggression within this cohort of involuntarily committed black patients with mental illness compared to baseline. Specifically, it helped lower the total number of PRN medication administrations and improved clinician-rated hostility scores on the BPRS.

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M93. EFFECT OF DURATION OF PRIOR PSYCHOTIC ILLNESS ON CLOZAPINE RESPONSE: A RETROSPECTIVE COHORT STUDY USING ELECTRONIC HEALTH RECORDS

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Background: There is evidence that early effective treatment of schizophrenia improves outcomes. Some researchers have argued for there being a 'critical period' of up to five years during which the course of future illness is set. Clozapine is the gold standard medication for treatment resistant schizophrenia, yet its use continues to be delayed beyond this period. There is

some evidence that earlier use of clozapine results in better clinical response. However, the number of patients in these studies has been limited.

Methods: The study was a 2 year retrospective cohort study of 425 patients who had their first adequate trial of clozapine whilst under the care of South London and Maudsley (SLaM) mental health services between 1st January 2007 and 31st December 2016 and remained on clozapine at the end of the study period. Data from electronic health records were extracted using the SLAM clinical records interactive search (CRIS) system. Dates of illness onset and clozapine commencement were manually extracted from anonymised case notes and correspondence. Clinical Global Improvement – Severity (CGI-S) scores were rated at the time of starting clozapine and at 2 years. The primary outcome variable was change in CGI-S score. Duration of illness prior to clozapine was used both as a continuous variable (years) and dichotomous variable (greater than or less than 5 years) in keeping with the critical period hypothesis. Ordinal logistic regression was performed using stata 15 statistical software to assess associations between illness duration prior to clozapine commencement and reduction in CGI-S score, adjusted for potential confounders namely severity of illness at trial onset, gender, socioeconomic status, ethnicity, age at illness onset and co-morbid substance use disorder.

Results: The mean duration of illness prior to clozapine was 10.33 years (SD = 8.40). The mean reduction in CGI-score was 1.86 (SD = 1.18).

There was a significant effect of duration of illness, with each year of delay in clozapine treatment associated less reduction in CGI-S (Adjusted OR 0.96 [95% CI 0.94, 0.98]). People who started clozapine within 5 years of illness onset enjoyed almost twice the improvement in CGI score after 2 years than people who started clozapine later (Adjusted OR 1.81 [95% CI 1.22, 2.70]).

Discussion: The study shows that duration of illness prior to clozapine remains long with a mean duration of 10.33 years. This is in line with the known literature on clozapine delay.

The regression analysis indicates that there is a significant and clinically relevant reduction in response to clozapine associated with longer duration of illness prior to clozapine prescription.

Clozapine appears to be significantly more likely to be effective if commenced within the first 5 years of illness. A similar study by Yoshimura et al showed similar results reporting an optimal response to clozapine when a cut off of 2.8 years from onset of treatment resistance to clozapine treatment was used.

Clinicians have a responsibility to consider clozapine at an early juncture if a patient is not responding adequately to first line treatments. This study provides further evidence that clozapine delay is likely to reduce potential for good outcome and supports initiatives to optimize clozapine prescribing.

M94. EFFECT OF BREXPIPRAZOLE ACROSS SYMPTOM DOMAINS IN PATIENTS WITH SCHIZOPHRENIA: POST HOC ANALYSIS OF SHORT- AND LONG-TERM STUDIES

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Background: Antipsychotics are efficacious in treating the overall symptoms of schizophrenia, as measured by the Positive and Negative Syndrome Scale (PANSS). However, PANSS subscales, such as the Marder factors, may better characterize the efficacy of antipsychotics across symptom domains.

Brexpiprazole is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, and an antagonist at serotonin 5-HT2A and noradrenaline alpha1B/2C receptors, all with subnanomolar affinity. The aim of the present post hoc analysis was to evaluate the short- and long-term effects of brexpiprazole across the spectrum of schizophrenia symptoms, using the five PANSS Marder factors.

Methods: Data were included from three 6-week, randomized, double-blind, placebo-controlled studies (Vector [ClinicalTrials.gov identifier: NCT01396421], Beacon [NCT01393613], and Lighthouse [NCT01810380]); a 52-week, randomized, double-blind, placebo-controlled maintenance treatment study (Equator [NCT01668797]); and two 52-week, open-label extension (OLEx) studies (Zenith [NCT01397786] and Study 14644B [NCT01810783]). All studies enrolled patients aged 18–65 years with an acute exacerbation of schizophrenia (DSM-IV-TR criteria). Patients allocated to oral brexpiprazole received 2–4 mg/day (short-term studies) or 1–4 mg/day (long-term studies).

The present analysis focused on PANSS Marder factors, which comprise the following domains of schizophrenia: positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression. Changes from baseline in each PANSS Marder factor score were analyzed using a mixed model repeated measures approach for short-term studies, an analysis of covariance model for the maintenance study, and were summarized using descriptive statistics for OLEx studies. Least squares mean differences (LSMDs) for brexpiprazole versus placebo with 95% confidence limits, p-values, and Cohen's d effect sizes (ES) were calculated for the short-term and maintenance studies.

Results: At Week 6, LSMDs for brexpiprazole (n=868) versus placebo (n=517) were: Positive symptoms: -1.55 (-2.30, -0.80), p<0.0001, ES=0.27; Negative symptoms: -1.12 (-1.63, -0.61), p<0.0001, ES=0.29; Disorganized thought: -1.26 (-1.78, -0.74), p<0.0001, ES=0.32; Uncontrolled hostility/excitement: -0.76 (-1.15, -0.37), p=0.0002, ES=0.26; Anxiety/depression: -0.56 (-0.91, -0.22), p=0.0014, ES=0.22. In the maintenance study, all Marder factors improved during stabilization with brexpiprazole. At last visit of the maintenance study, LSMDs for stabilized patients randomized to brexpiprazole (n=96) versus those randomized to placebo (n=104) were: Positive symptoms: -3.44 (-4.99, -1.89), p<0.0001, ES=0.62; Negative symptoms: -1.23 (-2.52, 0.07), p=0.063, ES=0.27; Disorganized thought: -1.69 (-2.81, -0.56), p=0.0035, ES=0.42; Uncontrolled hostility/excitement: -1.26 (-2.12, -0.39), p=0.0046, ES=0.41; Anxiety/depression: -0.72 (-1.47, 0.03), p=0.061, ES=0.27. In the OLEx studies, improvements in all Marder factors were maintained over 58 (6+52) weeks of brexpiprazole treatment.

Discussion: Brexpiprazole was associated with clinically relevant improvement in all five Marder factors in patients with acute schizophrenia, and maintenance of this improvement in stabilized patients. This analysis suggests that brexpiprazole has efficacy across the spectrum of schizophrenia symptoms in the short- and long-term. Further work is needed to determine if

brexpiprazole has a specific effect on non-positive symptoms, or whether improvement in psychosis during acute treatment leads to secondary improvement in other symptom domains.

M95. ASSOCIATIONS BETWEEN VITAMIN C LEVELS, DEMOGRAPHIC FACTORS AND TREATMENT RESPONSE IN ANTIPSYCHOTIC-NAïVE PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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Background: Alterations in the dopaminergic transmitter systems have been associated with psychosis. Ascorbic acid (vitamin C) plays a role as a co-factor in the dopaminergic pathway and may have an antagonistic effect on the dopaminergic systems. Patients with chronic schizophrenia generally present with low levels of vitamin C, and low vitamin C levels have also been observed in patients with first-episode schizophrenia. Antipsychotic medication acts by modulating striatal dopamine D2 receptors, but to what extend the effect of antipsychotic medication is affected by the levels of vitamin C is yet to be elucidated.
We here investigate the associations between levels of vitamin C, clinical symptoms and response to monotherapy with a partial dopamine D2 receptor agonist in initially antipsychotic-naïve patients with first-episode psychosis.

Methods: Vitamin C levels were measured in 52 patients (24 females, age 23.1 ± 5.2) and 57 matched healthy controls (20 females, age22.7 ± 4.3) at baseline and after 6 weeks. Demographic data, body mass index, smoking status, reports on fruit and vegetable intake were obtained on all participants. Patients' psychiatric symptoms were assessed with the Positive And Negative Syndrome Scale before and after treatment with aripiprazole (mean dose 10.41 mg, SD ±4.8 mg), and s-aripriprazole was measured at follow-up.
Results: Multiple regression with baseline vitamin C levels as dependent variable and group, sex, age, smoking, BMI, vitamin supply and intake of fruit and vegetables as independent variables showed that vitamin C was associated with group, age and intake of fruit and vegetables ($R2=0.24$, $F=10.7$, $p<0.001$). Patients displayed lower levels of vitamin C (57.4 ± 25.9) than controls (72.7 ± 21.4) ($t=3.4$, $p=0.001$). No associations were found between baseline vitamin C levels and symptom severity in patients.
In both patients and healthy controls vitamin C levels were stable over time, and patients improved in positive-, negative- and general symptoms (all p-values < 0.001). Higher baseline vitamin C levels were associated with improvement in negative symptoms ($R2=0.20$, $F=8.2$, $p=0.007$) but

not with age, sex or s-aripiprazole. There were no associations with improvement in positive or general symptoms.

Discussion: We found reduced levels of vitamin C in patients at their first presentation of psychosis, which was not associated with symptom severity. Nevertheless, higher levels of vitamin C was associated with improvement in negative symptoms during treatment with aripiprazole. Though this study found reduced negative symptoms in patients following aripiprazole treatment, negative symptoms are generally considered challenging to alleviate, and a potential adjunctive effect of vitamin C on treatment response should be tested in future randomized clinical trials.

M96. STRESS AND COPING WITH THE COVID-19 PANDEMIC: A SURVEY OF PSYCHIATRIC PATIENTS AT CLINICAL TRIAL SITES

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Background: Recent research on the COVID-19 pandemic suggests that individuals who suffer with serious mental illness (SMI) are at heightened risk of infection and have increased mortality, due to their illness or lack of access to healthcare. As a consequence, progress in developing new treatments for the SMI has been disrupted, with many interruptions and holds places on clinical trials in psychiatry due to concerns regarding the pandemic and its risks to SMI patients.
Methods: To investigate this further, we conducted, a multi-site cross-sectional survey of 94 clinical trial patients diagnosed with bipolar disorder (n=23), major depressive disorder (n=27), or schizophrenia (n=44) in three geographically-distinct clinical trial sites (Maryland, Georgia and Florida) between June and September 2020. The survey collected data on COVID health service utilization, COVID knowledge and concerns, risk perceptions, use of precautionary measures, and psychological distress. Prevalence rates were calculated for sample characteristics and demographics, and low vs high stress groups were compared on survey variables using the Pearson's Chi Squared Test of Independence.
Results: The results from the surveys indicate that COVID19 knowledge, awareness, and the use of precautionary safety measures (i.e. handwashing, personal protective equipment, and social distancing) were robust and mirrored the general population. While the majority of patients reported experiencing moderate or extreme levels of distress (61.5%, n=56), high levels of stress were correlated with positive coping skills.
Discussion: These findings suggest that clinical trial patients with SMI can participate safely in clinical trials despite the increase safety risks posed by the COVID-19 pandemic.

M97. MOLECULAR MECHANISMS INVOLVED IN THE PREVENTION AND REVERSAL OF KETAMINE-INDUCED SCHIZOPHRENIA-LIKE BEHAVIOR BY RUTIN: THE ROLE OF GLUTAMIC ACID DECARBOXYLASE ISOFORM-67, CHOLINERGIC, NOX-2-OXIDATIVE STRESS PATHWAYS IN MICE

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Background: Nicotinamide adenine dinucleotide phosphate oxidase-2 (Nox-2) signaling pathways have been identified as important targets for mitigating oxidative-nitrergic stress-induced alterations in GABAergic (Gamma aminobutyric acid) and cholinergic neurotransmissions. Previous studies have shown that derangement of glutamic-acid decarboxylase-67 (GAD67), the rate-limiting enzyme for the synthesis of GABA, and acetylcholinesterase activity have important implications in schizophrenia pathology. Thus, it has been hypothesized that suppressing Nox-2-oxidative may enhance GABAergic and cholinergic neurotransmissions and retard the progression of the disease. Rutin, a neuroactive antioxidant compound, with proven neuroprotective property has been shown to reduce schizophrenic-like behavior in mice. Hence, we evaluated the effects of rutin on the brain markers of GABAergic, cholinergic and oxidative/nitrergic stress in the preventive and reversal of schizophrenia-like behavior induced by ketamine (KET).

Methods: Male mice were given rutin (0.1, 0.2 and 0.4 mg/kg) or risperidone (0.5 mg/kg) orally for 14 days prior to ketamine (20 mg/kg, i.p.) treatment from the 8-14th day (prevention). Ketamine was given for 14 days prior to rutin and risperidone (reversal). Behavioral (open-field, social-interaction and Y-maze tests), biochemical (oxidative/nitrergic stress markers, acetylcholinesterase activity), histochemical (GAD67, Nox-2) and neuronal cell deaths in the striatum, prefrontal-cortex, and hippocampus were evaluated. Schizophrenic-like behaviors consisting of positive (open-field test), negative (social interaction test) and cognitive (Y-maze test) symptoms were evaluated. Afterwards, brain levels of biomarkers of GABAergic (Glutamic acid decarboxylase-67, GAD67), cholinergic (acetylcholinesterase activity), oxidative [glutathione (GSH), malondialdehyde (MDA)] and nitrergic alterations were measured in the striatum, prefrontal cortex (PFC) and hippocampus. Regional expressions of immunopositive cells of GAD67 and Nox-2 were determined using immunohistochemistry. Furthermore, neuronal cell deaths in the striatum, prefrontal-cortex, and hippocampus were also examined.

Results: Findings from the present study showed that the exposure of mice to KET causes hyperlocomotion, social interaction deficit and memory impairment, which were prevented and reversed treatments with rutin. Importantly, KET reduced the expressions of GAD67 enzyme in the striatum, prefrontal cortex and hippocampus indicating decreased GABAergic neurotransmission which was prevented by rutin administration. Also, the preventive and reversal treatments of mice with rutin attenuated KET-induced increased expression of the superoxide producing enzyme, Nox-2 when compared with KET-treated group. Moreover, exposure of mice to KET increased malondialdehyde, nitrite contents, acetylcholinesterase activity and neuronal cell death in the striatum, prefrontal-cortex and hippocampus. Conversely, these were significantly reduced by rutin in both the prevention and reversal studies. The decreased glutathione levels due to ketamine were marked increased by rutin in both studies.

Discussion: The study showed that rutin prevents and reverses KET-induced schizophrenia-like behavior via mechanisms linked to inhibition of Nox-2 expression, oxidative/nitrergic stress, down-regulation of acetylcholinesterase activity, and increased expression of GAD67 protein in the brains of rats.

M98. WHICH ARE THE BEST PREDICTORS OF FUNCTIONAL OUTCOME IN SCHIZOPHRENIA?

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Background: Functional impairment is a main feature of schizophrenia affecting personal and occupational areas that lead to a significant reduction in patients' quality of life. A large number of studies have reported different factors that could explain and predict functional disruption, such as cognitive and metacognitive abilities, demographical and clinical variables, and, in recent years, subthreshold Autistic Traits (ATs). However, previous research has not been exhaustive in assessing the range of possible difficulties experienced by patients in their own everyday life, often focusing only a specific or a subset of functional domains or influencing factors.
In this study, we perform a comprehensive analysis examining the combined influence of cognitive, metacognitive abilities, demographic and clinical variables as well as ATs on both global daily functioning and functional capacity in a sample of schizophrenia patients.

Methods: 123 patients with schizophrenia were assessed for psychopathology (Positive and Negative Syndrome Scale, PANSS), ATs (PANSS Autism Severity Score, PAUSS), intellectual level (Wechsler Adult Intelligence Scale–Revised), daily functioning (Quality of Life Scale, QLS; UCSD Performance based Skills Assessment–Brief, UPSA-B), neurocognition (Brief Assessment of Cognition in Schizophrenia, BACS) and sociocognitive domains (Interpersonal Reactivity Index - IRI, Theory of Mind Picture Sequencing Task, PST).
A two-step cluster analysis was conducted to identify groups of patients characterized by different functional profiles using QLS subscores and UPSA subscores as clustering variables. Differences between clusters were evaluated using Analyses of Variance (ANOVAs). In order to explore predictors of functional outcome, a backward stepwise logistic regression analyses were performed with demographic, clinical, cognitive and sociocognitive variables as predictor variables, and Cluster (high functioning vs low functioning) as the dependent variable.

Results: The Bayesian information criterion, two-step cluster analysis produced two clusters: A low functioning cluster (N=63) and a high functioning cluster (N=60). Compared to the high functioning cluster, the low functioning cluster showed more compromised cognitive and ToM abilities, fewer years of education, more severe clinical symptomatology, as well as a more disrupted functional outcome in all QLS and UPSA domains. No differences were found between the groups in age, sex distribution, and empathic abilities. The backward stepwise logistic regression analysis, explaining 39% of the variance and correctly classifying 76.6% of the cases, showed that the odds of being a member of the high functioning group are significantly higher for individuals with (i) more years of education (OR= 1.21, 95%CI [1.02, 1.44]); (ii) higher Theory of Mind scores (OR= 1.17, 95%CI [1.03, 1.33]); (iii) higher PAUSS Stereotypies/Narrowed Interests Score (OR= 1.33, 95%CI [1.09, 1.66]); (iv) lower PAUSS Difficulties in Social Interaction Score (OR= 0.79, 95%CI [0.64, 0.97); (v) lower PAUSS Difficulties in Communication Score (OR= 0.62, 95%CI [0.45, 0.84]), and with (vi) being male (OR= 3.79, 95%CI [1.35, 10.61]).

Discussion: In order to analyze an overall functional disruption in schizophrenia, we studied the impact of the key relevant factors on quality of life and functional capacity. Our results underline the role of metacognitive abilities, years of education, sex, and particularly the role of specific subdomains of ATs in predicting functional outcome in schizophrenia.

M99. ASSESSING SOCIAL FUNCTIONING IN YOUTH AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: It has been well established that youth at clinical high-risk (CHR) of psychosis already have impaired social functioning, that a decline in social functioning has been identified as a predictor of transition, and thirdly, that many CHR individuals demonstrate difficulties in social functioning independently of whether they transition to psychosis. The Global Functioning Scale: Social (GF:S), is the gold standard measure to examine social functioning in CHR youth. However, it does not provide specific details of where difficulties might be. The First Episode Social Functioning Scale (FESFS) was developed to measure social functioning in first episode psychosis (FEP) individuals and measures further domains of functioning.
Objective: to determine if using the FESFS in a CHR sample would add to our knowledge about the social functioning of this population. Aims: 1) to compare ratings on the FESFS with ratings on the GF:S to determine if the scales were tapping different domains; 2) to compared CHR ratings on the FESFS with those of a FEP sample since the FESFS has not been used in CHR or with a population younger than 18.

Methods: The CHR sample consisted of 98 youth who met the Criteria of Psychosis-Risk Syndromes (COPS) and rated 7 or less on the GF:S. The FEP participants were all within two years of onset, were currently being treated in a FEP clinic. The GF:S assesses peer relationships, peer conflict, age-appropriate intimate relationships, and involvement with family members. The GF:S provides a single score for social functioning on a 10-point Likert scale [10=superior social or role functioning to 1=extreme social isolation]. The FESFS is a 4-point Likert scale [1=totally disagree to 4=totally agree (score A: perceived ability); 1=never to 4=always (score B: behavior past 3 months)] with 34 items, which measure nine domains of social functioning: living skills, social interaction, friends and social activity, intimacy, family, school relationships, educational abilities, and work relationships and work abilities.
Results: Of the 96 CHR participants (age: M=17.1; SD=4.3), 68.8% were Caucasian, and 31.3% were other race. The majority of the participants were single (95.8%) and had completed an average of 10 (SD=2.5) years of education. Of the 78 FEP participants (age: M=24.6; SD=5.8), 67.1% were Caucasian and 32.9% other race. The majority of participants (88.6%) were single and had completed an average of 12.6 (SD=2.0) years of education. Both groups significantly differed in age ($p \leq .001$) and education ($p \leq .001$). There were very few differences on all ratings between the FEP and CHR groups suggesting that these two samples rate very similarly. High ratings on the GF:S was significantly associated with high ratings on all the total scores and on several individual items in the FESFS.

Discussion: This suggests that overall, both scales are capturing the quality of social functioning but that the FESFS may be capturing different social domains has some items that may not be captured in a global score such as the GF:S. Since the FESFS captures different social domains, it may be useful for use in a CHR clinical setting to determining specific social functioning difficulties for intervention is needed.

M100. VIRTUAL REALITY COGNITIVE BEHAVIORAL THERAPY FOR PARANOID DELUSIONS – A RANDOMIZED CONTROLLED COST-EFFECTIVENESS TRIAL

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Background: Seventy percent of patients with schizophrenia and other psychotic disorders has paranoid delusions. Paranoid delusions are associated with great distress, hospital admission and social isolation. Cognitive behavioral therapy (CBT) is the main psychological treatment, but the median effect size is only small to medium. Virtual reality (VR) has a great potential to improve psychological treatment of paranoid delusions. In a previous study, we found that VR based CBT (VRcbt) for paranoid delusions is effective compared to waiting list. As a next step, a direct comparison with standard CBT is needed. The aim of this project is to investigate if VRcbt is more (cost-)effective than standard CBT for treatment of paranoid delusions and improving daily life social functioning of patients with schizophrenia and related psychotic disorders. Three research questions will be addressed: 1. Does VRcbt lead to better clinical and social outcomes? 2. Are fewer treatment sessions needed to achieve meaningful clinical change? 3. Is VRcbt more cost-effective at 6 months follow-up?

Methods: A total of 106 patients with DSM-5 diagnosis of psychotic disorder and at least moderate level of paranoid ideations will be randomized to either VRcbt or standard CBT treatment for paranoid delusions. VRcbt consists of maximum 16 sessions in virtual social situations that trigger paranoid ideations and distress, delivered in an 8-12 week time frame. Standard CBT also consists of maximum 16 sessions, aiming at reappraisal of the meaning of paranoid beliefs to reduce distress and improve coping in daily life, including the use of exposure and behavioral experiments.

Participants will be interviewed and tested at baseline, post-treatment and at six months follow-up. Primary outcome is level of paranoid ideations in daily life social situations, measured with ecological momentary assessments (EMA) at semi-random moments ten times a day during seven days, before and after treatment. Every session, participants and therapists will rate level of paranoid ideation and global clinical impression.

Results: Seven mental health services throughout the Netherlands participate in this RCT. Up untill now, fourteen psychologists have been trained in VRcbt and the first patients have been included in the trial. Some preliminary results will be presented.

Discussion: Comparison of VRcbt and cbt will provide information about the relative (cost-)effectiveness of VRcbt for this population. VRcbt may become a preferred psychological treatment for paranoid delusions and social anxiety in patients with psychotic disorder.

M101. AN AUTOMATED LINGUISTIC ANALYSIS IN PEOPLE WITH SCHIZOPHRENIA: ASSOCIATION WITH DIAGNOSIS AND CLINICAL FEATURES TOWARD MARKERS OF ILLNESS

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Background: Language disturbances are a core symptom of schizophrenia. Currently, computational models, which provide quick quantitative analyses of speech, represent a promising tool for research with possible clinical impact. The aim of this study is two-fold. First, we investigated differences between people with schizophrenia and healthy controls in automatically derived language characteristics and evaluated their predictive role in discriminating the two populations. Second, we analyzed the relationship between linguistic and clinical characteristics in patients.

Methods: 67 Italian native-speaker outpatients with schizophrenia, age 18–65 years, were recruited at the Schizophrenia Research and Clinical Unit, IRCCS San Raffaele, Milan, Italy. 36 Italian native-speaker control subjects, selected for similarity in age and education, were also included. All subjects were administered the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) Interview to elicit spontaneous spoken language. All patients were assessed for pragmatics, neuro-social cognition, psychopathology, and quality of life at the baseline. Language characteristics were analyzed using the Linguistic Inquiry and Word Count program (LIWC); moreover the type token ratio (TTR) was computed as a measure of lexical richness. Differences in language characteristics between patients and healthy controls were analyzed with t-tests, while their predictive value in differentiating the two populations was evaluated with Receiver Operating Characteristic (ROC) curves. Last, Pearson's Product Moment Correlation was used to measure the relationship between language characteristics and clinical features in patients. All statistical analyses were performed using R software.

Results: Significant differences emerged between the two populations. In detail, people with schizophrenia showed more verbosity than healthy controls, but lower vocabulary variation. Patients also used more first-person pronouns (both plural and singular) and more affective words. Furthermore, ROC curves analysis highlighted that some of these language characteristics, namely word count, words per turn, TTR and pronouns, have a good predictive value in differentiating between patients and healthy controls. Finally, the data showed significant correlations between language characteristics and psychopathology, pragmatics, and quality of life in patients.

Discussion: Data showed significant differences between people with schizophrenia and healthy controls in several automatically derived aspects of language. Interestingly for clinical purposes, these linguistic measures also proved to be a predictive tool in the classification of the two populations and were related to clinical features and daily functioning in patients. These results represent an important step towards a standardized approach to linguistic alterations to aid clinical diagnosis, assessment, and monitoring of patients. The automated language analysis using LIWC is a non-invasive, quick and low-cost approach, thus representing a promising tool in schizophrenia, linked to both clinical and neurobiological data. The automated approach has also

the potential to improve prediction of psychosis outcome among at-risk youths and to identify linguistic targets for remediation and preventive interventions.

M102. ASSOCIATIONS BETWEEN PERCEIVED HOSTILITY, INTERPERSONAL RELATIONSHIPS, AND SOCIAL NETWORK SIZE

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Background: Paranoia has been associated with worse social functioning in individuals with schizophrenia (Pinkham et al., 2016). Persecutory delusions and paranoia have been shown to be related to greater levels of perceived hostility (Combs et al., 2009; Combs et al., 2013). Despite the link between paranoia and perceived hostility, research has not explored how perceived hostility directly relates to interpersonal functioning. Links between perceived hostility and interpersonal relationships could determine if interventions targeting high levels of perceived hostility could improve interpersonal functioning. Moreover, research has shown that paranoia is related to fewer social contacts and lower levels of social engagement (Combs et al., 2013). With the association between paranoia and perceived hostility, it is could be that perceived hostility will be related to social support in some way as well, such as in size of social networks.
The current study will explore possible relations between perceived hostility, interpersonal functioning, and social network size when controlling for paranoia. We hypothesize that 1) perceived hostility and paranoia will be positively related, 2) perceived hostility and interpersonal relationships will be negatively related when controlling for paranoia, and 3) perceived hostility and social network size will be negatively related when controlling for paranoia.

Methods: Participants from a transdiagnostic sample of individuals with psychosis and healthy controls completed multiple measures to assess our hypotheses. The Green Paranoid Thoughts Scale was used to examine levels of paranoid thoughts, subscales from the Adult Social Relationships Scale were used to examine feelings of perceived hostility, the Interpersonal Relationships subscale of the Specific Levels of Functioning Scale was used to assess interpersonal functioning, and the Social Network Index was used to determine the number of people in a social network.
Results: Analyses indicated that a positive correlation was present between perceived hostility and paranoia ($N=114$, $r = .54$, $p < .001$). A negative correlation was present between perceived hostility and interpersonal functioning ($N = 117$, $r = -.335$, $p < .001$). When controlling for paranoia, this relation attenuated, but was still significant ($N = 114$, $pr = -23$, $p = .012$). There was no significant correlation between perceived hostility and social network size. ($N = 118$, $p > .05$).
Discussion: Our first hypothesis between paranoia and perceived hostility was supported, replicating what previous research has shown. This finding shows that higher levels of paranoia are related to higher levels of perceived hostility. Our second hypothesis between perceived hostility and interpersonal functioning when controlling for paranoia was also supported. This means that higher levels of perceived hostility are related to lower levels of interpersonal functioning when controlling for the effect that paranoia could have on the relation. However, because the correlation was weaker compared to the analysis that did not control for paranoia, it means that paranoia does play some role in the relationship between perceived hostility and

interpersonal functioning. Our third hypothesis between perceived hostility and social network size was not supported, meaning that levels of perceived hostility are not related to the number of individuals in a social network. Based on these findings, research could investigate whether perceived hostility is a mechanism of paranoia, or vice versa. Furthermore, more research needs to be conducted on how perceived hostility relates to aspects of social support, such as loneliness, friendship, and rejection.

M103. THE ROLE OF LONELINESS IN PSYCHOSIS-PRONENESS DURING COVID-19: PRELIMINARY FINDINGS FROM CROATIA

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Background: While social withdrawal is often regarded as a prodromal symptom of psychosis, there is growing evidence that identifies loneliness itself as a reliable risk factor for an onset of psychosis, especially during the COVID-19 pandemic, which has disrupted almost every aspect of daily life. The present study investigated the role of loneliness in psychosis-risk, depression, anxiety and stress in the Croatian population. Because of Croatia's recent history of transgenerational war trauma and the relative lack of prodromal data, it presents a unique opportunity to examine the impact of loneliness and other psychosocial factors on psychosis-proneness.

Methods: We conducted an anonymous, online study of Croatian residents (age 18-73; 78% female). The survey link was distributed via social media and mass email lists between July and September 2020. Information collected included demographics, COVID-related questions, preferred interpersonal distance, general health, attitudes and practices related to social distancing, positive emotions, and past trauma. We also administered the Depression, Anxiety, and Stress Scales (DASS; Lovibond & Lovibond, 1995); the UCLA Loneliness Scale (Russell, 1996); and the Prodromal Questionnaire-16 (PQ-16; Ising et al., 2012).

Results: Out of 404 participants, 71-73% completed the mental health items. 16.7% met the criteria for psychosis high-risk on PQ-16. Loneliness had a statistically significant impact on PQ-total (β= 0.418; p< 0.001) and PQ-distress (β= 0.434; p< 0.001) scores. Gender impacted both PQ-total (β = -0.202; p <.001) and PQ-distress (β = -0.118; p =0.023), with women endorsing fewer items and reporting less distress but there was no statistical sex difference in levels of loneliness. Domestic abuse/violence was associated with PQ distress (β= 0.208; p< 0.001). Exposure to trauma and PQ total score (rho=0.15; p=0.012) and PQ-distress (rho=0.233, p< 0.001) were correlated, as were between exposure to trauma and loneliness (rho=0.224; p<0.001). COVID concern and PQ distress (rho=0.135; p=0.022) were also associated but preferred interpersonal distance was not associated with psychosis-risk. Importantly, the associations between PQ total scores and DASS Stress (r=0.275; p<0.001), DASS Anxiety (r=0.372; p< 0.001) and DASS Depression (r=0.343; p<0.001) were robust. Similarly, PQ distress and DASS Stress (r=0.460; p< 0.001), DASS Anxiety (r=0.568; p<0.001), and DASS Depression (r=0.501; p< 0.001) were also significantly correlated.

Discussion: These findings suggest an important role of loneliness in psychosis-proneness in Croatia. While depression, anxiety and stress were closely related to increased levels of psychosis-risk, surprisingly, the impact of exposure to trauma was relatively weak despite the history of wars

and recent natural disasters in Croatia. Psychosis-proneness did not have an effect on preferred interpersonal distance. To conclude, loneliness is a highly salient issue for individuals with psychosis and it is extremely important to assess and target loneliness within a multi-faceted psychosocial intervention for those at risk for schizophrenia.

M104. CORRELATES OF AUTOMATICITY/HABIT STRENGTH IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Poor adherence to prescribed medications is a significant public health problem across chronic illnesses, including SMI. Meanwhile, adherence is considered a modifiable risk factor that can lead to better health outcomes. Understanding habitual processes can shed light on strategies to improve adherence. The current study took the first step and investigated correlates of habit in SMI to enhance our understanding of its relationship with multiple facets of functioning.
Methods: The current study examined both self-report and clinician-rated data from 113 individuals (56% male, mean age 39 years) with SMI. We collected data on self-report of habits for taking medication, checking daily schedule and self-care (Self-Reported Habit Index), symptomology (BPRS), social and community functioning (SOFAS, MCAS), and cognitive functioning (BAC). Self-Reported Behavioral Automaticity Index assesses habit strength; lower scores indicate greater habit strength. An example item assessing habit strength is "I take medication without thinking."
Results: Preliminary results from the current study supported our hypothesis that habitual behaviors are related to medication adherence measured by both self-report ($r= 0.19$, $p<.05$) and clinician rating ($r= -0.52$, $p<.05$). Age is negatively associated with both automaticity and habit strength, which means the younger patients report that their behaviors are less guided by habit ($r= -0.33$, $p<.05$). Self-report of Automaticity in different habit areas is intra-correlated. This suggests that if a person exhibits a high level of Automaticity in one area, for example, maintaining self-hygiene, they also tend to take their medication and check the daily calendar more automatically. Findings also show that the stronger individuals' habits are, the better they function in the community ($r= -0.32$, $p<.05$). However, they also tend to be more symptomatic ($r= 0.35$, $p<.05$), and perform poorer on memory ($r= 0.25$, $p<.05$) and processing speed ($r= 0.22$, $p<.05$) tasks.
Discussion: Habit and habit strength have been found to correlate key functional measures. Future studies can focus on examining pathways to habit formation based on known factors. Understanding the active ingredient of habit can predict and modify future behavior to enhance treatment adherence and outcomes.

M105. CONTRIBUTIONS OF EMPATHY AND EMOTION IDENTIFICATION TO SUBCLINICAL PARANOIA

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Background: Paranoia is one of the most common psychotic experiences, occurring in over 50% of patients with schizophrenia and 10-15% of the general population. Paranoia has been associated

with a multitude of social cognitive deficits, and these relationships are observed in both clinical and non-clinical populations, suggesting a continuum of social cognitive impairment that contributes to paranoid thinking. Empathy is significantly and broadly impaired in schizophrenia, yet its relationship with paranoia is unknown. Empathy relies on the ability to accurately perceive another's emotions, beliefs and motivations such that deficits in empathy may exacerbate feelings of suspiciousness or mistrust. Furthermore, deficits in emotion identification – a very early component of empathic processing – are present in both clinical and non-clinical paranoia. Deficits in emotion identification may therefore underlie relationships between paranoia and empathic processing. The current investigation aims to add to the literature on social cognition and paranoia by: 1) characterizing the relationship between paranoid ideation and empathy, and 2) testing whether there is an indirect effect of emotion identification on the relationship between empathy and paranoia.

Methods: Paranoia, empathy, and emotion identification were assessed in a non-clinical sample of adults (n=226) from the Nathan Kline Institute-Rockland (NKI-Rockland) sample. Paranoia was measured using the Peters Delusions Inventory-21 (PDI-21), a self-report instrument designed for assessing distress, preoccupation, and conviction of delusional ideation in the general population. Empathy was measured using the Interpersonal Reactivity Index (IRI), a self-report instrument designed to assess empathy using four subscales: Personal Distress, Empathic Concern, Perspective Taking, and Fantasy. Emotion identification was assessed using the Penn Emotion Identification Test. Structural equation modeling was used to estimate relationships between the four measures of empathy and paranoia, including the indirect effect of emotion identification. Age and sex were included as covariates.

Results: Paranoia was associated with the fantasy subscale of the IRI, such that higher fantasy was correlated with more severe paranoia ($p = .003$). No other empathy subscales were associated with paranoia. The empathic concern subscale was negatively associated with emotion identification, with higher empathic concern related to worse emotion identification ($p = .003$). There was a trend-level association between higher fantasy and higher emotion identification ($p= .058$). Paranoia and emotion identification were not significantly associated and all indirect paths through emotion identification were non-significant.

Discussion: More severe paranoia was associated with greater endorsement of the fantasy sub-scale, a perspective-tasking, cognitive aspect of empathy that has been previously associated with greater delusion severity in both schizophrenia and psychosis-risk populations. These results add to the literature demonstrating imaginative perspective-taking contributes to delusional thinking, by suggesting it may also contribute to paranoia in the general population. These data do not, however, point to robust global relationships between empathy and paranoia or to emotion identification as an underlying mechanism. Deficits in empathy and emotion identification observed in schizophrenia may be associated with the broader pathology of schizophrenia, and therefore not detectable with non-clinical populations.

M106. FACETS OF PSYCHOPATHY IN PSYCHOTIC AND NON-PSYCHOTIC VIOLENT OFFENDERS

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Background: Persons with psychosis are at a small but increased risk of committing violence. Violence in psychosis has been linked to antisocial behavior and psychopathy traits. Psychopathy is a multi-faceted clinical construct comprising interpersonal, affective, lifestyle, and antisocial traits. These traits may contribute differently to violent offending among persons with psychotic disorders and among non-psychotic violent offenders. They may represent different targets for treatment and prevention. Here, we explored patterns of psychopathy subdomains among violent offenders with or without psychosis.

Methods: 49 males with a history of severe violence (murder, attempted murder, severe violence towards other persons, or sexual assaults) with (n=28, mean age 36.3 (SD19.4) years, schizophrenia spectrum n=24) or without (n=21, mean age 40.3 (SD 13.4) years) psychosis were recruited from high-security forensic psychiatry wards or preventive detention prison facilities. All participants underwent thorough clinical characterization and mapping of violence history from medical journals and court documents. Psychopathy traits were assessed with the Psychopathy checklist revised (PCL-R) by specifically trained medical doctors, psychiatrists, or psychologists, and split into subdomains following the four-facet model: Facet 1: Interpersonal (PCL items 1, 2, 4, 5); facet 2 Affective (items 6, 7, 8, 16); facet 3 Lifestyle (items 3, 9, 13, 14, 15); and facet 4 Antisocial (items 10, 12, 18, 19, 20). Group differences in total and subdomain scores were analyzed with non-parametric independent samples Mann Whitney U tests. Bonferroni adjustment for multiple comparisons was applied.

Results: Total PCL scores did not differ between the groups (U=283.5, p=0.832), mean 20.4 (SD 7.69) and 19.21 (SD 8.83) for the non-psychosis and psychosis group respectively. The non-psychotic violent offenders had significantly higher facet 2 scores, i.e. the affective traits comprising lack of remorse or guilt, shallowness, callous/lack of empathy, and failure to accept responsibility for own actions, than the psychosis group (U=143.5, Bonferroni corrected p-value=0.015, mean 6.81 (SD 1.57) and 4.93 (SD2.34) for the non-psychosis and psychosis group respectively). Facet 1, 3 or 4 scores did not differ between the groups (U=327.5 p=0.495; U=300.3, p=0.903; U=197.5, p=0.072, respectively).

Discussion: Psychosis patients with a history of severe violence show less affective psychopathy traits (i.e. lack of remorse or guilt, shallow affect, callous/lack of empathy, and failure to accept responsibility for own actions) than non-psychotic violent offenders, which may point towards specific underlying biological mechanisms and targets for treatment and prevention.

M107. THE ROLE OF NEGATIVE SYMPTOMS ON SOCIAL SKILLS AND PERCEPTIONS OF SOCIAL RELATIONSHIPS IN PSYCHOSIS

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Background: Negative symptoms are common in psychotic disorders and contribute to significant social impairment (Kalin et al., 2015; Ventura et al., 2014). Previous research has shown that negative symptoms are related to poorer observed social skills (Blanchard et al., 2015) and more negative perceptions of social partners (McCarthy et al., 2018). Negative symptoms also impact how those with psychosis are perceived by others. Riehle et al. (2018) found that raters were less willing to interact with those high in negative symptoms and that this relation was mediated by poorer social skills. However, findings are based on overall social skills ratings and the role of specific social skills in these relations is unclear. Additionally, research has not explored how social skills relate to perceptions of social relationships more broadly.

Methods: The current study seeks to extend the previous literature by exploring the relation between negative symptoms, specific social skills, and perceptions of social relationships in a transdiagnostic sample with psychosis. We hypothesize that: 1) poorer social skills will be related to greater motivation and pleasure (MAP) and expressivity (EXP) negative symptoms, 2) social skills deficits will be related to less positive perceptions of social relationships, and 3) social skills deficits will be related to less positive perceptions of social relationships when controlling for negative symptoms.

Data were collected from a transdiagnostic sample of adults with psychotic disorders and healthy controls. Negative symptoms were measured using the Clinical Assessment Interview for Negative Symptoms which measures MAP and EXP deficits. Perceptions of social relationships were assessed using the Adult Social Relationships Scale (ASRS). To measure social skills, participants responded to a short video of an outgoing female describing her social relationships and activities by detailing what they like to do with their friends and family. Responses were video recorded and scored by raters blind to psychiatric diagnosis of participants using a social skills manual adapted for this task (Garcia et al., 2018). Participants were rated on verbal and nonverbal skills.

Results: Analyses (N = 113) indicated that MAP deficits were universally related to poorer social skills (rs .19-.36, ps < .05), while EXP deficits were related to poorer spontaneous conversation, fluency, eye contact, and nonverbal expression (rs .20-.32, ps < .05). ASRS subscales were related to several social skills. Of note, greater emotional support related to more clarity, fluency, and eye contact (rs .20-.34, ps < .05), greater friendship related to more fluency and eye contact (rs .24-.26, ps < .05), both greater loneliness and greater perceived rejection related to less fluency more negative statements and less eye contact (rs = .23-.32, ps < .05), and greater perceived hostility related to more negative statements (r = .23, p = .01). After controlling for negative symptoms, greater emotional support was related to more clarity (r = .25, p = .01), greater loneliness was related to increased use of negative statements (r = .20, p = .04), and perceived rejection was related to both increased use of negative statements (r = .22, p = .04), and poorer eye contact (r = .22, p = .03).

Discussion: Findings suggest that negative symptoms contribute to deficits in social skills and some of these deficits uniquely contribute to less positive social experiences. It may be that those with high levels of negative symptoms and poor social skills act in ways that make it more difficult for others to socially engage with them; therefore, these individuals perceive others as less supportive and more socially rejecting. Results will be discussed further at time of presentation.

M108. OBJECTIVE NEUROPSYCHOLOGICAL FUNCTIONING PREDICTS FUNCTIONAL CAPACITY BUT NOT SUBJECTIVE FUNCTIONING IN INDIVIDUALS WITH HIGH LEVELS OF NEGATIVE SYMPTOMS

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Background: Individuals with schizophrenia and high levels of negative symptoms are at greater risk for poor functional outcomes. However, the strongest predictors of psychosocial functioning in this subgroup are not well-understood. The current study examined the strongest modifiable predictors of performance-based functional capacity and social skills, and self-reported functioning, in a negative symptom-enriched sample of individuals with schizophrenia and schizoaffective disorder.

Methods: 55 adults with moderate-to-severe negative symptoms were administered tests of neuropsychological performance (MATRICS Consensus Cognitive Battery along with a test of premorbid IQ), functional capacity (UCSD Performance-Based Skills Assessment-Brief [UPSA-B]), social skills (Social Skills Performance Assessment [SSPA]), self-reported functioning (Independent Living Skills Survey [ILSS]; Specific Levels of Functioning Scale [SLoF]), psychiatric symptom severity (Clinical Assessment Interview for Negative Symptoms [CAINS]; Scale for the Assessment of Negative Symptoms [SANS]), defeatist/asocial beliefs (Defeatist Performance Attitude Scale [DPAS]; Asocial Belief Scale [ABS]); derived 3-item measure of intrinsic motivation from the Heinrichs-Carpenter Quality of Life Scale [QLS-3]. Multiple linear regression was used to examine the strongest modifiable predictors of both performance-based and subjective indices of functioning. To minimize Type II error, covariates were selected based on bivariate significance at $p<.05$ via Pearson correlations.

Results: For the UPSA-B, bivariate correlations determined that race, premorbid IQ, MCCB global performance, and QLS-3 scores were associated with UPSA-B performance. Together, these variables explained 52% of the variance in UPSA-B performance [$F(4, 49)=13.39$, $p<.001$]. MCCB global performance and QLS-3 scores uniquely explained 21% of UPSA-B variance, with only the MCCB global score emerging as a significant predictor ($p<.001$). For the SSPA, bivariate correlations determined lower scores on the CAINS motivation/pleasure subscale, as well as higher QLS-3 and MCCB global scores, were associated with better social skills performance. Together, these variables explained 23% of variance in SSPA performance [$F(3, 50)=4.85$, $p=.005$], with CAINS motivation/pleasure and the MCCB global score emerging as the only significant predictors ($p=.034$ and $p=.011$, respectively). For the ILSS, bivariate correlations determined that lower scores on the SANS diminished expression subscale and higher QLS-3 scores were associated with better ILSS performance. Together, these variables explained 28% of the variance in ILSS scores [$F(2, 47)=9.01$, $p<.001$], with SANS diminished expression score emerging as the only significant predictor ($p=.005$). For the SLoF, bivariate correlations determined that lower scores on the CAINS motivation/pleasure subscale, ABS, and DPAS, and higher QLS-3 scores, were associated with higher SLoF scores. Together, these variables explained 39% of variance

[F(4, 50)=7.81, p<.001], with ABS and QLS-3 scores emerging as the only significant predictors (p=.034 and p=.009, respectively).
Discussion: Functional capacity and social skill performance were positively associated with neuropsychological functioning, with less severe negative symptoms (particularly diminished motivation/pleasure) also associated with better social skill performance. Intrinsic motivation, diminished expressivity, and asocial beliefs appear to play a stronger role in predicting perceived psychosocial functioning. Improving neuropsychological functioning and motivation may improve functioning in individuals with high negative symptom severity.

M109. CRITICAL APPRAISAL OF FAMILY INVOLVEMENT IN PRACTICE GUIDELINES FOR EARLY INTERVENTION SERVICES FOR PSYCHOSIS

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Background: Title: Critical appraisal of family involvement in practice guidelines for early intervention services for psychosis.
Clinical practice guidelines provide recommendations for delivering quality healthcare services. For treating first-episode psychosis, programs such as early intervention were scaled warranting evidence-based care to service users and their families. Despite the significant contributions yielded through family involvement, guideline developers are challenged to provide practical and useful guidance amidst varied evidence quality. Hence, we assessed the methodological quality and identified gaps in recommendation for implementation of Canadian guidelines as a base for future guideline development.

Methods: A systematic search was carried out in peer reviewed and non-peer reviewed guideline databases published between 2000 and 2020. Three independent reviewers assessed the methodological quality of the identified guidelines using the instruments "Appraisal of Guidelines for Research and Evaluation II" (AGREE II) and AGREE-REX (Recommendation EXcellence). Data were analysed using thematic analysis and based on consensuses domain scores.
Results: Eight Canadian guidelines published from 2006 to 2017, five by Ontario, Quebec, British Columbia, Nova Scotia and three national level guidelines were included. The highest scores were obtained by a Canadian Practice Guidelines for Comprehensive Community Treatment for Schizophrenia and Schizophrenia Spectrum Disorders fulfilling 53-100% of criteria in AGREE II and 30-50% for AGREE-REX. All guidelines lacked in the domains “rigour of development”, “clarity of presentation”, "editorial independence", "applicability", and "recommendation".
Discussion: The national Canadian guideline demonstrated the highest scores with both instruments and may serve as a basis for future guideline development in devising family recommendations. The domains "editorial independence", "recommendation", and "applicability" were identified as methodological weaknesses and require attention and improvement in future guidelines.

M110. SUBJECTIVE AND OBJECTIVE QUALITY OF LIFE PARAMETERS IN SCHIZOPHRENIA AND BIPOLAR-I-DISORDER: RELATIONSHIP WITH EMOTIONAL INTELLIGENCE

Beatrice Frajo-Apor*[1], Silvia Pardeller[1], Georg Kemmler[1], Moritz Mühlbacher[2], Anna-Sophia Welte[1], Christine Hörtnagl[1], Birgit Derntl[4], Alex Hofer[1]

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Background: Social cognitive skills and both psychosocial functioning and well-being of patients with serious mental illnesses have consistently been shown to be interrelated. While functional outcomes tend to be better in bipolar disorder (BD) than in schizophrenia (SZ), quality of life (QoL) seems to be comparable between patient groups when objective recovery is achieved. In order to explore the impact of the nature of the illness on the interrelation between subjective elements of recovery in more detail the current study investigated Emotional Intelligence (EI) and QoL in clinically stable SZ or BD patients.
Methods: Patients diagnosed with either SZ (n=63) or BD (n=60) as well as 80 healthy controls were included into a cross-sectional study. EI and QoL were assessed using the Mayer-Salovey-Caruso Emotional Intelligence Test and the German version of the Lancashire Quality of Life Profile.
Results: The two patient groups were comparable with regard to overall EI as well as subjective and objective QoL but indicated significantly lower levels of EI and QoL than healthy controls. Whereas EI was not associated with patients' subjective QoL, a significant correlation of EI with objective QoL was observed in SZ. However, overall effect sizes were small.
Discussion: Our findings point to a difference in the interrelation between EI and QoL in patients suffering from SZ and BD and suggest that they may have different needs to achieve recovery. It will be critical to develop training programs targeting EI in SZ and to examine their impact on objective QoL in these patients.

M111. HOW DO RESIDUAL SYMPTOMS AND INTERNALIZED STIGMA AFFECT QUALITY OF LIFE IN SCHIZOPHRENIA?

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Background: Quality of life (QOL) is seen as a key outcome variable in schizophrenia. Factors deemed relevant in this context include the severity of symptoms and internalized stigma.
Methods: Patients with schizophrenia (ICD-10) between the ages of 18 and 65 from outpatient mental health services were included into a cross-sectional study. Apart from the registration of demographic data, various rating scales were used: the Positive and Negative Syndrome Scale (PANSS), the Internalized Stigma of Mental Illness (ISMI) Scale, and the German version of the Lancashire Quality of Life Profile, the Berliner Lebensqualitätsprofil (BELP).
Results: 80 patients (47 males, 33 females) with a mean age of 43.0 ± 10.9 years took part in this study. The mean PANSS total score was 71.1 ±25.4, the mean ISMI score was 61.1 ± 14.7 (range: 29-116), and the BELP subscale overall QoL showed a mean score of 4.73 ± 1.17 (range 1-7). Statistical analysis showed a moderate correlation between QoL and internalized stigma (r=-0.468, correlation with general life satisfaction) and a weak correlation with the PANSS total score (r=-0.246, correlation with general life satisfaction). Internalized stigma but not residual symptoms of the disorder negatively predicted QoL

Discussion: Our results highlight the complex nature of QoL in individuals suffering from schizophrenia and indicate that outpatients' quality of life correlates moderately with internalized stigma, whereas residual symptoms of the disorder play a secondary role. Accordingly, psychotherapeutic approaches should be applied to reduce internalized stigma, and, ultimately, to improve quality of life.

M112. IMPROVING OUTCOMES FOR YOUNG ADULTS WITH FIRST EPISODE PSYCHOSIS FOLLOWING HOSPITAL ADMISSION: PILOTING A NEW BRIEF PSYCHOLOGICAL INTERVENTION

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Background: The first episode of psychosis (FEP) including first psychiatric admission can be a traumatic and distressing experience (Tan et al., 2014). Risk of suicide is at its highest in the 3 months post discharge (Walter et al., 2019). Black and ethnic minority (BAME) service users experience more compulsory admissions to inpatient care (Oduola et al., 2019) and achieve poorer clinical and social outcomes following a FEP than their white counterparts (Ajnakina et al., 2017; Morgan et al 2017). BAME service users are also less likely to be offered CBT (Das Munshi et al., 2018) and have higher dropout rates from psychological therapy (Rathod et al., 2010).
We aimed to evaluate a 6 session psychological intervention for FEP inpatients' nearing discharge from a specialist early intervention inpatient unit. The unit was based in a diverse area of London with high incidences of FEP (PHE, 2016). Specifically, we aimed to evaluate the feasibility of implementation and acceptability of the intervention.

Methods: Service users on the unit were offered the intervention, delivered by a clinical psychologist. The initial session occurred on the inpatient unit, the remaining 5 sessions in a community setting. The intervention applied a CBT approach. A moving on plan was utilised to develop goals including processing the admission, making sense of the crisis and reconnecting with what's important.
Outcome measures exploring wellbeing, social functioning, process of recovery, beliefs about illness, and symptoms (CORE-5; WEMWBS; SFQ; QPR; BIPQ; PANSS-6) were completed pre and during therapy, and at 1 month follow up. The satisfaction with therapy questionnaire, and qualitative interviews were completed. Feedback from community care coordinators was collected.

Results: Over a period of 7 months 38 people were approached; Nine declined (23%), 7 (18%) were unable to start and 5 (13%) disengaged.
Seventeen participants completed all 6 sessions. Fourteen (82%) were from a BAME background; 10 (59%) of whom identified as Black Caribbean, Black African or Black other. Ten participants (59%) were male and the mean age was 29.6 years. The mean length of admission was 159 days. All were admitted to inpatient care involuntarily. Ethnicity, age, gender nor length of stay were predictors of engagement (n=38; X2 (3) = .91, p = .82).

The PANSS-6 demonstrated that participants symptoms significantly reduced from pre-therapy to the final session ($t(15) = 8.66$, $p < 0.001$). The QPR scores significantly reduced ($t(14) = 2.64$, $p < 0.05$) between session 6 and follow up, indicating positive perceptions of recovery reduced during this time. No other measures yielded significant differences.

Participants were very satisfied with the therapy (mean-4.76 out of 5). Qualitative feedback highlighted the intervention helped people make sense of the crisis, develop coping strategies and shift negative self-views. Participants noted the intervention should have been longer.

Feedback was collected from seven care coordinators; they rated the intervention as helpful for service users (mean 4.14 out of 5).

Discussion: The low disengagement rates, high uptake from individuals from a minority ethnic background, satisfaction with therapy, and qualitative data indicate that the intervention was feasible in implementation and acceptable to service users. Wellbeing was maintained throughout indicating the intervention helped maintain a sense of stability in wellbeing for participants, at a time when an individual sense of identity can be challenged (Fenton et al., 2014). The main critique of the intervention was that the intervention should be longer. Positive perceptions of recovery reducing in the month after the intervention also indicate increasing the number of sessions.

M113. IMPLEMENTATION OF NAVIGATE FOR FIRST EPISODE PSYCHOSIS IN ISRAEL: INSIGHTS AND LESSONS LEARNED

David Roe[1], Michal Mashiach–Eizenberg[2], Paula Garber Epstein[3], Amit Yamin[3], Gili Gili Hoter Ishay[1], Yaara Zisman-Ilani*[4]

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Background: NAVIGATE is a comprehensive treatment program for first episode psychosis developed and implemented in the US that has been found to be effective. The purpose of the present study was to describe the first initiative of NAVIGATE's implementation outside the US, and to present data collected in Israel from the first two clinics focusing on NAVIGATE clients' characteristics, components utilization, and retrospective clinician ratings of change.

Methods: Administrative data for 61 NAVIGATE clients in Israel and retrospective ratings of NAVIGATE clinicians were analyzed.

Results: The duration of untreated psychosis was 4.4 months (SD = 6.8). Clients were mostly referred to NAVIGATE from psychiatric hospitals (n = 29, 50.9%) and community mental health agencies (n = 20, 35.1%). The individualized resiliency training (IRT) component had the highest client utilization rate (n = 53, 98.1%) with a monthly average of M = 2.32 sessions (SD = 2.75). Clinicians' retrospective ratings indicated that 66% of the clients (n = 33) had improved in at least one life domain, with the most common improvement in employment (n = 28, 56%), recovery (n = 24, 50%), and symptoms severity (n = 23, 47%).

Discussion: Our findings reveal that NAVIGATE can be implemented outside the US within a different social and cultural context and different mental health system. The utilization rates of the program components and clinicians' retrospective ratings indicated positive change among most of NAVIGATE clients, pointing to the potential value of NAVIGATE above and beyond different countries and health systems.

M114. PERSON-CENTERED PSYCHOSIS CARE –HOW INCREASING PERSON-CENTEREDNESS IN PSYCHOSIS INPATIENT CARE RELATE TO CARE CONSUMPTION AND STAFF WORKLOAD

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Background: Person-centered care (PCC) is widely embraced and considered to increase effectiveness and quality of health care. We developed an educational intervention for hospital staff, using a participatory design, intended to increase person-centeredness of care at four psychosis wards. 6 conference days spread over a 6-month period interspersed with practical projects at home wards provided the opportunity for staff to discuss and test principles of PCC, including acknowledging patients' resources, preferences and experiences, working in partnership with patients to co-create the care plan, and documenting agreements. From this new knowledge staff initiated projects tailored to their own wards to increase person-centeredness in the everyday care. Here we investigate aspects of care consumption and staff-perceived workload in relation to this intervention called Person-Centered Psychosis Care.

Methods: LoS, length of involuntary stay (LoIS) and number of involuntary treatments (specified as restraints, seclusions and forced injections) were measured for all patients at the inpatient services during a yearlong data collection period before, and respectively after the intervention. Data was extracted from the clinic registry. During data collection periods one staff member per day and ward filled out a VAS rating (1 = no burden – 10 =highest imaginable burden) capturing perceived workload (n = 505, 60% response rate vs n = 465, 45% response rate). Mean or median of each variable was used for comparative analysis.

Results: LoS was longer after implementation (Md =34.2 days, n = 385 vs Md = 25.2, n = 366 before), U = 81409.5, p = <.0005, r = .13, as was LoIS (Md =25, n = 385 vs Md = 16.1, n = 366 before), U =76260.5, p = .047, r = .04. There were no significant group differences in the number of involuntary treatments. Staff perceived workload was rated significantly lower after implementation (M = 5.4, SD = 1.94 vs M = 4.5, SD = 2.08), t = 7.5 (968), p <.0005.

Discussion: Although study design prevents conclusions on cause and effect, the Results: indicate a beneficial development of perceived staff workload after implementation of PCC. The increased LoS is more challenging to interpret but could be a result of more thorough attention to patient needs. Both LoS and LoIS could also be due to differences between groups in terms of severity of symptom and functional ability at admission. The level of actual uptake of PCC and application in care situations is another point of uncertainty to be addressed in a coming study.

M115. GENDER DIFFERENCES IN PROFILES OF SOCIAL COGNITION AND METACOGNITION IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS

Marta Ferrer-Quintero*[1], Daniel Fernández[2], Raquel Lopez Carrilero[3], Luciana Díaz[4], Helena García-Mieres[4], Marina Verdaguer[4], Irene Birulés[4], Ana Barajas[5], Esther Lorente-Rovira[6], Ana

Luengo[6], Alfonso Gutiérrez-Zotes[7], Eva Grasa[8], Esther Pousa[8], Elena Huerta-Ramos[4], Trinidad Peláez[3], Maria Luisa Barrigón[9], Juana Gómez-Benito[10], Fermín González-Higueras[11], Isabel Ruiz-Delgado[12], Jordi Cid[13], Steffen Moritz[14], Susana Ochoa[3]

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Background: Deficits in social cognition and metacognition impact the course of psychosis. Heterogeneity in the disease could be explained by distinct profiles of social cognition and metacognition. However, well-known gender differences are apparent in psychosis, and profiles of impairment may not be equal in both genders. The current study explored profiles of social cognition and metacognition according to gender.

Methods: A total of 174 (58 females) patients with first-episode psychosis were included. A latent profile analysis split by gender was performed with the Faces Test, the Hinting Task, the Internal, Personal and Situational Attributions Questionnaire and the Beck's Cognitive Insight Scale (BCIS) and the three conditions of the Beads Task. The sample also completed a full clinical and neuropsychological battery.

Results: We found 2 clusters (homogeneous and indecisive) that were common to both genders. We found a specific male cluster characterized by presenting jumping to conclusions and a specific female cluster characterized by cognitive biases. Males and females in the homogeneous cluster seem to have a more benign course of illness. Conversely, males with jumping to conclusions had more clinical symptoms and more neuropsychological deficits. Females with cognitive biases were younger and had less self-esteem.

Discussion: Our results suggest that males and females differ in their presentation of social cognition and metacognition variables and that each profile may have specific correlates. Each profile may benefit from specific targeted treatment.

Tuesday Poster Session

T1. THE DIFFERENTIAL IMPACT OF SEVERE CHILDHOOD TRAUMA ON EMOTION RECOGNITION IN MALES AND FEMALES WITH FIRST-EPISODE PSYCHOSIS

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Background: Childhood trauma increases social functioning deficits, which in turn negatively impact social inclusion and the transition to typical social roles in those experiencing a first episode of psychosis (FEP). In nonclinical populations, individuals with chronic childhood trauma histories typically present with social cognitive deficits. Such deficits are also observed in FEP and across the psychosis spectrum, with pervasive deficits in higher-order social cognitive processes such as emotion recognition. Associations between aberrant emotion recognition and childhood trauma severity may be one pathway by which trauma negatively impacts social functioning. While sex differences are largely unapparent in emotion recognition in FEP, given identified sex-specific experiences in childhood trauma and its negative impact on social cognition more broadly, it remains to be clarified whether the severity of childhood trauma exposure may differentially impact emotion recognition in males and females.

Methods: Eighty-three FEP participants (52 males, 31 females) completed the CogState Research Battery (CRB) and the Childhood Trauma Questionnaire as part of an exhaustive clinical and neuropsychological assessment. Demographic and clinical variables found to be significantly different between the sexes were correlated with the Social Emotional Cognition Task (SECT) of the CRB, by sex, to assess for potential covariates. FEP participants were matched on age and sex with 69 nonclinical controls (49 males, 20 females) who also completed the CRB. A sex × group (FEP, controls) ANOVA first examined emotion recognition differences between groups. A two-way ANCOVA then investigated the effects of sex and childhood trauma severity (none, low, moderate, severe) on the SECT in the FEP sample. A follow-up ANCOVA was run using a global index of cognition (verbal, visual, and working memory, attention, executive function, processing speed) as a control measure to assess whether potential effects were selective to emotion recognition.

Results: Age at psychosis onset significantly correlated with the SECT in males with childhood trauma and was treated as a covariate. FEP participants had significantly lower scores on the SECT than nonclinical controls ($p = .035$). No significant sex × group interaction emerged for emotion recognition $F(3, 147) = .496$, $p = .438$, partial $\eta 2 = .003$. In FEP, a significant interaction emerged between sex and childhood trauma severity $F(3, 71) = 3.173$, $p = .029$, partial $\eta 2 = .118$, while controlling for age at onset. Simple effects analyses revealed that females in the severe trauma category exhibited superior emotion recognition capacity relative to males ($p = .011$). No significant sex × childhood trauma severity interaction was observed for the global index of cognition when controlling for age at psychosis onset $F(3, 69) = 2.410$, $p = .074$, partial $\eta 2 = .095$. No significant main effects emerged for either sex or trauma severity (p's $> .47$).

Discussion: This study presents a novel association between sex and childhood trauma, demonstrating that severe trauma may differentially impact emotion recognition capacity in males and females with FEP. This finding may be theoretically interpreted as the distinct way that hypervigilance affects the sexes. The female advantage we observed in those with severe childhood trauma can be understood as a form of exaggerated risk assessment, while in severely

traumatized males, emotional numbing or avoidance may be factors contributing to deficient emotion recognition. Social cognitive and trauma-focused interventions should thus consider the impact of these sex-specific differences to facilitate the personalization of therapeutic services in FEP.

T2. CLOZAPINE RECHALLENGE FOLLOWING EXERCISE-TRIGGERED RHABDOMYOLYSIS: A CASE REPORT

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Background: Clozapine is well known for its unique efficacy in resistant schizophrenia. Its widespread use is limited by its tolerability profile, particularly hematological. Data remain sparse for rare adverse events that can lead to serious complications. Among these, rhabdomyolysis has been reported and its management represents a challenge for clinicians. Considering rhabdomyolysis can lead to severe consequences and safety of using clozapine after such an occurrence remains unknown, case reports can help clinicians to identify aspects that need to be taken into account in similar cases.

Methods: A case of possible clozapine induced rhabdomyolysis was described based on the patient's file and a systematic review was conducted using the terms "rhabdomyolysis AND clozapine" in MEDLINE database. Search yielded 23 results. Titles, abstracts and articles were analyzed to identify every published case of clozapine-induced rhabdomyolysis, from which data were subsequently extracted.

Results: A 20-year-old Caucasian male diagnosed with resistant schizophrenia developed, after a 5 months total exposition and a significant response to clozapine, a marked creatine kinase (CK) elevation and an important myalgia following a recent increase of clozapine daily dose (from 175 mg to 200 mg). The CK elevation also coincided with weight training as reported by the patient. Rhabdomyolysis was diagnosed (CK 7499 U/L, normal values 50–200 U/L), the patient was hospitalized, and clozapine was stopped. On 3rd day of hospitalization, his CK levels rose to 45564 U/L. Rhabdomyolysis etiology was thoroughly investigated and clozapine was held accountable despite other possible contributing factors, including concurrent training. Clozapine cessation rapidly led to patient's significant mental deterioration. Fortunately, 3 months later, clozapine rechallenge with strict monitoring of CK levels and liver enzymes, led to a robust favourable response. Clozapine was pursued despite 2 other mild CK elevations, again, following weight training. Since FDA approval in 1989, only 7 case reports of clozapine induced rhabdomyolysis have been published (8 including this case report). Clozapine was withdrawn in 5/8 cases despite the presence, in most case reports, of contributing factors that prevent drawing firm conclusions on clozapine accountability. Clozapine rechallenge was attempted in 4/8 cases with a 50% success rate, with no further complications.

Discussion: Rhabdomyolysis is a rare and poorly understood adverse event of clozapine. Among the uncertainties surrounding its management, there is a need to propose a more specific CK threshold that would warrant clozapine withdrawal. Also, clinical guidelines should address how to manage CK elevations that can result from exercise while exposed to clozapine. Furthermore, determining the rhabdomyolysis cause can be challenging, as other contributing factors need to be taken into account before only incriminating clozapine. Once medication accountability is established, a risk-benefit assessment should be undertaken using a shared decision process including both patient and family, before attempting clozapine rechallenge, in light of the unknown safety of this approach. In such cases, a careful monitoring

protocol should be elaborated, jointly with specialists, and followed. The unique aspect of the case described herein is that clozapine was pursued following a rechallenge despite two more CK elevations, given their occurrence following physical activity and the patient's significant treatment response. This case also highlights that more research is needed in order to provide more robust evidence-based guidelines to help clinicians and their patients in confronting this clinical dilemma.

T3. ALTERED RANGE-ADAPTIVE VALUE REPRESENTATION IN DIFFERENT STAGES OF SCHIZOPHRENIA

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Background: Amotivation in schizophrenia (SCZ) has been shown to correlate with the representation of value. Patients with SCZ are less discriminative when they are required to make decisions or pay effort to obtain rewards. To guarantee maximal value discriminability while still being able to representing all possible values, the brain's valuation system adapts its coding sensitivity dynamically to the range of values available in any given condition. Any impaired range-adaptive coding may lead to the observed amotivation in SCZ patients. However, previous studies on value processing in SCZ have mostly been limited to the absolute magnitude of rewards and neglect the importance of how the value is represented in its comparative range. The present study aimed to investigate the relationship between range adaptive coding of value and the manifestation of amotivation in individuals in different stages of schizophrenia.

Methods: Thirty chronic patients with SCZ (CP-SCZ), 30 first-episode patients with SCZ (FEP-SCZ), 34 individuals with high social anhedonia (HSoA) and their paired controls were recruited to perform the E-pet task. They were requested to choose between high/low effort task with different values and rate consummatory pleasure experience after seeing the outcomes. Outcome values were derived from two ranges and the pleasure ratings provided the measure of subjective value representation.

Results: Over-adaptation to the value range was found in the CP-SCZ group and was positively correlated with their self-reported consummatory interpersonal pleasure scores. However, the FEP-SCZ group exhibited reduced adaptation and such reduced adaptation was negatively associated with SANS avolition severity and the proportion of choosing hard effort task. Although the range adaptation performance was comparable within the HSoA group, it was negatively correlated with the proportion of choosing hard effort task under the lowest value condition.

Discussion: Our results suggest that the range adaptive coding deficit correlate significantly with the manifestation of amotivation. Such deficits in range adaptive coding have been present but in different patterns across the different stages of SCZ. The results indicate that range adaptive coding may serve as a potential marker of the amotivation in patients with SCZ.

T4. MOLECULAR EVIDENCE THAT MACROPHAGES CONTRIBUTE MORE TO CORTICAL NEUROINFLAMMATION IN PEOPLE WITH SCHIZOPHRENIA THAN DO MICROGLIA

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Background: Neuroinflammation exists in cortical and subcortical regions in schizophrenia, and mRNA levels of inflammatory cytokines and immune regulators can define inflammation subgroups. Elevated levels of cytokines are found in ~40% of those with schizophrenia, defined as a "high inflammation" schizophrenia subgroup (SCZ-HI). Since microglia and macrophages perpetrate tissue inflammation, we tested how they may contribute to cortical inflammation in controls compared to schizophrenia. Previously, we found elevated macrophage marker CD163 mRNA, but no change in the microglial marker IBA1 mRNA in schizophrenia. While we do not know if these putative macrophages are pro- or anti-inflammatory, we hypothesized that people with schizophrenia and heightened inflammation may have increased proinflammatory macrophage markers without a corresponding increase in anti-inflammatory markers or changes in microglial markers.

Methods: We investigated mRNA levels of macrophage and microglial markers in postmortem DLPFC tissue (n=141) and compared diagnostic and inflammation groups (schizophrenia cases [n=72] including 42 low inflammation [SCZ-LI] and 30 SCZ-HI; and controls [n=69] including 57 low inflammation [CON-LI] and 12 high inflammation [CON HI]). The mRNA levels for microglia (IBA1, Hexb, CD11c, CD68), macrophages (CD163, CD64, CD206, CD86 and CCL2) or both (CD68, TSPO) were measured by Fluidigm multiplex RT-PCR using pre-designed Taqman assays. Normalized RNA levels were analyzed by diagnosis and inflammation by 2 way ANOVA/ANCOVA. Pearson's correlation were run.

Results: Microglia markers were unchanged or suppressed in SCZ-HI compared to CON-HI. IBA1 mRNA did not differ between groups ($p>0.26$). Hexb mRNA was elevated in CON-HI compared to CON-LI (>300% $p<0.001$) but it was not elevated in SCZ-HI ($p=0.89$). CD11c mRNA was decreased in SCZ-HI compared to CON-HI (<60%, $p< 0.001$). However, mRNA of markers for both microglia and macrophages were unchanged (CD68) or elevated (TSPO) (>130% all $p<0.05$) in both SCZ-HI and CON-HI compared to SCZ-LI and CON-LI. CD163 mRNA was robustly elevated in schizophrenia, particularly in SCZ-HI compared to SCZ-LI and CON-LI (>250%, $p<0.0001$). CD163 mRNA was positively correlated with a macrophage recruitment marker, CCL2 mRNA ($r=0.46$, $p<0.0001$). One pro-inflammatory macrophage marker, CD64 mRNA, was elevated in SCZ-HI compared to all other subgroups (>200%, $p<0.0001$). However, mRNA of anti-inflammatory markers were unchanged (CD206) or elevated (IL-10 >220%, $p<0.01$) in CON-HI compared to CON-LI, but did not differ between SCZ-LI and SCZ-HI ($p=0.17$). We also found macrophage and microglia marker mRNAs were positively correlated in CON-HI, but not in SCZ-HI ($Z>2.38$, $p<0.018$).

Discussion: Our results demonstrate that microglia do not appear to be reactive in SCZ-HI, indicating that there may be a paucity of appropriate microglia response to inflammation in schizophrenia. Since microglia are a major source of inflammatory cytokines in the brain, lack of microglia activation is surprising. Our findings of elevated chemokine and macrophage-related mRNA support the hypothesis that macrophages may be recruited into the brain in schizophrenia during inflammation. These macrophages are likely to have elevated proinflammatory markers and relatively suppressed anti-inflammatory markers. However, mapping of transcripts and proteins to individual cells is needed to confirm this interpretation. We plan to confirm the macrophage cell types, density and their positions in the brain in the future. This would allow us to better determine which inflammatory cells and signals need to be blocked or boosted in the brain of people with schizophrenia.

T5. BRAIN-PREDICTED AGE DIFFERENCE AND PERIPHERAL INFLAMMATION IN SCHIZOPHRENIA

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Background: Evidence suggests a dysregulation in peripheral inflammatory markers among patients with schizophrenia (SZ). Higher levels of peripheral pro-inflammatory mediators, among them interleukin (IL)-6 and C reactive protein (CRP), were demonstrated to be associated with altered brain morphology and cognitive impairment in non-mentally ill comparison (NC) participants. Furthermore, in SZ, brain morphological changes reflecting an advanced aging process have been observed, as measured by a ~3 year gap between age predicted by brain structural features and actual chronological age (brain-predicted age difference; brain-PAD). These changes seem more evident in younger participants than in older ones, and were demonstrated to be associated with reduced cognitive performance. Brain-PAD represents an accurate and reliable phenotype, which, in combination with measures of peripheral biomarkers such as inflammatory mediators, has the potential to provide real-time information on brain health in mental illnesses such as schizophrenia. The relationship of inflammation and brain-PAD in SZ has not previously been examined. We therefore hypothesized to find a higher positive brain-PAD in SZ vs NC and furthermore that higher peripheral inflammation would be associated with advanced brain age (i.e., a higher and more positive brain-PAD).

Methods: We analyzed cross-sectional data from patients with SZ (n=20; M/F: 12/8) and NC (n=20; 15/5), aged 21-55 years. Plasma levels of cytokine, chemokine, and vascular biomarkers (CRP, Eotaxin, Fractalkine, IP10, IL6, IL10, ICAM1, IFNγ, MCP1, MIP1β, SAA, TNFα, VEGF, VCAM1) were quantified. Brain-predicted age was calculated using a modelling approach based on Gaussian process regression applied to raw T1-weighted MRI data (4), with brain-PAD (predicted brain age - chronological age) as the main variable of interest. Rank analysis of covariance correcting for age was used to investigate group differences (5) and Spearman correlations using the residualized brain-PAD were used to investigate the relationship of inflammation to age-corrected brain-PAD in the combined group and separately in SZ and NC. Multiple testing was corrected for using FDR.

Results: A strong correlation between brain-predicted age and chronological age ($r=0.78$, $p<0.001$) in the combined group indicated validity of the model. The gap between brain-predicted age and chronological age was significantly higher in SZ vs NC ($F(1, 37)=10.7$, $p=0.002$) with a mean brain-PAD of -5.8 (SD: 14.2) in the NC group (indicating a younger brain) and of 8.3 (12.8) in the SZ group, indicating an older brain than expected by chronological age. After correction for multiple testing, significant correlations between age-corrected brain-PAD and IL-6 ($r=0.52$, $p=0.005$), TNFα ($r=0.61$, $p<0.001$), MIP1β ($r=0.45$, $p=0.02$), Eotaxin-3 ($r=0.61$, $p<0.001$) and ICAM-1 ($r=0.41$, $p=0.04$) were observed in the overall group. Upon investigating the SZ and NC group separately, a significant correlation was present in the SZ group of brain-PAD and TNFα ($r=0.65$, $p=0.03$).

Discussion: These results support our hypothesis of advanced brain aging in SZ vs NC as reflected in a larger, positive brain-PAD in SZ. Furthermore, our hypothesis of an association between higher peripheral inflammation and older-than-chronological brain is supported by our finding of positive correlations in the combined group for many markers and of the pro-inflammatory cytokine TNFα in the SZ group only. Further research into the possible mechanisms of interplay between peripheral inflammation and brain aging are warranted, with special attention to the possible role of TNFα in neuroprogression in SZ.

T6. THE ROLE OF ABCB1 AND CYP3A GENE VARIATIONS IN CLINICAL RESPONSE TO ANTIPSYCHOTIC TREATMENT IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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Background: Allelic variants of the ATP-binding cassette, subfamily B member 1 (ABCB1), also known as the multidrug resistance gene (MDR1), encode a membrane-bound efflux transporter known as P-glycoprotein. This protein is located both on the intestinal lining and on the blood-brain barrier, playing an important role in the absorption and penetration of antipsychotics into the central nervous system.
The variant T allele for the C3435T ABCB1 SNP has been reported to be associated with reduced activity in PGP, leading to higher plasma concentrations of antipsychotics. Genetic variations in cytochrome enzymes are known to influence drug metabolism and treatment response too. The rs472660 CYP3A43 variant has been shown to influence clinical response to antipsychotics. However, few studies have investigated the relationship between PGP or CYP3A4 polymorphisms and the antipsychotic response and functionality in schizophrenia.

This study aimed to evaluate whether the rs1045642 ABCB1, rs2032582 ABCB1, and rs2740574 CYP3A4*1B genetic polymorphisms were associated with improved clinical response of psychotic symptoms as measured with standardized PANNSS and CGI scales.

Methods: Two hundred and forty-five patients with a diagnosis of schizophrenia were recruited. Mostly were outpatients (55% male, mean age 47,5 ± 13,77 years). Every subject received treatment with a variety of antipsychotic drugs (37% clozapine, 15% olanzapine, 11% paliperidone, 9% risperidone, 7% aripiprazole, 7% quetiapine, 14% others). Measurements: The degree of clinical response was measured using the PANSS and CGI scales, as well as the psychotic symptoms dimensions described by Van der Gaag (2006), at baseline and 12-weeks of follow-up.Genotyping techniques for ABCB1 rs1045642, ABCB1 rs2032582, and CYP3A4*1B rs2740574 polymorphisms were performed using iPlex® Gold chemistry and the MassARRAY platform. Statistical analysis: Linear regression analyses were performed considering the changes (week 12 - baseline) in PANSS and CGI scores and the emotional distress, excitement, disorganization, negative and positive symptoms dimensions as dependent variables; and age, sex, and antipsychotic drug were taken as co-variables for each genetic polymorphism. Software used: SPSS (IBM, v. 23) and PLINK.
Results: The presence of the rs2032582 allele (A/A or A/- individuals) for ABCB1 was associated with a greater improvement in the PANSS positive score (13-17 vs 11-7, p=0,01). This polymorphism was also associated with changes in the excitement (p=0,006) and

emotional distress (p=0,01) domains, with subjects with the A/A or A/- genotypes showing the greatest improvements. Additionally, the CYP3A4*1B allele was associated with worse clinical responses as measured with the PANSS general score (p=0,05) and in the negative symptoms dimension (p=0,01). No other significant resultswere observed in the clinical response as measured with the PANSS general score.

Discussion: Genetic variability in the ABCB1 and CYP3A4 enzymes may influence the clinical response to treatment with different antipsychotics. This association seems to be particularly strong in the subgroup of individuals with an illness of multi-episodic, chronic course. Further studies about the role of CYP polymorphisms and treatment efficacy will help to clear up whether pharmacogenetic studies of candidate genes can be used as reliable clinical markers.

T7. MICROBIOME-GENERATED CHEMICALS ASSOCIATED WITH SCHIZOPHRENIA: CEREBROSPINAL FLUID LEVELS V. BIOACTIVITY

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Background: Levels of numerous phenolic and indolic chemicals such as 3,3-hydroxyphenylpropionic acid (3,3-HPPA), 3,4-dihydroxycinnamic acid (3,4-DHCA) and indole-3-propionic-acid (I3PA) i) are part of the human urinary and/or serum metabolome, ii) are generated largely by gut microbiota (GMB), iii) are associated with schizophrenia. Whether such chemicals can reach and act on the brain directly is not known.

Methods: We conducted targeted, quantitative analysis of levels of over 70 phenolic and indolic metabolites in human cerebrospinal fluid (CSF), using liquid chromatography/ mass spectrometry.

We then conducted a PubMed search for the reported bioactivity of those chemicals across various human in vitro studies (e.g. cell culture), and then compared levels in human CSF to those known to be bioactive.

Results: Over 20 GMB-related chemicals, including 3,3-HPPA, 3,4-DHCA and I3PA have been both confirmed in human CSF (concentrations ranging from micromolar to nanomolar) and have been studied in various in vitro assays using human cells (e.g. antioxidant effects, interleukin response, inhibition of alpha-synuclein aggregation). In many cases, the levels present in CSF are in the range of those reported to be bioactive in vitro.

Discussion: The levels of numerous gut microbiota-derived chemicals, known to be associated with the serum or urinary metabolome in schizophrenia, are present in human cerebrospinal fluid at concentrations in the range of known bioactivity on human cells. We conclude that GMB-responsive chemicals, and hence the GMB itself, have the potential to act directly on the brain. Given their association with schizophrenia, the bioactivity of these chemicals and their relation to the GMB needs to be more extensively investigated and their levels quantified in CSF as well as brain tissue from different groups of patients with schizophrenia. The role of these chemicals as potential diagnostic or therapeutic biomarkers remains to be determined.

T8. RELATIONSHIP BETWEEN STRIATAL DOPAMINE SYNTHESIS CAPACITY AND COGNITIVE FUNCTIONS IN PSYCHOTIC DISORDERS: THE EFFECTS OF AGE

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Background: Cognitive impairments are key features in psychotic disorders. Some cognitive functions have been linked to dopamine activities. Recent studies have proposed striatal dopamine synthesis capacity (DSC) as a final common pathway towards psychosis onset in both early-onset and late-onset psychotic disorders. As dopamine in healthy subjects is modulated by age, the relationship between DSC and cognition is likely to be different in different age groups.

Methods: We analyzed data from a prospective cohort of 35 patients with first-episode psychosis (FEP). All patients received an 18F-DOPA positron emission tomography (PET) scan within one month of antipsychotic treatment. We compared the levels of striatal DSC (Kocc;30–60 value) and cognitive function for younger patients below 40 years (early-onset) and those at 40 years or above (late-onset). Cognitive measures included Digit Span Forward (DS-F), Digit Span Backwards (DS-B), Visual Patterns Test (VPT), Digit Symbol Substitution Test (DSST), Monotone Counting Test, Verbal Fluency Test (VFT; which yielded scores for total correct, duplicate error, and semantic error), and Modified-Wisconsin Card Sorting Test (M-WCST; which yielded scores for correct responses, perseverative error, and non-perseverative error). Verbal memory retention was calculated from the difference between the delayed recall and immediate recall scores of the Logical Memory test. This measure specifically addressed the ability of patients to hold information over time. The associations between baseline striatal DSC and cognitive function were examined using Spearman's correlation coefficient.

Results: Compared with early-onset patients, cognitive performance was significantly worse in late-onset patients, as indicated by lower scores in DS-F (mean=12.87 vs mean=11.25, p=0.032), DS-B (mean=8.80 vs mean=5.40, p=0.012), DSST (mean=79.71 vs mean=52.45, p=0.001), and VFT correct responses (mean=22.77 vs mean=17.63, p=0.033). In those with early onset, Kocc;30–60 showed significant positive correlations with duplicate errors in the VFT (average putamen: rho=0.691, $p<0.01$; average caudate: rho=0.635, p=0.02). Among late-onset patients, DSC in the putamen region was negatively correlated with verbal memory retention (rho=-0.540, p=0.017) and positively correlated with duplicate errors in the VFT (rho=0.468, p=0.050). Negative trends were observed between DSC and DS-B in both putamen (rho=-0.390, p=0.089) and caudate (rho=-0.393, p=0.087) regions.

Discussion: We showed that cognitive functions were significantly more impaired in late-onset FEP patients compared to those with an early onset. Importantly, elevated dopamine activity in the striatum was associated with poorer cognitive performance and more duplicate errors in the VFT. However, negative associations between DSC and memory retention ability as well as DS-B were found only in late-onset but not early-onset patients. This suggests that there exists differentiations in the effects of dopamine activity on FEP as a function of age on onset and that both elevated and diminished DSC can be associated with differential cognitive impairments in FEP patients.

T9. HIGH INFLAMMATION AND METABOLIC DYSFUNCTION ARE ASSOCIATED WITH INCREASED NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Bidirectional relationships between inflammation and metabolic dysfunction may contribute to the pathophysiology of psychiatric illnesses like schizophrenia. Inflammation has been implicated in the development of schizophrenia and recent data supports an association between increased inflammation and negative symptoms. This is significant given the lack of current effective treatments for negative symptoms, which are associated with poor outcomes. Many individuals with schizophrenia have metabolic abnormalities that may be further exacerbated by antipsychotics. Previous data in patients with depression have demonstrated that altered glucose metabolism defined a subset of depressed patients with high inflammation and anhedonia. Similarly, we have shown that inflammation and metabolic dysfunction are associated with disruptions in circuits that are relevant for reward and motivation. Motivational deficits are a core negative symptom of schizophrenia and we thus hypothesized that individuals with schizophrenia who had high inflammation and metabolic dysfunction will have increased negative symptoms.

Methods: 53 patients with schizophrenia were recruited from the Atlanta VA. Concentrations of TNF, IL-6, IL-1beta were Z-scored and added to create an inflammatory composite score. Lipid panels were obtained from the electronic medical record. Total negative symptom (PANSS) were significantly correlated with total cholesterol ($r=0.401$, $p=0.002$) and low density lipoprotein (LDL; $r=0.427$, $p=0.002$) and were used in subsequent analyses. Median splits of the inflammatory composite score, cholesterol, and LDL were used to define groups. Independent t-tests were used to test differences in negative symptoms between individuals with: a) high inflammation and high metabolic dysfunction vs low inflammation and low metabolic dysfunction; b) high inflammation and high metabolic dysfunction vs high inflammation and low metabolic dysfunction; and c) high inflammation and high metabolic dysfunction vs low inflammation and high metabolic dysfunction. A 2-Way ANOVA was conducted to test the interaction between inflammation and cholesterol/LDL on negative symptoms.

Results: Subjects in the high inflammation and high metabolic dysfunction group had worse negative symptoms compared to the low inflammation and low metabolic dysfunction group for both total cholesterol ($t=-2.34$, $p=0.028$) and LDL ($t=-2.35$, $p=0.028$). Subjects in the high inflammation and high metabolic dysfunction group had worse negative symptoms compared to the high inflammation and low metabolic dysfunction group for both total cholesterol ($t=-3.73$, $p=0.001$) and LDL ($t=-3.24$, $p=0.004$). There were no significant differences between subjects with high inflammation and high metabolic dysfunction vs subjects with low inflammation and high metabolic dysfunction. The two way ANOVA showed a statistically significant interaction between the effects of inflammation and cholesterol on negative symptoms, $F(1, 47) = 5.42$, $p = .024$.

Discussion: Individuals with high inflammation and dyslipidemia/metabolic dysfunction may represent a subset of individuals with schizophrenia who have worse negative symptoms. Future work should seek to replicate these findings in larger samples. High inflammation and metabolic dysfunction may represent a transdiagnostic signature for symptoms related to

positive valence systems (i.e., anhedonia and motivational deficits) and could represent novel therapeutic targets for these difficult to treat symptoms.

T10. ANTERIOR CINGULATE GLUTAMATE AND GLX AT FIRST EPISODE ARE ASSOCIATED WITH SUBSEQUENT ANTIPSYCHOTIC RESPONSE: FINDINGS FROM THE UK STRATA-2 STUDY

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Background: The overall aim of the STRATA consortium is to identify biomarkers that can predict antipsychotic non-response and treatment resistance. Accurate predictors of response from first presentation could inform clinical decision making. Cross-sectional studies have indicated that elevated anterior cingulate cortex (ACC) glutamatergic metabolites could be one feature of antipsychotic non-responsive illness (Egerton et al., 2012; 2020; Iwata et al., 2019; Mouchliantis et al., 2016; Tarumi et al., 2020), and there is some evidence that glutamate may predict outcome from the first episode of psychosis (Egerton et al., 2018).
Methods: Recruitment and assessment occurred at two UK sites. Criteria for participation included being within the first episode of psychosis (<2 years of illness onset), <4 weeks antipsychotic medication exposure and not meeting modified remission criteria. Participants were assessed at baseline, 2 and 6 weeks during which they received antipsychotic medication according to normal clinical care. Glutamate and Glx (glutamate + glutamine) were measured using 1H-MRS in the ACC and right caudate nucleus. Symptoms were primarily rated using the PANSS. Response was primarily defined as >20% reduction from baseline in PANSS total score.
Results: Baseline ACC glutamate and Glx was significantly elevated in non-responders (NR) compared to in responders (R) at 6 weeks (17 NR; 25 R) ($p < 0.05$). ACC glutamate and Glx at baseline were also negatively correlated with the percentage change in PANSS and improvement in CGI score over 6 weeks ($p<0.05$). In the caudate, glutamate and Glx were not associated with response. The effect of time on glutamate and Glx was non-significant.
Discussion: ACC glutamate was higher in patients within the first episode of psychosis who subsequently showed less symptomatic improvement. Associations between elevated ACC glutamate at first episode and poorer symptomatic or functional outcome have been observed in other studies (Egerton et al. 2018; Dempster et al., 2020) although there are inconsistencies (Dempster et al., 2020; Li et al., 2020; Bojesen et al., 2020). Combination of glutamate measures with other STRATA biomarkers may increase predictive accuracy, and this work is on-going.

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T11. SMALLER SUBCORTICAL VOLUMES AND ENLARGED LATERAL VENTRICLES ARE ASSOCIATED WITH HIGHER GLOBAL FUNCTIONING IN YOUNG ADULTS WITH 22Q11.2 DELETION SYNDROME WITH PRODROMAL SYMPTOMS OF SCHIZOPHRENIA

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Background: Enlarged lateral ventricles and abnormal subcortical volumes are among the most frequently observed morphometric abnormalities in schizophrenia (SZ). Enlarged lateral ventricles have been associated with reductions in subcortical gray matter volume in SZ, as well as with less improvement in global functioning over time. These findings have been observed in early onset, first episode, and chronic SZ. However, it is not known whether associations between enlarged lateral ventricles and changes in subcortical structures are present before psychosis onset in individuals at genetic high-risk for SZ. This may be elucidated by investigating individuals with the 22q11.2 deletion syndrome (22q11DS), a rare genetic syndrome associated with a 30% risk for developing SZ. Here, we investigated whether lateral ventricles and subcortical volumes are associated in young adults with 22q11DS both with and without PS for SZ, and whether abnormalities in the volumes are associated with global functioning.

Methods: MR images were acquired on a 3T scanner from 51 individuals with 22q11DS and 30 healthy controls (age: M=20.9). FreeSurfer, version 6.0, was employed for segmentation. Correlations were performed to evaluate the relationship between ventricular and subcortical volumes, as well as between Global Assessment of Functioning (GAF) in each group. Post-hoc correlations were conducted separately for individuals with 22q11DS both with PS (n=21) and without PS (n=30).

Results: Lateral ventricular volumes correlated negatively with subcortical volumes in young adults with 22q11DS, suggesting that larger lateral ventricles are associated with smaller subcortical volumes. In individuals with 22q11DS with PS, GAF ratings correlated positively with the volumes of the lateral ventricles and negatively with volumes of subcortical structures, suggesting that higher global functioning is associated with enlarged lateral ventricles and smaller subcortical volumes. No such associations were found in individuals with 22q11DS without PS or in healthy controls.

Discussion: Enlarged lateral ventricular volumes are associated with smaller subcortical volumes in 22q11DS with and without PS. This suggests a possible neurodevelopmental

pathology of these structures in young adults with this genetic syndrome, as the relationship between these structures is not present in healthy controls. Further, in 22q11DS with PS, larger lateral ventricles and smaller subcortical structures are associated with higher global functioning. Based on published studies of smaller subcortical structures in SZ in comparison to healthy controls, we would have expected smaller subcortical structures to be associated with lower functioning in young adults with 22q11DS and PS. However, our results are in line with a report that enlarged lateral ventricles are associated with better, not worse, disease outcome in SZ. Additionally, recently published resultsstate that reductions in subcortical volumes are associated with improvement in global functioning in SZ. Given that our study is the first to report significant correlations of functional measures with lateral ventricular and subcortical volumes in individuals with 22q11DS with PS, further studies are encouraged to replicate and extend these resultsin individuals at clinical and genetic risk to develop SZ. The findings of this study demonstrate the importance of monitoring changes of lateral ventricular and subcortical volumes as well as associations with functional measures in respect to understand the neurodevelopmental aspects of SZ.

T12. THE KYNURENINE PATHWAY IN MAJOR DEPRESSIVE DISORDER, BIPOLAR DISORDER, AND SCHIZOPHRENIA: A META-ANALYSIS OF 101 STUDIES

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Background: The importance of tryptophan as a precursor for neuroactive compounds has long been acknowledged. The metabolism of tryptophan along the kynurenine pathway and its involvement in mental disorders is an emerging area in psychiatry. We performed a meta-analysis to examine the differences in kynurenine metabolites in major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ).

Methods: Electronic databases were searched for studies that assessed metabolites involved in the kynurenine pathway (tryptophan, kynurenine, kynurenic acid, quinolinic acid, 3-hydroxykynurenine, and their associate ratios) in people with MDD, SZ, or BD, compared to controls. We computed the difference in metabolite concentrations between people with MDD, BD, or SZ, and controls, presented as Hedges' g with 95% confidence intervals.

Results: A total of 101 studies with 10,912 participants were included. Tryptophan and kynurenine are decreased across MDD, BD, and SZ (tryptophan in MDD: g= -0.51, 95% CI= -0.63 to -0.39, p= <0.001; BD: g= -0.56, 95% CI= -0.76 to -0.35, p= <0.001; SZ: g= -0.24, 95% CI= -0.46 to -0.01, p= 0.04. Kynurenine in MDD: g= -0.26, 95% CI= -0.35 to -0.16, p= <0.001; BD: g= -0.34, 95% CI= -0.62 to -0.061, p= 0.02; SZ: g= -0.27, 95% CI= -0.53 to -0.01, p=0.046). Kynurenic acid and the kynurenic acid to quinolinic acid ratio are decreased in mood disorders (i.e., MDD and BD), (kynurenic acid in MDD: g= -0.37, 95% CI= -0.52 to -0.21, p= 0.001; BD: g= -0.44, 95% CI= -0.65 to -0.24, p= <0.001. Kynurenic acid to quinolinic acid ratio in MDD: g= -0.54, 95% CI= -0.82 to -0.27, p= <0.001; BD: g= -0.44, 95% CI= -0.67 to -0.21, p= <0.0001), whereas kynurenic acid is not altered in SZ (g= 0.06, 95% CI= -0.36 to 0.48, p= 0.78). Kynurenic acid to 3-hydroxykynurenine ratio is decreased in MDD (g= -0.42, 95% CI= -0.63 to -0.21, p= <0.001) but not SZ (g= -0.53, 95% CI= -1.11 to 0.05, p= 0.07). Kynurenic acid to kynurenine ratio is decreased in MDD (g= -0.39, 95% CI= -0.73 to -0.04, p= 0.03) and SZ (g= -0.49, 95% CI= -0.85 to -0.12, p= 0.01). Finally, the kynurenine to tryptophan ratio is increased in MDD (g= 0.15, 95% CI= 0.007 to 0.291, p= 0.04) and SZ (g= 0.36, 95% CI= 0.004 to -0.626, p= 0.05).

Discussion: Our results suggest that there is a shift in the tryptophan metabolism from serotonin to the kynurenine pathway, across these psychiatric disorders. In addition, a differential pattern exists between mood disorders and SZ, with a preferential metabolism of kynurenine to the potentially neurotoxic quinolinic acid instead of the neuroprotective kynurenic acid in mood disorders but not in SZ. Our results suggest that the metabolites of the kynurenine pathway might be promising new targets for clinical trials guided by the specific molecular profile of a sub-group of patients, or molecularly-guided clinical trials, as preconized by precision medicine.

T13. BULLYING AND SOCIAL FUNCTIONING, SCHEMAS, AND BELIEFS AMONG YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Individuals at clinical high-risk (CHR) for psychosis experience high rates of bullying. There is little research on the differences between CHR who did and did not experience bullying. However, there is evidence that bullying may be related to negative schemas and social impairment. Objectives: To examine differences in core schemas, asocial and defeatist beliefs, and social functioning between those who did and did not report bullying experiences in a large sample of CHR individuals. We hypothesized that bullying in CHR youth would be associated with poorer social functioning, increased maladaptive beliefs, and negative core schemas.
Methods: CHR participants (N=203) were split into those who did and did not report experiencing bullying. The two groups were compared on demographic characteristics, social functioning, and belief variables, using the Brief Core Schemas Scale, the Asocial Beliefs Scale, the Defeatist Performance Attitudes Scale, and the First Episode Social Functioning Scale.
Results: 72.9% reported experiencing bullying. These participants had greater severity of negative schemas about others and asocial and defeatist performance beliefs, and lower social functioning scores. Of those who reported bullying, 55.4% reported experiencing a high-perceived impact from bullying.
Discussion: Prevalence of bullying among CHR participants is high. Bullying may be a risk factor for increased asocial and defeatist beliefs, negative core schemas, and poor social functioning. Targeting maladaptive schemas and beliefs during treatment may serve to improve functional outcomes in this group.

T14. TRAUMATIC STRESSFUL EVENTS AND SCHIZOTYPAL SYMPTOMS: MEDIATION BY EXECUTIVE FUNCTION AND SOCIAL COGNITION

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Background: Certain individuals who were exposed to traumatic stressful events (TSEs) exhibit schizotypal symptoms subsequently. The mechanism linking TSEs to schizotypy is as

yet unknown. One possible mechanism is the neuropsychological process during adolescence. Increasing evidence has shown that TSEs contribute to functional alterations of brain regions such as the posterior cingulate cortex, and the dorsomedial prefrontal cortex, which are essential for effective executive function (EF) and social cognition (SC). Therefore, our hypotheses that EF or SC could mediate the association between TSEs and schizotypal symptoms. This study aims to examine the potential mediating effect of EF or SC deficits in the association between TSEs and schizotypal symptoms in a longitudinal design.
Methods: A sub-sample of 426 adolescents (mean age 15.2 at baseline, 51.6% female, 43.7% Black, 46.5% White, 9.8% Other) were from the Philadelphia Neurodevelopmental Cohort study whom a two-year longitudinal follow-up data were available. Adolescents completed measures of demographic, TSEs, EF and SC, family history, and other psychopathology information (e.g., psychosis spectrum symptoms, mood disorder, anxiety disorder, and behavior disorder) at baseline. Schizotypy dimensions (cognitive-perceptual, interpersonal, and disorganized) were evaluated approximately two years later.
Results: The prevalence of TSEs was high (54%) in the current population. Aggregate TSEs had a significant negative association with baseline EF and SC, and a significant positive association with each dimension of schizotypal symptoms in a two-year follow-up. There were significant mediation effects of EF on the relationship between TSEs and cognitive-perceptual schizotypy dimension when adjusting for demographic and family history variables; however, this mediation effect did not hold when adding baseline psychopathology variables. No mediation effect of EF was found in associations between TSEs and interpersonal symptoms or disorganized symptoms. No mediation effect of SC was found in the association between TSEs and any of the schizotypy dimensions.
Discussion: The findings of our study suggest that cognitive-perceptual symptoms are closely related to aggregate TSEs. Moreover, the study provides preliminary evidence for a partial mediation effect of EF in the connection between TSEs and cognitive-perceptual symptoms though the mediation effect is not robust when considering the baseline psychopathology. Thus, health providers should first raise awareness of screening trauma history and its consequences, particularly in adolescents at risk for schizotypal symptoms. Early intervention to improve the ability of EF might be helpful to mitigate the occurrence of the cognitive-perceptual symptoms in adolescents. And More research is needed to explore the mechanisms between TSEs and schizotypy.

T15. DEVELOPMENTAL LAG FOR CROSS-MODAL ABILITIES IN FAMILIAL HIGH-RISK CHILDREN FOR SCHIZOPHRENIA, BIPOLAR DISORDER AND RECURRENT MAJOR DEPRESSIVE DISORDER: A NEW RISK MARKER FOR DISEASES' VULNERABILITY

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Background: Major psychiatric disorders (MPD) including schizophrenia, bipolar disorder and major depression disorder have shared neurodevelopmental vulnerability due to early sensory defect as revealed by sensory and cognitive endophenotypes observed in our cohorts (e.g. Gagné et al., Schizophr. Res., 2020). There is considerable evidence that a harmonious self-development - known to be disrupted in MPDs - requires a synchronized multisensory

perception and an adequate interplay of sensory afferences across modalities (e.g. tactile, visual and auditory). Early impairment in cross-modal abilities namely in intermodal transfer (IMT) may jeopardize a stable and unified self's and world's representation and then would undermine self-development (Salomon et al., Schizophr Bull., 2020) representing thus a risk factor for MPD. IMT is the capability to transfer a percept coming exclusively from a sensory modality (e.g. tactile) to another modality (e.g. visual). This study aims to determine if IMT may be a vulnerability marker in Familial High-Risk (FHR) children.

Methods: Sample:

Twenty-six FHR offspring (17 girls) of patients suffering from bipolar disorder or schizophrenia (BP/SZ-HR, mean age = 12.08), twenty-height FHR offspring (13 girls) for major depression disorder (RMD-HR, mean age = 12.28) were recruited from the cohort study INTERCEPT through the HoPE program of the CIUSSS de la Capitale-Nationale. Twenty-nine controls (20 girls) with no family history of MPD and no DSM-V disorder (CTL, mean age = 12.64) were recruited using advertisements or control bank. All participants were aged between 9-15 years old and had no personal history of affective or psychotic DSM-V disorder.

IMT Task:

Each condition has 12 trials (0 or 1, scores /12) and the shapes are hidden from sight during palpation.

- Tactile-Tactile, T-T condition: The subject has to palpate a 3D target shape for 10s and must then recognize it by touch from among a distractor. Note that this corresponds to an intramodal practice condition.

- Tactile-Visual, T-V condition: The subject has to palpate a 3D target shape for 10s and must then recognize it visually from among a distractor.

- Visual-Tactile, V-T condition: A 3D target shape is presented visually for 10s and the subject must then recognize it by touch from among a distractor.

Results: For the whole sample, no significant difference between groups was observed for T-T condition (BP/SZ-HR: 9.81; DMR-HR: 9.82; CTL: 10.24, $F(2,82) = 1.57$, $p = .214$), nor for T-V condition (BP/SZ-HR: 10.00; DMR-HR: 9.71; CTL: 9.93, $F(2,82) = .037$, $p = .964$. However, for V-T condition, both BP/SZ-HR (9.31) and DMR-HR (9.04) were significantly impaired ($F(2,82) = 3.35$, $p = .040$) compared to controls (9.97). Note that age, sex and socio-economic status are not significant confounders according to ANCOVA. Moreover, only for V-T condition, the subsample of 29 subjects aged from 13 to 15 showed particular impairment ($F(2,28) = 6.60$, $p = .005$) with a score of 8.86 for BP/SZ-HR and 9.00 for DMR-HR (controls score: 10.5).

Discussion: FHR children showed impairment in cross-modal abilities and specially in V-T IMT. Whereas T-V transfer is widely used in daily life (e.g. to grasp something out of sight and then use it), V-T transfer seems to be a more fragile ability and then to be more prone to being impaired in FHR. Interestingly, the impairment in V-T for FHR is magnified in 13–15 y.o subsample. This result suggests a developmental lag in FHR for V-T condition that could lead to a new risk marker for MPD sensitive many years before attenuated or prodromal symptom onset. Developmentally FHR children would show significant impairments in IMT that might enter into the group of indicators of brain dysfunctions, or risk endophenotypes, that both children HR and adult patients carry.

T16. ELUCIDATING SCHIZOPHRENIA-RELATED BEHAVIORS IN LARVAL ZEBRAFISH (DANIO RERIO) ON SHORT TERM AND WITHDRAWAL BASE DRUG INDUCTION

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Background: The link between the use of substances and the development of psychoses is demonstrated by the high prevalence of substance abuse in schizophrenia. Objective: To understand the relationship between addiction and schizophrenia, several avenues of investigation on the molecular mechanisms of the short-term (3 days) behavioral and physiological alterations are to be interpreted.

Methods: Thirty embryos at 48 hours post-fertilization (hpf) larvae were exposed to Domperidone (DMP), Morphine sulphate, and Dizocilpine hydrogen maleate (MK-801). Administration of each drug was according to the Maximum Tolerated Concentration of the larvae to observe the difference in the locomotor activity and their social behavior using the mirror biting test (n=30). The withdrawal group for morphine was done by replacing embryo media every other day for 5 days, after the 3 days exposure. This study measured the mRNA levels of DRD2, PI3K, AKT1, and SLC6A4 in the head part of the larvae (n=50, pooled) using real-time polymerase chain reaction and further biochemical test using ELISA on serotonin level.

Results: Here we demonstrate that in zebrafish larvae, different drugs DMP (5.0±0.45μM), Morphine sulphate (3.125±0.71μM), and MK-801 (0.8±0.2μM) resulted in significant ($p<0.05$) alterations in locomotor activity and social behavior, transmitting with the upregulation of DRD2, PI3K, AKT1 and SLC6A4 gene expressions ($p<0.05$). Equally, a progressive significant increase during mirror biting and locomotion of larvae reflected behavioral hyperactivity in the withdrawal of the morphine group. The biochemical test has shown a significant increase in the levels of serotonin when compared to control at 39.0±0.3%, for MK801 treated group, and 23.0±0.12%, for DMP treated group. While morphine treated group at 1.0±0.5% was not significant compared to the control. Conversely, the highest percentage was recorded in the morphine withdrawal group at 56.4±0.3% of serotonin compared to the control.

Discussion: The regulation of PI3K/AKT signaling has also been implicated in the etiology of mood disorders and depression. In fact, molecular AKT deletion evokes a change in behavior reflecting the psychiatric appearance reminiscent of schizophrenia, anxiety, and depression. While it is reinforced by drug-induced reward and the emotionally negative state of drug withdrawal, which includes anxiety. The increase in serotonin levels is also aggravated by the SLC6A4 gene expression positively correlating with the basal activity. The biochemical assays showed reduced serotonin levels in the brain, thus, altering the behavior of the exposed zebrafish larvae.

T17. LONG-TERM ANTIPSYCHOTIC EFFICACY OF OLANZAPINE AND SAMIDORPHAN COMBINATION IN PATIENTS WITH SCHIZOPHRENIA: POOLED ANALYSES FROM PHASE 3 STUDIES

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Background: The combination of olanzapine and samidorphan (OLZ/SAM) is in development for treatment of schizophrenia and bipolar I disorder. In 2 respective phase 3 studies, OLZ/SAM treatment resulted in similar antipsychotic efficacy to olanzapine and mitigated

olanzapine-associated weight gain. This analysis describes the long-term (up to 76 weeks) antipsychotic effect of OLZ/SAM integrated from these 2 phase 3 studies and their extensions in patients with schizophrenia.
Methods: Resultsfrom 2 pivotal studies and their respective extension studies were integrated longitudinally into 2 groups. Group 1 included patients from ENLIGHTEN-1 (NCT02634346), a 4-week, randomized, double-blind study evaluating antipsychotic efficacy of OLZ/SAM, placebo, and olanzapine in patients with an acute exacerbation of schizophrenia, who could enroll in a 52-week, single-arm, open-label safety extension (NCT02669758) and a 48-month follow-on study (NCT03201757, ongoing). Group 2 included patients from ENLIGHTEN-2 (NCT02694328), a 24-week, randomized, double-blind study evaluating mitigation of olanzapine-associated weight gain by OLZ/SAM in adult outpatients with schizophrenia, who could enroll in a 52-week, single-arm, open-label OLZ/SAM extension (NCT02873208, ongoing) and 48 month follow-on study (NCT03201757, ongoing; this study also includes patients from group 1). Long-term efficacy was assessed descriptively via Positive and Negative Syndrome Scale (PANSS) total and Clinical Global Impression-Severity (CGI-S) scores using observed data without imputation for missing values. The analysis included all patients exposed to OLZ/SAM with ≥1 postbaseline PANSS and body weight assessment. Baseline was relative to the start of OLZ/SAM exposure.
Results: Groups 1 and 2 included 281 and 381 patients, respectively. As of April 2019, mean OLZ/SAM exposure was 479.1 days in group 1; 64.1% of patients received ≥52 weeks of OLZ/SAM. In group 2, mean OLZ/SAM exposure was 348.1 days; 42% were treated for ≥52 weeks. In group 1 (acute), mean (SD) PANSS total score was 89.4 (18.63) at baseline (n=281) and 61.3 (11.99) at week 52 (n=183); mean (SD) change from baseline was −25.3 (20.49) points. In group 2 (stable), mean (SD) PANSS total score was 65.2 (11.03) at baseline (n=381) and 57.9 (12.12) at week 52 (n=174); mean (SD) change from baseline was −6.0 (11.50) points. In group 1 at baseline, 144/281 (51.2%) patients were markedly to extremely ill (CGI-S score ≥5). At week 76, only 1/133 (0.8%) met this criterion. In group 2, 206/381 (54.1%) were normal to mildly ill (CGI-S score of ≤3) at baseline. After 76 weeks, 87/105 (82.9%) met this criterion. The mean (SD) change from baseline to week 76 in CGI-S score was −1.46 (1.22) for group 1 and −0.45 (0.65) for group 2.
Discussion: Integrated data from multiple studies provided evidence of enduring antipsychotic effectiveness in patients with schizophrenia who continued long-term OLZ/SAM treatment.

T18. A META-ANALYTIC REVIEW OF THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) ON CLINICAL SYMPTOMS OF SCHIZOPHRENIA WITH A FOCUS ON THE GENERAL PSYCHOPATHOLOGY SCALE

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Background: In the past decade, transcranial direct current stimulation (tDCS) has emerged as a promising and safe treatment tool for alleviating neurocognitive symptoms of schizophrenia, but its efficacy with respect to positive, negative, and general psychopathology symptoms are unclear. Whilst positive and negative symptoms remain primary treatment targets, the role of general psychopathological symptoms in recovery has been largely overlooked. However, aspects of general psychopathology such as poor insight, anxiety, somatic concerns, motor retardation and preoccupation are likely to interfere with daily life

and adversely affect functional outcome. In this meta-analysis, we focused on the general psychopathology scale of the Positive and Negative Syndrome Scale (PANSS).
Methods: A literature search based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015) yielded 8 randomized controlled trial studies of tDCS and the PANSS. There were 164 patients in the active and 165 patients in the sham conditions. Differences in pre and post treatment data (mean and standard deviation values) of the PANSS were extracted. Random-effects model was used to test the standardized mean differences (SMD) and variance-weighted variability ratios for each study. For studies that reported one-month or longer follow-up data (5 studies with 108 and 110 patients in active and sham condition, respectively), SMD of general psychopathology score was also evaluated.
Results: This meta-analysis showed that the general psychopathology symptoms assessed with PANSS were significantly reduced after tDCS active condition compared to the sham condition. However, we did not find evidence for long-term treatment effects. Given that only a small subset of studies reported follow-up data, long-term treatment effect needs to be evaluated further in future studies. Interestingly, the treatment group showed a significantly higher variability in general psychopathology scale than the control group.
Discussion: Interventions using tDCS appear to be effective for the treatment of general psychopathology symptoms as measured by the PANSS in schizophrenia. However, the long-term treatment effects of tDCS are unknown and it is unclear which aspect of the general psychopathology symptoms respond to tDCS. Lastly, the variability analysis suggests that individual differences in response to tDCS needs to be investigated to develop a more personalized intervention strategy.

T19. HANDWRITING KINEMATICS IN SCHIZOPHRENIA PATIENTS TREATED WITH LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTICS: RESULTSFROM THE ALPINE STUDY

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Background: Handwriting movements, which are mediated by striatal dopaminergic mechanisms, may provide insight into the therapeutic response to antipsychotics. Handwriting kinematic (HWK) assessments were administered in the ALPINE study, a randomized controlled trial of 2 long-acting injectable (LAI) antipsychotics started during an acute psychotic episode of schizophrenia. This exploratory analysis of ALPINE data examined blinded baseline HWKs as a potential biomarker for short-term therapeutic response to acute antipsychotic treatment.
Methods: Adults with an acute exacerbation of schizophrenia were enrolled as inpatients and randomly assigned to an LAI treatment (aripiprazole lauroxil or paliperidone palmitate; combined for this analysis). Patients were discharged 2 weeks later, if clinically stable, and followed for an additional 23 weeks. This post hoc exploratory analysis evaluated the relationship between baseline HWKs and treatment response at week 4, defined as: (1) ≥20% reduction from baseline in Positive and Negative Syndrome Scale (PANSS) total score, or (2) ≥2-point improvement from baseline in Clinical Global Impression–Severity (CGI-S) score. HWKs were assessed as an exploratory measure at baseline and at several visits over the treatment period; only the baseline HWK assessment was included in this analysis. HWK parameters were captured in 4 handwriting tasks (complex loops, maximum speed circle drawing, overlay circles, and left-right loops) found in prior studies to be proxies of dopamine dysfunction. Two kinematic measures were considered for this exploratory study: peak velocity (lower score corresponds with greater dysfunction) and percentage of nonballistic movements

(%NBM; higher percentage corresponds with greater dysfunction). Baseline scores for peak velocity and %NBM in the complex loops, maximum speed circle drawing, and combined overlay circles and left-right loops tasks were compared between week 4 treatment responders and nonresponders.
Results: A total of 143 patients had baseline HWK assessments and week 4 efficacy assessments and were included in this exploratory analysis (76% men; mean age, 43 years; mean PANSS total score at baseline, 94.5). At week 4, 46.9% and 28.7% of patients showed responses on the PANSS and CGI-S scales, respectively. Responders were similar to nonresponders on severity of baseline psychopathology or prior exposure to anticholinergics. PANSS responders had a lower mean peak velocity (ie, slower pen movements) on all HWK tasks at baseline compared with nonresponders (PANSS responders [n=67] vs nonresponders [n=76]: complex loops, 8.8 vs 12.2 cm/s; combined loops, 11.9 vs 15.8 cm/s). PANSS responders had a greater %NBM compared with nonresponders on the complex loops (57.1% vs 47.4%) and combined loops (44.7% vs 35.8%) tasks. Similar resultswere observed in CGI-S responders and nonresponders, respectively. PANSS response generally did not appear to vary according to other baseline clinical or demographic characteristics.
Discussion: In this exploratory analysis, ALPINE study participants who achieved PANSS or CGI-S response after 4 weeks of LAI treatment had lower movement velocities and a greater %NBM in HWK tasks at baseline than those who did not. This pattern suggests that baseline HWKs may reflect striatal dopamine dysfunction and could be a useful predictor of antipsychotic therapeutic response at 4 weeks of treatment.

T20. CLINICALLY RELEVANT WEIGHT CHANGE ASSOCIATED WITH ANTIPSYCHOTICS: A META-ANALYSIS

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Background: Antipsychotics induced weight gain (AIWG) is an important problem associated with decreased life expectancy and non-compliance. Our previous meta-analysis showed that almost all antipsychotics are associated with clinically relevant weight gain (CRWG) and that data on clinically relevant weight loss (CRWL) is sparse. Here we present an update as new antipsychotics are available.
Methods: CRWG or CRWL are defined as ≥7% weight gain or loss. PubMed, Embase and PsycINFO were searched for randomized clinical trials of AP that reported ≥7% weight change in study populations aged ≥15 years. We performed meta-analyses stratified by study duration (<6 weeks, 6-16 weeks, 16-38 weeks and >38 weeks) with a random-effects model. Additionally, meta-regression analyses are executed to test for 'duration' as a modifier for AP use, and baseline BMI to control for the influence of weight gain before the start or switch of AP. At the moment this is in process.
Results: The search yielded 2594 articles in total. After checking all papers on the eligibility of data, 198 articles could be included in the meta-analysis, resulting in 545 records of AP in the data set on clinically relevant weight change. CRWG differed per antipsychotic: the proportion of patients with CRWG was most pronounced for clozapine (<6 weeks: 27,5%; 6-16 weeks: 40%; 16-38 weeks: 47%; >38 weeks: 76,3%) and olanzapine (17,2%; 24,5%; 22,7%; 36,9%) whereas relatively low proportions of CRWG were seen for lurasidone (<6 weeks: 4,3%; >38 weeks: 7,4%) and ziprasidone (2,5%; 8,7%; 2,8%; 7,6%). CRWL occurred with all antipsychotic drugs; after > 38 weeks of treatment, the proportion of patients with CRWL was most pronounced for lurasidone (12.6%) and ziprasidone (28.6%). However, data are limited to draw firm conclusions. During SIRS final and complete resultswill be presented.

Discussion: Switching of AP can result in both weight gain and weight loss, although weight gain is more prominent than weight loss. This questions whether changing an AP because of weight gain is a sensible strategy.

T21. EXECUTIVE DYSFUNCTIONS IN FIRST EPISODE OF SCHIZOPHRENIA - IMPLICATIONS FOR SOCIAL REINTEGRATION

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Background: Patients with first episode of schizophrenia (FES) perform worse on executive dysfunction (ED) tests regarding planning, spatial working memory, and attentional set-shifting when compared to normal volunteers, matched for age and IQ [1]. Neuropsychological deficits seem to predate the clinical symptoms of FES, therefore their evaluation is very important both initially and during the evolution of the disorder [2]. The evaluation of these aspects in clinical practice should be more frequently implemented, because it may offer an image about the patients' ability to cope with new situations, stressful events, social challenges being included [3].

Methods: A case series of 5 patients (mean age 25.6, male: female= 2:3) diagnosed with FES is presented in order to evaluate the correlation between ED and social performance. All patients were evaluated using verbal fluency tests- Controlled Word Association Test (COWAT) consisting of two tasks- first letter (FAS) production and categorial fluency (CF), as well as clock-drawing test (CDT), scored on a 1 to 10 scale. These tests were selected for determining the level of language and executive function (selective attention, set-shifting, self-monitoring, visuospatial coordination, planning abilities, lexical access speed), while for social abilities, the Personal and Social Performance (PSP) scale was administered. Positive and Negative Syndrome Scale (PANSS) was also administered, and N4 (passive /apathetic social withdrawal), N5 (difficulty in abstract thinking), G11 (poor attention) G14 (poor impulse control), and G16 (active social avoidance) items were monitored separately. All patients were evaluated in the first 7 days after their atypical antipsychotic treatment initiation and at 24 weeks after their baseline visit.

Results: At the initial evaluation, all 5 patients recorded low performance on ED tests- COWAT- FAS total score= 13.5, COWAT-CF total score=7.3, CDT mean value=6.2, and the PSP mean score was 52. On the PANSS, the mean score was 95.4, and the sum of items indicating ED (N5, G11, G14) was 14.7, while the sum of N4 and G16 was 12.5. The correlation between PSP and ED was not consistent at the baseline visit ($p=0.022$). The analysis after 24 weeks of antipsychotic treatment reflected a significant improvement of the PANSS total score ($p<0.01$), ED-PANSS subscale ($p<0.001$), and social performance-PANSS subscale ($p<0.001$). However, the COWAT-FAS and COWAT-CF scores improved at a nonsignificant level (+1.3, and +0.9, respectively), and the CDT also showed little improvement (+1.2) which indicates the need for more detailed ED exploration in FES patients. The PSP scores improved significantly at week 24 (+12.8, $p<0.01$), but patients with higher ED at baseline had a lower level of PSP improvement at week 24 ($p<0.01$).

Discussion: Exploration of ED is an important aspect of the social functioning prognosis on medium-term in patients diagnosed with FES. Although initially ED and social performance may not be correlated in this population, the strength of their relationship tends to increase in time. Targeted social reintegration interventions can be initiated in FES patients with ED, as part of functional prognosis improvement and anti-stigmatization policies.

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T22. EMOTIONAL MEMORY FOR FACIAL STIMULI IN SCHIZOPHRENIA: THE ROLE OF DIFFERENT ENCODING STRATEGIES

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Background: The emotional enhancement of memory (EEM) is a socially adaptive phenomenon by which emotional materials are better remembered than neutral ones. There is evidence that the EEM remains intact in schizophrenia (SCZ) despite known emotional disturbances and memory impairment in this population. However, some contradictory findings suggest this is not the case and present the need for further research. This study tested the primary hypothesis that different encoding strategies may differentially influence the EEM for facial stimuli in SCZ. Encoding strategies are likely to be particularly relevant for the EEM with facial expressions as SCZ involves selective facial emotion perception deficits. More specifically, emotion perception appears impaired when expressions are encoded directly (by attending directly to emotional content; emotion-discrimination decisions) but intact when encoded indirectly (by attending to non-emotional content; sex-discrimination decisions). Given that intact emotion perception appears necessary for the EEM with faces, we hypothesized that the EEM would be present in SCZ when stimuli were encoded indirectly but not directly.

Methods: A SCZ (N = 28) and healthy adult group (N = 29) performed an incidental recognition task with faces showing happy, angry, fearful, and neutral expressions. Faces were encoded in two conditions: indirect and direct. After a distraction phase, participants were shown the faces from encoding intermixed with new faces and indicated which they recognized using the Remember/Know paradigm.

Results: Encoding method did not influence the EEM in SCZ when examining within-group comparisons. However, between-group contrasts showed that overall memory performance (for all emotions) was only significantly impaired in SCZ comparatively to healthy adults when faces were encoded directly, whereas indirect encoding resulted in similar recognition accuracy between groups. Beyond this, an intact EEM effect (irrespective of encoding) was found in SCZ that mirrored the healthy adult group's: all participants had better memory for angry and fearful faces. Further, both participant groups showed an EEM effect for Remember responses only.

Discussion: These findings have important implications for understanding emotional memory in SCZ. Our resultssuggest that different encoding strategies do not modulate EEM patterns in SCZ. Interestingly, however, encoding method appeared to influence overall memory in SCZ. When comparing memory performance between groups for all facial expressions, SCZ showed poorer overall memory performance than healthy adults in the direct encoding condition only, whereas memory accuracy was similar in both groups in the indirect condition. Our findings

also show that the EEM is intact in SCZ but only in one recognition domain (Remember not know). This may explain past inconsistencies in the literature: previous work that failed to differentiate between recollection and familiarity memory may not have been able to detect the EEM in this population. The finding of intact EEM for facial expressions in SCZ informs an area of cognition worth harnessing in social and neurocognitive remediation approaches. Given the socially adaptive nature of emotional memory for faces, this has implications for improving social function in SCZ.

T23. DOES COGNITION FOLLOW THE CORTICAL STRUCTURE? NEUROANATOMICAL SUBGROUPS BASED ON CORTICAL THICKNESS IN SCHIZOPHRENIA

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Background: One of the challenges in schizophrenia research is heterogeneity present in this disorder, which points to the need for data-driven approaches to tackle this problem. Cortical thinning has been proposed as an expression of the neurobiological pathogenesis of the illness insofar as it reflects both gene-mediated and progressive deficits in neurodevelopment. Regional cortical thinning has been found in schizophrenia patients compared to healthy controls. However, case-control paradigms that subsume the illness into a single disease entity ignore the within-group variability of cortical thinning patterns. Therefore, this study set out to address heterogeneity by applying cluster analysis to cortical thickness data from both chronic schizophrenia-spectrum patients and healthy control participants to determine clinical and cognitive correlates of neuroanatomical-derived subgroups.

Methods: 63 healthy control participants and 73 patients diagnosed with schizophrenia or schizoaffective disorder were recruited from outpatient programs in Hamilton, Ontario, Canada. Demographic, clinical (PANSS), cognitive (MCCB) and functional competence (COALS) measurements were collected. Participants underwent 3T MRI scans, which were processed with FreeSurfer to generate average cortical thickness values in 148 cortical regions of interest (Destrieux et al., 2010). We carried out agglomerative hierarchical cluster analysis using Ward's method with Euclidean distance on age-corrected thickness values. The optimal number of clusters was determined by 16 validity indices. Chi-square and ANOVA were used for group comparisons, and Bonferroni correction was performed when appropriate.

Results: 12 out of the 16 clustering validity indices suggested a 2-cluster solution. The first subgroup (n1=53) was primarily composed of patients (75%), whereas approximately two-thirds of the other subgroup (n2=83) were healthy controls. The patient/control ratio was significantly different across subgroups, $X2$ (1, $N = 136$) = 15.186, $p < .0001$.

Subgroup 1 showed a significantly lower MCCB composite T score ($M = 30.23$) than subgroup 2 ($M = 37.84$), $p = 0.003$. Subgroup 1 also displayed significantly lower cortical thickness values across 110/148 regions ($p<0.001$; 84/148 regions with Bonferroni correction). However, there was no significant difference in MCCB between the patients in subgroup 1 ($M = 29.18$) compared to patients in subgroup 2 ($M = 29.36$), $p = 0.95$. Likewise, no significant difference was found in terms of COALS and PANSS scores. Additionally, patients in subgroup 2 were more cognitively impaired than controls in subgroup 2 (MCCB 29.36 vs. 43.44).

Discussion: Cluster analytic algorithms revealed two clusters. The lower cortical thickness subgroup was over-represented by schizophrenia patients and demonstrated lower cognitive ability. Patients in this subgroup displayed cortical thinning patterns distinguishable from most

of the healthy population and characterized by cognitive impairment. This result is consistent with the previous finding that cognitive impairment is a correlate of cortical structural integrity. However, this association is only present in a subpopulation of schizophrenia spectrum patients. In the second cluster subgroup, which aggregated roughly balanced numbers of patients and controls, patients had impaired cognitive performance despite thickness patterns being indistinguishable from healthy controls. This implies that the impoverished brain structure is not a prerequisite for impaired cognition in schizophrenia. In addition, our data illustrate the potential value of fractionating schizophrenia based on brain morphology to pursue novel hypotheses on the pathogenesis of schizophrenia.

T24. UNDERSTANDING THE VARIABILITY OF THEORY OF MIND IN SCHIZOPHRENIA THROUGH A CLINICAL LIABILITY APPROACH: A SIB-PAIR STUDY

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Background: There is consistent evidence that Theory of Mind (ToM) is impaired in schizophrenia (SZ) (Bora & Pantelis, 2013; Chung et al., 2014); however, it remains unclear whether such deficits are trait- or state-dependent. To further investigate such dichotomy, a key aspect is to look at the performance of healthy relatives as compared to patients. Also, the analysis of the association of ToM with known clinical vulnerability markers of SZ has shown to be useful in the study of the role of ToM as an adequate intermediate phenotype of SZ risk (Giralt-López et al., 2020; Soler et al., 2017). Then, in the current approach, we aimed to investigate whether ToM is modified by clinical liability markers (basic symptoms and psychotic-like experiences) in individuals with a diagnosis of schizophrenia and their healthy relatives (siblings).

Methods: The sample comprised 65 individuals: 38 patients with a diagnosis of a schizophrenia-spectrum disorder (SSD) and 27 healthy siblings. ToM was assessed using the Hinting Task (HT) (Corcoran et al., 1995; Gil et al., 2012) and the Intellectual quotient (IQ) was estimated using the Block Design and Vocabulary/Information WAIS-III subtests (Weschsler 1997). Basic symptoms (BS) were evaluated with the 4 factors of "The Frankfurt Complaint Questionnaire" (FCQ; Peralta and Cuesta, 2003): Central cognitive disorders, Perception and motor skills, depressiveness, Internal and external overstimulation. Psychotic-like-experiences (PLEs) were assessed using the Community Assessment of Psychic Experiences (CAPE), which reports scores on two dimensions (positive and negative) (Stefanis et al., 2002). Family history was assessed with the Family Interview for Genetic Studies (Maxwell, 1992).

Results: First, we tested whether ToM performance in healthy siblings is modulated by BS and/or PLEs. Linear regression analyses (adjusted for age, sex, IQ and family history) showed that higher scores of FCQ Depressiveness factor) and CAPE negative dimension were related

to poorer ToM performance in siblings (β=-0.77, p=0.041 Radj2=36.3%; β=-2.91, p=0.032 Radj2=47%, respectively). Second, a comparison of HT performance between patients and siblings (linear mixed model adjusted for age, sex, IQ and family history) showed significant group effects (F=5.49 p=0.023): patients presented lower scores than siblings (estimated mean difference=-2.21). However, after adjusting also for clinical vulnerability markers such as basic symptoms and PLEs the differences in HT performance between patients and siblings became not significant.

Discussion: Our data indicate the usefulness of clinical liability markers to characterise differences in ToM abilities within healthy individuals. Furthermore, our resultssuggest that deficits in ToM are not only associated with schizophrenia, but with clinical vulnerability for this disorder. These findings support the potential role of ToM as a marker that could contribute discriminating especially vulnerable subjects from a population at risk, in this case at genetic risk (siblings). Nevertheless, new analyses in larger samples are needed.

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T25. COMBINED EFFECT OF TREATMENT-RESISTANCE AND AUTISTIC TRAITS ON THEORY OF MIND IN SCHIZOPHRENIA

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Background: : Patients affected by schizophrenia show highly different clinical, cognitive, sociocognitive, and functional outcomes, highlighting the heterogeneity that characterizes the disorder. Around 30% of patients are defined treatment-resistant, as they never show a significant response to first-line antipsychotics. Treatment-resistant schizophrenia (TRS) is associated with worse course of illness and functional outcome, as well as with a more severe impairment in cognitive and sociocognitive abilities.

The disruption of sociocognitive skills is a hallmark not only of schizophrenia, but also of autism spectrum disorder (ASD). Growing evidence shows the presence of autistic-like symptoms (i.e., autistic traits, ATs), of the same quality as ASD clinical manifestations but not reaching diagnostic threshold, in a subgroup of patients with schizophrenia. The severity of ATs in schizophrenia has been associated with a more significant impairment of sociocognitive abilities, especially Theory of Mind (ToM), supporting the hypothesis that the presence of ATs would be associated with a 'double dose' of deficit in schizophrenia. While it has been shown only in one study that TRS patients exhibit higher severity of ATs and sociocognitive difficulties, the combined effect of both TRS and ATs on sociocognitive skills has not been investigated.

Thus, the aim of this study is to evaluate the combined effect of treatment response and ATs on ToM abilities in schizophrenia.

Methods: 172 patients with schizophrenia were enrolled and stratified into two groups: 85 first-line responders (FLR), and 87 TRS. Patients were assessed for ATs severity (PANSS Autism Severity Score, PAUSS) and allocated either to ATs+ group (patients with ATs) or

ATs- group (patients without ATs), according to PAUSS cut-off score of 30. Intellectual level was evaluated with the Wechsler Adult Intelligence Scale–Revised, and ToM was evaluated by means of Picture Sequencing Task (PST), evaluating cognitive (PST Questionnaire), affective (PST Sequencing), and global (PST Total) ToM abilities. Analysis of variance (ANOVA) was run to evaluate differences in PST scores between FLR and TRS patients. General linear models (GLMs) were conducted with PST scores as dependent variables, treatment (FLR/TRS) and ATs (ATs+/ATs-) as categorical variables, and age, duration of illness, education, and I.Q. as covariates.

Results: ANOVA showed significant differences between FLR and TRS in all PST scores: Questionnaire (p=.04), Sequencing (p=.02), and Total score (p=.01). The GLM on PST Questionnaire revealed a significant effect of treatment (p=.002), ATs (p=.0005), and treatment*ATs interaction (p=.02), with worse cognitive ToM abilities in TRS patients with ATs. The GLM on PST Sequencing showed an effect of treatment, with worse affective ToM in TRS patients. Lastly, GLM on PST Total score showed a significant effect of treatment (p=.001), ATs (p=.01), and treatment*ATs interaction (p=.02), with worse global ToM abilities in TRS patients with ATs.

Discussion: This is the first study to evaluate the interactive effect of treatment response and ATs on ToM abilities. We showed that the interaction between treatment resistance and ATs is associated with a more severe disruption of both cognitive and global ToM abilities, with worse outcome among TRS patients with autistic traits. As for affective ToM, we only found an effect of treatment, showing that TRS patients have a more significant disruption. These resultshighlight the need of further research on ATs in schizophrenia, as well as the necessity of early individuation and tailored pharmacological treatment for TRS patients, in order to improve sociocognitive abilities, with consequent beneficial effects on functioning.

T26. INVESTIGATING THE INTENTIONALITY BIAS IN SUBCLINICAL PARANOIA

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Background: Recent research has emphasized conceptualizing psychopathology as a continuum ranging from absent to severe (Clark et al., 2017), suggesting it may be beneficial to investigate symptoms present in subclinical populations. Regarding schizophrenia, social cognitive biases such as hostile and negative attributions have been linked to paranoia in both patients (Pinkham et al., 2016) and populations with high subclinical paranoia (Combs et al., 2007; Klein et al., 2018). A perhaps broader version of these biases is the intentionality bias, wherein individuals attribute intentionality to apparently accidental, neutral situations rather than just negative situations. This bias has been previously demonstrated in both schizophrenia (Buck et al., 2018) and schizotypy (Fyfe et al., 2008; Moore & Pope, 2014). Given the relationship between paranoia and related social cognitive biases in both clinical and subclinical populations, we sought to investigate the intentionality bias in a sample with heightened subclinical paranoia.

Methods: We recruited 40 undergraduates with high levels of paranoia, defined as a score of 52 or higher on the Paranoia Scale (PS; Fenigstein and Vanable, 1992). Participants completed the Intentionality Bias Task (IBT; Rosset 2008) in which individuals rate a series of events as occurring “on purpose” or “by accident.” We summed each participant’s total “on purpose” responses and analyzed the bivariate correlation between this value and paranoia. We also aimed to compare our analyses to previous findings on the relationship between paranoia and hostile attributions and to examine the relationship between the intentionality bias and hostile

attributions. To this end, participants completed the Ambiguous Intentions Hostility Questionnaire (AIHQ; Combs et al., 2007). Here, participants are presented with ambiguous situations involving another individual and are asked to rate how intentional they believe the situation to be, how angry the situation would make them, and how much they would blame the individual involved. An overall blame score is calculated by combining these three aspects. We calculated the bivariate correlation between paranoia and the AIHQ blame score, as well as the correlation between the IBT and AIHQ.
Results: Participants were 62.5% female, 40% Caucasian, with an average age of 20.15 (SD=2.19). We did not find a significant relationship between IBT performance and paranoia, r=0.20, p=.21. Consistent with previous findings, we observed a relationship between the AIHQ blame score and paranoia (r=0.47, p<.01). However, the IBT and AIHQ were not significantly related to each other (r=0.19, p=.24).
Discussion: Although we found a correlation between paranoia and hostile attributions in this subclinical sample, our findings do not support a relationship between either paranoia and the intentionality bias, or between hostile attributions and the intentionality bias in a subclinical sample. This may indicate that, while hostile attributions are rooted in paranoia, a separate dimension of schizotypy and schizophrenia gives rise to the intentionality bias. Future research may benefit from directly investigating how other symptoms (e.g., odd beliefs, abnormal perceptual experiences) relate to the intentionality bias.

T27. DETERMINING RISK VERSUS PROTECTION OF EXECUTIVE FUNCTION IN INDIVIDUALS AT-RISK FOR PSYCHOSIS: THE ROLE OF OBSESSIVE COMPULSIVE SYMPTOMOLOGY

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Background: Failures of executive functioning (EF) have been found across the illness course of schizophrenia (SZ) and obsessive-compulsive disorder (OCD), and are associated with depression, anxiety, poorer quality of life, and pronounced impairment in social and role function. When SZ and OCD arise comorbidly, some research suggests that individuals have greater global EF deficits than those who have SZ or OCD alone. However, other evidence suggests that obsessive-compulsive symptoms (OCS) instead may function as a protective factor from EF deficits when co-occurring with SZ, especially in the at-risk and early stages of illness. Therefore, the role of OC symptoms as they covary with EF performance, particularly in the risk-stages of SZ, warrants further clarification. As such, the primary aim of this study is to determine how OCS may influence the well-known EF impairment in individuals at-risk (AR) for developing a psychosis-spectrum disorder.
Methods: Participants completed two self-report screening measures, the Prodromal Questionnaire Brief (PQ-B) and the Yale Brown Obsessive-Compulsive Scale (Y-BOCS), which determined the preliminary AR and OCS groups: AR with OCS (AR+OCS; n=12), AR without OCS (AR-OCS; n=3), and healthy comparisons (HC; n=12). Eligible participants then met virtually to complete EF tasks, including a modified cued task switching paradigm. On each trial of this task, a letter-digit pair was presented and participants responded to the stimuli according to the applicable cue rule. Trial cues pseudorandomly alternated as either an in-category switch (i.e. odd to even or consonant to vowel), an out-of-category switch (i.e. number

to letter or letter to number), or a non-switch. We assessed the relationship between AR and OC symptom severity and accuracy on in-category, out-of-category, and non-switch trials. Subsequently, moderating effects of OC symptom severity on the relationship between AR symptoms and accuracy on each task switching condition were assessed. Lastly, protective versus vulnerability factors in EF performance were assessed across groups.
Results: Preliminary findings revealed a negative relationship between OC symptom severity and accuracy in out-of-category switch trials ($r=-.447$, $p<.015$) and non-switch trials ($r=-.446$, $p<.015$). Additionally, correlational analyses show a negative association between AR symptom severity and accuracy on in-category switch trials ($r=-.408$, $p<.028$), however, when OCS severity is controlled for, this relationship is no longer present ($r=-.303$, $p<.117$). Group differences were observed between AR+OCS and AR-OCS in accuracy on out-of-category switching trials ($F(1,13)=4.852$, $p<.046$), with AR+OCS performing worse. Analyses also revealed group differences between AR+OCS and HC in accuracy on non-switch trials ($F(1,22)=4.575$, $p<.044$) and in-category switch trials ($F(1,22)=4.688$, $p<.041$), with AR+OCS demonstrating poorer performance.
Discussion: The overall goal of the current study is to identify potential risk and/or protective factors of OCS in AR individuals to aid in early identification and prognosis. Preliminary findings here replicate the well-established report of EF impairment in AR individuals. Additionally, these findings suggest that OCS may negatively contribute, to some degree, to EF impairments in the comorbid presentation of these symptoms. However, data collection is ongoing to further clarify the potential risk or protective effect of OCS, in addition to how the interaction of EF performance and OC symptomology may impact social and role function. Such findings may aid in AR intervention efforts as the currently available treatments may not be effective across all patients with varying comorbid presentations.

T28. STRATEGY MONITORING AND TRANSFER IN COGNITIVE REMEDIATION

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Background: Cognitive Remediation (CR) is an effective treatment for cognitive deficits in schizophrenia, and its effects are associated with improvements in everyday functioning. A CR expert working group recently identified four core features of the treatment: facilitation by a trained CR therapist, cognitive exercises, as well as procedures to develop awareness of problem-solving strategies (i.e., strategy monitoring) and facilitate the application of strategies to real-world activities (i.e., transfer). This study aimed to provide further insight into the importance of strategy monitoring and transfer in CR by addressing two research questions:
i) Are changes in the ability to develop quality strategies and transfer ideas associated with changes in neurocognition and real-world functioning?

ii) Which participant characteristics predict the ability to develop quality strategies and transfer ideas at the beginning of CR treatment?

Methods: Individuals with Schizophrenia or Schizoaffective Disorder (n=55) participated in 12 weeks of CR. All participants completed assessments of cognition, clinical symptoms, social competence, and real-world functioning at baseline and post-CR. At each session, the clinician rated the quality of participants' strategies and transfer ideas on a scale from 1 (irrelevant) to 10 (clear application).
Results: Changes in strategy quality were significantly correlated with changes in neurocognition, $r(53) = .40$, $p = .003$, but not with changes in real-world functioning, $r(53) = -$

.10, p = .481. Steiger's test of the difference between two dependent correlations revealed that the former relationship is significantly greater than the latter (z=2.79, p=.003).
Changes in transfer quality were significantly correlated with changes in real-world functioning, r(53) = .45, p = .001, but not with changes in neurocognition, r(53) = .05, p = .708. Steiger's test indicated that the former relationship is significantly greater than the latter (z=2.31, p=.011).

The multiple regression conducted to predict strategy quality at Session 1 of CR from premorbid functioning, age of onset, baseline negative symptoms, and baseline neurocognitive performance was statistically significant, R2=.45, F(4,47)=9.71, p<.001. Baseline neurocognitive performance was the only significant predictor of strategy quality at Session 1 of CR, b= 1.28, p<.001.

The multiple regression conducted to predict transfer quality at Session 1 of CR from baseline negative symptoms, baseline neurocognitive performance, and baseline social competence was statistically significant, R2=.38, F(3,51)=10.39, p<.001. Baseline neurocognitive performance was a significant predictor of strategy transfer at Session 1, b= .63, p=.003, as was baseline social competence, b= .06, p=.002.

Discussion: Strategy monitoring and transfer processes in CR differentially relate to treatment outcomes. Specifically, improved ability to develop quality strategies over CR is related to improvement in neurocognition, while improved ability to transfer these strategies to everyday activities is related to improvement in real-world functioning. Further, participant characteristics, such as neurocognitive performance and social competence at baseline, may affect individuals' ability to develop quality strategies and transfer ideas at the start of treatment. Given that these processes are related to treatment outcomes, CR therapists may consider these factors as risks for poorer treatment response and allocate resources to assist those patients more with strategy monitoring and transfer ability.

T29. IMPAIRMENT OF MOTIVATION MAY CONTRIBUTE TO EMPATHY DEFICITS IN INDIVIDUALS WITH HIGH LEVEL OF SOCIAL ANHEDONIA

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Background: Empathy, the ability to share and understand others' emotion states, is a goal-directed, effortful behaviours and recent findings have suggested that empathy may be affected by motivation. Although previous studies have documented impairments of empathy in individuals with high level social anhedonia, the relationship between motivation and empathy remains unclear. The present study examined the associations between self-reported empathy and social/non-social motivation in individuals with high level social anhedonia compared to those with low level social anhedonia to examine the mechanism of empathic impairments.
Methods: Thirty-nine individuals with high level social anhedonia (> MEAN+SD) and 57 controls (< MEAN) were recruited based on their scores on the Revised Social Anhedonia Scale of the Chapman Psychosis Proneness Scales. Monetary Incentive Delay (MID) and Social Incentive Delay (SID) tasks were administered to assess non-social and social motivation respectively. Cognitive and affective empathy was assessed with the Interpersonal Reactivity Index (IRI) and the Questionnaire of Cognitive and Affective Empathy (QCAE). Independent sample t tests were used to examine the group differences on cognitive and

affective empathy, and repeated-measures analysis of variance (ANOVAs) were conducted to examine the main effects of Group and its interaction effects on MID/SID task performances. Stepwise linear regression analyses were also performed to examine the contributions of motivation measured by the MID/SID task performances to cognitive and affective empathy.
Results: Individuals with high social anhedonia reported lower scores on both affective empathy (IRI empathic concern: $t = 4.10$, $p < 0.001$; QCAE proximal responsivity: $t = 2.39$, $p = 0.021$) and cognitive empathy (QCAE cognitive empathy: $t = 2.28$, $p = 0.026$; QCAE online simulation: $t = 3.22$, $p = 0.002$) than individuals with low level social anhedonia. On anticipatory ratings of the MID/SID tasks, the main effect of Group was significant ($F(1, 90) = 7.12$, $p = 0.009$), indicating that individuals with high social anhedonia exhibited lower level of anticipatory pleasure than individuals with low level social anhedonia. Moreover, individuals with high social anhedonia also exhibited lower hit rate on the SID task ($p = 0.001$) but comparable hit rates on the MID task. Regression analysis in individuals with high social anhedonia further indicated that anticipatory pleasure of reward condition in the MID task significantly predicted cognitive empathy (IRI perspective taking: $\beta = 0.37$, $t = 2.38$, $p = 0.023$, $R2 = 0.139$). Consummatory pleasure ratings in hit trials of reward condition of the SID task also significantly predicted affective empathy (IRI empathic concern: $\beta = 0.34$, $t = 2.10$, $p = 0.043$, $R2 = 0.115$).
Discussion: Our results indicated poorer empathy and lack of motivation, particularly social motivation, in individuals with high level social anhedonia. More importantly, our findings suggested that both social and non-social motivation may contribute to empathic impairments in these individuals.

T30. METACOGNITIVE WCST PERFORMANCE, MOMENTARY JUDGMENTS OF PERFORMANCE AND CONFIDENCE, AND GLOBAL ASSESSMENTS OF ABILITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: People with schizophrenia (SCZ) and bipolar disorder (BPI) have challenges in accurate evaluation of their cognitive performance. In addition to mis-estimation, they also manifest response biases, with a general tendency toward overconfidence. We have previously found that over-confidence, assessed on a momentary basis, was associated with poorer performance on social cognitive and neurocognitive tests. In this study, we examined performance, momentary judgments of performance, and confidence in correctness of responses on a meta-cognitive version of the Wisconsin Card Sorting Test (WCST). After each of the 64 trials, participants reported on whether they believed that they were correct, how confident they were in that judgment, and then received performance feedback. After completion of the assessment, participants were asked to rate how well they did and how well "the average person would do".
Methods: 99 participants with SCZ and 67 participants with BPI completed the study. Data collected in the study were the number of correct sorts on the meta-cognitive WCST, the number of sorts they believed that they were correct, the confidence ratings collected on a trial

by trial basis, and the participants' global judgments about how they did and how a normative individual would perform.
Results: Participants with SCZ got 31 WCST sorts correct and reported that they were correct on 49. Participants with bipolar BPI got 37 sorts correct and reported that they were correct on 53. Bipolar patients performed significantly (p=.009) better, but both groups overestimated equivalently. For participants with bipolar disorder, momentary confidence was associated with WCST accuracy and momentary judgments. For SCZ participants, WCST performance was not independently related to momentary confidence or global judgments. For prediction of global judgments compared to normative standards, for participants with BPI WCST performance and trial x trial confidence were predictors.
Discussion: Participants in both groups equivalently overestimated their performance on average on a momentary basis. However, confidence in BPI patients was correlated with actual WCST performance, whereas in SCZ it was only associated with self-reported performance. Thus, SCZ participants appear to have challenges in both momentary estimation of accuracy and utilization of available information to guide other future behavior. For BPI participants, momentary judgments of performance were inflated, but performance predicted confidence and global judgments. This may be due to differences in responding to feedback, because the momentary accuracy judgments were produced prior to feedback regarding correctness of responses.

T31. DO PERSONAL GOALS INFLUENCE MENTAL TIME TRAVEL IN INDIVIDUALS WITH AND WITHOUT SCHIZOTYPY?

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Background: The ability to project oneself into the past to re-experience the past or into the future to pre-experience the future is referred to mental time travel (MTT). Many MTT are related to personal goals. Previous studies on MTT in schizotypy revealed inconsistent results,it is not clear whether personal goal relevance played a role in explaining the inconsistent results, the present study aimed to examine this issue.
Methods: Individuals with schizotypy (n=39) and non-schizotypy (n=21) participated in the study and finished the MTT task in which participants were required to generate personal goals and non-goal events first, and then to generate specific possible future events or past events related to the personal-goals or non-goal events. Outcome measures include specificity, vividness, sense of experience, emotional valence, emotional intensity, proportion of first-person visual perspective, and difficulty in MTT.
Results: A 2 (group: schizotypy, non-schizotypy) x 2 (event type: personal goal, non-goal) x 2 (time orientation: past, future) ANOVA was conducted for each index. Results revealed that individuals with schizotypy generated fewer specific events than non-schizotypy. Personal goal related MTT were more specific, more vivid, more emotional intensive, and had more sense of experience than non-goal related MTT. Compared with remembering past events, individuals generated fewer specific events, and are less vivid, had less sense of experience, reported more difficulty, but more positive in future thinking. Moreover, the event type x time orientation interaction was significant in sense of experience, emotional valence, and emotional intensity. Personal goal related MTT had more sense of experience and emotional intensity than non-goal related MTT, and this difference was more prominent in future thinking than remembering the past. In addition, imagining personal goal related events were more positive than remembering past personal goal related events, but this difference was not significant in non-goal related events.

Discussion: These findings suggest that individuals with schizotypy were less specific than non-schizotypy individuals in MTT. Participants exhibited better performance in personal goal related MTT than non-personal goal related MTT, and individuals with schizotypy showed a similar pattern to non-schizotypy individuals.

T32. STRESS-SENSITIVITY IN SCHIZOPHRENIA APPEARS TO BE PART OF DIFFERENTIAL SUSCEPTIBILITY TO ANY ENVIRONMENTAL INFLUENCE: PRELIMINARY FINDINGS FROM AN EXPERIMENTAL VIGNETTE STUDY

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Background: While there is a broad consensus regarding the role of stress-sensitivity in schizophrenia, there is little, if any at all, attention to the possibility that it is part of a broader picture of differential susceptibility to any environmental influence (i.e., both negative and positive). More specifically, to the possibility that patients with schizophrenia are more susceptible than healthy controls not only to stressful environmental influences but also to positive or supportive ones. This presentation aims to introduce this notion and to present pilot data that provide preliminary support for its plausibility.
Methods: To test the above hypothesis, a sample of 186 mental health professionals was randomly assigned to read one of two experimental vignettes describing a young adult diagnosed with schizophrenia or a healthy young adult and answered questions about their evaluation of the individual in the vignette's functioning in an occupational assessment which consists neuropsychological tests examining neurocognition and social cognition. Afterward, the participants read a sequel vignette describing an experimentally induced situation. The individual from the first vignette receives either a positive reinforcement on his performance in the tests, creating a supportive environment, or negative feedback on his performance, producing a stressful environment. Following, the participants answered the same questions about their evaluation of the individual in the vignette's functioning in the occupational assessment.
Results: As would be expected, there was a significant group (schizophrenia versus healthy) effect on the estimated level of performance in both domains (i.e., neurocognition and social cognition). Moreover, consistent with our hypotheses, there was a significant feedback effect on the level of performance in both groups and both domains. However, inconsistent with our hypotheses, only the simple main effect of positive feedback was significant, whereas the simple main effect of negative feedback was not significant. These resultsremain unchanged after controlling for level of experience with patients with psychosis and schizophrenia.
Discussion: To the best of our knowledge, these pilot results provide a first indirect empirical support for the notion of differential susceptibility in schizophrenia. Moreover, they suggest that patients with schizophrenia are more susceptible to positive environmental influences (e.g., supportive feedback) than to stress (e.g., negative feedback). If further replicated in future studies among mental health professionals who specialize in the diagnosis and treatment of schizophrenia patients, the present results will lay the theoretical and methodological foundation for future studies that will test the above notion among patients with schizophrenia.

T33. RELATIONSHIP BETWEEN SOCIAL COGNITION AN EXECUTIVE FUNCTION IN PEOPLE WITH A RECENT-ONSET PSYCHOSIS

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Background: Social cognition is defined as the mental processes underlying people's capacity to perceive, process and comprehend social information. (Ludwig et al., 2017). Executive functions are high-level cognitive processes that enable individuals to regulate their thoughts and actions during goal-directed behavior (Berberian et al., 2019; Friedman 2017). Some studies have related the association between neurocognitive performance and social cognition in first episode psychosis (FEP) (Ayesa-Arriola.,et al 2016; González-Ortega., et al 2019) . Studies that focus on executive functioning and social cognition are needed because their relationship is unclear. On the other hand it is unclear whether males and females with FEP differ in their executive function and social cognitive abilities. The aim of this study was to assess the relationship between executive function and different domains of social cognition in patients with a recent-onset psychosis. As a secondary objective is to evaluate the relationship of these variables split by gender.

Methods: A cross-sectional study was performed based in the data of 2 mains multicenter clinical trials. The sample was composed of people with a recent onset of psychosis, recruited from 10 public centers in Spain. A total of 191 patients compose the sample. A battery of questionnaires regarding social cognition was included: Emotional perception (Face Test), Theory of Mind (Hinting Task), Attributional style (IPSAQ). Assessment of executive function included: Trail Making Test, Wisconsin Card Sorting Test (WSCT), Stroop Test, Digits Wais. The statistical analysis was done using SPSS.

Results: : TMT B was related to attributional style, specially to internal attribution (p=0.002). Some scores in Stroop Test were related to Emotional recognition: word (p=0.020), colour (p=0.028), word/colour (p=0.058). Regarding the correlations split by gender: In the men´s sample we find a association between digits scores and attributional style (p= 0.051). WSCT was related to emotional recognition (p=0.049). Interference score of Stroop test was related to Attributional style (p=0.026). Regarding to women TMT B was related to Internal Attribution for positive events (p=0.055) and to emotional recognition (p=0.008). Stroop test was related to emotional recognition in word score (p= 0.030), word/colour (p=0.007) and interference (p=0.027).

Discussion: Social cognition and executive function have been described in psychosis being variables of importance in social functioning and recovery of the patients (Hajdúkt,. et al 2018). Although that few studies have reported the relationship between them, and those that do compared specific domains of Social cognition or general neurocognition. Studies focus on the different domains of Social cognition and executive functioning are needed in order to improve treatments to patients in the early stages of psychosis.

T34. DIFFERENTIAL ASSOCIATION OF GRANDIOSITY AND PASSIVITY WITH ALTERED JUDGMENTS OF AGENCY

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Background: Have you ever pressed a button at a pedestrian crossing and believed you caused the traffic lights to change? These buttons are usually ineffective and the changing of the traffic lights is actually linked to timers. This is an example of where the sense of agency(SoA) can be quite disconnected from objective reality. Although we all fall prey to such perceptions from time to time, in disorders like schizophrenia, symptoms related to impaired SoA are highly distressing. Psychotic symptoms are marked by aberrant sensory perceptions and a disturbance in SoA, whereby patients believe that their actions/thoughts are controlled by external forces (delusions of passivity), or they may ascribe agency to events which are independent of their actions (e.g. grandiosity). One approach to investigating SoA is the exposure of participants to experimental conditions that differ in the temporal proximity between actions and consequences. Here, we used an agency-attribution task that evaluated explicit experiences of the temporal causal relations between an intentional action and an external event.
Methods: In each trial, a square object appeared at the bottom of a computer screen and moved straight upward at uniform speed. Participants were instructed to press a key immediately upon hearing a beep. When the key was pressed, the object jumped forward with various temporal biases. Participants were instructed to make a judgment for each trial about whether (or not)they caused the object to jump. A total of 43 people with schizophrenia (/schizoaffective disorder) (PSZ), 21 nonclinical voice-hearers(NCV) varying in delusional beliefs, and 37 control subjects participated. The Peters Delusion Inventory (PDI) was used to quantify delusional ideation.
Results: We indexed agency attribution as area under the % Yes responses against temporal bias curve (AUC) and found that PSZ and NCV, particularly those endorsing grandiose beliefs, tended to give more yes responses than control subjects at larger temporal biases ($F=3.37, p=0.039$, indicating that they over-associate their actions with subsequent events. Critically, the AUC was associated with grandiosity type delusions($r=0.35$, $p=0.01$), while this measure was negatively associated with delusions of control across PSZ and NCV($r=-0.29$, $p=0.04$).
Discussion: These results suggest that aberrant experiences of temporal-causal relationships can differentially be associated with distinct types of delusional ideation. Specifically, the data show that disturbances in SOA may be a continuous dimension ranging from grandiosity to passivity and these two types of delusions are usually anticorrelated.

T35. CROSS-DIAGNOSTIC COMPARISONS OF INTELLECTUAL ABILITY AND WORK OUTCOME IN PATIENTS WITH MENTAL DISORDERS: A MULTI-CENTER STUDY

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Background: Cognitive impairment is common in people with mental disorders, leading to cross-diagnostic classification based on cognitive characteristics (Lewandowski et al., 2018). Although cognition and intelligence are different in nature, some domains are overlapped (Wechsler, 2008). So far, few studies addressed cross-diagnostic classification based on intellectual abilities in people with mental disorders. Also, functional outcome has rarely been considered in cross-diagnostic studies. The present study was conducted to address the above two issues taking data-driven approach.

Methods: Subjects: Data from 779 patients (60 years old or younger), diagnosed with schizophrenia (SCZ, n=542), bipolar disorder (BD, n=57), major depressive disorder (MDD, n=93), or autism spectrum disorder (ASD, n=87), and healthy control subjects (HC, n=1046) were used for analyses. They were recruited from 13 facilities in Japan. The study protocol was approved by ethical committees at each site.

Assessment: Current IQ was assessed by an abbreviated version of the WAIS-3, consisting of Symbol search and Similarities (Sumiyoshi et al., 2016). Premorbid IQ was estimated using Japanese version of the Adult Reading Test (Matsuoka, et al., 2006). IQ discrepancy was estimated by subtracting Premorbid IQ from Current estimated IQ. Total work hours per week (Work), based on the Modified Social Adjustment Scale -Work Outcome (Subotnik, et al., 2008; Sumiyoshi et al., 2011), were obtained as a measure of functional outcome.

Analyses: Two independent k-means cluster analyses were performed. First, intelligence variables (Current estimated IQ, Premorbid IQ, and IQ discrepancy) were included. In the second analysis, Work was added.

Results: Cluster by intelligence : Linear discriminant analysis indicated a good fit of the 4 cluster solution with 98.7 % classification accuracy on average. Current estimated IQ lowered linearly from Cluster 1 to Cluster 4 with about 10-15 point decrement. Furthermore, clusters were halved into the “Preserved” (Cluster 1, 2: IQ discrepancy was less than 10 points) and “Deteriorated” (Cluster 3, 4: IQ discrepancy was greater than 10 points) groups (Weickert et al., 2000). Overall, SCZ was more prevalent in the Deteriorated group while other diagnoses were more frequent in the Preserved group.

Cluster by work outcome : Classification accuracy for the 4 cluster solution was 99.0% on average. Clusters were dichotomized into “Better” (Cluster 1) and “Poor” clusters (Cluster 2, 3, 4). Work hours in the former group (44.3 hrs/wk) were slightly longer than those of HC (40.3 hrs/wk) while work hours in the latter group were below 10 hours/week (8.29 hrs/wk on average). Cluster 1 and Cluster 4 showed similar intellectual abilities with HC although the latter cluster belonged to the Poor group. Roughly, distribution was unimodal in SCZ with its

peak in in the Poor cluster. In contrast, distributions were bimodal for BP, MDD and ASD with the peaks both in the Poor and Better groups.

Discussion: Characteristics of the clusters based on intelligence variables were in accord with those in a previous cross-diagnostic study that showed gradual decrement in cognition across 4 clusters (Lewandowski et al., 2018). We further characterized the clusters according to the IQ discrepancy. The cluster analysis including work outcome did not reflect the intellectual status, as a large proportion of subjects with BP, MDD, or ASD was distributed in the Poor cluster irrespective of their preserved intelligence. Thus, despite the importance of dimensional classification of mental disorders (e.g. RDoC, Insel, 2014), alternative strategies based on functionality should also be pursued to support recovery for patients with mental disorders.

T36. EFFECTS OF SCHEMAS, INTERNALIZED STIGMA, AND SYMPTOMS ON THE EXPERIENCE OF SOCIAL EXCLUSION IN PSYCHOSIS

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Background: Social exclusion has immediate negative effects on healthy individuals' sense of belonging, sense of control, self-esteem, and cognitive functioning. Individuals with psychosis are more likely to be ostracized than healthy individuals. Moreover, social exclusion plays a role in the development, maintenance, and severity of psychosis. However, social exclusion has rarely been experimentally examined, and to our knowledge, social exclusion has never been experimentally examined in psychosis. Internalized stigma is associated with numerous negative outcomes and may be associated with how individuals react to social exclusion. Schemas are cognitive constructs that provide a framework for understanding the world. It is likely that schemas of the self and others may influence how individuals respond to social exclusion. Furthermore, effects of these factors in relation to overinclusion in psychosis have not been studied. The goal of the current study was to examine the effects of schemas, internalized stigma, and symptoms on the experience of social exclusion and overinclusion for individuals with psychosis.

Methods: 27 participants diagnosed with schizophrenia, ages 18 to 65, completed a computerized Cyberball game in which they passed a ball with two other players. Participants were led to believe that the two other players were in the lab with them and that they could meet the other players after the game. Participants completed three blocks of Cyberball; an exclusion, fairplay and overinclusion block. The participant received approximately one-fifth of the throws in the exclusion block, and four-fifths of the throws in the overinclusion block. In the fairplay block, the participant received approximately one-third of throws. The Need Threat Questionnaire (NTQ) was used to measure the emotional impact of the manipulation. Schemas about the self and others were measured with the Brief Core Schema Scale, internalized stigma was measured with the Internalized Stigma of Mental Illness Scale, and symptoms were measured with the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms.

Results: Individuals with psychosis with greater negative self-schemas and lower positive self-schemas were more likely to experience greater need threat when socially excluded ($r= -0.488$, $p= .022$; $r= 0.440$, $p=.025$). However, other-schemas were not significantly correlated with need threat in the social exclusion condition. Neither self-schemas nor other-schemas were significantly associated with need threat in the overinclusion condition. Individuals who reported greater internalized stigma experienced greater need threat when socially excluded ($r= -5.61$, $p= .004$). Whereas, internalized stigma was not associated with need threat in the social

overinclusion condition. In the social overinclusion condition, individuals with greater positive symptoms experienced more negative emotionality (r= -0.399, p= .044), whereas, negative symptoms did not significantly influence emotionality. In the social exclusion condition, individuals with greater negative symptoms experienced more negative emotionality (r= -0.455, p= .02), whereas, positive symptoms did not influence individuals' emotional reaction.
Discussion: Self-schemas, internalized stigma, and negative symptoms were associated with greater negative experience in response to social exclusion. These resultssuggest that therapies targeting self-esteem, internalized stigma, and negative symptoms may be beneficial in protecting against the negative consequences of social exclusion. Interestingly, overt social inclusion may be experienced negatively by individuals with psychosis with greater positive symptoms.

T37. COGNITIVE IMPAIRMENT DUE TO ANTICHOLINERGIC BURDEN IN SCHIZOPHRENIA: IS IT EVIDENT IN PATIENTS WITH LOW EDUCATIONAL STATUS?

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Background: Cognitive impairment is a major predictor of everyday functioning in schizophrenia (SCZ). It has a relatively stable course throughout life, settling between -0,75 and -1,5 standard deviation in cognitive tests. The iatrogenic cognitive effect of anticholinergic burden (ACB) has been investigated in studies focused on cognitive remediation. Extrinsic ACB associated with first-generation antipsychotic turned out to be one main reason for the claimed superiority of second-generation antipsychotic (SGA) in cognitive performance. ACB has been associated with worse performance on long-term spatial and declarative memory, complex attention and speed of processing. The aim of this research is to replicate this evidence in a low educational context. Our hypothesis is that ACB iatrogenic cognitive impairment may be masked by a floor-effect.
Methods: We assessed 94 stable patients with SCZ, with a mean age of 40.9 years (standard deviation-SD=12.3), a mean educational level (EL) of 7.9 years (SD=3.8), a mean age of onset (AoO) of 27.5 years (SD=11) and a mean length of disease (LoD) of 13.4 years (SD=10.4). Overall, 39.4% were on SGA regimen, and the mean antipsychotic dose was 415.6mg/day of chlorpromazine equivalents. Symptoms and cognitive performance were assessed by the Positive and Negative Syndrome Scale and the Brief Assessment of Cognition in Schizophrenia (BACS). We assessed ACB through a pharmacological index based on in vitro acetylcholine receptor binding studies, converted to relative "benztropine equivalents" (BE). Student's t test compared BACS scores between groups with at least one psychotropic medication with ACB, and without ACB. Pearson correlation or Spearman's rho coefficient analyzed correlation between ACB and BACS. In multiple regression models, we examined the variance in cognitive performance which remained to be explained by ACB, after controlling for covariates.
Results: Sixty-three patients (67%) taking at least one medication with ACB had a mean dose of 3.15mg/day (SD=2.61) of BE. BACS mean composite score was -1.28 (SD=0,84). No differences were found between groups with or without ACB for BACS composite score (t=0.875; p=0.384), or its subdomains. ACB was mildly correlated with verbal memory (rho=-0.258; $p<0.05$) and attention and speed of processing (rho=-0.258; $p<0.05$), but uncorrelated with BACS composite score. Verbal memory also had a moderate correlation with age (r=-0.338; $p<0.01$) and EL (rho=-0.364; $p<0.01$), and when these covariates entered in the multiple regression model (R2=0,204; F=7,421, df=2, 58, p=0,001), no variance in verbal memory

(dependent variable) remained to be explained by ACB (R2 change=0,012; F=0,870, df=1, 57, p=0,355). Attention and speed of processing correlated with age (r=-0.569; p<0.01), EL (rho=-0.566; p<0.01), LoD (r=0.417; p<0.01) and AoO (rho=-0.267; p<0.05). When these covariates were entered in the multiple regression model (R2=0.484; F=14.841, df=4, 55, p=0.000), no additional variance in attention and speed of processing (dependent variable) remained to be explained by ACB (R2 change=0.027; F=3.227, df=1, 54, p=0.078).

Discussion: International studies have revealed a consistent relationship between ACB and cognitive impairment in SCZ, even though with small effect sizes. Our study failed to replicate this pattern, when comparing people with and without ACB. A common feature in the previous studies is the EL of the sample, ranging from 12 to 13 years of formal education. Patients enrolled in our sample had only 7.9 years of education, consistent with the Brazilian low educational attainment. We suggest that a floor-effect might have masked the iatrogenic potential of ACB over cognitive performance in SCZ.

T38. ALTERED PERCEPTION OF ENVIRONMENTAL VOLATILITY DURING SOCIAL LEARNING IN EMERGING PSYCHOSIS

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Background: Paranoid delusions (PD), defined as unfounded beliefs that others intend to deliberately cause harm, are a frequent and burdensome symptom in early psychosis. About 50% of first-episode psychosis patients (FEP) with PD report well-being lower than 2% of the general population. Despite this urgent clinical need, emergence and consolidation of PD remains opaque. Recent theories suggest that aberrantly salient prediction errors (PEs) lead to a brittle model of the world providing a breeding ground for delusions to form. Here, we test this hypothesis with a Bayesian model of perception to investigate the computational mechanisms of emerging paranoia.

Methods: We analyzed 15 unmedicated FEP (≤ 7 days of antipsychotic medication), 16 individuals at clinical high-risk for psychosis (CHR), and 16 healthy controls (HC) that were matched to CHR for age, gender, handedness, and cannabis consumption. We examined participants' behavior during a social learning task, designed to probe learning about others' intentions under a stable and volatile environment. Subsequently, we investigated underlying computational mechanisms with the Hierarchical Gaussian Filter (HGF), which assumes that individuals do not only learn about another person's intentions (helpful or misleading), but also about their volatility over time. We formulated two competing hypotheses about computational mechanisms, comparing the standard HGF with a mean-reverting HGF, thereby formalizing the notion that altered perception of environmental volatility may explain the emergence of aberrantly salient PEs in psychosis. These models along with two simpler (control) models were fit to participants' behavior and compared with Bayesian model selection (BMS). We computed protected exceedance probabilities (φ) and estimated model frequencies (f) to measure the effect size of each model.

Results: Groups did not differ with respect to working memory ($F = 0.71$, $p = 0.499$) or IQ ($F = 1.00$, $p = 0.385$). However, behaviorally, FEP displayed reduced flexibility to take environmental volatility into account (group-by-volatility interaction: $F = 4.27$, $p = 0.020$). BMS suggested that HC were best explained by the standard HGF ($\varphi = 86\%$, $f = 0.95$). Conversely, FEP were best described by the mean-reverting HGF ($\varphi > 99\%$, $f = 0.95$) in line

with an altered perception of volatility in this population. Thirdly, CHR were better explained by the standard HGF (φ = 94%, f = 0.79), although model frequencies were indicative of a more heterogenous group.
We then investigated, whether model parameters also captured behavioral effects. We found group differences in parameter (κ) determining the coupling strength between hierarchical levels of the model ($\eta 2$ = 0.17, p = 0.013, pbf = 0.132), and the attractor point of the mean-reverting process (m3) ($\eta 2$ = 0.17, p = 0.019, pbf = 0.115), although these effects did not survive Bonferroni correction. Post-hoc tests indicated that FEP perceived the environment as more volatile over time (p = 0.004, pbf = 0.013) and showed a reduced coupling strength between hierarchical levels (p = 0.012, pbf = 0.036) compared to HC. Lastly, we observed correlations between m3 and PANSS positive symptoms (r = 0.32, p = 0.026, pbf = 0.158), and between κ and negative (r = -0.39, p = 0.008, pbf = 0.048), as well as general symptoms (r = -0.34, p = 0.022, pbf = 0.130).

Discussion: Our results suggest that FEP may be characterized by a different computational mechanism – perceiving the environment as increasingly volatile – which may give rise to aberrantly salient PEs in emerging psychosis. Furthermore, we observed greater heterogeneity in CHR, suggesting that this modeling approach may prove useful to investigate heterogeneity in CHR and identify vulnerability for transition to psychosis.

T39. METACOGNITION & SOCIAL COGNITION DIFFERENTIALLY INFLUENCE EXPERIENTIAL & EXPRESSIVE NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Negative symptoms in schizophrenia are core to the disorder, but existing interventions have had limited success in ameliorating their impact. Recently, the field has moved towards more nuanced assessment of negative symptoms, breaking them into experiential and expressive domains. Identification of unique factors contributing to each of these domains may help to identity more precise intervention targets. This study aimed to investigate the relationship between experiential and expressive negative symptoms and two factors repeatedly found to contribute to overall negative symptoms: metacognition and social cognition.
Methods: In fifty-eight people with schizophrenia-spectrum disorders, we used correlational and regression analyses to examine the associations of metacognition and social cognition with experiential and expressive negative symptoms. We further compared the strength of associations between negative symptoms domains.
Results: Results indicate that, in our data, metacognition was not associated with experiential negative symptoms. Instead, we found a moderate, negative association between metacognition and expressive negative symptoms. Social cognition was related to both domains of negative symptoms, but associations were not maintained in regression analyses.
Discussion: Together, these findings suggest that metacognition and social cognition seem to be differentially linked to negative symptom domains, such that metacognition is more closely tied to expressive symptoms, while social cognition is more closely tied to experiential symptoms. With replication, our findings point to metacognition and social cognition as potential treatment targets to improve expressive and experiential negative symptoms, respectively.

T40. WORKING MEMORY PERFORMANCE IS RELATED TO CHILDHOOD TRAUMA IN FEMALES WITH PSYCHOTIC-LIKE EXPERIENCES

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Background: Childhood trauma (CT) has been repeatedly associated with the whole psychosis spectrum and has been found to differentially affect males and females. CT also has adverse effects on a range of cognitive outcomes and correlates with poorer working memory (WM) performance in individuals with psychotic disorders, at clinical high-risk for psychosis, and non-psychiatric controls. However, the effect of CT on WM performance, and sex differences in this relationship, have yet to be explored in individuals experiencing psychotic-like experiences (PLEs).
Methods: In 466 undergraduates at a large, urban university, the influence of PLEs (Prodromal Questionnaire) and CT (Childhood Trauma Questionnaire) were examined to determine their contributions to WM performance on a spatial n-back task. A working memory sensitivity d' score was the dependent variable, calculating (Zhits – Zfalse alarms) for each trial type and controlling 2-back d' for 0-back d'. We conducted linear regressions on the total sample, as well as stratified by sex, to examine the effects of CT, PLEs, and their interaction on WM performance.
Results: Controlling for age (which significantly predicted WM performance), CT was significantly associated with WM in the total sample [unstandardized B=-.09, p=.045. After stratifying for sex, we found that CT was associated with poor WM performance in females only [unstandardized B=-.11, p=.028]. There was no significant main effect of PLEs or interaction of CT and PLEs on WM in the whole sample or either sex.
Discussion: Results indicate that CT accounts for lower WM performance in individuals, particularly females, experiencing PLEs. Females who have experienced CT may be at greater risk for WM problems, irrespective of co-occurring PLEs.

T41. INTELLIGENCE DECLINE ACROSS MAJOR DEPRESSIVE DISORDER, BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: Major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ) are associated with impaired intelligence that predicts poor functional outcomes.
Methods: Premorbid IQ, present IQ and intelligence decline were compared across patients with MDD (n=45), BD (n=30) and SCZ (n=139) and healthy controls (HCs) (n=135). Furthermore, we investigated which factors contribute to the intelligence decline in each diagnostic group.
Results: Significant differences were observed in premorbid IQ, present IQ and intelligence decline across the diagnostic groups. Patients with each psychiatric disorder displayed lower premorbid and present IQ and more intelligence decline than HCs. Patients with SCZ displayed lower premorbid and present IQ and more intelligence decline than patients with MDD and BD, while there were no significant differences between patients with MDD and BD. When

patients with BD were divided based on bipolar I (BD-I) and II (BD-II) disorders, degrees of intelligence decline were similar between MDD and BD-II and between BD-I and SCZ. Lower educational attainment was correlated with a greater degree of intelligence decline in patients with SCZ and BD but not MDD.
Discussion: These findings confirm that although all psychiatric disorders display intelligence decline, the severity of intelligence decline differs across psychiatric disorders (SCZ, BD-I>BD-II, MDD>HCs). Higher educational attainment as cognitive reserve contributes to protection against intelligence decline in BD and SCZ.

T42. MORTALITY AND PHYSICAL MULTI-MORBIDITY IN PEOPLE WITH SCHIZOPHRENIA: A POPULATION-BASED COHORT STUDY

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Background: People with schizophrenia have reduced life expectancy of 10-15 years compared with the general population. Accumulating evidence further suggests an increased prevalence of physical morbidity prior to onset of schizophrenia. Investigation on pre-existing physical diseases provides critical information about how multi-morbidity would impact upon premature mortality risk over time. This study aimed to examine the prevalence of pre-existing physical multi-morbidity and its impact on increased all-cause and cause-specific mortality rates among patients with first-recorded schizophrenia.
Methods: This population-based cohort study comprised 13945 patients with first-recorded diagnosis of schizophrenia between January 2006 and December 2016. Study cohort data were extracted from a territory-wide medical-record database for public healthcare services in Hong Kong. Pre-existing chronic physical multi-morbidities were captured with modified Charlson Comorbidity Index (CCI), which takes into account both number and severity of physical diseases. Individual CCI-identified diseases were further grouped into nine broad physical morbidity categories for mortality outcome analyses. Physical multi-morbidity was classified into three levels according calculated CCI score=0, =1 or ≥2. Cox proportional hazards regression models were used to estimate association between physical morbidity and all-cause and cause-specific mortality rates among schizophrenia patients during the study period.
Results: A total of 967 deaths were recorded during the study period. Majority of patients did not have any pre-existing chronic physical morbidity (91.3%), while 5.8% and 2.8% had CCI score of 1 and ≥2, respectively. Among CCI-identified diseases, peptic ulcer disease (3.3%) was the most frequently diagnosed chronic physical morbidity prior to schizophrenia diagnosis. Among the nine broad physical morbidity categories, cancers were associated with the highest all-cause mortality rate during follow-up (adjusted HR 2.60 [95% CI 1.93 – 3.51]). Patients having pre-existing CCI-identified physical morbidity were 2 to 3 times more likely to die during follow-up (1.98 [1.64 – 2.40] for CCI score=1; 3.08 [2.51 – 3.77] for CCI score ≥2), relative to those without any baseline chronic physical morbidity. Progressive increase in mortality risk was observed among schizophrenia patients with physical multi-morbidity, compared with those without pre-existing physical diseases, with higher CCI scores associated with higher mortality rate during study period (i.e., patients with CCI score≥2 exhibited the highest mortality rate relative to those with CCI score=1 and =0 [with 4-fold increased mortality risk]).
Discussion: Our findings indicate the burden of pre-existing physical morbidity on schizophrenia patients, whose premature mortality risk increased with greater levels of chronic

physical multi-morbidity. More intensive physical health monitoring and medical care should be provided to those suffering from pre-existing physical diseases to reduce avoidable premature mortality. Regular screening should be conducted for early identification and hence prompt medical intervention of physical morbidity during the early course of schizophrenia.

T43. EXCESS LIFE-YEARS LOST IN PATIENTS WITH SCHIZOPHRENIA AND DIABETES MELLITUS: A POPULATION-BASED COHORT STUDY

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Background: Schizophrenia is a severe mental illness affecting approximately 1% of the population. Evidence has shown that people with diabetes mellitus and co-occurring schizophrenia are associated with 1.1- to 4-fold higher mortality rate, compared with those with diabetes only. Recently, there is a growing interest in estimating average lifespan of individuals in severe mental illness using a new method – life-years lost (LYLs), which provides a more precise estimate for life expectancy by taking into account the distribution of age of illness onset. This study aimed to examine life expectancy gap in patients with incident diabetes with versus without pre-existing schizophrenia by utilizing the method of LYLs. We also decomposed excess LYLs into specific causes of death.

Methods: This population-based cohort study comprised propensity-score matched 6991 patients with incident diabetes and pre-existing schizophrenia, and 68682 patients with incident diabetes only during a study period between January 2006 and December 2016. Study data were derived from a territory-wide medical-record database of public healthcare services in Hong Kong. The average life expectancy at recorded schizophrenia diagnosis was determined by weighting life expectancy at every single age starting from 18 years until 95 years by the number of patients at that age of diagnosis. LYLs denotes the number of years between average life expectancy and 95 years, whereas excess LYLs refers to the average number of years that the schizophrenia group lost in excess of that observed in the comparison group. 95% CIs of excess LYLs were estimated from non-parametric bootstraps with 500 iterations. LYLs were computed using the lilies package on R version 4.0.2.

Results: Men and women with diabetes and pre-existing schizophrenia had 5.95 and 5.46 years excess LYLs, respectively, compared with individuals of the same sex with diabetes only. Excess LYLs were mainly attributable to respiratory diseases (1.97 [0.90 – 2.86] for men; 1.76 [1.06 – 2.45] for women). In men, cardiovascular diseases (1.15 [0.28 – 1.85]) and unnatural causes (0.91 [0.61 – 1.26]) also contributed to longevity gap in schizophrenia, whereas genitourinary diseases (0.47 [0.03 – 0.84]) and unnatural causes (0.57 [0.31 – 0.87]) produced a significant but mild effect in women. Respiratory diseases (30.8% vs 25.1%), cardiovascular diseases (20.8% vs 20.4%) and cancers (18.5% vs 30.1%) accounted for the majority of known-cause deaths in both schizophrenia and comparison groups.

Discussion: Our study is the first to estimate LYLs to evaluate shortened life expectancy associated with schizophrenia patients with diabetes. We showed that the mortality gap in schizophrenia corresponded to an approximately five life-years. Further investigation is required to identify underlying factors that contribute to premature mortality among patients with diabetes and concurrent schizophrenia.

T44. TRANSDIAGNOSTIC DIMENSIONS OF PSYCHIATRIC COMORBIDITY IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: A PRELIMINARY STUDY INFORMED BY HITOP

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Background: Although psychiatric comorbidity is the norm among individuals at clinical high risk for psychotic disorders (CHR), research has yet to examine transdiagnostic dimensional models of comorbidity in this critical population.
Methods: This study analyzed quantitative measures of eleven psychiatric syndromes in a group at CHR (n = 71) and a matched healthy comparison group (n = 73) to determine these syndromes' dimensional structure and relationships to cognition, functioning, and risk of conversion to psychotic disorders.
Results: Relative to the comparison group, the CHR group was elevated on all eleven psychiatric syndromes. Exploratory factor analysis found three psychopathology dimensions: internalizing, negative symptoms, and positive symptoms. Depression cross-loaded onto the internalizing and negative symptom dimensions. Hypomania loaded positively on positive symptoms but negatively on negative symptoms. The negative symptom factor was associated with poorer cognition and functioning and a higher risk of conversion to psychosis.
Discussion: These dimensions align with internalizing, detachment, and thought disorder, three of the five spectra in higher-order models such as the Hierarchical Taxonomy of Psychopathology (HiTOP). In the CHR state, detachment appears to be particularly insidious and predictive of psychosis. Further research is required to distinguish depression and hypomania from attenuated psychotic symptoms in this population.

T45. PREVALENCE AND FUNCTIONAL CONSEQUENCES OF SOCIAL ANXIETY IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS: PERSPECTIVE FROM A COMMUNITY SAMPLE COMPARISON

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Background: Social anxiety commonly occurs among individuals at clinical high-risk (CHR) for psychosis. However, extant research has yet to examine the prevalence and clinical/functional correlates of social anxiety in this population compared to a community control (CC) sample. This comparison may improve generalizability that a traditional non-psychiatric, "healthy" control sample cannot provide. Additionally, it remains unknown how social anxiety may contribute to clinical outcomes (symptom severity and clinical course) and social impairments in those meeting criteria for a CHR syndrome.
Methods: Both CHR and CC participants were recruited from general community sources; CC participants were not excluded in this analysis on the basis of any psychopathology except psychosis. A total of 245 young adults (CHR=81; CC=164) were administered the Social Phobia Scale (SPS), the Structured Interview for Psychosis-risk Syndromes (SIPS), Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV), and the Social Functioning Scale (SFS).
Results: When compared to CC, CHR participants were approximately five times more likely to have a diagnosis of social anxiety (d=0.63; CHR prevalence=42%). Greater social anxiety

was related to higher levels of negative (r=0.29) but not positive (r=0.05) symptoms within the CHR group. Furthermore, social anxiety was found to be negatively associated with social functioning (r=-0.31).
Discussion: Findings suggesting substantially elevated rates of social anxiety in those at CHR in comparison to a CC group highlight the significance of this comorbidity, and links between symptoms and function speak to the need for future assessments and intervention approaches.

T46. PROCESS EVALUATION OF A SMOKING CESSATION GROUP FOR ADULTS WITH SERIOUS MENTAL ILLNESS

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Background: Tobacco use is pervasive among adults with serious mental illness (SMI) with approximately half of all deaths attributable to smoking. Few behavioral smoking cessation interventions have been implemented for this population. In order to address existing cancer prevention disparities, a smoking cessation group was adapted and added to existing psychosocial programming within a community mental healthcare system. This quality improvement project was designed to assess the feasibility and implementation of a 10-week smoking cessation group for individuals with SMI.
Methods: Smoking cessation groups were designed to be delivered in ten (45-60 minute) sessions conducted on a weekly basis. Content was derived from a previously-published smoking cessation therapy manual (Stritzke et al., 2009) and was adapted to address the ways mental health symptoms impacted cessation attempts and to increase self-efficacy. Groups were conducted at a community clubhouse, which annually serves approximately 800 adults with serious mental illness and is affiliated with a community mental health center. Groups were open-ended, meaning participants could attend sessions at any time. The group facilitator administered a nine-question quality improvement survey on a 5-point Likert scale after sessions 4 and 6. Process notes were written after each group.
Results: In total, seven sessions were delivered over two months before the group was suspended due to COVID-19 restrictions. Group attendance varied throughout implementation with an average of 4.43 participants (range 2-11 participants) per session. Five surveys were completed; all responses indicated that members agreed or strongly agreed that the group provided smoking cessation information and increased confidence to quit smoking. Two of the five responses reflected that members felt unsure if the group supported them with others agreeing or strongly agreeing that they felt supported. All respondents indicated that they had tried to quit or reduce nicotine intake. Process notes reflected that group members readily identified a variety of smoking triggers which included social pressure (i.e., peers and/or family members who were also smokers), meal-times, morning rituals, boredom, etc. Though the majority made connections between generalized symptoms (i.e., stress and anxiety) and nicotine urges, one group member in the second session shared their experience of nicotine urges as an auditory hallucination. Group members identified reasons for quitting, which included often emphasized financial and health reasons. Group members' preferences for smoking cessation techniques varied between "cold-turkey", harm reduction, and pharmacological strategies. Others reported having success in using behavioral strategies, such as delaying smoking when faced with urges. The open-ended aspect of the group allowed group members to present psychoeducational material to new attendees, which was encouraged to foster increases in self-efficacy and knowledge.
Discussion: Initial results indicate a smoking cessation group is feasible and acceptable to adults with SMI. Quality improvement survey responses indicated that the smoking cessation

group increased group members' self-efficacy to quit and their knowledge of smoking cessation information. Additionally, responses suggest future implementation efforts should emphasize group cohesion as some members were unsure if they felt supported. The project demonstrates that tailored smoking cessation interventions can address patient-level barriers including low self-efficacy, while increasing knowledge and use of behavioral strategies even among those who may be exhibiting symptoms.

T47. DATA FROM A FEASIBILITY AND ACCEPTABILITY STUDY USING A MOBILE APP FOR EMOTION REGULATION WITH DUAL DISORDERS

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Background: Recent studies reported that interventions for emotional regulation can help reduce distress related to psychotic symptoms. Emotional regulation may also be one of the pathways involved in addictions and their resolution. Recently developed technologies allow us to carry out psychological interventions in other useful formats. Indeed, more data supports smart phone apps effective and particularly promising methods in the field of prevention and intervention. This research aims to evaluate the acceptability, and feasibility of a new app to promote emotional regulation for individuals with psychotic disorders and comorbid substance misuse.

Methods: The Chill Time mobile app includes a module dedicated to assessment of distress and a module offering different intervention strategies (cognitive, behavioural, emotional & spiritual) based on strategies from cognitive behavioural and mindfulness-based therapies. Fourteen people with dual diagnosis of psychosis and substance use disorder were recruited from first psychosis episode clinics and were asked to use the application over a 30-day trial period. The sample consisted of 11 men and 2 women [mean age 28 (SD: 4.12)]. The study followed a pre-post design. Clinical scales were administered at the two measurement periods [i.e. Brief Psychiatric Rating Scale-Expanded (BPRS-E) , Difficulties in Emotion Regulation Scale, Cognitive Emotion Regulation Questionnaire & Alcohol, smoking and substance involvement screening test (ASSIST)]. In order to obtain information on the application's appreciation, a user satisfaction measure and a qualitative questionnaire assessing participants' impressions were administered at the end of study. Descriptive statistics were used to assess the acceptability and feasibility.

Results: Outcomes on clinical scales are not presented given the lack of statistical power and low reliability. Two participants dropped out after the first week. Analyses were performed on data from 12 subjects. Participants used the application an average of 33% of the days comprised in the trial period and completed one to two exercises per use. There was a low response rate to notifications (fewer than 10 answers in all trail period). In order, the most frequently used exercises were cognitive (36%), affective (34%), behavioral (21%) and spiritual (9%). The majority of participants reported that the application was simple to use and were satisfied with the app. Most mentioned that ChillTime was useful, particularly for managing anxiety.

Discussion: Results suggest that there is a greater preference for cognitive and affective techniques, especially those including guidance with a recorded voice. Furthermore, these exercises would, according to participants, could be useful in managing anxiety symptoms, which can be a reason for substance use. The contrast between the low frequency of use and the relatively high satisfaction with the application could be partly explained by the fact that the app was mostly offered to participants living in an environment with frequent distractions.

It is also possible that frequency of use is not necessarily a predictor of perceived usefulness. A future study taking the best moments to send notifications according to needs or specific time in their day to use the app could potentially increase adherence.

T48. AUDITORY DIGITAL BIOMARKERS IN SCHIZOPHRENIA AND THEIR RELATIONS TO CLINICIAN-RATED NEGATIVE SYMPTOMS AND EMOTION RECOGNITION PERFORMANCE

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Background: Around 60% of people with schizophrenia (SCZ) have clinically significant negative symptoms (e.g. affective flattening, alogia, avolition, and asociality). However, objective psychometric tools for assessment are limited, even though negative symptoms lead to impaired functional outcome and poor treatment response. Available treatments for negative symptoms are only modestly effective and around 35-70% of people experience persistent negative symptoms even with treatment. Valid psychometric assessment for negative symptoms is crucial for the development of effective treatments. The gold standard assessment of negative symptoms is the clinician-rated interview which is limited to only capture recent and biased recall of symptoms. The development of an objective measure of negative symptoms would be a valuable psychometric assessment method. In this study, we used a computerized software that analyzes audio to produce digital biomarkers as a novel objective method of assessment of negative symptoms to explore correlations to clinical measures and social cognitive performance.

Methods: Fourteen individuals diagnosed with SCZ or schizoaffective disorder were administered the Social Skills Performance Assessment (SSPA), during which participants engage in a role play about meeting a new neighbor. For the current project, three-minute audio recordings of the participant's side of the role play were extracted from this assessment. The audio files were analyzed using the AiCure OpenDBM software package and several acoustic variables were computed (e.g. harmonics-to-noise ratio or a measure of additive noise, glottal-to-noise excitation ratio or a measure of breathiness, jitter or voice frequency variation, pause characteristics and voice prevalence). We examined correlations between the auditory digital biomarkers and clinician ratings on the Positive and Negative Syndrome Scale (PANSS) and Scale for Assessment of Negative Symptoms (SANS) as well as performance on the Emotion Recognition Task (ERT), a social cognitive task in which participants are exposed to a brief facial stimulus. Accuracy scores are computed based on percent of correct facial expression recognition.

Results: Correlation analyses revealed that the glottal-to-noise excitation ratio mean was positively correlated with ERT total accuracy ($r=0.742$, $p<0.01$) and negatively correlated with the SANS total ($r=-0.559$, $p<0.05$), while the harmonics-to-noise ratio mean was negatively correlated with the PANSS negative total score ($r=-0.697$, $p<0.01$), but was not correlated with ERT accuracy. The percentage of the audio recording that consisted of pauses in speech was correlated with PANSS negative and SANS total scores ($r=0.551$, $p<0.05$), but no significant correlations were found with ERT accuracy. Also, ERT accuracy for disgust and fear stimuli were correlated with glottal-to-noise excitation ratio ($p<0.05$), ERT accuracy for happiness stimuli was correlated with jitter (i.e. voice frequency variation or lack of control over vocal cords) ($p<0.05$), and ERT accuracy for anger stimuli was negatively correlated with the total time of the audio recording ($p<0.05$).

Discussion: These findings indicate that breathiness, additive noise and greater voice frequency are related to less severe negative symptoms, while frequency of pauses in speech are related to increased negative symptom severity, and ERT accuracy is related to some digital biomarkers (e.g. breathiness) but not others (e.g. speech pauses). These findings highlight the multidimensional nature of negative symptoms and the importance of using digital technology to improve upon traditional psychometric assessments for SCZ.

T49. E-NAVIGATE: STUDY PROTOCOL FOR ADAPTING EVIDENCE-BASED EARLY PSYCHOSIS INTERVENTION SERVICES FOR VIRTUAL DELIVERY

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Background: Early comprehensive psychosis intervention (EPI) has become the standard of care for youth with psychosis. NAVIGATE is a modular form of EPI with 4 key intervention components: individualized medication management; psychoeducation and a blend of evidence-based psychotherapies (individual resiliency training); supported employment and education; and family education.
During the COVID-19 pandemic most mental health care was switched to virtual delivery despite little knowledge on how to administer core components virtually and whether doing so would be feasible and yield similar outcomes to in-person delivery. Therefore, we are conducting the e-NAVIGATE study, an evaluation of implementation effectiveness of NAVIGATE for virtual delivery ("e-NAVIGATE") in the context of the COVID-19 pandemic.

Aims:

1. To explore adaptations required for e-NAVIGATE and its implementation.

2. To evaluate implementation outcomes of e-NAVIGATE including fidelity to the EPI model and acceptability among patients, family members and clinicians.

3. To explore implementation facilitators and barriers that may alter service engagement in e-NAVIGATE, to guide iterative development and implementation.

Methods:
The study setting will be a large EPI Service at CAMH Toronto, Canada, providing comprehensive EPI care for youth with early psychosis aged 16-29.

Intervention and Implementation Approach:

NAVIGATE is a highly structured model of coordinated specialty care, designed for in-person care. We will adapt and refine the new e-NAVIGATE informed by the Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions (FRAME) to confirm that e-NAVIGATE retains the core components of NAVIGATE. We will implement and explore implementation barriers and facilitators using The Consolidated Framework for Implementation Research (CFIR).

Implementation Evaluation:

- E-NAVIGATE's fidelity to the EPI model will be assessed using the First-Episode Psychosis Services Fidelity Scale (FEPS-FS).

- Acceptability of e-NAVIGATE by patients and family members will be measured using the validated Virtual Client Experience Survey (VCES).

- Facilitators and barriers. Health equity factors and indicators of service engagement will be extracted from health records and examined to evaluate barriers to adoption. The CFIR will be used to systematically assess contextual factors that are associated with effective implementation in relation to five major domains: intervention characteristics (e.g. complexity); outer setting (e.g. external policy); inner setting (e.g. resources); staff characteristics (e.g. knowledge); and implementation process (e.g. facilitation). A semi-structured interview will guide data collection with 8 clinicians, 4 patients and 4 family members.

Results: A comprehensive research team, consisting of researchers, clinicians, administrators, youth and family members with lived experience, and decision makers, has achieved consensus on study design and outcomes. The intervention model is currently in the implementation stage with planned analyses throughout 2021.

Discussion: Youth with psychosis have acute mental health needs exacerbated by the COVID-19 pandemic. Results from this work may demonstrate that a virtual model may meet the pre-existing standard of care for this population. It can also identify patients who are not well-served by the model in order to guide future iterations and blended in-person/virtual approaches. This work may support the continued delivery of high-quality services to youth with psychosis in the context of the COVID-19 pandemic; its format may also be more accessible to youth and adaptable to low-resource settings well beyond the pandemic.

T50. DIGITAL PHENOTYPING ADHERENCE, FEASIBILITY, AND TOLERABILITY IN OUTPATIENTS WITH SCHIZOPHRENIA

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Background: Digital phenotyping has potential for use as an objective and ecologically valid form of symptom assessment in clinical trials for schizophrenia that has potential for incorporating precision medicine based approaches. However, there are critical methodological factors that must be addressed before digital phenotyping can be used for this purpose.

Methods: The current study evaluated levels of adherence, feasibility, and tolerability for active (i.e., signal and event contingent ecological momentary assessment surveys) and passive (i.e., geolocation, accelerometry, and ambulatory psychophysiology) digital phenotyping methods recorded from smartphone and smartband devices. Participants included outpatients diagnosed with schizophrenia (SZ: n = 54) and demographically matched healthy controls (CN: n = 55), who completed 6 days of digital phenotyping.

Results: Adherence was significantly lower in SZ than CN for active recordings, but not markedly different for passive recordings. Some forms of passive recordings had lower adherence (ambulatory psychophysiology) than others (accelerometry and geolocation). Active digital phenotyping adherence was predicted by higher psychosocial functioning, whereas passive digital phenotyping adherence was predicted by education, positive symptoms, negative symptoms, and psychosocial functioning in people with SZ. Both groups found digital phenotyping methods tolerable and feasibility was supported by low frequency of invalid responding, brief survey completion times, and similar impediments to study completion.

Discussion: Digital phenotyping methods can be completed by individuals with SZ with good adherence, feasibility, and tolerability. Recommendations are provided for using digital phenotyping methods in clinical trials for SZ based on a precision medicine model.

T51. PRODROMAL SYMPTOMS OF FIRST EPISODE MANIA OR FIRST EPISODE PSYCHOSIS

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Background: Bipolar disorder and schizophrenia represent two of the most severe mental disorders and are responsible for high burden of disease and psychosocial dysfunction (Vieta et al., 2018., Kahn et. Al., 2015). Preventive strategies of treatment and early detection of symptoms are crucial (Arango et al., 2018). The identification of prodromic symptoms capable to differentiate the occurrence of a first episode mania (FEM) or a first episode psychosis (FEP) could be of help.

Methods: Patients with a FEM or a FEP have been evaluated with the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R) (Correll et al., 2007). X2 tests were conducted to assess if prodromic symptoms were more reported in FEM or FEP. Depressive prodromes were excluded from the analysis. A linear regression model has been conducted in order to assess which were the prodromic symptoms that were more associated with a FEM or a FEP (after Bonferroni correction was applied). All data were analyzed with the Statistic Package for Social Sciences (SPSS v.23 for Windows). All the analyses were two-tailed with alpha set at $p < 0.05$.

Results: The total sample included 104 patients, 71 presenting a FEM and 31 a FEP. Social isolation ($X2=11.311$, $p=0.0007$), decreased school or work functioning ($X2=3.839$, $p=0.050$), difficulty thinking or communicating clearly ($X2=7.643$, $p=0.017$), anxiety or nervousness ($X2=4.368$, $p=0.037$) and ambivalence ($X2=7.915$, $p=0.011$) were more frequently reported in patients presenting a FEP. On the contrary, being physically agitated ($X2=6.042$, $p=0.010$), overly cheerful or happy ($X2=6.042$, $p=0.010$), presenting frequent mood swings or mood lability ($X2=5.056$, $p=0.025$), increased energy or goal-directed activity ($X2=16.809$, $p<0.001$) and decreased need for sleep ($X2=6.541$, $p=0.011$) were more frequently reported in patients presenting a FEM. The logistic regression model was significant ($X2=30.326$, $df=2$, $p<0.001$). Social isolation was associated with FEP (OR=5.267, CI=1.700-16.316, $p=0.004$) and increased energy or goal-directed activity with FEM (OR=0.093, CI=0.025-0.347, $p<0.001$).

Discussion: Manic and psychotic prodromes are sufficiently characterized in order to make early identification and intervention programs feasible.

T52. CLINICALLY RELEVANT OR NORMATIVE FUNCTIONING? EVALUATING FREQUENTLY ENDORSED ITEMS ON THE PRODROMAL QUESTIONNAIRE IN AN URBAN UNDERGRADUATE SAMPLE

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Background: Brief questionnaires, such as the Prodromal Questionnaire (PQ) positive scale, have been used to pre-screen individuals who may be at clinical high-risk (CHR) for psychosis and identify those most in need of further assessment. Despite the apparent utility of the measure, few studies have examined response styles on the PQ positive subscale in a general community sample. Therefore, this study sought to identify if certain items on the PQ positive subscale were overly endorsed in a normative sample and to evaluate how these items were associated with symptom ratings on an established clinician-administered risk interview.
Methods: Response frequencies were examined for each of the 45 PQ positive subscale items in a sample of 3584 students (age 18-35; female n=2653) from a nationally representative, semi-public undergraduate institution. Items endorsed by over 20 and 30 percent of the sample were identified as commonly endorsed and evaluated further in conjunction with established cutoffs and associated symptom ratings from the Structured Interview for Psychosis-risk Syndromes (SIPS) on a smaller subset of participants (n=162). PQ responses were also evaluated by gender.
Results: Fifteen symptoms were identified as commonly endorsed with as high as 71 percent of respondents endorsing them. Individuals who endorsed 11 of these items were not significantly associated with clinically relevant ratings on the SIPS. Additionally, male participants endorsed more symptoms than female participants, although females endorsed items as distressing more often.
Discussion: A series of commonly endorsed items were identified, 6 of which were not overly endorsed in previous undergraduate samples. Items endorsed by a high proportion of individuals have a high probability of resulting in false positive identification of those at CHR for psychosis, given the probable base rates of CHR in the population. These overly endorsed items may be more indicative of normative functioning. Future work should evaluate if removing these items increases the positive predictive power and specificity of the PQ.

T53. CONTRIBUTORY CAUSAL FACTORS OF PARANOIA IN THE GENERAL POPULATION

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Background: Persecutory delusions are among the most common symptoms of schizophrenia, contributing to suicide, hospitalization and serious violence. Psychological models of persecutory delusions identify several causal factors that contribute to their onset, maintenance, and severity. These factors include worry, negative self-beliefs, and sleep disturbance, all of which have been shown to be efficacious targets of treatment in schizophrenia. Persecutory delusions represent the extreme end of a paranoia spectrum that exists in the general population. At least 10-15% of individuals endorse paranoid thoughts, and even fleeting paranoid thoughts can cause distress. It is therefore critical to understand whether the factors that contribute to persecutory delusions also contribute to paranoia. Furthermore, few investigations have examined specificity of these contributory causal factors to paranoia versus other types of

delusional ideation. Understanding whether worry, negative self-beliefs and sleep disturbance are specific to paranoia will help refine psychological models of psychosis.
Methods: Delusional ideation, worry, negative self-beliefs, and sleep quality were assessed in adults from the Nathan Kline Institute-Rockland (NKI-Rockland) sample. Paranoid and grandiose ideation were assessed using the Peters Delusion Inventory-21 (PDI), a self-report designed to measure distress, conviction, and preoccupation of delusional beliefs in the general population. Worry was measured using the Perseverative Thinking Questionnaire (PTQ) & Penn State Worry Questionnaire (PSWQ) (N=228). Negative self-beliefs were measured through specific items on the Beck Depression Inventory (BDI) and Achenbach Adult Self-Report Measure (ASRM) (N=439). The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality (N=655). Pairwise relationships between contributory causal factors and paranoia/grandiosity were first assessed in pairwise correlations. Then, 56 individuals with self-report data from all 6 measures were included in linear and step-wise regressions with age, sex, and race as covariates, to determine the absolute and relative contribution of the causal factors to paranoia and grandiosity.
Results: Paranoia was significantly associated with worry ($r=.45$, $p<.001$), negative self-belief ($r=.27$, $p<.001$) and sleep ($r=.15$, $p<.001$). Regression revealed that causal factors and covariates contributed significant variance to paranoia ($R2=.27$, $p=.001$); however, when included in a stepwise regression, only worry was identified as a significant predictor (Beta=.494, $t=4.22$, $p<.001$), explaining approximately 24% of the variance in paranoia. Grandiosity demonstrated attenuated relationships with worry ($r=.12$, $p=.07$), negative self-beliefs ($r=.10$, $p=.024$), and sleep ($r=.12$, $p=.002$). When included together in a model, causal factors explained only approximately 2% of variance in grandiosity ($R2=.023$, $p=.747$) and step-wise regression retained no causal factors when predicting grandiosity.
Discussion: Causal factors of persecutory delusions contribute to paranoia in the general population and are specific to paranoia, not extending to grandiosity. Of these causal factors, worry may be the most important contributor to non-clinical paranoia. Worry brings threat beliefs to mind and keeps them there, limiting exploration of other perspectives. Targeting worry processes in the general population may help minimize the prevalence and distress of paranoid thinking.

T54. THE M1/M4 AGONIST XANOMELINE IN COMBINATION WITH TROSPIUM IS EFFECTIVE FOR ACUTE TREATMENT OF SCHIZOPHRENIA: PANSS RESPONDER AND PANSS 5-FACTOR ANALYSES OF A PHASE 2 PLACEBO-CONTROLLED INPATIENT TRIAL

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Background: KarXT (xanomeline-trospium) is a non-dopaminergic investigational antipsychotic that preferentially activates muscarinic receptors in the CNS. In a Phase 2 trial in acutely psychotic patients with schizophrenia (EMERGENT-1; NCT03697252), KarXT treatment was associated with statistically significant and clinically meaningful improvements relative to placebo on the primary endpoint (change from baseline in total PANSS score at week 5) and four out of five secondary efficacy measures. KarXT was well-tolerated; the most common (>5%) adverse events (AEs) were primarily pro- or anti-cholinergic, were rated as mild or moderate in severity, decreased in incidence during the trial, and were unassociated with treatment discontinuation.

Here we present post hoc efficacy analyses from EMERGENT-1, including (1) categorical responses with ascending PANSS cutoffs at week 5 and associated number needed to treat (NNT) estimates, and (2) 5-factor PANSS Marder analyses to further delineate specific domains in which KarXT treatment was associated with improved outcomes relative to placebo.

Methods: EMERGENT-1 was a double-blind, placebo-controlled, 5-week inpatient trial conducted at 12 US sites. Participants discontinued any prior antipsychotic medication, then were randomized 1:1 to receive flexibly dosed KarXT or matched placebo. BID dosing began at 50mg xanomeline/20mg trospium for two days, then increased to 100mg/20mg for 5 days, with an optional increase to 125mg/30mg on day 8 based on tolerability.
All efficacy analyses included participants who received ≥ 1 dose of study medication and had a baseline and ≥ 1 post-baseline PANSS assessment (mITT population). Differences in the proportion of PANSS responders for each group and cutoff were analyzed using a logistic regression model with factors of treatment group, age, and gender; missing data were imputed using last observation carried forward methodology. PANSS scaling used 0-6 item scoring (range 0-180) and PANSS response cutoffs (% reduction from baseline score) were ≥20%, ≥30%, ≥40% and ≥50%. NNTs were calculated as 1/(KarXT responder rate- placebo responder rate). For the PANSS Marder analyses, least-square mean (LSM) changes from baseline were derived from a mixed model for repeated measures and Cohen's d (CD) effect sizes were based on the LSM estimates.

Results: 170 out of 182 randomized participants met mITT criteria (n= 83 KarXT; 87 placebo). At week 5, greater proportions of participants in the KarXT arm met response criteria compared with placebo arm for all PANSS cutoffs: ≥20% (59% vs 23%, $p<0.0001$); ≥30% (39% vs 12%, $p=0.0001$); ≥40% (24% vs 8%, $p=0.006$); ≥50% (16% vs 6%, $p<0.05$). The NNT [95% CI] for one participant to achieve ≥20%, ≥30%, ≥40%, and ≥50% responses were: 3 [3-5], 4 [3-7], 7 [4-20], and 11 [6-145].
For Marder factor outcomes, treatment differences between KarXT and placebo arms at week 5 were: (1) Positive symptoms: -2.96 points ($p<0.0001$; CD=0.64); (2) Negative symptoms: -2.53 points ($p=0.0002$, CD=0.59); (3) Disorganized thoughts: -2.13 points ($p=0.0003$, CD=0.58); (4) Hostility: -1.52 points ($p=0.002$, CD=0.48); (5) Depression/anxiety: - 2.12 points ($p<0.0001$, CD=0.66).

Discussion: KarXT treatment was associated with higher response rates compared with placebo across PANSS cutoff criteria (all $p<0.05$), with NNTs ranging from 3 (≥20% response) to 11 (≥50% response). All PANSS Marder analyses showed improvements in the KarXT relative to the placebo arm (all $p\leq0.002$), providing important information on the efficacy of a non-dopaminergic antipsychotic over a range of outcome domains. Together, these post hoc analyses substantiate and extend the EMERGENT-1 primary analyses and support Phase 3 development of KarXT as a treatment for schizophrenia.

T55. PREVALENCE PSYCHOTIC EXPERIENCES IN A COHORT OF CHILDREN AND ADOLESCENTS OVER TIME AND ITS ASSOCIATION WITH GENERAL PSYCHOPATHOLOGY

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Background: Psychotic experiences (PE) are attenuated symptoms, below the threshold for clinical psychosis. Studies show that up to 17% of community youths (ages 9 to 12) report PE, but this prevalence decreases with age, reaching 7.2% in adult samples. The persistence, frequency and intensity of PE over time are associated not only with psychosis, but also with general psychopathology and occupational and social impairments. In youths, the presence of significant emotional complications and maladaptive behavior is associated with psychiatric disorders and can be assessed through the scores obtained from the Child Behavior Checklist (CBCL). Here, our objective is to evaluate the prevalence of PE in a community sample of children and adolescents (aged 6-14 y/o at baseline) assessed in three different time-points (T0 – 2011, T1 – 2014 and T2 – 2017), and to investigate if the presence of PE is associated with the development of general psychopathology.
Methods: We analyzed data from the Brazilian High-Risk Cohort Study for Psychiatric Disorders, comprised of 2,511 youths recruited in São Paulo and Porto Alegre, both urban centers. Psychotic experiences were evaluated and rated by trained psychologists through the positive subscale of the Community Assessment of Psychic Experiences (CAPE), and categorized into: 1) never PE (no report of any PE at T0, T1 and T2); 2) transitory (report of at least one PE at T0 and/or T1, but none at T2); and 3) current (report of at least one PE at T2). General psychopathology was assessed through parental report, using the total scores of the Child Behavior Checklist (CBCL) collected at T2. We performed an ANCOVA to test if the CBCL scores differed across PE categories, using age, recruitment site and sex as covariates and Bonferroni adjustment for multiple comparisons. All analyses were conducted on SPSS v.24.
Results: At T0, T1 and T2, 2,511 (6 to 14 y/o, mean age = 10.2, SD = 1.9, 54.8% male), 2,010 (9 to 17 y/o, mean age = 13.5, SD = 1.9) and 1,801 (13 to 23 y/o, mean age = 18.2, SD = 2.0) youths were assessed, respectively. In our sample, PE prevalence was 10% at T0, 8.7% at T1 and 8.4% at T2 and, considering subjects that were assessed in all time-points, we found 994 never presented PE, 218 presented transitory PE and 119 presented PE at W2 (current). Regarding CBCL means, a significant difference emerged in univariate tests between PE categories (mean square = 1254.1, df = 2, F = 3.4, p = 0.34); never PE showed lower scores (mean = 23.1, SE = 0.9), transitory PE had intermediate scores (mean = 27.1, SE = 2.3) and current PE presented higher scores (mean = 30.6, SE = 3.3), although differences in pairwise comparisons were only significant between the never PE and current PE groups (p = 0.31, SE = 3.4).
Discussion: In line with previous studies, we found an association between PE with general psychopathology. The occurrence of these symptoms in childhood and adolescence, especially when persistent, can be understood as a marker for psychiatric disorders in general. In our sample, young people who never had PE or who had transient and self-limited PE did not show significant psychopathological symptoms in T2. In contrast, individuals who presented PE in T2 showed a noticeably clear and significant association with psychopathological symptoms assessed by CBCL. This study is the largest longitudinal work with children and adolescents conducted in a developing country. Our findings indicate that not only the presence of PE in younger individuals, but its persistence throughout development, can be understood as an early marker for psychiatric disorders in general. The early identification of individuals at risk for psychiatric disorders is essential for the development of more effective programs towards the prevention of mental illness.

T56. REAL-WORLD OUTCOMES FOR SCHIZOPHRENIA PATIENTS AND CAREGIVERS BY DISEASE SEVERITY

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Background: Schizophrenia is a severe long-term condition associated with decreased quality of life (QoL) and ability to work for both patients and their caregivers. The objective of this survey was to assess patient and caregiver outcomes according to patients' severity of schizophrenia.

Methods: A point-in-time survey was conducted across the US between July and October 2019 via the Adelphi Schizophrenia Disease Specific Programme™. Participating psychiatrists provided information on their next 10 eligible patients with schizophrenia in real-world clinical practice. The same patients and their caregivers were invited to voluntarily complete a Patient self-completion form (PSC) or Caregiver self-completion form (CSC). Patients and caregivers were stratified for analyses as mild, moderate and severe based on patients' schizophrenia severity which was reported by psychiatrists according to the Clinical Global Impression (CGI) Severity Scale (normal-mild=mild, moderate=moderate, markedly-most extremely severe=severe). Multiple regression was used to model the association between CGI-severity and outcomes, while adjusting for age and gender.

Results: Psychiatrists (n = 124) provided data for 468 mild, 408 moderate and 270 severe patients with schizophrenia. PSCs were completed by 222 mild, 202 moderate and 90 severe patients, and 36, 56 and 39 caregivers of mild, moderate and severe patients respectively completed a CSC. Worsening CGI-severity was associated with an increased number of hospitalizations in the previous 12 months (2.37 incidence rate ratio (IRR), $p<0.0001$ moderate vs. mild; 5.99 IRR, $p<0.0001$ severe vs. mild), as well as increased overall work impairment (10.81 IRR, $p=0.010$ moderate vs. mild; 23.32 IRR, $p=0.034$ severe vs. mild) and activity impairment in the past week (17.80 IRR, $p<0.0001$ moderate vs. mild; 31.63 IRR, $p<0.0001$ severe vs. mild) according to the Work Productivity and Activity Impairment Questionnaire. Compared to mild disease severity, severe disease severity was associated with poorer QoL according to EuroQoL 5 Dimension (EQ-5D) Health Index (-.153 IRR; $p<0.0001$) and EQ-5D Visual Analogue Scale (VAS) (-13.49 IRR, $p=0.002$) as well as decreased overall life satisfaction according to the Quality of Life Enjoyment and Satisfaction Questionnaire (-15.15, $p<0.0001$ severe vs. mild). Increasing CGI-severity was associated with patients requiring a caregiver (3.48 IRR, $p=<0.0001$ moderate vs. mild; 6.28 IRR, $p<0.0001$ severe vs. mild) and number of average hours spent by caregivers per week (3.53 IRR, $p<0.0001$ moderate vs. mild; 7.45 IRR, $p<0.0001$ severe vs. mild). Compared to mild patients, caregivers of severe patients tended to have worse QoL according to EQ-5D Health Index (-.012, $p=0.887$) and EQ-5D VAS (-3.38 IRR, $p=0.534$) though this was not significant.

Discussion: Worsening schizophrenia severity was significantly associated with greater hospitalizations in the previous 12 months and increased work and activity impairment in the past week. Compared to mild severity, severe severity was significantly associated with poorer QoL and lower overall life satisfaction for patients. Requiring a caregiver and number of hours spent by caregivers per week were also significantly associated with worsening severity.

T57. THE CAT IS BACK: CAT OWNERSHIP IN CHILDHOOD HAS SEX-SPECIFIC ASSOCIATIONS WITH PSYCHOTIC EXPERIENCES AND INTERACTS WITH OTHER RISK FACTORS IN A COMMUNITY SAMPLE

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Background: Meta-analyses have demonstrated an association between Toxoplasma gondii seropositivity and the risk for schizophrenia. This parasite is generally transmitted to humans by domestic cats. However, there is mixed evidence of an association between cat ownership in childhood and the later risk of schizophrenia. Here, we aimed to examine the association between cat ownership in childhood and psychotic experiences (PE) in adults from the community. Since cats typically shed the parasite after feeding on rodents, we examined whether ownership of rodent-hunting cats, versus non-hunting cats or no cats, was associated with more PE. We also evaluated the sex-specific effects of cat ownership, and explored potential interactions with other risk factors for schizophrenia.
Methods: Adults aged between 18 and 40 years old were approached in public places in downtown Montreal to complete a brief survey. The frequency of PE was measured using the Community Assessment of Psychic Experiences – 15-item positive scale. Participants were asked about cat ownership before age 13 and whether the cat hunted rodents, as well as demographic characteristics, number of house moves before age 15, history of head trauma, and smoking status. Associations between each risk factor and PE standard scores were examined in linear regressions adjusted for age and sex. The interaction between cat ownership and sex was tested. Other possible interactions among the variables were explored using a conditional inference tree (CTree). CTree is a decision tree regression model that performs recursive partitioning of the data to identify subgroups of participants with homogeneous characteristics. CTree selects covariables using Bonferroni-corrected permutation tests.
Results: Of 2,206 participants, 1,986 (90%) had complete data and were retained in the analyses. Rodent-hunting cat ownership ("cat+rodent"), as well as younger age, more house moves, history of head trauma, and smoking were associated with more frequent PE. Winter birth and non-rodent-hunting cat ownership ("cat only") were not associated with PE. Interaction analysis revealed that the effect of cat+rodent was specific to men. In men, cat+rodent was associated with more PE compared to cat only or no cat: standardized mean difference (SMD) = 0.57 (95% confidence interval [CI]: 0.27, 0.86); in women, this difference was not significant: SMD = 0.10 (95% CI: -0.18, 0.38). Next, in the CTree, all variables, except winter birth and sex, were retained. The highest mean PE score was found in the class comprised of non-smokers with more than one house move, head trauma history, and cat+rodent (n = 22; mean standard score = 0.96). On cross-validation, the CTree explained 5.8% of the variance in PE scores.
Discussion: These findings support that early T. gondii exposure, through contact with potentially infected cats, is associated with PE in adulthood. Interaction with sex suggests that the putative effect of T. gondii might be specific to, or stronger among, men. This is consistent with previous evidence of sex-specific effects of T. gondii on human behavior. CTree corroborated the association between cat+rodent and PE, but not its interaction with sex. Rather, it pointed to interactions between smoking, head trauma and cat+rodent. As such, in post-hoc linear regressions, we found a significant interaction between head trauma and cat+rodent, suggesting that head trauma had synergistic effects with T. gondii. Our cross-sectional study is limited by its inability to ascertain the occurrence and timing of T. gondii exposure. Nevertheless, we bring a new line of evidence for the link between this parasite and psychosis, and illustrate the utility of decision trees in uncovering interactions among risk factors.

T58. INSOMNIA, SUICIDAL IDEATION, AND PSYCHOPATHOLOGY IN FIRST-EPISODE PSYCHOSIS

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Background: Insomnia occurs frequently in the clinical course of schizophrenia. A growing literature has found associations between insomnia, suicidal ideation, and psychopathology in patients with schizophrenia. We explored these associations in a cohort of patients with first-episode psychosis. We hypothesized that insomnia would be associated with an increased odds of suicidal ideation and higher psychopathology scores.
Methods: We investigated relationships between sleep problems (terminal insomnia or difficulty sleeping) and suicidal ideation over the past two weeks (assessed by either the Calgary Depression Scale for Schizophrenia or self-report), and current psychopathology for n=404 subjects with data from the Recovery After an Initial Schizophrenia Episode (RAISE) study using regression models.
Results: After controlling for multiple potential confounding factors, baseline sleep problems were associated with an over two-fold increased odds of current suicidal ideation (OR=2.25, 95% CI 1.17-4.34, p=0.016). Over the 24 months of the study, sleep problems at any time point were associated with four-fold increased odds of concurrent suicidal ideation (OR=4.01, 95% CI 1.84-8.77, p<0.001). Sleep problems were also a significant indicator of higher Positive and Negative Syndrome Scale total (β=0.13-0.21, p<0.01), positive (β=0.15-0.26, p<0.01) and general (β=0.14-0.29, p<0.01) subscale scores at baseline, as well as 6, 18, and 24 months.
Discussion: Insomnia is associated with suicidal ideation and greater psychopathology in first-episode psychosis. Formal assessment of insomnia appears relevant to the clinical care of patients with psychosis as an indicator of suicidal ideation and symptom severity.

T59. ANTI-STIGMATISATION APPROACHES FOR SCHIZOPHRENIA-DIAGNOSED PATIENTS- A NARRATIVE LITERATURE REVIEW

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Background: Discrimination against patients with schizophrenia may influence social interactions with peers, job applications, professional networking, even their close relationships [1]. Mass-media coverage of tragic events involving psychotic patients may be at least partially responsible for the fact that more than 70% of the general population in the United Kingdom consider schizophrenia-diagnosed patients as dangerous or unpredictable [2]. Treatment adherence may be impacted by the perceived stigmatization, therefore this social phenomenon may translate in very concrete effects at the therapeutic level, and the percentage of more resistant cases may increase [3]. Also, the stress related to stigmatization may explain the transition to schizophrenia in young people at risk of psychosis [4]. Therefore, anti-stigmatization policies are important for preserving treatment adherence, quality of life, and chances for social and professional re-integration in patients with schizophrenia.
Methods: A literature review was conducted through main electronic databases (PubMed, Cochrane, EMBASE, CINAHL, Thomson Reuters/Web of Knowledge) using the search paradigm “schizophrenia” OR “chronic psychosis” AND “de-stigmatization”. All papers published between January 2000 and August 2020 were included in the primary analysis.
Results: A number of 412 papers surfaced after the primary search, with only 16 remaining after filtering them out according to the inclusion and exclusion criteria. An electronic tool that simulates psychotic symptoms has been proposed as a method to increase awareness about personal experiences in patients with schizophrenia, using immersion glasses and an embedded camera. Re-naming psychotic disorders has also been suggested as a possible way to decrease

the social negative perception of schizophrenia. Educational measures focused on increasing social awareness of the biological origin of this disorder, and decreasing misconceptions related to it (e.g., symptoms perceived as being voluntarily produced, or hostility as an intrinsic feature of schizophrenia) have also been applied. Social skills training and cognitive rehabilitation therapy increase the chances of a successful re-integration at the professional, familial, and social level. Family therapy focused on understanding the symptoms of schizophrenia is also an important way to increase the chances of de-stigmatization. Patients advocacy groups are also a possible method to fight against the stigmatization of schizophrenia-diagnosed patients. International programs (e.g., World Psychiatric Association Global Programme against Stigma and Discrimination because of Schizophrenia) have been implemented but the quantification of their efficacy is difficult.

Discussion: De-stigmatization policies in schizophrenia have a long history, and although many methods for reaching this objective have been suggested, the research methodology is far from being solid. Therefore, the results of already implemented strategies are difficult to evaluate.

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T60. SPEECH DISTURBANCES IN SCHIZOPHRENIA: A CROSS-LINGUISTIC REPLICATION OF AUTOMATED ANALYSIS OF COHERENCE

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Background: Speech and language disturbances are considered a hallmark of schizophrenia (SCZ). Speech disturbances mainly occur at the discourse level, include reduced semantic coherence, and are often associated with specific symptoms, e.g. thought disorder.

Recently, natural language processing (NLP) techniques have been applied to the analysis of schizophrenic speech, showing decreased number of words, reduced linguistic cohesion and coherence, with measures of coherence argued to reliably identify patients with SCZ and to predict psychosis onset.

However, heterogeneity across studies was large, replications almost nonexistent, and the association between NLP measures and clinical symptoms uncertain. In addition, there is a lack

of concern with cross-linguistic generalizability, that is, comparing linguistic features in SCZ across different linguistic groups.

In this research we analyzed a large cross-linguistic corpus of speech transcripts of patients with SCZ, to systematically assess the replicability of previous results, and to test whether the patterns are distinctive of SCZ in general, or specific to linguistic and/or cultural groups.

Methods: We reviewed the literature to identify automated NLP measures of schizophrenic speech that could be reproduced in our study. We collected a Danish (DK) and Chinese (CH) cross-linguistic dataset involving 161 participants with SCZ (111 DK, 60 CH) and 168 controls (HC) (129 DK, 39 CH). Data were collected using the Animated Triangle Task, and the following measures of coherence were computed from transcripts:
Mean similarity - average semantic similarity of each word to the immediately preceding word; coherence-5 and coherence-10 - average semantic similarity of each word in 5- or 10-word windows; coherence K5, K6, K7, K8 - word-to-word variability at "k" inter-word distances (k-range: 5-8); first-order semantic coherence - similarity of consecutive phrase vectors -, second-order semantic coherence, - similarity between phrases separated by another intervening phrase.

We ran multilevel regression models with coherence measures as outcome, and language (DK, CH), diagnosis (SCZ, HC) or symptoms (SANS/SAPS; PANSS), and their interaction as predictors.

Results: We replicated previous findings for reduced number of words ($\beta = -0.2$, SE = 0.01, $p < .001$) and reduced first-order semantic coherence ($\beta = -0.01$, SE = 0.01, $p = .024$) in SCZ for both languages. Decreased measures of other forms of semantic coherence in SCZ were only found in Chinese, but not Danish, patients with schizophrenia: similarity mean ($\beta = -0.02$, SE = 0.003, $p < .001$), coherence-5 ($\beta = -0.02$, SE = 0.003, $p < .001$), coherence-10 ($\beta = -0.018$, SE = 0.002, $p < .001$), K5 ($\beta = -0.02$, SE = 0.004, $p < .001$), K6 ($\beta = -0.01$, SE = 0.004, $p < .001$), K7 ($\beta = -0.02$, SE = 0.004, $p < 0.001$) and K8 ($\beta = -0.01$, SE = 0.004, $p < .001$). We did not replicate any result for second-order semantic coherence, which showed no significant effect of diagnosis.
Associations between symptoms and coherence measures were only inconsistently replicated, and no consistent pattern emerged.

Discussion: We replicate previous results for lower number of words and reduced first-order semantic coherence in SCZ in both languages. However, other measures of coherence and the relations between NLP measures and clinical features could not be coherently replicated across datasets.
We argue that automated NLP measures are promising, but we need to combine current exploratory research with more rigorous tests of reproducibility and generalizability: open NLP tools, and tests across samples, tasks and languages. More work is also needed in validating NLP measures, and clarifying what aspects of the different psychopathological manifestations the different coherence measures reflect.

T61. THE GLYCINE TRANSPORT INHIBITOR BI 425809 RESTORES TRANSLATABLE EEG DEFICITS IN AN ACUTE MOUSE MODEL FOR SCHIZOPHRENIA-RELATED SENSORY PROCESSING AND CORTICAL NETWORK DYSFUNCTION

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Background: Patients with schizophrenia show alterations in integration and processing of sensory information, which can be monitored by electroencephalography (EEG). Deficits can be revealed as changes in auditory event-related potentials (AERP), 40 Hz auditory steady-state response (ASSR), sensory gating as well as increased basal gamma oscillation. Such EEG recordings can also be performed in animals, representing highly translatable biomarkers. There is growing evidence that dysfunctions in N-methyl-D-aspartate (NMDA) receptors contribute to the pathophysiology of schizophrenia, and hence NMDA receptor antagonists such as MK-801 or ketamine induce symptoms in animals and humans that closely resemble those of patients with schizophrenia. Thus, schizophrenia-linked EEG deficits can be induced by administration of MK-801 [1] presumably by disturbing the balance between cortical interneuron inhibition and pyramidal neuron excitation. Inhibition of the Glycine transporter 1 (GlyT1) is being discussed as an effective tool to facilitate NMDA receptor function via increasing its co-agonist glycine in the synaptic cleft. In this study, we tested the ability of the novel GlyT1 inhibitor BI 425809 [2] to reverse MK-801 induced deficits on AERPs, ASSR and basal Gamma oscillation.
Methods: EEG and AERP were measured in mice by a novel wireless recording technique [1]. We implanted epidural electrodes above the primary auditory cortex and the medial prefrontal cortex. BI 425809 was tested in a 5-arm cross-over design in 3 different doses. Animals were placed in a sound attenuated cubicle for recordings. A white-noise double-click paradigm and a 40 Hz ASSR paradigm was presented to obtain all readouts.
Results: BI 425809 reversed MK-801-induced deficits in several EEG readouts like N1 amplitude, N1-Gating and 40Hz ASSR power and inter-trial coherence. Additionally, BI 425809 significantly attenuated MK-801-induced basal gamma increase.
Discussion: Our study indicated that elevation of the glycine level by BI 425809 to facilitate NMDA receptor function is sufficient to attenuate MK-801 induced deficits in translatable EEG readouts with relevance to schizophrenia. Thus, GlyT1 inhibition could be a promising therapeutic approach to improve cognitive function in patients with schizophrenia as recently shown in a phase 2 trial with BI 425809 [3].

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T62. ELECTROENCEPHALOGRAPHY AS A CLINICAL BIOMARKER IN A BI 425809 PHASE II SUBSTUDY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia exhibit a diminished pre-attentive sensation response to deviating auditory stimuli and a reduced auditory steady-state response, detectable by electroencephalography (EEG). As part of a Phase II trial investigating the efficacy and safety of the novel glycine transporter 1 (GlyT1) inhibitor BI 425809 in patients with schizophrenia, this substudy evaluated EEG parameters as potential diagnostic, predictive or treatment response biomarkers. Objectives were to gain insight on EEG methodologies, neurophysiological changes in schizophrenia, and the influence of treatment with BI 425809 on these measures.

Methods: The Phase II, double-blind, placebo-controlled, parallel-group study (NCT02832037) recruited adult patients (18–50 years of age) with schizophrenia. Eligible patients were randomized (1:1:1:1:2) to oral BI 425809 (2, 5, 10, or 25 mg) or placebo once daily (plus standard of care as adjunctive to antipsychotic treatment) for 12 weeks. Those who consented to participate in the substudy had EEG measurements made within a 14-day period prior to randomization (baseline) and again within 7 days before the end of the trial (Week 12). EEG assessments included resting-state EEG to assess brain activity at rest and any correlation with cognitive readouts; mismatch negativity to assess pre-attentive sensation of deviating auditory stimuli; and 40 Hz auditory steady-state response to assess cortical network function. EEG assessments at baseline and their change from baseline were compared with clinical assessments from the same trial visits, including the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), the Positive and Negative Syndrome Scale (PANSS) and the Schizophrenia Cognition Rating Scale (SCoRS).

Results: Overall, 79 patients from 17 sites (USA and EU) participated in the EEG substudy. Fifty-seven patients completed the substudy (BI 425809 2 mg, n=10; 5 mg, n=6; 10 mg, n=13; 25 mg, n=13; placebo, n=15) and were evaluated. Slightly more males, European and African American patients, and current smokers participated in the EEG substudy vs the full analysis set of the parent study. Mean baseline MCCB, SCoRS and PANSS data were similar between the substudy and parent study. Weak to moderate correlations of EEG parameters with clinical scores (MCCB composite, PANSS total and SCoRS) at baseline and change from baseline were determined. Some associations, however, indicate a diagnostic, prognostic and predictive potential of EEG as clinical biomarker.

Discussion: In this multicenter substudy in patients with schizophrenia, the association of EEG parameters with clinical scores indicates the potential of EEG as clinical biomarker. However, strength of correlations was often limited possibly due to high variability of EEG parameters. EEG variability may, in part, be due to the involvement of multiple sites with different levels of expertise in quantitative EEG or event-related potential recording. Restricting EEG assessment to fewer, high-quality sites, with a minimum number of patients, could reduce inter-site variability providing more robust data to inform on the value of EEG in supporting clinical drug development. In conclusion, these encouraging results support further exploration and optimization of EEG as relevant biomarker for future studies in patients with schizophrenia.

T63. FUNCTIONAL CONNECTIVITY DURING CONTOUR OBJECT PERCEPTION IN PSYCHOSIS

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Background: Contour integration, the process of joining spatially separated elements into a single unified edge, has consistently been found to be impaired in schizophrenia. Recent work suggests that this deficit could be associated with psychotic symptoms more generally, rather than specific psychosis-spectrum diagnoses.
Methods: We examined a transdiagnostic sample of 45 participants with psychosis (16 schizophrenia, 14 schizoaffective disorder, 15 bipolar disorder), 33 first degree biological relatives without psychosis, and 26 healthy controls with no family history as a part of the Psychosis Human Connectome Project. We obtained quantitative indices of contour perception by measuring discrimination accuracy and orientation jitter thresholds in a behavioural psychophysics task. We also used 7 tesla functional MRI (fMRI) to measure neural responses during an analogous task inside the scanner. Our fMRI analyses focused on three visual regions of interest (ROIs; primary visual cortex [V1], the lateral geniculate nucleus of the thalamus [LGN], and the lateral occipital complex [LOC]) chosen a priori based on their known roles in visual perception and contour integration. Our first-level GLM analysis quantified response magnitude for each trial of aligned and scrambled contours with and without background elements. We then carried out a task-based functional connectivity analysis (beta series method) to quantify changes in connectivity between ROIs across different task conditions.
Results: People with psychosis showed impaired contour perception (i.e., lower accuracy) in agreement with previous findings. However, we found no relationship between task performance and severity of symptoms measured using the Scale for Assessment of Positive Symptoms, the Brief Psychiatric Rating Scale, and the Sensory Gating Inventory. People with psychosis showed lower LGN-V1 functional connectivity, which may represent dysfunctional thalamocortical connectivity in psychosis. More subtle abnormalities in connectivity between LGN and V1 were observed among relatives of people with psychosis. Functional connectivity between V1 and LOC was also abnormal in people with psychosis, consistent with the idea that patients show impaired contour integration during shape discrimination.
Discussion: Our results may suggest a relationship between functional connectivity deficits and well-known contour integration impairments among people with psychosis.

T64. EFFECTS OF SCHIZOPHRENIA GENETIC RISK ON MULTI-MODAL ASSESSMENT OF COGNITIVE FLEXIBILITY AND TASK RELATED BRAIN ACTIVATION

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Background: Schizophrenia is a highly heritable disorder; however, understanding how genetic variation contributes to schizophrenia pathology is not well understood. Behavioral performance on tasks of cognitive flexibility may be a useful endophenotype as poor performance on this domain is shown not only in individuals with schizophrenia but also their family members. However, the extent to which brain activation during a cognitive flexibility task is affected by genetic risk for schizophrenia is less clear. The present study sought to examine the degree to which cognitive flexibility performance and its related brain activation may reflect effects of schizophrenia genetic risk using an extended pedigree design.
Methods: A total of 521 participants, 30 schizophrenia probands, 202 of their relatives (1st to 4th degree), and 289 unrelated controls from the Multiplex Genetic Investigation (MGI) study, completed similar versions of a computerized cognitive flexibility task (Penn Conditional

Exclusion Test, PCET) both out of and in an MRI scanner. Brain activation measures comparing task activation to a fixation baseline were extracted for five regions of interest: left and right frontal pole, left and right middle frontal gyrus, and bilateral anterior cingulate cortex. The genetic correlations between all measures and schizophrenia were computed. In order to examine diagnostic specificity, we also investigated genetic correlations between diagnosed depression and PCET performance and brain activation.
Results: Cognitive flexibility performance was significantly genetically correlated with schizophrenia both out of (Rg=-0.65, p=0.005) and in the scanner (Rg=-0.56, p<0.001) after false discovery rate (FDR) correction. In contrast, genetic correlations between schizophrenia and ROI brain activation in the Frontal Pole (right Rg=0.30, p=0.30, left Rg=1.00, p=0.01), Anterior Cingulate Gyrus (bilateral Rg=0.39, p=0.18), and Middle Frontal Gyrus (right Rg=1.00, p=0.04, left Rg=0.60, p=0.12) were either not nominally significant or were not significant after FDR correction. Neither behavioral performance nor brain activation measures were significantly genetically correlated with depression.
Discussion: Cognitive flexibility performance both out of and in scanner was sensitive to schizophrenia genetic risk. However, shared genetic effects between schizophrenia and regional brain activation measures were not significant. In contrast to some hypotheses, these results suggest that behavioral performance on this measure of cognitive flexibility (PCET) is more sensitive (and also specific compared with depression) to schizophrenia genetic risk effects than fMRI measures of its regional brain activation.

T65. EVIDENCE FOR SCHIZOPHRENIA-SPECIFIC PATHOPHYSIOLOGY OF NICOTINE DEPENDENCE

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Background: The prevalence of smoking in schizophrenia is three-times higher than the general population. Prior imaging studies of candidate brain circuits have not converged on a biological basis for schizophrenia's link to nicotine addiction. We therefore employed an entirely data-driven analysis of the connectome to identify schizophrenia-specific circuits of nicotine dependence.
Methods: We reanalyzed existing data from two neuroimaging studies using a data-driven approach. In the first cohort, 35 smokers (18 schizophrenia, 17 controls) underwent resting-state fMRI and clinical characterization. A multivariate pattern analysis of whole-connectome data was used to identify the strongest links between daily cigarette consumption and functional connectivity. In the second cohort, 12 participants with schizophrenia and 12 controls were enrolled in a randomized, controlled crossover study of transdermal nicotine patch with resting-state fMRI. We calculated mean change in default mode network connectivity (FCnicotine – FCplacebo) and correlated change in whole-network functional connectivity with nicotine dose.
Results: In cohort 1, the strongest (p<.001) correlate between functional connectivity and daily cigarette consumption was driven by individual variation in the topography of the default mode network. This effect was entirely driven by participants with schizophrenia despite the fact that groups were matched for severity of nicotine dependence. In cohort 2, we observed a linear relationship between nicotine dose and reduction in default mode network connectivity (R=-0.50; 95% CI -0.75 to -0.12, p<.05). There was a significant effect of diagnosis on default mode

network connectivity. Schizophrenia subjects had hyperconnectivity compared to controls in the placebo condition ($p<.05$), which was no longer significant during nicotine administration. **Discussion:** It has been hypothesized that the biological basis of nicotine dependence is different in schizophrenia and in non-schizophrenia populations. We here provide direct evidence in support of this hypothesis by demonstrating that tobacco use is strongly linked to brain network organization only in participants with schizophrenia. Our results suggest that the high prevalence of nicotine use in schizophrenia may be a product of both a hyperconnected default mode network that both interferes with cognitive performance and is more sensitive to nicotine in schizophrenia compared to controls. Future experiments will directly test the acute effect of nicotine on this network in schizophrenia and control populations.

T66. AMYGDALA HYPERCONNECTIVITY IN THE PARANOID STATE: A TRANSDIAGNOSTIC STUDY

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Background: Paranoia, the delusional fear that people are harming you deliberately, is linked with significant distress and social dysfunction across various clinical diagnoses. Previous research has suggested abnormal functioning of the amygdala as a potential mechanism underlying paranoia ideation. Amygdala is involved in several processes that are associated with paranoia, including interpersonal trust, vigilance, and fear conditioning. Additionally, amygdala also interacts with the prefrontal cortex (PFC) to process negative emotional stimuli, including the context of threat exposure, suggesting that abnormal amygdala-PFC circuits may also be associated with paranoid ideation. However, such hypothesis has not been tested yet. Therefore, the aim of the current study is to investigate amygdala functional connectivity in paranoia across different diagnoses using resting-state functional magnetic resonance imaging (R-fMRI). Understanding the role of amygdala-PFC functional connectivity in the neuropathology of paranoia across populations with different diagnoses has important implications for mechanism and intervention.

Methods: Forty-five patients with a recent history of clinically significant paranoid ideation and a current DSM-5 diagnosis of any disorder underwent resting-state functional magnetic resonance imaging while either in a paranoid (N=23) or non-paranoid (N=22) state. The preprocessing procedure includes slice-timing, realignment, coregistration using a T1-weighted structural image, normalization to MNI space, smoothing (FWHM=4mm), detrending, nuisance regression (Friston 24 head motion parameters, white matter signal, and cerebrospinal fluid signal), and filtering (0.01-0.08 Hz). Seed-based whole-brain functional connectivity (FC) analyses were then performed using bilateral amygdala as the seed regions of interest (ROIs). For each seed ROI, a whole-brain FC map was calculated by correlating the mean BOLD time series of the given seed ROI with all other voxels in the gray matter mask. FC patterns between amygdala and the rest of the brain were then compared between paranoid and non-paranoid patient groups using voxel-wise general linear models (GLM) with age, gender, medication, and framewise displacement as covariates. The significance threshold for between-group differences was set at $p<0.01$, combined with an individual voxel threshold of $p<0.001$ based on 3dClusterSim. Supplementary analyses considering additional covariates (i.e. diagnoses and state anxiety) and head motion effects (i.e. scrubbing) were also performed.

Results: Increased functional connectivity was found between right amygdala and the prefrontal cortex (PFC) [bilateral medial superior frontal gyrus, anterior cingulate, medial frontal gyrus, the triangular part and the opercular part of the inferior frontal gyrus (IFG); right orbital part of IFG], the frontal cortex (bilateral median cingulate, left precentral gyrus), and subcortical areas (right insula) in the paranoid group compared with the non-paranoid group. These between-group differences had large effect sizes (d>0.8). No significant between-group differences were observed in left amygdala functional connectivity. Similar results were present in the supplementary analyses.
Discussion: The current findings suggest that paranoia is associated with hyperconnectivity between right amygdala and PFC, frontal cortex, and insula. These increases were evident regardless of diagnosis and therefore identify a likely transdiagnostic neural mechanism. These findings may help to identify treatment targets, which could potentially improve the social functioning of people with clinical diagnoses.

T67. COMBINING PHYSICAL EXERCISE AND THE SIMPLE HEALTHY LIVING INTERVENTION MITIGATE HELTH RISK FACTORS IN SCHIZOPHRENIA

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Background: Metabolic syndrome is common in adults with psychosis, and of grave concern as it has been linked to increased mortality. Behavioral interventions such as healthy lifestyle groups and physical exercise (PE) have separately been shown to improve health outcomes such as obesity, eating behavior, and physical fitness. We sought to compare each intervention against a combined of the two, to determine if the latter would be associated with greater reductions in modifiable health risk factors.
Methods: Thirty-two outpatient adults with schizophrenia were randomized to either 4 months of a weekly 90-min healthy living skills group (n=11), twice weekly 45-min PE sessions (n=12), or a combination of the two consisting of weekly 45-min PE plus 45-min healthy living (n=9). The healthy living group was the "Simplified Intervention to Modify Physical activity, Lifestyle & Eating behavior" (SIMPLE), a healthy lifestyle program designed to reduce metabolic syndrome risk factors in adults with schizophrenia. SIMPLE is designed specifically to accommodate cognitive impairments common in this population by not assuming prior nutritional knowledge, presenting concepts in their most basic forms, and repeating information to facilitate encoding. For the PE sessions, participants chose from a menu of loosely supervised group PE activities. These included aerobic exercises such as the treadmill, elliptical and rowing machines, stationary bikes, weight training using nautilus equipment and free weights, and outdoor activities such as basketball or power walking around the campus. Assessments of body mass index (BMI), healthy eating, symptoms, and physical activity were administered at baseline and post treatment (4 mo). Two-month follow-up measures of healthy eating and physical activity were administered remotely, due to the outpatient program closing down for in-person visits due to COVID.
Results: Compared to either intervention alone, the SIMPLE+PE group demonstrated greater improvements in BMI, healthy eating, and physical activity at post (F=4.03-6.71, p's<.010).

Most striking was that these gains endured during the two-month follow-up, when the outpatient program was closed down to face-to-face visits due to COVID. At follow-up, there was an overall increase in psychotic symptoms in all three groups. Nevertheless, the SIMPLE+PE group still maintained better eating habits and a more active lifestyle (F=2.86-2.95, p's<.039).

Discussion: SIMPLE+PE was associated with greater improvement in healthy living habits and a reduction of risk factors associated with premature mortality. These gains persisted in the face of increased symptoms and social isolation during the COVID lockdown. Limitations include a small community sample and follow-up measures that were modified for remote assessment. Nevertheless, results suggest that combining PE and a healthy lifestyle program specifically developed for people with schizophrenia may mitigate health risk factors.

T68. LIFESTYLE AND STRESSFUL LIFE CIRCUMSTANCES IN FIRST-EPISODE PSYCHOSIS

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Background: Patients with a first-episode psychosis (FEP) often have a less favorable lifestyle and higher stress levels than the general population. However, whether diet and physical activity are associated with stress levels, cognitive and clinical features in FEP remains to be established.

Methods: We studied diet, physical activity and stress in 191 patients with a FEP and 144 healthy controls. The eating pattern was assessed with the Dietary Instrument for Nutrition Education (DINE), and physical activity was assessed with the International Physical Activity Questionnaire. Details about recent stressful life events were obtained using the List of Threatening Experiences questionnaire, while perceived stress was evaluated using the Perceived Stress Scale. History of childhood sexual abuse was obtained with the Childhood Experience of Care and Abuse Questionnaire (CECA-Q). We estimated hypothalamic-pituitary-adrenal (HPA) activity by measuring salivary cortisol at awakening; at 15, 30, and 60 minutes after awakening; at noon; and at 8 pm. An Area Under the Curve analysis was performed to estimate the awakening response (AUCi) and cortisol levels during the day (AUCg). A subgroup of the patients (N=85) also underwent a standardised neuropsychological assessment. Statistics: Linear regression was used to investigate eating patterns, physical activity and cognitive features of psychosis. Since age and sex are associated with cognitive function, analyses were adjusted for age and sex. Assumptions for linear regression was checked and found satisfactory. T-test was applied to investigate eating patterns in patients with and without childhood abuse, as well as eating patterns in patients compared to controls. Spearman's correlation was run for all other analysis.

Results: Patients as a group had a less healthy diet than healthy controls, characterised by higher sugar and fat intake. Patients with higher sugar and fat intake also had higher stress levels. For example, patients with higher sugar and fat intake had higher cortisol level during the day (AUCg; respective Spearman's correlations r=0.45, p=0.001; and r=0.32, p=0.03). Moreover, patients with a history of childhood sexual abuse had higher sugar intake than patients without childhood sexual abuse (t=2.19, DF=67, p=0.006). Patients with higher sugar

and fat consumption also showed worse performance on verbal memory immediate recall (β: -0.25; 95% CI: -0.61 to -0.02; p=0.04) and verbal memory delayed recall (β: -0.25; 95% CI: -0.88 to -0.016; p=0.04). Patients with high sugar and fat intake also had poorer performance on perception and visuospatial abilities (block design, β: -0.28; 95% CI: -0.48 to -0.07; p=0.008, and matrix reasoning, β: -0.23; 95% CI:-1.24 to -0.06; p=0.03), as well as general information (β: -0.32; 95% CI: -1.42 to -0.29; p=0.004). Finally, walking at least 10 min per day was associated with better functioning and lower symptom severity (p<0.05).
Discussion: Poorer lifestyles in patients with psychosis seem associated with activation of the stress system and worse cognitive function. Further work should establish whether interventions aiming at stress management and promotion of healthy lifestyles could work synergistically early in the illness to promote good physical health.

T69. BASELINE FALFF DERIVED FROM RESTING-STATE FMRI PREDICTS ACUTE TREATMENT RESPONSE IN FIRST EPISODE PSYCHOSIS

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Background: Clinical response to antipsychotic (AP) drug treatment is highly variable, yet prognostic biomarkers are lacking. The goal of the present study was to test whether fractional amplitude of low frequency fluctuations (fALFF), as measured from resting state fMRI data, can serve as a potential biomarker of treatment response to APs.
Methods: Subjects included 130 patients with first episode psychotic disorders (mean age = 22 years) and minimal exposure to APs (median exposure = 5 days; all patients <2 years). All subjects underwent scanning while entering 12 weeks of prospective treatment with second-generation APs (risperidone or aripiprazole). Consistent with our prior studies, stringent treatment response criteria were applied for ratings obtained on weeks 1, 2, 3, 4, 6, 8, 10, and 12: response required 2 consecutive ratings of much or very much improved on the CGI, as well as a rating of ≤3 on psychosis-related items of the BPRS-A. By these criteria, 84 patients were classified as responders; these subjects did not differ from 46 non-responders on age, sex, medication, or scan movement (FD and DVARS).
All fMRI exams were conducted on a 3T scanner (GE Signa HDx, n=77; Siemens PRISMA, n=53). On the Signa, the resting-state scan lasted 5 minutes, during which 150 EPI volumes were obtained (TR = 2000 ms, TE = 30 ms, matrix = 64*64, FOV = 240 mm; 40 contiguous 3mm oblique axial slices). On the PRISMA, two 7-minute 17-second resting-state runs were obtained, one each with AP and PA phase encoding directions. Resting scans contained 594 whole-brain volumes, each with 72 contiguous axial/oblique slices in the AC-PC orientation (TR=720ms, TE=33.1ms, matrix = 104x90, FOV = 208mm, voxel = 2x2x2mm, multi-band acceleration factor=8).

Raw resting state data were preprocessed with despiking, linear trend removal, spatial smoothing, and grand mean scaling. Utilizing Fourier Transformation at every voxel, we calculated the power of BOLD signal in the low frequency range of 0.01–0.10 Hz and divided it by the power of BOLD signal across the entire frequency range (0–0.25 Hz) to calculate fALFF. Voxelwise fALFF was compared between responders and non-responders using t-tests implemented in SPM with age, sex, scanner, and movement (FD) as nuisance covariates, and applying a height threshold of p<0.005 and FDR-corrected cluster size p<.05.

Results: Compared to non-responders, patients who would later meet strict criteria for clinical response demonstrated significantly greater baseline fALFF in five brain regions: bilateral orbitofrontal cortex, bilateral superior frontal cortex, and right pars opercularis. Additionally, one large (k=203) region in the left posterior temporal cortex demonstrated greater baseline fALFF in non-responders compared to responders, although this region did not meet FDR-corrected significance.
Discussion: Baseline resting state measures, obtained relatively easily even in impaired, early-phase patients with schizophrenia show promise as prognostic biomarkers. Combined with prior literature, results suggest that prefrontal deficits may be a critical target for antipsychotic treatment, whereas temporal abnormalities may be associated with lingering positive symptoms.

T70. THE NEURAL SUBSTRATES OF NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Neurological soft signs (NSS) are abnormalities in motor coordination, sensory integration, sequencing of complex motor movements, and the disinhibition of those movements, which are common in patients with schizophrenia. A meta-analysis of published literature on NSS in patients with schizophrenia and healthy controls found that on average, 73% of patients perform outside the range of healthy participants on aggregate NSS measures (Chan, Xu et al. 2010). The presence of NSS has been found to be independent of demographic variables and most medication variables (Bombin, Arango et al. 2005), supporting the idea that NSS are related to the pathophysiology of schizophrenia. However, the neural substrates of NSS remain poorly understood.
Methods: Here, we performed a systematic review and included studies that assessed neurological soft signs and obtained neuroimaging data in patients with a schizophrenia spectrum disorder published up to June 2020. Using legacy PubMed, we screened titles and abstracts, applied eligibility criteria, and excluded irrelevant articles to reach consensus on eligible full text articles. From these articles, we extracted relevant information, including author name, publication year, number of participants per diagnostic category, NSS instrument, and neuroimaging modality.
Results: Of the potentially relevant 464 articles, we systematically reviewed 35 relevant articles, including 29 structural MRI studies, 5 functional MRI (fMRI), and one molecular imaging study. Studies consistently implicate the basal ganglia and cerebellum as structural substrates of NSS, and suggest that somatomotor and somatosensory regions as well as areas involved in visual processing and spatial orientation may underlie NSS in psychosis spectrum disorders. Additionally, dysfunction of fronto-parietal and cerebellar networks has been implicated in the pathophysiology of NSS in several studies. In contrast, white matter volume deficits and dopamine D2 receptor dysfunction may not play a primary role in development of NSS.
Discussion: The current literature outlines several structural and functional brain signatures that are relevant for NSS in schizophrenia spectrum disorder. The vast majority of studies assessed gray matter structure, but only few studies leveraged other imaging methods such as diffusion weighted imaging, or molecular imaging. Due to this, it remains unclear if white matter integrity deficits or neurometabolic alterations contribute to NSS in the illness. While a substantial portion of the literature has been conducted in patients in the early illness stages, mitigating confounds of illness chronicity, only two studies have been conducted in

antipsychotic medication-naïve patients, which is a clear limitation. Furthermore, only little is known about the temporal evolution of NSS and associated brain signatures. Future studies addressing these pivotal gaps in our mechanistic understanding of NSS will be important.

T71. WHITE MATTER INTEGRITY, CLINICAL SYMPTOMS AND QUALITY OF LIFE IN SCHIZOPHRENIA: A DTI STUDY

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Background: White matter (WM) alterations have been consistently described both in first-episode and chronic psychosis. In particular, previous diffusion tensor imaging (DTI) studies of patients with schizophrenia reported widespread fractional anisotropy (FA) alterations, differing with respect to extent and location. Consistently with the disconnectivity hypothesis of the disorder, these microstructural abnormalities could underlie an inefficient communication between functional brain regions, thus contributing to the cognitive and behavioral alterations reported in schizophrenia. Accordingly, recent evidence suggests that WM measures may be correlated with the severity of clinical features, especially negative symptoms. However, up to date, there are only few studies addressing this topic and none of them evaluated the direct impact of WM disruption on quality of life of patients with schizophrenia.
The aim of the study is to comprehensively investigate the relationship between microstructural WM alterations and both psychopathology and quality of life in a sample of patients with chronic schizophrenia.

Methods: Seventeen patients with schizophrenia were enrolled for this study. All patients were evaluated with the Positive and Negative Syndrome Scale (PANSS), providing a global and domain specific measure of symptoms, and with the Quality of Life Scale (QLS), assessing subjective perception of daily functioning and quality of life.
DTI data were collected with a 3.0 Tesla Philips scanner. Whole brain tract-based spatial statistics were performed in the WM skeleton with threshold-free cluster enhancement of DTI measures of WM microstructure: axial (AD), radial (RD) and mean diffusivity (MD), and FA.

GLMs were performed with the DTI measurements (FA, AD, MD, RD) as dependent variables and PANSS and QLS as independent variables.

Results: A significant negative correlation emerged between AD values and PANSS Total, Negative and General scores, with main effects localized in the right cerebral peduncle, anterior/posterior limb of internal capsule, corticospinal tract, anterior thalamic radiation, external capsule, forceps minor, and anterior thalamic radiation.
Moreover, the analysis revealed significant associations between DTI measures and total QLS score. Specifically, higher QLS scores correlated with higher FA and lower AD, RD and MD values in the inferior/superior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps minor, forceps major, uncinate fasciculus, anterior thalamic radiation and body of corpus callosum, with a lateralized effect on the left hemisphere.

Discussion: Consistently with previous literature, results suggest that greater WM integrity and thus better brain connectivity in patients with schizophrenia are associated with better

psychopathological status and, more specifically, lower severity of negative symptoms. Interestingly and innovatively with respect to previous works, this study highlights a significant association between WM integrity and quality of life. These preliminary results thus suggest that, besides being associated with more severe clinical symptomatology, altered WM microstructure, especially in critical areas for subcortical connection, should be considered as one of the underlying neural mechanisms of the compromised functioning and quality of life observed in patients with schizophrenia.

T72. A LONGITUDINAL STUDY OF WHITE MATTER PROGRESSION AMONG PATIENTS WHO RECENTLY EXPERIENCED A FIRST-EPISODE OF PSYCHOSIS

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Background: For several years now, schizophrenia and related psychoses have been hypothesized to be disorders of disconnectivity. Diffusion imaging is a technique that allows for in vivo quantification of water molecules in the brain and enables assessment of the structure of white matter. Studies using this technique to identify white matter differences in patients with enduring psychosis have identified widespread robust differences in comparison with healthy controls (HC). However, studies in patients who have recently been treated for a first-episode of psychosis (FEP) have led to mixed results. It remains then to identify when patients begin to show white matter differences following a FEP. The current study examined white matter differences, as quantified through fractional anisotropy (FA), between FEP patients and HC using a longitudinal design with four assessments over 15 months.

Methods: Diffusion-weighted images were acquired on a 3.0 Tesla scanner for patients (n=54) and non-clinical controls (n=55) at baseline, 3, 9, and 15 months. Patients aged 24.60 ± 4.28 years old had less than a month of antipsychotic treatment before entering the program and less than 4 months of exposure to pharmacological treatment at the baseline scan. Preprocessing was performed using MRtrix3.0, which recruits the FSL software library tools for eddy current correction. A multi-shell acquisition was used to collect data across two phase encoding directions, and corrected for distortions using FSL topup. FA was computed by fitting a diffusion tensor model at each voxel with MRtrix3.0. Tract-Based Spatial Statistics were calculated using the procedure recommended by the ENIGMA Consortium-DTI, using a study-specific template. Precisely, the FA map for each subject was skeletonized and used to extract the average FA per white matter region using the JHU-White matter parcellation. Statistical analyses were performed in R, where a linear model was applied to identify group differences in all 24 tracts of the JHU parcellation, accounting for age and sex as covariates. False discovery rate (FDR) was used to correct for multiple comparisons.

Results: Regional group differences in FA over time were observed in the anterior cingulum, where patients showed a slow decrease in FA while HC's FA remained constant. At baseline, patients show a slightly lower FA in 13 regions of the JHU atlas, all with small effect sizes ($d \leq 0.3$). At 15 months, patients show lower FA compared with non-clinical controls on 15 regions of the JHU atlas, all with similarly small effect sizes ($d \leq 0.4$). Nevertheless, linear mixed effect model showed no significant main effect of group after correction for multiple comparisons.

Discussion: To our knowledge, there are a limited number of longitudinal studies investigating white matter changes in well-characterized FEP patients. This study suggests that there are trending decreases in FA among FEP patients in comparison with HC. Brain analyses are consistent with other cross-sectional studies that did not identify statistically significant group

differences in FA recently after a FEP. Furthermore, we demonstrate that the cingulum is potentially among the first tracts to be significantly affected after a FEP. Consistently, the cingulum has also been identified as a tract with reduced FA in psychosis, including both high-risk and enduring patients populations. Our future analyses will investigate how white matter changes relate to cognition and clinical symptoms.

T73. GLUTATHIONE AS A MOLECULAR MARKER OF FUNCTIONAL IMPAIRMENT IN PATIENTS WITH AT-RISK MENTAL STATE: 7-TESLA 1H-MRS STUDY

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Background: A substantial number of individuals with clinical high-risk (CHR) mental state do not transition to psychosis. However, regardless of future diagnostic trajectories, many of these individuals develop poor social and occupational functional outcomes. The levels of glutathione (GSH), a crucial cortical antioxidant, may track variations in functional outcomes in early psychosis and prodromal states.
Methods: Thirteen clinical high-risk and 30 healthy control volunteers were recruited for a 7-Tesla magnetic resonance spectroscopy scan with voxel positioned within the dorsal anterior cingulate cortex (ACC). Clinical assessment scores were collected to determine if any association was observable with glutathione levels.
Results: Bayesian Spearman test revealed a positive association between the Social and Occupational Functioning Assessment Scale (SOFAS) and the glutathione concentration in the clinical high-risk group (mode $\rho = 0.58$, posterior proportion [PP] = 0.98, Bayesian Factor in favour of H1 over the null H0 [BF10] = 2.1) but not in the healthy control group (mode $\rho = 0.11$, PP = 0.44, BF10 =0.23). After accounting for variations in SOFAS, CHR group had higher GSH levels than the healthy subjects (mode difference = -0.26, PP = 0.96; effect size -1.04, PP = 0.96).
Discussion: This study is the first to use 7-Tesla magnetic resonance spectroscopy to test whether ACC glutathione levels related to social and occupational functioning in a clinically high-risk group and offers preliminary support for glutathione levels as a clinically actionable marker of prognosis in emerging adults presenting with risk features for various severe mental illnesses.

T74. N-METHYL-D-ASPARTATE RECEPTORS IN FIRST-EPISODE PSYCHOSIS: A PET-MR BRAIN IMAGING STUDY

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Background: Evidence from genetics, post-mortem and animal studies suggest that N-Methyl-D-Aspartate Receptor (NMDAR) hypofunction has an important role in the pathophysiology

of psychosis. However, it is not known if NMDAR activity is altered in the early stages of psychosis or if this links to symptom severity. Our aim was to investigate NMDAR availability in first-episode psychosis (FEP) and to determine if they are associated with symptom severity.
Methods: We studied 40 volunteers (21 patients with first episode psychosis and 19 matched healthy controls) using a cross-sectional, case-control study design. The uptake of an NMDAR selective ligand, [18F]GE179, was measured using positron emission tomography (PET) and indexed using the distribution volume ratio (DVR) and volume of distribution (VT, in millilitres per cubic centimetre) of [18F]GE179 in the hippocampus and additional exploratory regions (anterior cingulate cortex (ACC), thalamus, striatum and temporal lobe). Symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS).
Results: Data from 37 participants (18 controls, 19 patients) could be analyzed. There was a significant reduction in hippocampal DVR in the patients with schizophrenia relative to healthy controls ($p = 0.02$, Cohen's $d = 0.81$). Although the VT of [18F]GE179 was lower in absolute terms in patients, there was no significant effect of group on VT in the hippocampus ($p = 0.15$, Cohen's $d = 0.49$) or the exploratory brain regions. There was a negative association between hippocampal DVR and total PANSS symptoms (rho = -0.47, $p = 0.04$), depressive symptoms (rho = -0.67, $p = 0.002$), and general PANSS symptoms (rho = -0.74, $p = 0.001$).
Discussion: These results indicate lower hippocampal NMDAR availability in schizophrenia relative to controls with a large effect size, and that lower NMDAR availability is associated with greater levels of symptom severity. These findings are consistent with the role of NMDAR hypofunction in the pathophysiology of schizophrenia; however, further work is required to test specificity and causal relationships.

T75. GLUTAMATE CONNECTIVITY ASSOCIATIONS CONVERGE UPON THE THE SALIENCE NETWORK IN SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Alterations in cortical inter-areal functional connectivity, and aberrant glutamatergic signalling are implicated in the pathophysiology of schizophrenia but the relationship between the two is unclear. We used multimodal imaging to identify areas of convergence between the two systems.
Methods: Two separate cohorts were examined, comprising 195 participants in total. All participants received resting state functional MRI to characterise functional brain networks and proton magnetic resonance spectroscopy (1H-MRS) to measure glutamate concentrations in the frontal cortex. Study A investigated the relationship between frontal cortex glutamate concentrations and network connectivity in individuals with schizophrenia and healthy controls. Study B also used 1H-MRS, and scanned individuals with schizophrenia and healthy controls before and after a challenge with the glutamatergic modulator riluzole, to investigate the relationship between changes in glutamate concentrations and changes in network connectivity. In both studies the network-based statistic was used to probe associations between glutamate and connectivity, and glutamate associated networks were then characterised in terms of their overlap with canonical functional networks.
Results: Study A involved 76 individuals with schizophrenia and 82 controls, and identified a functional network negatively associated with glutamate concentrations that was concentrated within the salience network ($p<0.05$) and did not differ significantly between patients and

controls (p>0.85). Study B involved 19 individuals with schizophrenia and 17 controls and found that increases in glutamate concentrations induced by riluzole were linked to increases in connectivity localised to the salience network (p<0.05), and the relationship did not differ between patients and controls (P>0.4).
Discussion: Frontal cortex glutamate concentrations are associated with inter-areal functional connectivity of a network that localises to the salience network. Changes in network connectivity in response to glutamate modulation show an opposite effect compared to the relationship observed at baseline, which may complicate pharmacological attempts to simultaneously correct glutamatergic and connectivity aberrations.

T76. NEURAL CORRELATES OF RELAPSE IN PSYCHOTIC DEPRESSION

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Background: Psychotic depression is a severe and impairing mental disorder. Even after remission is achieved, patients with psychotic depression are at a high risk of relapse. Relapse prevention is therefore crucial and neuroimaging biomarkers may prove useful in predicting future relapse. Our group recently examined psychotic depression in the context of a multi-site, randomized, placebo-controlled trial (Study of Pharmacotherapy of Psychotic Depression II; STOP-PD II). A magnetic resonance imaging (MRI) study was embedded within the design of STOP-PD II, and recent work by our group demonstrated that thinner cortex in an insular-limbic network was related to treatment outcome. Based on these structural MRI results, we sought to examine resting state functional connectivity (rsFC) from this insular-limbic network to determine associations with relapse.
Methods: Fifty-five participants (mean (SD) age = 54.2 (15.5) years; M/F = 24/31) in the randomized olanzapine (n = 25) and placebo (n = 30) groups of STOP-PD II had rsFC data of sufficient quality. Based on our previous rsFC work, we hypothesized that increased rsFC between an insular-limbic (IL) network and the dorsal attention (DAN) and somatosensory/motor (SMN) networks are a neurobiological vulnerability for relapse. We examined rsFC between the IL network and the whole brain to identify clusters of functional connectivity that differed between those who subsequently relapsed (N=22 [olanzapine n = 4 and placebo n = 18]) and those who sustained remission (N = 33 [olanzapine n = 21 and placebo n = 12]). We then compared relapsers to remitters.
Results: Increased rsFC in relapsers (relative to remitters) was observed between the IL and three clusters. Cluster 1 (t=1.782, p=0.04, d=0.5) was located within the right parietal cortex and overlapped with the DAN. Cluster 2 (t=3.491, p<0.001, d=1.3) was located in the left parietal cortex and overlapped with the DAN, SMN, and fronto-parietal control network (FPCN). Cluster 3 (t=3.880, p<0.001, d=1.1) was located in the right frontal and parietal cortex and also overlapped with the DAN, SMN, and FPCN.
Discussion: Our functional MRI results converge with previous structural MRI results. Increased resting state functional connectivity between the IL and brain regions that overlapped with the DAN, SMN, and FPCN was observed in relapsers when compared to remitters. Future work will examine the relationship of this pattern of rsFC with psychomotor disturbance and risk of relapse, as well as whether this rsFC generalizes to risk of relapse of psychotic

depression that remits with electroconvulsive therapy. Ultimately, these structural and functional findings may guide relapse prevention, reduce unnecessary exposure to antipsychotics in people who do not need them, and inform the development of novel interventions to prevent relapse.

T77. POLYMORPHISM OF THE MTHFR1 GENE IS ASSOCIATED WITH DECREASED INTRACORTICAL MYELINATION IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a severe mental disorder that affects a person's thoughts, moods, and behavior. The MTHFR 1 gene is critical for the health of the brain and body, as it converts folate to the active 5-methyltetrahydrofolate. This active form of folate is important for methylation in the body, which is required for nerve mylenation among various other biological functions. Increased negative symptoms have been shown in schizophrenia patients who have a relatively rare homozygote, TT, for the MTHFR 1 gene for SNP C677T. Given the known role of the MTHFR 1 gene in disorders of myelination, the relationships of the TT homozygote to levels of intracortical myelination (ICM) in schizophrenia was examined here.
Methods: Data were acquired with a novel MRI method from 78 individuals with recent onset of SZ who were participants in the Aftercare Research Program at the Semel Institute for Neuroscience and Human Behavior at UCLA. A manual quantification method delineated MRI images into grey and white matter. Samples of the control's DNA were sequenced, extended with primers, and then run through gel electrophoresis to classify the single nucleotide polymorphism.
Results: Based on literature indicating that the TT genotype was associated with myelination deficits in multiple sclerosis, the TT allele group was compared to the combined TC and CC alleles group. The ICM volume for the TT genotype was lower (M=1049.833 cm3, SD=836.5107) that that of the TC genotype patients (M= 2615.333 cm3, SD=1098.2675), and the CC genotype patients (M=2531.300 cm3, SD=1056.4347). The significant mean TT vs TC + CC difference ((t(36)=3.309, P=.002)) reveals that there was significantly less intracortical myelination for individuals with the rare homozygote, TT, as compared to those with the CC or CT alleles on the MTHFR1 gene.
Discussion: We speculate that this lower level is also an underlying contributor to the greater levels of negative symptoms seen in schizophrenia patients with the rare allele for the MTHFR 1 gene. Further examination of the role of the MTHFR 1 gene in the methylation pathway must be studied in order to better understand the interplay between the pathway and ICM. Going forward, as compounds are developed for multiple sclerosis, they could potentially be used to target the decreased amount of intracortical myelination for those individuals with schizophrenia and the rare TT genotype as well. As the MTHFR 1 mutation also contributes to folate metabolism, more studies should be done to understand if increasing or decreasing dietary folate or folate supplementation would increase ICM. Additionally, this specific polymorphism is a potential target for gene therapy for individuals with schizophrenia.

T78. CHARACTERIZING AGE-DEPENDENT PATTERNS OF SCHIZOPHRENIA GENETIC EFFECTS ON GENERAL COGNITION

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Background: Cognition shares extensive genetic overlap with schizophrenia and can thus be a useful proxy for examining patterns of genetic risk for schizophrenia. Thus, examining genetic effects on cognition across age of risk can help with parsing the timing of key developmental events contributing to the peak age of onset of schizophrenia during young adulthood. Specifically, early neurodevelopmental models suggest that genetic effects on schizophrenia risk are evident well before the peak age of risk (Murray & Lewis, 1987; Weinberger, 1987), whereas late neurodevelopmental models suggest that genetic effects on schizophrenia risk may not be evident until around the peak age of risk (Feinberg, 1983). In addition, neurodegenerative models suggest that genetic effects on schizophrenia risk may increase long after the peak age of risk (Lieberman, 1999). However, no study to date has directly addressed how genetic effects shared between cognition and schizophrenia may shift before, during, and after peak age of risk for schizophrenia in late adolescence and early adulthood. We therefore examined the extent to which the genetic relationship between general cognition and schizophrenia may change across age.

Methods: As part of the Multiplex Genetic Investigation of Schizophrenia (MGI), 533 participants from 42 families with at least two first-degree schizophrenia relatives and 135 unrelated controls underwent structured diagnostic interview and cognitive assessment using the Penn Computerized Neurocognitive Battery, Trails A and B, and California Verbal Learning Test. We first conducted exploratory factor analysis of cognitive test scores to extract a general cognition factor. We then conducted quantitative genetic variance decomposition analyses on this general cognition factor to examine schizophrenia developmental neurocognitive effects that arise before schizophrenia peak age of risk (age under 22 years: early neurodevelopmental effects), during peak age of risk (age 22-42 years: late neurodevelopmental effects), and after peak age of risk (age over 42 years: neurodegenerative effects).

Results: General cognition was significantly heritable across all age periods ($h^2 = 0.40$-0.84, $p < 0.04$). Most importantly, genetic effects shared between general cognition and schizophrenia were low before peak age of onset ($Rg = -0.41$, $p = 0.03$), increased after peak age of onset ($Rg = -0.87$, $p < 0.01$), and decreased somewhat in later adulthood ($Rg = -0.71$, $p < 0.01$). This pattern of findings was diagnostically specific to schizophrenia and not found in non-psychotic depression, where genetic effects shared between cognition and depression remained low before peak age of onset for schizophrenia, ($Rg = -0.11$, $p = 0.73$), during peak age of onset ($Rg = -0.07$, $p = 0.81$), and in later adulthood ($Rg = -0.26$, $p = 0.25$).

Discussion: This is the first study to our knowledge to demonstrate that schizophrenia liability, as indexed by shared genetic effects with cognition, shows increased effects around the peak age of onset. Our findings supported both early and late neurodevelopmental models: although schizophrenia genetic risk effects were present during adolescence, genetic effects increased around the peak age of onset of schizophrenia during young adulthood and then persisted but did not increase in later adulthood. This suggests the utility of examining expression levels of

schizophrenia risk variants identified in genome-wide association studies during the critical neurodevelopmental period spanning late adolescence and early adulthood. More broadly, our findings promote the importance of adopting developmentally-informed approaches to identify genetic risk factors for schizophrenia.

T79. RARE GENOMIC VARIANTS DRIVING SEVERE PSYCHOSIS: RESULTS FROM A PILOT STUDY

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Background: Even in diseases thought to be primarily characterized by high common polygenic risk burden, individuals with "extreme phenotypes" of illness are more likely to harbor mechanistically potent, rare or de novo variants. We looked for these variants in a deeply phenotyped cohort of 25 individuals with severe psychosis, using whole genome (WGS) and RNA sequencing (RNA-seq), and intensive genotype-phenotype correlation.

Methods: Participants with schizophrenia and schizoaffective disorder were enrolled in our pilot precision medicine study while admitted to the BC Psychosis Program, the tertiary inpatient adult refractory psychosis research and clinical care unit for the Canadian province of British Columbia. Phenotyping includes admission and discharge PANSS scores and functional ratings; detailed perinatal and developmental, and psychiatric and medication histories; structured neurological and dysmorphology-oriented physical examinations; neurocognitive assessments; and M.I.N.I. research diagnostic interview and multidisciplinary consensus-based DSM-5 diagnoses. Extensive clinical biochemical screens for inborn errors of metabolism, and chromosomal microarrays (CMAs) are performed at entry. A cytokine and inflammatory marker panel was performed on 24 participants, and clinical MRI scans are available on most.

Illumina next generation sequencing is performed on genomic DNA and whole blood RNA at Canada's Michael Smith Genome Sciences Centre at BC Cancer, and analyzed in UBC's Michael Smith Laboratories. Variants are filtered and prioritized by pathogenicity prediction, allele frequency and conservation. RNA-seq data and phasing from linked-read WGS enables identification of allelic expression imbalances. Bioinformatically prioritized exonic variants are validated by IGV review of DNA and RNA reads, and curated using databases (e.g. SCHEMA, Varsome, SZGR2, OMIM, UniProt, SwissProt), literature review, and correlation with phenotype data. Pharmacogenomic (PGx) variants are extracted from WGS data using Stargazer, and clinical PGx reports are generated using Sequence2Script after integration of medication phenocopy data. Clinically relevant copy number and single nucleotide variants

(CNVs and SNVs) are returned to participating patients and family members through psychiatric genetic counselling.

Results: Phenotyping, CMAs, WGS and RNA-seq has been completed on 25 participants. Mean admission and discharge total PANSS scores were 91.9 and 69.5, respectively.
CMA revealed 10 clinically reportable CNVs, including a 346 kb 3p26.3 duplication partially overlapping and potentially disrupting CHL1, and a 1.3 Mb 22q11.23 duplication, both considered as likely pathogenic.

Exonic sequence variant annotation and curation has been completed for the first 10 participants, harboring between 12 and 42 (mean 19.5) prioritized variants each. 12 loss-of-function (LoF) variants impact genes including SETD1A (the schizophrenia risk gene most significantly enriched in LoF variants to date), the neurodevelopmental risk gene FOXP1, and ATP7B (heterozygous; biallelic ATP7B mutations cause Wilson's disease). Protein-altering variants were found in many mutation-intolerant genes potentially relevant to the neurobiology of schizophrenia, including MDGA1, GGA1, CNOT1, GRK2, ATR, NCDN, PI4KA, and WDR20. Analysis for the remaining 15 participants is underway, and will be presented.

Discussion: While individually rare, as a class, potent single gene variants may not be uncommon in treatment-resistant psychosis, and can pinpoint personalized medicine treatment targets for further study. We will outline the potential for a precision medicine approach to SETD1A haploinsufficiency as an example.

T80. TOBACCO SMOKING IS ASSOCIATED WITH ADVERSE EFFECTS ON THE MICROBIOME IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Individuals with schizophrenia are three times more likely to smoke tobacco than persons in the general population. While adverse health outcomes have been associated with smoking, no previous studies have specifically examined the effects of cigarette smoking on the microbiome in this population.
Methods: The sample consisted of 138 schizophrenia patients and 100 non-psychiatric controls from whom an oropharyngeal throat swab sample was taken for measurement of the microbiome. 16S rRNA gene sequencing was performed on DNA eluted from the swabs. The resulting sequences were clustered into operational taxonomic units (OTUs) using QIIME and metabolic pathways were inferred using PICRUSt. Participants were assessed as to their current tobacco smoking along with demographic and clinical variables. Differences in the microbiome were assessed using regression models adjusted for relevant covariates.
Results: A total of 58% of the schizophrenia participants and 11% of the controls reported current smoking. In the schizophrenia group, a total of 7 bacterial genera differed significantly in abundance between the smokers and the non-smokers ($p<.05$). Genera that were enriched in schizophrenia smokers predominantly consisted of pathogenic organisms (e.g. Treponema, Arvimonas) while those that were depleted consisted largely of non-pathogenic organisms (e.g. Neisseria, Abiotrophia). Functional analysis inferred from the microbial sequences showed alterations in metabolic pathways related to utilization of essential nutrients and energy metabolism. Only 2 of these taxa were found to be altered in the control population.
Discussion: Tobacco smoking in schizophrenia alters the oropharyngeal microbiome, potentially leading to shifts in functional pathways with implications for smoking-related diseases.

T81. SUBCHRONIC PHENCYCLIDINE ENHANCES DNA METHYLATION OF NMDAR SUBUNITS IN RAT BRAIN

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Background: The glutamate/N-methyl-d-aspartate receptor (NMDAR) plays an important role in brain development, synaptic plasticity, stress response and cognitive function. Dysfunction of the NMDAR is implicated in the neurobiology of schizophrenia, and NMDAR antagonists, such as phencyclidine (PCP), can induce behaviours that mimic aspects of the disease. Environmental risk factors for psychiatric disorders, such as early-life stress, may affect methylation of DNA, and this epigenetic mechanism can alter the expression of several candidate genes, indicating how environmental factors might interact with the genomic risk contributing schizophrenia. As we previously found increased promoter methylation of the Grin1 and Grin2b NMDAR genes in the brains of isolation-reared rats (Loureiro et al., 2020, Epigenomics, ahead of print), and decreased GRIN2B methylation in first-episode schizophrenia patients when compared to controls (Fachim et al., 2019, Epigenomics, 11(4):401-410); we sought to extend our previous findings to investigate the involvement of NMDAR hypofunction regulated by DNA methylation of NMDAR genes (Grin1, Grin2a and Grin2b) in a pharmacologic animal model of schizophrenia.

Methods: Lister-hooded female rats received 2 mg/kg PCP (n=10) or vehicle (0.9% saline, n=10) both twice a day, i.p. for seven days. Novel object recognition (NOR) was tested six weeks after PCP treatment. After behavioural testing, genomic DNA was extracted from rat brain (prefrontal cortex and hippocampus) and bisulfite converted for following pyrosequencing analysis to quantify DNA methylation in equivalent CpGs sites, previously investigated in humans, of NMDAR genes. Line-1 methylation was also determined as a measure of global methylation. Data were analysed by parametric tests using Student's t-test and Pearson correlation coefficient. Values of $p<0.05$ were considered significant for two-tailed tests.

Results: Rats undergoing subchronic PCP administration had an impairment in NOR when compared to the vehicle as demonstrated by a deficit in the discrimination index in the task retention phase (vehicle: 0.35±0.04 versus PCP: 0.08±0.04, $p<0.01$). Moreover, PCP rats showed hypermethylation of DNA in Grin1 and Grin2b in the prefrontal cortex [Grin1: CpG3 ($p=0.05$); Grin2b: CpG3 ($p=0.006$) and CpG4 ($p=0.036$)], and hippocampus [Grin1: CpG3 ($p=0.023$) and CpG4 ($p=0.041$); Grin2b: CpG4 ($p=0.031$)] when compared to vehicle. However, no significant differences were observed in the Line-1 and Grin2a methylation.

Discussion: Our study showed that animals undergoing subchronic PCP treatment have increased DNA methylation at promoter sites of Grin1 and Grin2b NMDAR subunits in two brain areas implicated in schizophrenia. These findings are independent of any global change in DNA methylation determined by Line-1 methylation, and are similar to our observations in another animal model of schizophrenia - exposure to social isolation rearing post-weaning (Loureiro et al., 2020, Epigenomics, ahead of print). Moreover, our findings support partly our previous human data that showed hypomethylation of the GRIN2B promoter in schizophrenia patients when compared to controls (Fachim et al., 2019, Epigenomics, 11(4):401-410). Thus, these two different animal models demonstrate consistent DNA methylation changes in

NMDAR genes that are likely to influence receptor expression and function, demonstrating the potential importance of epigenetic mechanisms in the pathophysiology of schizophrenia.

T82. ALTERED MICROGLIAL MORPHOLOGY IN PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Microglia are the principal immune cells in the brain, and respond to pathological events or disruptions in homeostasis by initiating concomitant structural and functional changes. It is now apparent that microglial cells are highly heterogeneous and can adopt a diverse range of morphological and molecular phenotypes depending on context. While alterations in microglial density have previously been reported in schizophrenia (SCZ), findings are inconsistent, and prior studies of microglia have not adequately considered whether changes are restricted to specific morphological subtypes. In order to further elucidate microglial disturbances in SCZ we quantified the density and distribution of morphologically distinct subpopulations of microglia in postmortem brain tissue.
Methods: Paraffin sections of prefrontal cortex from SCZ and control subjects were acquired from the Stanley Medical Research Institute. Microglia were identified using immunohistochemistry for IBA-1. Mean densities of microglial subpopulations, IBA-1 area fraction and measures of cell clustering were compared between groups using mixed models.
Results: Immunoreactive cells displayed a variety of morphologies, including ramified, primed/reactive, ameboid, rod, dystrophic and perivascular subtypes. While total microglial density was unaltered in SCZ compared to controls, the density of microglia with dystrophic morphology was significantly increased in SCZ. In addition, significant deficits in IBA-1 area fraction were observed in the SCZ group, providing further evidence for anomalous microglial morphology in this disorder, while clustering of IBA-1 positive cells was also increased in SCZ.
Discussion: Microglial morphology and spatial distribution is disturbed in SCZ. In particular, we report an increase in microglial dystrophy, proposed to represent cellular senescence, and increased microglial clustering, providing evidence for aberrant microglial function in this disorder.

T83. BIRTH ASPHYXIA IS ASSOCIATED WITH WHITE MATTER MICROSTRUCTURAL DIFFERENCES IN THE POSTERIOR LIMB OF THE INTERNAL CAPSULE OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS

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Background: Worldwide, newborn infants experience birth asphyxia (ASP), a condition with a clinically relevant deficiency in the supply of oxygen reaching the brain around the time of birth. White matter (WM), specifically myelin, is a primary target for neural injury due to ASP, which is associated with a particular pattern of acute lesions detectable on neonatal magnetic resonance imaging (MRI). In term infants, the combination of ASP-related MRI findings that leads to the poorest functional outcomes are prominent basal ganglia and thalamic lesions and abnormal MRI signal in the posterior limb of the internal capsule (PLIC) (1). Myelination of the PLIC begins at 39-40 weeks gestational age (2). Since the average human gestation is 40 weeks, the PLIC might be particularly vulnerable to ASP. Previously, we reported smaller basal ganglia and thalamic volumes across adult patients with schizophrenia (SZ) and bipolar disorders (BD) and healthy controls (HC) who experienced ASP, wherein smaller caudate volumes were specifically found in patients with ASP (+) compared to patients without ASP (-), a difference not found in HC (3). In this study we explored the effect of a history of ASP on adult WM of patients and HC.
Methods: We utilized prospective data from the Medical Birth Registry of Norway to identify incidences of ASP in 579 HC and 271 patients with SZ or BD (age range: 18-72 years). Participants underwent diffusion tensor imaging, and mean diffusion metrics, fractional anisotropy (FA, WM integrity), axial diffusivity (AD, axonal damage) and radial diffusivity (RD, demyelination) (4), were extracted based on atlas-defined WM tracts and labels. 25 WM region of interest ANCOVAs, adjusted for age, sex and age-squared, were used to examine ASP related WM abnormalities between patients and HC. Comparing FA estimates in ASP+ versus ASP- participants between groups, interaction effects were declared significant with a correction for multiple comparisons.
Results: ASP was identified in 16% of participants in each group. In the PLIC, a significant FA reduction was detected in ASP+ patients compared to ASP- patients, which was not found among the HC ($F(1, 843) = 11.46$, $p = .001$). Effect sizes for the PLIC varied in ASP+ patient groups, with largest effects ($d = -0.46$) in the SZ group. Both left and right hemisphere PLIC showed effects of ASP, but the left PLIC had a greater effect size in SZ ($d = -0.44$) and the right had a greater effect size in BD ($d = -0.55$). RD, not AD, displayed significant results ($F(1, 843) = 9.28$, $p = .002$) and similar effect sizes as FA. In follow-up analyses, subtracting the right from the left hemisphere PLIC, difference scores were associated with positive symptoms in the BD group (FA: $t(106) = 2.91$, $p = .004$; RD: $t(106) = -2.89$, $p = .005$), where increasing left/right PLIC abnormalities were related to increasing positive symptoms.
Discussion: Despite similar frequencies of ASP, only patients had indications of compromised WM integrity in the PLIC consistent with previous findings on MRI patterns of asphyxiated infants with the poorest outcome (1). Myelination of PLIC tracts is considered an important sign of brain development (2), and alterations due to ASP in adult patients might indicate early damage or impeded brain development. Disproportion of right compared to left PLIC abnormalities in BD that associate with positive symptoms might be related to the psychotic features of this disorder. These findings should be replicated in an independent sample.

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T84. AUTOMATED THEMATIC ANNOTATIONS FOR OUTCOME PREDICTION OF VIRTUAL REALITY-ASSISTED THERAPY: A MACHINE LEARNING STUDY

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Background: It is well-known that many patients with schizophrenia will not respond to conventional treatments recommended by treatment guidelines. Novel interventions are needed to remediate the limitations of standard treatments. In this sense, Virtual Reality (VR)-assisted Therapy (VRT) is a modern and innovative therapeutic alternative for patients with treatment-resistant schizophrenia who continue to suffer from persistent persecutory voices. This approach allows patients to enter in a dialogue with a virtual representation of their persecutory voice (avatar) controlled in real-time by the therapist. The results of this approach have shown effects that appear larger than those of conventional treatments. While these effects are promising, the therapeutic processes are just now beginning to be defined and there remains uncertainties as to the factors that lead to the best treatment response. Artificial intelligence may aid to fill this gap and move towards precision medicine. The objective of this study was thus to predict treatment response based on the patient-avatar interaction during the sessions of VRT. To do so, we followed three steps. The first step was to determine a machine learning algorithm for automated text classification applicable for small databases, such as the one obtained via the transcripts of VRT sessions. The second step was then to implement this algorithm and examine the predictive score and inter-rater agreement for the automated text classification of patient-avatar interactions. The third step was to predict the principal therapeutic outcome consisting of auditory verbal hallucinations as measured by the Psychotic Symptoms Rating Scale.

Methods: A systematic review on such use of machine learning in the fields of psychiatry, psychology, and social sciences was conducted to help determine the available algorithms that may be used for on the transcripts of the interaction between patient and avatar. The systematic search was performed in the electronic databases of PubMed, Web of Science, PsycINFO and Google Scholar from their inception dates until 2020. The Linear Support Vector Classifier (LSVC) was selected from this search and implemented. Predictive algorithm was implemented using a logistic regression algorithm.

Results: The systematic review showed that limited literature existed on the subject. Though, few algorithms tended to display accuracy of interest when performing text classification on small datasets. The performance test enabled to establish that LSVC tended to yield better accuracy than the other algorithms for smaller datasets such as ours. Consequently, our choice of selecting LSVC was appropriate considering support vector machine algorithms tend to have the best performances with smaller subsets as compared to other alternatives. LSVC was suited to perform automated theme classifications on VRT transcripts with the use of limited datasets with an accuracy of 73% and a substantial classification Scott's Pi agreement of 0.71. We combined our previous algorithm to a logistic regression to predict the treatment response of patients (e.g. treatment responders vs non-treatment responders) based on the patient-avatar interaction they held during the immersive sessions of VRT. Using our algorithm, 88% of patients' therapeutic outcomes were correctly predicted.

Discussion: The results of this project showed that it is, on one hand, possible to annotate automatically an un-annotated transcript from a small database and that it is also possible, on another hand, to predict treatment response based on the patient-avatar interaction during VRT. Artificial intelligence in VRT may pinpoint who will or will not respond to treatment, which will help maximize treatment success.

T85. IMMERSIVE, MINDFULNESS-BASED VIRTUAL REALITY (VR) TO IMPROVE AGGRESSIVE BEHAVIORS IN AN INPATIENT SETTING: PRELIMINARY PILOT DATA

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Background: Aggressive behavior in the context of psychotic illness is a complex and multifactorial issue with severe public health and social consequences. While treatment options exist to reduce aggression, most are pharmacological interventions. Virtual reality (VR) appears to be a unique possibility as a mindfulness-based intervention, which has been used as an adjunctive treatment for a variety of mental health conditions including anxiety, substance use disorders, and in improving clinical features of psychiatric disorders. The main objective of the study is to explore the feasibility and the potential benefits of using mindfulness-based VR in inpatients with schizophrenia and a recent history of aggressive behaviors.

Methods: In this randomized controlled trial at Manhattan Psychiatric Center, inpatients with ICD-10 schizophrenia and aggressive behaviors were randomly assigned to either mindfulness-based VR with the TRIPP™ device, or a mindfulness-based auditory app. VR consisted of 18 sessions of 8-minute individual treatment given three times a week for 6 weeks. The auditory app was presented to subjects at the same frequency and duration. Assessments were done at baseline, weekly, and at endpoint. Primary outcome measures were aggressive behavior measured with the modified Overt Aggression Scale (OAS), Oxford Daily Mood Scale (ODMS), State-Trait Anxiety Inventory (STAI-VR), self-reported aggression, PANSS, and Mobile Application Rating Scale (MARS). The ODMS and STAI-VR were completed before and after each VR session. Due to small sample size, data will be presented for the TRIPP™ VR only.

Results: Of the 9 participants receiving TRIPP™, the mean age is 35.34±8.10. Baseline State Anxiety (STAI-S) was 17.0 (7.07) and Trait Anxiety (STAI-T) was 21.0 (8.49). Mean PANSS positive scores at baseline was 17.0 (4.24), negative = 23.5 (0.71), total PANSS = 80.5 (4.95). Chi Square indicated improved change in mood from baseline to endpoint ($X2 = 18.23$ (1), $p < 0.05$). Change from baseline (CFB) show individuals who initially reported negative moods at the beginning of the VR session had increases in positive mood at the end of the VR session on the ODMS (mean = 2.162 (±1.113)). No significant differences were noted on the modified Overt Aggression Scale (mOAS) from baseline to endpoint ($p = 0.124$). During the 6-week study period, no participant dropped out, nor reported verbal or physical aggression or required PRNs medication for aggressive incidents. In terms of feasibility, in all quadrants of the MARS (engagement, functionality, aesthetics, information and subjectivity) VR received the highest scores ranging from 3.40 (1.13) for Engagement to 4.00 (1.41) for Aesthetics indicating high participant acceptability.

Discussion: The results suggested that there were subjective improvements in mood following the use of TRIPP™ VR with improvements noted on both STAI-VR and the ODMS. The VR device was well tolerated by acute inpatients with psychosis. With a small sample size, VR has shown reductions in PRNs for aggressive behavior. The plan is to have a larger sample size of 25 participants by April 2021.

T86. COMPUTER CODING FOR EARLY PSYCHOSIS - AN INNOVATIVE PILOT STUDY

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Background: People with psychotic disorders are at higher risk of not completing an educational degree and tend to get low-wage jobs. Computer coding could help develop skills that increase one's education and employment opportunities. Offering computer coding training to students at risk of dropping out of school seems to increase their interest in education. This study's objectives were threefold 1) to determine the feasibility of adapting and delivering a computer coding training typically offered in schools to youth with a psychotic disorder, 2) to measure the acceptability, from the youth's perspective, of the training and 3) to estimate the potential impact of such a training on the youth's self-esteem, motivation, and education/vocational aspirations.

Methods: We offered computer coding classes to 14 participants. This was a mixed-method pilot study with pre-post measures as well as a three-month telephone follow-up. Participants were recruited from two early psychosis clinics in Montreal. The average age was 25 (S.D.: 3.4), French was the mother-tongue for 64% of our sample (n=9). The computer coding training was offered by Kids Code Jeunesse (KCJ), a not-for-profit organization that teaches computer coding to elementary and high school students and teachers across Canada. The trainer was a qualified KCJ trainer who had previous knowledge in mental health. The training was offered in small classes of 4 to 6. Feasibility was measured at each session, via feedback collected at the end of each class from participants. Acceptability was measured by the actual presence in the training (attendance) as well as individual qualitative interviews conducted with each participating youth in the coding training. The potential impact: self-esteem was assessed with the Self-Esteem Rating Scale-short-form; work and school motivation were assessed with The Motivation to Find a Job or Motivation for School questionnaires.

Results: Participants were all able to complete their project and the trainer was able to adjust the training to the pace of each class as needed. Feedback addressed for example the pace or clarity of explanations by the trainer ('explains really well'), that 'all is well', 'nothing to change', or 'starting to get better at scratch program'. As for acceptability, out of the initial participants who agreed to take part (n=26), 13 never showed up, 6 attended all sessions, and 7 missed at least one class. Three months after the training, the participants were contacted again to see if the training had had any impact on their lives or goals. The comments mention a high appreciation for the training and motivation to complete a degree for most of the sample. Regarding potential impact, our sample was too small to detect any statistically significant Results:. Nonetheless, when looking at the effect sizes we notice a small-medium effect size for each of these variables (self-esteem (E.S.= 0.37), school motivation (E.S.= 0.46) and work motivation (E.S.= 0.41)), suggesting noticeable improvements between before and after the training.

Discussion: This is to our knowledge the first initiative to teach computer coding to individuals with psychosis. We have demonstrated that such skills, formerly considered too complex, can be adapted for people with psychiatric problems, such as psychotic disorders, and help them develop school and work goals. Computer coding might be a stepping stone towards better employment opportunities or, at least, increased motivation for educational goals. The preliminary results of this study may eventually be reinforced by larger studies with a randomized controlled design.

T87. THE IMPACT OF THE COVID-19 PANDEMIC ON TREATMENT-RESISTANT SCHIZOPHRENIA PATIENTS HAVING FOLLOWED AVATAR THERAPY OR CBT: A CONTENT ANALYSIS

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Background: It has been estimated that 20 to 50% of patients suffering from schizophrenia will have treatment resistant schizophrenia (TRS), meaning they do not respond to antipsychotic medication. They are likely to experience high levels of distress in relation to their auditory verbal hallucinations (AVH). Avatar Therapy (AT) is a psychosocial therapy using virtual reality and exposure-based interventions to establish an intimate dialogue with patients' voice, which has shown to improve AVH in TRS patients, in comparison to Cognitive behavioral therapy (CBT). CBT is a therapy that engages the patient in examining and challenging their psychotic experiences and developing coping strategies to manage symptoms. The COVID-19 pandemic being an important stressor for the general population and more specifically for schizophrenia patients, the exploration of its impacts on patients having followed AT and CBT therapy was examined.

Methods: We conducted open interviews with 23 TRS patients having followed CBT and 18 TRS patients having followed AT over the past 3 years. Patients were asked to discuss the general impact of COVID-19, its impacts on their daily lives, hallucinatory experiences and affective symptoms including suicidal thoughts, their psychiatric follow-up, as well as their personal experience of AT or CBT. All the interviews were transcribed and a content analysis was conducted in order to extract predominant themes. All of the patients' verbatims in each transcript were coded by 2 people in function of these themes using QDA miner. The total agreement for the classification of all our verbatims was substantial (Scott's Pi = 0.806).

Results: Four predominant themes emerged from this content analysis. First, whatever the therapy, the COVID-19 pandemic did not lead to a change in the frequency of voices perceived by a majority of patients. In relation to the pandemic, depressive symptoms were more experienced by patients having followed CBT, whereas more patients having followed AT felt anxious symptoms directly caused by COVID-19. In both groups, patients expressed a positive appreciation of the therapy they had previously followed, this theme seeming more expressed by AT patients.

Discussion: According to current literature, the pandemic has increased hallucinatory symptoms in many schizophrenia patients, which was not seen in both of the groups studied. This may show that having followed CBT or AT may acts as a protective factor in the face of important stressors and that their positive impacts are maintained throughout these major events. Current literature studying the impact of the pandemic on the general population also shows that increased symptoms of anxiety are common, which is then the expected response in all individuals and may explain the increase in anxiety symptoms experienced by AT patients. However, an increase in depressive symptoms was less common in the general population, and their higher prevalence in the CBT group compared to the AT group may show the positive impact that AT has on affective symptoms when exposed to a major stressor, which was not seen with CBT.

T88. THE THERAPEUTIC PROCESSES OF VIRTUAL REALITY-ASSISTED THERAPY: A CONTENT ANALYSIS OF THE DIALOGUE BETWEEN TREATMENT RESISTANT PATIENTS WITH SCHIZOPHRENIA AND THEIR AVATAR

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Background: Several therapies have been developed to embrace the communicative aspect of the voice-hearing experience and modify how patients respond to their distressing auditory verbal hallucination (i.e., voices). Notably, these therapies use different techniques (e.g., role-play with the therapist, empty-chair work) to allow patients to engage with their voices, while increasing both awareness and understanding of their experience. As the phenomenon of voice-hearing is highly heterogeneous, these therapies require a great deal of flexibility on the part of the therapist, and variation in how they are delivered could be significant. One of these approaches, that is Virtual Reality (VR)-assisted Therapy (VRT), has gone further to enable patients to engage with an audio-visual depiction of their persecutory voices (an avatar) in real time. Such technological advances have led to large therapeutic outcomes as shown in previous trials. Though, the underlying therapeutic processes of VRT remain largely unknown. Notably, no analysis has yet been conducted to evaluate the key elements in the dialogue between the patients and their avatar. The current study therefore used mixed-method analyses to analyze the evolution of both the avatars' and patients' speech and, the changes in patients' responses as sessions of VRT progressed. The aims were thus threefold: (i) identify the main themes characterizing the avatar's and the patients' speech, (ii) observe how these themes vary over the sessions, and (iii) analyze how patients respond to each of the avatar's themes.
Methods: Eighteen patients having followed VRT were selected. A qualitative content analysis of the sessions' transcript was conducted to identify the main themes that emerged from the dialogue between the patients and their avatars. Three coders then classified each verbatim into one of the identified themes, which allowed the quantification and graphic representation of their evolution through the immersive VR sessions. The patients' responses to the utterances of their avatar were also quantified using a frequency matrix.
Results: Our analyses enabled the categorization of the avatar's discourse into confrontational techniques (e.g., provocation) and positive techniques (e.g., reinforcement). Patients responded to these latter utterances by using coping mechanisms or by expressing emotions, beliefs, self-perceptions, or aspirations. Through the identification of mutual changes in the patient-avatar interaction, a shift was observed over the sessions beginning from a more confrontational dialogue to a more constructive dialogue. Assertiveness, emotional responses, and prevention strategies seemed to be central to the therapeutic process, and these usually occurred in response to the avatar's positive techniques.
Discussion: This study allowed for a deeper understanding of the therapeutic processes underlying VRT. These findings are pertinent as investigating VRT's therapeutic process may help to identify components to achieve better therapeutic outcomes and it can also help to develop more effective treatments.

T89. UNDERSTANDING PERSONAL RECOVERY IN PSYCHOSIS: A COMPARISON BETWEEN FIRST EPISODE AND CHRONIC PSYCHOSIS

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Background: Our aim was to investigate whether personal recovery levels differ between those in the early vs prolonged phase of psychosis and if there are different associations with objective outcomes of recovery, as defined by symptom severity and level of functioning.
Methods: Data of 131 patients with early psychosis and 83 patients with prolonged psychosis was collected. The domains of the Recovery Assessment Scale were used to assess personal recovery in both samples. The MIRECC-GAF and the CGI-S were used as measures of objective recovery in the early psychosis group. The PANSS and the QoL scales were used as measures of objective recovery in the prolonged psychosis group.
Results: People with early reported better personal recovery scores in all domains except willingness to ask for help in contrast to individuals with prolonged psychosis. Markers of objective recovery were not correlated with personal recovery in the early psychosis sample, but were significantly correlated within the prolonged sample. Depressive symptoms were negatively correlated with personal recovery in the prolonged psychosis group.
Discussion: The relationship between personal and objective recovery may change over time and be dependent on the phase of illness the individual is in. As individuals experience dysfunction over time, they may be more likely to be demoralized and experience less personal recovery. This suggests the importance of promoting hope-oriented and phase-specific treatment and social connections in the early treatment of psychosis to hopefully stave off the potentially deleterious effects of becoming demoralized during the illness progression

T90. DIMINISHED POSITIVITY OFFSET AND INCREASED AMBIVALENCE – A LABORATORY-BASED INVESTIGATION OF EMOTIONAL RESPONDING IN ATTENUATED NEGATIVE SYMPTOMS

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Background: In laboratory studies, people with and without schizophrenia typically activate similar levels of positive emotion in response to pleasant stimuli, which has led to the notion that hedonic responding is intact in schizophrenia. However, a recent study (Strauss et al., The positivity offset theory of anhedonia in schizophrenia, Clinical Psychological Science, 2017, 5(2), 226-38) found that people with schizophrenia and motivational negative symptoms (NES; i.e. reduced anticipation of pleasure, avolition, asociality) showed a diminished positivity offset, i.e. they did not show the normative surplus of positive over negative emotional activation in low arousing contexts. They also showed increased ambivalence, i.e. patients co-activated positive and negative emotion more often. In another recent study, we found that diminished positivity offset and increased ambivalence were related to higher levels of psychosis proneness along the continuum of psychotic symptoms (Riehle et al., in preparation). The present study follows up on these findings to test whether attenuated negative symptoms predict reduced positivity offset and increased ambivalence and to explore to which degree alterations in emotional responding in attenuated negative symptoms are related to altered visceral responding (i.e. skin conductance response, SCR, and heart rate, HR).
Methods: Participants were 57 people with low and 46 people with high proneness for negative symptoms (scoring in the bottom or top 10%, respectively, on the Community Assessment of Psychic Experiences negative symptoms subscale). All participants completed the Clinical Assessment Interview for Negative Symptoms (CAINS) Motivation and Anticipation of Pleasure scale as a measure of motivational NES, a measure of depression, and an emotional experience task in which they rated their positive, negative, and arousal responses to pleasant, neutral, and unpleasant pictorial stimuli (i.e., “how positive/how negative/how calm/excited does this picture make you feel?”). Psychophysiological measures were taken throughout the

task. Mixed linear models (responses nested in participants) were used to test for group differences (high NES vs. low NES) in emotional responding (including ambivalence and positivity offset) and to test whether current levels of motivational NES and/or depression accounted for group differences in emotional responding.
Results: We found that high NES participants compared to low NES participants responded with diminished positive emotion (Cohen's d = -0.70) and increased ambivalence (d = 0.45) for pleasant stimuli and with diminished negative emotion (d = -0.68) and arousal (d = -0.53) as well as increased ambivalence (d = 0.39) for unpleasant stimuli. These group differences were largely accounted for by group differences in motivational NES, but were not related to depression. We did not find group differences for positivity offset. However, across groups, higher levels of motivational NES, but not of depression, predicted a diminished positivity offset. Psychophysiological data backed up the validity of the stimuli, but did not mirror the differences found between groups.
Discussion: Our findings suggest that attenuated motivational NES are associated with alterations of emotional responding, including diminished positivity offset and increased ambivalence. The latter two constructs appear to be distributed on a continuum from low to high motivational NES, making them likely vulnerability factors for amotivation in schizophrenia. The finding that self-report results were not reflected in visceral responses could indicate top-down modulation (e.g. by defeatist beliefs) of self-reported emotional experience in motivational NES.

T91. DIFFERING POSITIVE SYMPTOM PROFILES IN PSYCHOSIS: COMPARING PRIMARY VOICE-HEARERS VERSUS THOSE WITH HALLUCINATIONS ACROSS MULTIPLE SENSORY MODALITIES

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Background: There has been burgeoning interest in studying hallucinations in psychosis occurring across multiple sensory modalities. The current study aimed to characterise the positive symptom profile in patients with auditory hallucinations only versus those with multisensory hallucinations.
Methods: Participants with psychosis were partitioned into groups with voices only (AVH; n=50) versus voices plus hallucinations in at least one other sensory modality (AVH+; n=50), based on their responses on the Scale for the Assessment of Positive Symptoms (SAPS). Basic demographic and clinical information was collected, and the Questionnaire for Psychotic Experiences (QPE) was used to assess psychosis phenomenology.
Results: Relative to the AVH group, greater compliance to perceived commands, auditory illusions and sensed presences were significantly elevated in the AVH+ group. The latter group also had greater levels of delusion-related distress and functional impairment and were more likely to endorse delusions of reference and misidentification.
Discussion: This preliminary study uncovered important phenomenological differences in those with multisensory hallucinations. Future hallucination research extending beyond the auditory modality is needed.

T92. IN VIVO CHARACTERIZATION OF THE OPIOID RECEPTOR BINDING PROFILES OF SAMIDORPHAN AND NALTREXONE IN RATS: COMPARISONS AT CLINICALLY RELEVANT CONCENTRATIONS

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Background: A combination of olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM) is under development for the treatment of schizophrenia and bipolar I disorder. Samidorphan is a new molecular entity structurally related to naltrexone, but with differentiated characteristics. OLZ/SAM is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. In vitro, samidorphan binds with high affinity to mu (MOR), kappa (KOR), and delta (DOR) opioid receptors and functions as a MOR antagonist with partial agonist activity at KOR and DOR. Samidorphan binds with higher affinity to MOR, KOR, and DOR than naltrexone and functions as a more potent opioid receptor antagonist. The current studies characterize and compare the in vivo binding profiles of samidorphan and naltrexone at clinically relevant concentrations.
Methods: Two cohorts of male Sprague-Dawley rats were injected with 0.03-3 mg/kg SC samidorphan or 0.01-1 mg/kg SC naltrexone. The first cohort of rats was sacrificed to measure plasma and brain uptake. In the second cohort, thirty minutes after receiving samidorphan or naltrexone, rats were IV injected with a triple tracer of NTX-D3, naltriben, and GR103545 to measure MOR, DOR, and KOR occupancy, respectively. Brains were dissected and receptor occupancy of MOR, DOR, and KOR was measured using LC-MS.
Results: At clinically relevant concentrations, samidorphan occupied MOR, DOR, and KOR whereas naltrexone occupied only MOR and KOR. Corrected for free brain concentration, samidorphan also has higher in vivo affinity for MORs, KORs and DORs than naltrexone.
Discussion: Based on these data, samidorphan has a differentiated binding profile from naltrexone.

T93. EFFICACY AND SAFETY OF LURASIDONE IN ADOLESCENTS AND YOUNG ADULTS WITH SCHIZOPHRENIA: POOLED ANALYSIS OF DOUBLE-BLIND, PLACEBO-CONTROLLED 6-WEEK STUDIES

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Background: Onset of schizophrenia commonly occurs during late adolescence or early adulthood and is often characterized by greater illness severity, chronicity, and functional impairment with a less favorable prognosis than later onset schizophrenia.1,2 The aim of this pooled post-hoc analysis was to evaluate the efficacy and safety of lurasidone in the treatment of an acute exacerbation of schizophrenia in adolescents and young adults.
Methods: The 6 pooled studies in this analysis used similar study designs and outcome measures. Patients (ages 13-25 years) were randomized to 6 weeks of double-blind, placebo-controlled treatment with once-daily lurasidone in fixed doses of 40 mg, 80 mg, 120 mg, or 160 mg. The primary efficacy endpoint was week 6 change in the Positive and Negative Syndrome Scale (PANSS) total score; secondary efficacy endpoints included week 6 change in the Clinical Global Impression, Severity scale (CGI-S), and the PANSS positive and negative subscales; and week 6 responder rates defined as ≥20% reduction in PANSS total score. Change scores were evaluated using mixed-model repeated-measures (MMRM) analysis; responder rates were analyzed using a logistic model.
Results: The safety population consisted of 537 patients (69.8% male; mean age, 18.1 years; mean baseline PANSS total score, 95.75); 82.6% of patients completed the studies. Treatment with lurasidone was significant at all doses ($P<0.001$) for change in the PANSS total score at

Week 6 endpoint, with higher effect sizes (ES) at higher doses (40 mg, 0.53; 80 mg, 0.57; 120 mg, 0.67; 160 mg, 1.35). Significance was also observed at all doses for change in the CGI-S with medium to large effect sizes (40 mg, 0.51; 80 mg, 0.49; 120 mg, 0.57; 160 mg, 1.75). Treatment with lurasidone was significant at all doses on the PANSS positive subscale ($P<0.001$); and was significant ($P<0.001$) on all but the 120 mg dose on the PANSS negative subscale. Responder rates were significant for lurasidone 40 mg (NNT=5), 80 mg (NNT=5), and 160 mg (NNT=3), but not for lurasidone 120 mg (NNT=6). For lurasidone (combined doses), 3 adverse events occurred with a frequency ≥5% (nausea, 13.5%; somnolence, 12.1%; akathisia, 10.1%); 4.8% of patients discontinued due to an adverse event. At LOCF-endpoint, 3.6% of patients had weight gain ≥7%, and 1.5% had weight loss ≥7%. For lurasidone (combined doses), minimal median changes were observed at endpoint in metabolic lab values (cholesterol, -2.0 mg/dL; triglycerides and glucose, 0.0 mg/dL).
Discussion: In adolescents and young adults with schizophrenia, treatment with lurasidone in doses of 40-160 mg/d was a safe, well-tolerated, and effective treatment. Short-term treatment with lurasidone was associated with minimal effects on weight and metabolic parameters.
Supported by Funding from Angelini Pharma S.p.A. and Sunovion Pharmaceuticals Inc.

T94. SEASONAL ANTIPSYCHOTIC IN SCHIZOPHRENIA - OUTCOMES IN NATURALISTIC SETTINGS IN CANADA (SEASONS): REAL-LIFE RESULTS OF THE SWITCH FROM 1-MONTH PALIPERIDONE TO 3-MONTH PALIPERIDONE LONG ACTING INJECTABLE FORMULATION

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Background: Medication adherence and long-term treatment continuation are critical goals for patients' remission and recovery, requiring efficacious, well-tolerated drugs, and support of a qualified treatment team. Development of long-acting injectable (LAI) antipsychotics has led to improvement in treatment adherence and continuation. In 2016, a 3-monthly LAI formulation of paliperidone palmitate (Invega Trinza®) was introduced as a new therapeutic tool for schizophrenia treatment. This novel formulation may promote treatment continuation and engagement, both critical for patients' recovery. Yet, assessment of clinical outcomes for patients treated with Invega Trinza® in real-life settings presenting comorbidities and sometimes more complex clinical profile is warranted.
Methods: This retrospective chart review examined the first uses of Invega Trinza® in 4 sites across Canada since 2016. Broad inclusion/exclusion criteria allowed the inclusion of patients typically left out from randomized controlled trials (RCTs) (e.g. dual diagnosis, community treatment order). Primary outcome was a composite including both treatment discontinuation and psychotic relapse (defined as an increase of psychotic symptoms requiring either: i) stopping Invega Trinza® for another antipsychotic; ii) increasing Invega Trinza® dose; iii) supplementing with oral medication; iv) hospitalization).
Results: Studied population includes 180 patients, 34-year-old on average, mostly Caucasian and men (72.8% and 83.9%, respectively). At 12-months, there were 53 composite events (29.4%), including 15 treatment discontinuations (8.3%) and 38 psychotic relapses (21.1%).

Throughout the entire follow-up period, there were 71 composite events. Compared with patients who were still on Invega Trinza® at the end of follow-up (n = 109), those who relapsed (n = 52) were more frequently suffering from comorbid substance use disorder (SUD) (52% vs 25%, p = .001) and personality disorder (31% vs 12%, p = .004). Other characteristics, such as ethnicity, duration of psychotic illness, main psychiatric diagnosis, and psychopathology severity, were similar across both groups. In regard to previous antipsychotic treatment, patients had been receiving Invega Sustenna® for 2.3 years on average and only initial Invega Trinza® mean dose differed between those who relapsed and those who did not (430mg vs 381mg, p = .013).

Discussion: In a previous RCT, only 8.1% of patients receiving Invega Trinza® relapsed at 12-months. Due to major differences regarding relapse criteria, caution should be applied when comparing this relapse rate with the one herein reported. Notwithstanding this issue, this higher relapse rate may be partly explained by differences in the populations studied. First and foremost, this study was conducted in a naturalistic setting and included patients who are usually excluded from RCTs (e.g. active comorbid SUD). As such, comorbid SUD and personality disorder were both significantly associated with relapse. Second, patients recruited for RCTs differ from those for whom clinicians may judge that a 3-month LAI would be most beneficial; subjects recruited in RCTs are typically collaborative patients, relatively free of comorbidity and show higher adherence level to any therapeutic approach. While adequate compliance to Invega Trinza® treatment was thoroughly documented in the present study, adherence to other pharmacological and non-pharmacological treatments, such as psychotherapy, was not. Although other components of this study are still ongoing, results available so far highlight the importance of considering population characteristics included in RCTs before generalizing findings to real-life clinical settings.

T95. OPTIC: OFFERING PATIENTS THERAPEUTIC INFORMATION ABOUT CLOZAPINE, A SHARED DECISION-MAKING TOOL

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Background: Patients suffering from treatment resistance schizophrenia (TRS) often have an inadequate clinical response and a less favorable functional outcome. Therefore, it is important to use the most effective treatment available. Although clozapine has proven benefits in treating TRS compared to other antipsychotics, it is only prescribed in less than 50% of eligible patients. Clozapine's list of side effects and blood monitoring requirements give it a negative reputation amongst patients and some physicians. The primary focus of the OPTIC (Offering Patients Therapeutic Information about Clozapine) tool is to facilitate a balanced discussion between clinicians and patients that emphasizes the benefits of clozapine as the gold standard treatment for TRS. When clinicians are confident that clozapine is the best treatment for their patients, their genuine approach to offering clozapine will be better received. The OPTIC shared decision-making tool guides clinicians on how to discuss the important information surrounding clozapine acceptance, initiation and adverse effects with their patients.

Methods: A thorough literature review was performed to gain insight on clozapine, its effects and common barriers to its prescription for clozapine eligible patients suffering from TRS. The information obtained was compiled and presented in a comprehensive and succinct fashion to help guide the clinician-patient discussion. Based on both literature and clinical experience, various communication methods and different approaches are suggested throughout the document.

Results: The OPTIC tool is composed of three parts, a clinician information handout, a patient handout and patient questionnaire. The clinician handout discusses the benefits of clozapine in TRS, how to offer clozapine to patients as well as how to best manage the side effects with lifestyle changes and medications. There is also a guide to initiating clozapine. The two patient focused parts were developed to assist patients in deciding if clozapine is right for them. The patient handout clearly highlights the benefits of clozapine compared to other treatments for TRS and discusses how clozapine's side effects can be managed. The clinician administered questionnaire uses motivational interviewing concepts to guide the iscussion thereby allowing the patient to reflect on their treatment goals and determine if clozapine is suited to help them. These documents educate patients on the benefits of well-managed schizophrenia, making them more receptive when they are offered clozapine. It is also hoped that if patients, even if psychotic, better understand their treatment options, they will be more engaged in their overall care.

Discussion: OPTIC provides the necessary information to initiate a balanced discussion between clinician and clozapine eligible patient. It changes the conversation from a list of clozapine's many side effects to a discussion about how its benefits on reducing TRS symptoms significantly outweigh its side effects. The main objective is for clozapine to be adequately offered systematically to people with TRS as soon as they become eligible. This tool can facilitate a positive offer and increase acceptance of clozapine. The OPTIC tool has not yet been distributed as it was just recently completed, therefore its impact on clozapine prescription rates among eligible patients cannot be measured at this time. The three components of the OPTIC shared decision-making tool will be presented as part of this poster presentation.

T96. A TWO-WAVE NETWORK ANALYSIS OF COVID-19'S IMPACT ON SCHIZOTYPAL TRAITS AND MENTAL HEALTH

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Background: The novel coronavirus (COVID-19) pandemic has negatively impacted the livelihoods of many individuals globally. This naturalistic stressor being the 'pandemic' may be an opportunity to shed light on how stress impacts people's mental health – in particular, whether levels of paranoia/schizotypal traits are increased during times of uncertainty. There is longitudinal evidence showing that early childhood life stressors predict psychosis (Varese et al., 2012) and schizotypal traits and externalising problems (Wong & Raine, 2019) in adulthood. These findings are replicated cross-sectionally and for both genders and ages (Barrantes-Vidal et al., 2013; Le et al., 2020).

Holmes et al's (2020) April position paper on COVID research spawned a slew of psychological studies reporting poor mental health in key sub-groups (e.g., keyworkers/BAME) and populations across countries. These studies focus on prevalence rates and account for background confounders, but most do not control for comorbid mental health variables and are limited to short time-lagged designs that do not inform longer-term changes and effects of COVID. Several studies have addressed this comorbidity issue using network analysis, which maps all relationships between variables relative to other variables in the whole network - yet the narrow focus on mental health variables (anxiety/depression) is limited (Hung et al., 2020; Jia et al., 2020).

This study applies network analysis to test the relationship between paranoia/schizotypy and psychopathology. Understanding how mental health variables relate to paranoia/schizotypal

traits during the pandemic may inform how resources should be directed to help individuals and develop targeted interventions in the future. We hypothesize that paranoia/schizotypal traits will be positively related to internalising/externalising problems across ages and gender. However, stronger networks will be found in younger than in older people due to youths self-reporting higher levels of mental health issues overall.

Methods: Participants (M=36.4, SD=13.53; range=18–89 years) from Wave 1 (N=1559) and 2 (N=1000) of the UCL-Penn Global COVID Study (Wong et al., 2020) completed a 30-minute online survey on the study website (GlobalCOVIDStudy.com). This convenience sample is not representative of the population and are from the countries with N >50 (UK, Greece, Italy, USA, HK). The survey assessed participant's background variables, levels of schizotypy, paranoia, anxiety, depression, aggression, loneliness and stress. Complete data on all variables of interest were used in our network analyses (in R) which were compared across ages (=<35 years, >=35 years) and gender.

Results: All variables were positively related in the expected way, such that higher levels of paranoia/schizotypy were associated with poorer mental health, specifically with levels of loneliness (Wave 1). For age, network structures were not different (M=0.10, p=0.58) but a network invariance test by age suggests stronger connections in the older (S=0.63, p=0.02) than the younger group. In terms of gender, both network structures (M=.08, p=.95) and connections (S=.02, p=.95) were not significant.

Discussion: This network analysis study demonstrated that general psychopathology, particularly loneliness, was strongly associated with paranoia/schizotypal traits, though this did not differ by gender. Contrary to prediction, network strengths were stronger in older than in younger individuals, suggesting strong inter-node network connections. Replication of findings in Wave 2 awaits. Our study relies on self-report which may have inflated observed relationships but this is the first COVID study examining the mental health-schizotypy relationship.

T97. EXPLORING SLEEP, SOCIAL ANXIETY, AND SOCIAL SKILLS DURING SOCIAL INTERACTIONS IN PSYCHOSIS

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Background: Sleep problems, such as trouble initiating or maintain sleep, have been associated with social anxiety (Cox & Olatunji, 2020; Cox & Olatunji, 2016; Horenstein et al., 2019; Kushnir et al., 2014; Pires et al., 2016). However, findings are mixed and there is limited research exploring this relation in adults with psychosis. Social anxiety disorders are one of the most common comorbid anxiety disorders in people with schizophrenia, with both disorders showing similar characteristics, such as poor social skills, fear, avoidance, and withdrawal of social situations (Sutliff et al., 2015). In the general population, sleep problems are associated with worse social interactions with others (Gordon et al., 2017) and lead to behavioral consequences, such as social withdrawal (Simon & Walker, 2018). Recent literature has found sleep disturbances and sleep related impairments are associated with several social domains in individuals with psychosis, such as worse community functioning (Blanchard et al., 2020). However, this study did not explore social skills, which are essential in effective social interactions. Previous studies have shown that persons with schizophrenia demonstrate social skills deficits, but few studies have examined this deficit in persons with psychosis (Blanchard et al., 2015).

To address the gaps in the literature, the current study will explore how sleep problems and social anxiety relate to social skills in persons with psychosis. We hypothesized that 1) greater sleep problems are related to greater social anxiety, and 2) greater sleep problems and social anxiety contribute to lower ratings of social skills during an affiliative task.

Methods: Data were collected from a transdiagnostic sample of adults with psychosis (N = 119). We used the PROMIS™ Sleep Related-Impairment-Short Form and Sleep Disturbance-Short Form scales (Yu et al., 2012) to measure sleep problems. For social anxiety, we used the Social Interaction Anxiety Scale (Heimberg et al., 1992). To measure social skills, participants were first asked to watch a short video of a female confederate sharing activities that she enjoys doing during her free time. At the end of the video, participants were asked to respond as if they were talking to this person in real life. Using a social skills rating manual, raters coded the participants' video recorded response to the confederate on overall social skills (Garcia et al., 2018).

Results: Multiple regression analyses were conducted to explore the relation between sleep disturbance, sleep impairment, and social anxiety. Sleep disturbance and sleep-related impairment were significantly associated to social anxiety $F(2, 116) = 16.78$, $p < .001$, $R2 = .22$. Multiple regression analyses used to test our second hypothesis investigating the association of social skills with sleep disturbances, sleep impairment, and social anxiety, were not significant.

Discussion: Our first hypothesis examining the relation between sleep-related impairment and sleep disturbance on social anxiety was supported. These findings contribute to the existing literature that sleep problems contribute to symptom severity in social anxiety and extends it by using a sample of adults with psychosis. This points to the importance of treatments targeting sleep problems in this population, as they might serve to reduce symptoms of social anxiety. Our second hypothesis was not supported, future studies should explore how these variables independently relate to social skills, as social deficits are considered to be a common deficit in persons with psychosis.

T98. PARANOIA AND TRUSTWORTHINESS: AN EYE TRACKING STUDY ON THE NON-CLINICAL SAMPLE

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Background: Paranoia, unfounded belief that other people have malevolent intentions, refers to symptoms spanning across the continuum from the healthy population to people with identified mental illness. Current theoretical models of the persecutory delusions proposed importance of various social - cognitive biases as a risk factor for the development and maintenance of delusional ideas. Previous studies have suggested that people with high levels of paranoia showed aberrant perception of the face and have difficulties in the emotion recognition from facial expression. In the current study, we plan to test, whether paranoia in the non-clinical sample is related to the perception of the trust from the neutral facial expression. Secondary aim is to evaluate if eye - tracking parameters - number of fixations on salient feature of face (eyes and mouth) are related to paranoid beliefs and trustworthiness rating.

Methods: The sample consisted of 25 participants without history of mental illness validated with the Mini International Neuropsychiatric Interview. Mean age was M=32.12, SD=11.38.

60% of sample were females. Paranoia was measured with Paranoia Scale, Perception of trust from the neutral facial expression was measured using 24 pictures of people (balanced for age: young, middle age, elderly; and gender). Stimuli were presented for 2.5 seconds. Eye movements were measured via Tobii X-120 eye tracking device. Areas of interest (AoI) around eyes and mouth were constructed for each stimulus separately. Mean number of fixations per region across trials was used in the further analysis. Due to non - normal distribution of some variables, 95% CI for correlation coefficients were calculated using bias - corrected bootstrap method on the 5000 samples.

Results: We found that severity of the paranoia was related to perception of faces as less trustworthy (r=-0.399, p=0.048, 95CI [-0.001; -0.628]). Perception of faces was not related to number of fixations on the eyes (r=0.001, p=0.997) or mouth area (r=288, p=0.163). Paranoia severity was positively associated with number of fixations on the eyes (r=0.421, p=0.036, 95% CI [0.027; 0.691]).

Discussion: Our preliminary results supported association between subclinical levels of paranoia and social - cognitive biases. In line with our expectation, highly paranoid healthy people tend to perceive neutral faces as less trustworthy. We also found that they allocated much more attention to the area around eyes. Paranoia is thus related to intensive scanning of salient feature of the face. Simultaneously we found no evidence of associations between the number of fixations on salient face areas and ratings of trustworthiness in non-clinical sample. Other variables than visual attention to faces are crucial for making social trait judgements in healthy people.

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T99. OBSESSIVE-COMPULSIVE SYMPTOMS AND THEORY OF MIND IN PSYCHOSIS

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Background: Prior research has demonstrated a negative relationship between social cognition and obsessive-compulsive symptoms (OCS) in various stages of schizophrenia (SCZ), although a majority of the literature has focused on first-episode psychosis patients. The goal of the current study was to examine the relationship between OCS and social cognition at various stages of psychosis, from clinical high risk (CHR), to first episode psychosis (FEP), to SCZ. We hypothesized that OCS would be negatively correlated to Theory of Mind (ToM) at each stage. In exploratory fashion, we also compared the strength of the OCS-ToM relationship between stages.

Methods: Participants were 52 teenagers at CHR (14-19yo), 35 young adults with FEP (18-25yo), and 49 adults with SCZ (21-55yo) enrolled in a larger cognitive training study. This cross-sectional assessment at baseline included the Yale-Brown OCS scale (Y-BOCS), Hinting Task (ToM), and PANSS/SOPS (symptoms). Non-parametric correlations between OCS and ToM were calculated for each stage of psychosis. Strength of correlations between psychosis stages were evaluated using Fisher r-to-z transformation.
Results: While CHR reported much greater OCS on the Y-BOCS than FEP or SCZ (F=57.815, p=0.000), they demonstrated nearly perfect ToM on the Hinting Task (total score max is 20; M=18.53, SD=1.21). In terms of OCS-ToM correlation, there were significant negative correlations between the Y-BOCS and Hinting Task in FEP (rho=-0.21, p=0.035) and SCZ (rh0=-0.28, p=0.012), while no such correlation was found in CHR (rho=0.07, p=0.691). The strength of the OCS-ToM negative correlation in SCZ was greater than in FEP (Fisher r-to-z transformation: Z=1.70, p=.042).
Discussion: We found significant negative correlations between OCS and ToM in FEP and SCZ, but not in CHR. This may be due to ceiling effects on Hinting Task scores in CHR and the significantly higher score on the YBOC compared to other stages of psychosis. CHR participants scored in the moderate range for YBOC, while FEP and SCZ were within the mild range. The relationship between ToM and OCS was stronger in SCZ than FEP. However, since these results are cross-sectional, they cannot establish a causal relationship between the progression of OCS and ToM scores across stages of psychosis. Nevertheless, results replicate previous findings that the presence of OCS is linked to decreases in social cognition in SCZ. Furthermore, they replicate prior findings that some SCZ patients may experience increased OCS in early stages as a form of prodromal SCZ. This suggests that the CHR population, especially those with OCS, should be targeted for earlier, preventative measures. Additional work is needed to investigate a longitudinal relationship between OCS and ToM in those with psychosis as well as possible effects of cognition on ToM.

T100. THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT): PSYCHOMETRIC AND VALIDATION DATA IN SUPPORT OF AN ACCEPTED APPLICATION FOR THE FDA CLINICAL OUTCOME ASSESSMENT QUALIFICATION PROGRAM

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Background: The FDA requires drug developers focused on cognitive improvement in schizophrenia to demonstrate the functional relevance of any improvements with a co-primary measure of functional capacity. The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) uses a realistic simulated environment to create a series of routine activities of daily living. The FDA recently accepted the VRFCAT into its Clinical Outcome Assessment (COA) Qualification Program as a co-primary measure of functional capacity in schizophrenia. This program is intended to qualify COAs that can be relied on to have a specific interpretation and application in any drug development program and regulatory review. This presentation describes data supporting the successful application for the VRFCAT to enter into the FDA COA Qualification Program and reports on recent developments in the validation and implementation of the VRFCAT.

Methods: The VRFCAT is a digital performance-based outcome measure that assesses the ability to prepare a meal, shop, use transportation, and handle money, four of the key functional outcome challenges in schizophrenia. It is one of only four Psychiatry COAs that have been accepted into the FDA Qualification Program. Following a series of method development studies, data were collected in a large (N=334) psychometric and validation study of the VRFCAT in primarily chronically ill patients with schizophrenia and healthy controls that also assessed participants with the MATRICS battery (MCCB) and the UCSD Performance-based Skills Assessment (UPSA), a conventional measure of functional capacity. Complementary studies subsequently examined the VRFCAT's latent structure, convergent validity in recent-onset patients, and sensitivity to treatment effects in schizophrenia. Results from all four of those studies will be presented here.
Results: In a large study of primarily chronically ill patients, the VRFCAT demonstrated high sensitivity to impairment in patients vs. healthy controls (d=1.2), high test-retest reliability (ICC=0.81), minimal practice effects (d=-0.04 compared to d = 0.35 for the UPSA), and large correlations with the MCCB (r = −0.57) and UPSA (r=−0.56). Regarding latent structure, the best fitting models indicated the VRFCAT and the MCCB each reflected separable unidimensional factors whereas the UPSA and MCCB shared a single factor. In recent-onset patients, the VRFCAT demonstrated a large patient vs. control difference (d = .82) and large correlations with the MCCB (r = - .70) and UPSA (r = -0.66), as well as strong correlations with real-world role (r = -.52) and social (r= -0.41) functioning. Regarding treatment sensitivity, a RCT of computerized social cognition training found that social cognition and VRFCAT performance showed training-related improvements, whereas UPSA performance did not.
Discussion: The VRFCAT demonstrates good psychometric characteristics, strong convergent validity evidence, and practical strengths in early and late phases of schizophrenia. The FDA requires additional data analyses and further data collection to support a full qualification package submission. At this stage, we have completed a normative study of the VRFCAT in over 650 healthy adults (18 to 80+ years old), as well as translation and cultural adaptations for over 25 languages. We will also report progress from on-going efforts that include a content validation study of the VRFCAT using qualitative methods in patients and caregivers, evaluation of the VRFCAT's psychometrics in a large multi-site RCT, and the roll-out of a remote assessment version of the VRFCAT.

T101. EXAMINING THE EFFICACY OF COGNITIVE REMEDIATION FOR SCHIZOPHRENIA-SPECTRUM DISORDERS DELIVERED THROUGH VIRTUAL CARE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Individuals with severe mental illnesses such as schizophrenia-spectrum disorders are among the most affected by the COVID-19 pandemic. Cognitive remediation (CR) is an effective treatment for schizophrenia. However, social restrictions associated with COVID-19 have made delivering in-person CR problematic, as most services have moved to virtual delivery. Yet, the evidence-base for virtual delivery of CR is limited and it is unclear how effective virtual delivery of CR is. Thus, we sought to examine 1) the extent to which virtual delivery of CR has been examined and any adaptations required for virtual delivery; and 2) determine the efficacy of virtual-CR.

Methods: This review was pre-registered in the PROSPERO database (CRD42020189460). A literature search was conducted following PRISMA guidelines using four databases, Ovid, MEDLINE, EMBASE, and PsycINFO from January 1990 to May 2020. To be included in the review, studies had to meet the following criteria: 1) At least 50% of participants were diagnosed schizophrenia-spectrum disorders, 2) the treatment delivered was CR, 3) CR must be delivered by some form of remote method that was not in-person, and 6) only full papers (no conference abstracts or clinical trial registrations) were selected.
Results: Seven studies (N = 418) met inclusion criteria for virtual-CR. The studies utilized a variety of training approaches to CR including working memory training and perceptual training. Only one study directly compared at-home iPad-based CR to CR delivered in-person in a laboratory setting and this was a non-randomized trial. The primary outcome measures assessed were neurocognition and functioning. When raw change was analyzed, without reference to a comparison condition, virtual-CR produced moderate effects on neurocognition (g=0.34) and functioning (g=0.33).
Discussion: Few studies have examined the efficacy of virtual-CR, however, preliminary evidence suggests that effect sizes on both neurocognition and functioning are similar to when CR is delivered in-person (neurocognition g = 0.45, functioning g = 0.37). As a primary focus of in-person CR is computerized practice of cognitive training, this component was most commonly used in virtual delivery, however, other therapeutic components of CR such as strategy monitoring and generalizing to the real world were less commonly used virtually. Limited evidence thus far suggests that virtual-CR may be effective, however, further research is required to directly compare virtual-CR to in-person CR and examine the long-term follow-up effects of virtual treatment.

T102. INTROSPECTIVE ACCURACY FOR SOCIAL COMPETENCE IN SCHIZOPHRENIA

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Background: Deficits in introspective accuracy (IA), the ability to accurately estimate one's own abilities and skills, have been identified in schizophrenia across social cognitive and neurocognitive domains. Importantly, this discrepancy between self-assessment and objective performance has been identified as a better predictor of functional outcome than objectively measured ability and informant reports of functioning. The purpose of the current study was to examine if these findings extend to more discrete domains of IA, specifically IA for social competence.
Methods: 55 individuals with schizophrenia and 69 healthy comparison participants completed the SSPA roleplay assessment to objectively assess social skills. After completion, participants evaluated their performance on discrete aspects of social skill (e.g., fluency, focus, affect, etc.). An independent expert rater also scored their performance on the task. Introspective accuracy (IA) was conceptualized and calculated as the discrepancy between self-reported and objective scores (self-report – objective score). IA was compared between patients with schizophrenia and healthy controls. Additionally, an informant rated participants' social functioning on the specific levels of functioning (SLOF) scale.
Results: A 2 (Task Type: self-report vs. objective score) x 2 (Group: SCZ vs. HC) RM ANOVA revealed both a significant main effect of group ($F=46.86$, $p<.001$) and a significant interaction effect ($F=8.38$, $p=.005$), indicating that both groups showed impairments in IA. Discrepancy scores revealed that patients tended to overestimate their performance on the task ($M=.13$, $SD=.64$) whereas healthy controls underestimated their performance ($M=-.16$,

SD=.49). Patients also showed poorer social functioning, and importantly, IA was identified as a significant predictor of functioning in interpersonal relationships in the patient group (r^2= .089, F=5.197, p=.027, B=.299).
Discussion: Results from the current study support a growing body of literature indicating that introspective accuracy is impaired in schizophrenia and in healthy populations, but in opposite directions. These findings suggest that individuals with schizophrenia overestimate their social competence, which may negatively impact interpersonal relationships. Thus, accurate self-evaluation of social skill ability should be considered in interventions aimed at improving social functioning in this population.

T103. 'MINDS@WORK': NOVEL INTEGRATIVE MANUALIZED INTERVENTION IMPROVING JOB TENURE IN PSYCHOSIS

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Background: Only a small proportion of individuals living with psychosis satisfactorily maintain employment, despite the majority of them wishing to work. Previous studies have repeatedly demonstrated the multiple individual and societal benefits of work for people living with psychosis. Based on a systematic literature review from our group, we synthesized results using the logic models methodology and developed a new manualized integrative group intervention aimed at improving job tenure in severe mental illness, such as psychosis and schizophrenia. We tested this new psychosocial intervention in a real-world work setting in collaboration with social firms in Quebec, Canada.
Methods: We conducted a pilot study aimed at verifying the feasibility, acceptability and preliminary efficacy of our new psychosocial group intervention for job tenure in severe mental illness. We used a multiple case study design over 15 weeks (3 weeks pre-intervention, 9 weeks intervention, 3 weeks post-intervention). In total, 5 participants completed the study and filled 8 self-reported questionnaires every week, which measured: motivation to work and maintain employment, cognitive biases and subjective cognitive complaints, socioemotional skills, work-related self-efficacy, and satisfaction of the basic psychological needs under the self-determination theory (i.e., autonomy, competence, social affiliation). Two follow-up phone interviews were conducted at 3- and 6-month post-intervention. Participants were employees of two collaborating social firms in Quebec, Canada, and the co-facilitators of the group were psychosocial workers employed by the organizations. Statistical analyses were conducted using linear mixed effect models for repeated measures.
Results: Preliminary analyses of qualitative data suggest that the intervention is acceptable by both workers and immediate supervisors, and that its implementation in social firms is feasible. Quantitative results provide preliminary evidence for the efficacy of our intervention with workers significantly reporting greater motivation to keep their job and greater feeling of self-efficacy to plan and secure their career. Satisfaction of basic psychological needs also appears to have significantly improved over the course of the intervention. Analyses further indicate a significant decrease in cognitive biases and subjective cognitive complaints, as well as significant improvements in emotion recognition and empathy. Follow-up interviews revealed that 2 participants maintained employment, and that the other 3 preferred to suspend their job seeking efforts following the end of their work experience in social firms because of the COVID-19 pandemic.

Discussion: Our novel psychosocial intervention capitalizes on putative mechanisms of action to address identified predictors of job tenure. A detailed accompanying manual provides exercises that can be personalized to participants' experiences and is readily usable by various work stakeholders (e.g., job coaches, workers of supported employment programs, psychologists). Pilot results are encouraging, which warrants further validation. This work complements current supported employment programs and it would be of great interest to verify its adaptability to other populations (e.g., return-to-work following a leave of absence due to common mental illness).

T104. EFFECT OF BREXPIPRAZOLE ON FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA: POST HOC ANALYSIS OF SHORT- AND LONG-TERM STUDIES

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Background: Deficits in psychosocial functioning are a core feature of schizophrenia. Although antipsychotics are efficacious in treating positive symptoms, patients may remain functionally impaired due to persistent negative and cognitive symptoms. Side effects of antipsychotics can also contribute to impaired functioning. Clinical guidelines emphasize that improving functioning in the acute phase, and maintaining or improving functioning in the maintenance phase, should be key goals of schizophrenia management.
The aim of the present post hoc analysis was to evaluate the short- and long-term effects of brexpiprazole on patient functioning. Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, and an antagonist at serotonin 5-HT2A and noradrenaline alpha1B/2C receptors, all with subnanomolar affinity. The efficacy and safety of brexpiprazole for the treatment of schizophrenia have previously been demonstrated.

Methods: Data were included from three 6-week, randomized, double-blind, placebo-controlled studies (Vector [ClinicalTrials.gov identifier: NCT01396421], Beacon [NCT01393613], and Lighthouse [NCT01810380]); a 52-week, randomized, double-blind, placebo-controlled maintenance treatment study (Equator [NCT01668797]); and two 52-week, open-label extension (OLEx) studies (Zenith [NCT01397786] and Study 14644B [NCT01810783]). All studies enrolled patients aged 18–65 years with an acute exacerbation of schizophrenia (DSM-IV-TR criteria). Patients allocated to oral brexpiprazole received 2–4 mg/day (short-term studies) or 1–4 mg/day (long-term studies).
The present analysis focused on functioning outcomes, measured using the Personal and Social Performance (PSP) scale (short-term and OLEx studies) and Global Assessment of Functioning (GAF) scale (maintenance study).

Changes from baseline in PSP score and PSP domain scores were analyzed using a mixed model repeated measures approach for short-term data and were summarized using descriptive statistics for long-term data. Change from baseline in GAF score was calculated using an

analysis of covariance model. Cohen's d effect sizes were also determined. Functional response and remission rates were calculated, along with the number needed to treat (NNT) to achieve response or remission. Functional response was defined as an increase in PSP or GAF score ≥10 points, and remission as PSP score ≥71 or GAF score ≥61.

Results: Brexpiprazole (n=831) showed greater improvement than placebo (n=490) from baseline to Week 6 in PSP score (least squares mean difference, 3.20; 95% confidence interval, 1.82–4.58; p<0.0001; Cohen's d=0.31), and in all four PSP domains. In the maintenance study, GAF score improved during stabilization with brexpiprazole, and was maintained for patients subsequently randomized to brexpiprazole, but worsened for those randomized to placebo. At Week 52, GAF functional remission was achieved by 65.3% (62/95) of stabilized patients randomized to brexpiprazole, and 47.1% (48/102) of stabilized patients randomized to placebo, with an NNT of 6 (95% confidence interval, 4–22; p=0.0076). At Week 52 of the OLEx studies (n=177), PSP functional response and remission were achieved by 84.2% and 41.8% of patients receiving brexpiprazole, respectively.

Discussion: Brexpiprazole treatment was associated with clinically relevant improvement in functioning among patients with acute schizophrenia, and maintenance of this improvement in stabilized patients. High rates of functional response and remission suggest that brexpiprazole may assist with functional recovery, as well as reducing symptoms of schizophrenia.

T105. METACOGNITION ACROSS PROFILES OF CLINICAL AND COGNITIVE INSIGHT IN PROLONGED SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Clinical insight is the recognition of psychopathology, loss of function, or impairments in mental processes in relation to changes in the trajectory of a person's life. In the context of psychosis, when clinical insight is poor, individuals engage less with treatment, have poorer therapeutic alliance with clinicians, and experience greater symptom severity. When clinical insight is good, depression and demoralization can follow, especially when a person experiencing stigma or social disadvantage, as well as reduced quality of life.

The study of clinical insight in severe mental illness has become more nuanced in recent years, and multiple domains of insight are now regularly examined. Cognitive insight refers to people's abilities to recognize changes in their own thoughts and beliefs. Like clinical insight, cognitive insight is important in the context of psychosis because of the clinically relevant correlates when present at low or high levels. When cognitive insight is poor, it is associated with the presence of delusions in people with schizophrenia and at-risk groups, more severe symptoms during first episodes of psychosis, and poorer outcomes from cognitive remediation. When cognitive insight is good, it is associated with depression, poorer sense of personal recovery, and reduced quality of life.

If clinical and cognitive insight covary, the conditions under which people are likely to have both low clinical and cognitive insight should be identified. Doing so could have practical implications for engaging people who struggle to make sense of and manage their recovery. Mixtures of high and low cognitive and clinical insight might lead to different treatment strategies or the development of different interventions.

Methods: A median-based form cluster analysis that is robust to outliers was used to identify groups in the data. We considered the number of groups that were theoretically interpretable, whether there was an even distribution in the sample, and where the clusters had an efficient reduction of the within-group variance in clinical and cognitive insight. We also characterized each group with regard to levels of neurocognition, social cognition, and metacognition. We confirmed the relevance of the clusters and characterized the groups using Kruskal-Wallis tests and post hoc Dunn's tests, with all tests using false discovery rate corrections for multiple comparisons.
Results: Three groups emerged and based on multiple comparisons were ranked as high clinical and cognitive insight, high clinical insight and low cognitive insight, and low clinical and cognitive insight. There were large main effects for the cognitive insight ($H(2) = 61.57$, p. adj. $< .001$), self-reflection ($H(2) = 30.79$, p. adj. $< .001$), and self-certainty ($H(2) = 20.46$, p. adj. $< .001$). There was also a large main effect for clinical insight ($H(2) = 64.42$, p. adj. $< .001$), but not overall psychopathology ($H(2) = 2.13$, p. adj. $= .421$). There were no main effect for neurocognition or social cognition. There was a moderate main effect for metacognition in terms of self-reflection ($H(2) = 11.46$, p. adj. $= .007$), a large main effect for understanding others' minds ($H(2) = 17.36$, $p < .001$), as well as a moderate main effect for decentration ($H(2) = 8.57$, $p = .029$) and total metacognition ($H(2) = 13.22$, p. adj. $= .004$). There was no main effect for mastery of psychological problems ($H(2) = 3.69$, p. adj. $= .268$). Multiple comparisons for metacognition indicated that the lowest ranked group differed from the others in that they had poor metacognition.
Discussion: This study indicates that low levels of metacognition might lead to the confluence of low clinical and cognitive insight. Interventions targeting metacognition may be of particular use for this group.

T106. EXAMINATION OF POOR SLEEP QUALITY ON SUBJECTIVE WELL-BEING AND OBJECTIVE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia are affected with sleep disruptions, with 30-80% of patients reporting difficulties (Cohrs, 2008). Poor sleep quality has been related to symptom severity in schizophrenia (Afonso et al., 2014) as well as quality of life and coping (Hofstetter et al. 2005). Severity of negative symptoms as well as mood symptoms such as depression have also been found to be related to quality of life (Huppert et al. 2001) and psychological well-being in patients with schizophrenia (Strauss et al., 2012). The objective of the present study was to investigate the impact of sleep quality in patients with schizophrenia and to explore whether poor sleep quality contributed to subjective measures of well-being and objective measures of functioning independent of symptom severity.
Methods: Data was collected from 67 outpatients with a diagnosis of schizophrenia or schizoaffective disorder who completed a baseline assessment for a study of cognitive remediation (Clinical Trial # NCT 00995553). Symptom severity and sleep quality were assessed with the Brief Psychiatric Rating Scale (BPRS) and the Pittsburgh Sleep Quality Index (PSQI). Well-being was measured with participant report on the Basic Psychological Needs Scale (BPNS) and the Measure of Insight into Cognition (MIC-SR). Self-reported community functioning was measured with the Social Functioning Scale (SFS). Objective functioning was assessed with the MATRICS Consensus Cognitive Battery (MCCB), the Social Skill Performance Assessment (SSPA), and the University of California Performance-Based Skills Assessment (UPSA).

Results: Over half of the sample reported having poor sleep quality. Sleep quality and mood symptom severity were related to each other and were found to be related negatively to frequency of perceived cognitive problems, psychological well-being, and self-reported effectiveness in interpersonal interactions on the SFS. Regression analyses revealed that sleep quality (β = -.37, p = .003) but not mood symptoms made an independent contribution to the prediction of perceived cognitive problems, R2 = .19, F(2, 64) = 7.25, p = .001. With regard to psychological well-being, both sleep quality (β = -.35, p < .01) and mood symptom severity (β = - .30, p = .01) made significant contributions to the prediction of BPNS Relatedness, R2 = .29, F(2, 64) = 12.82, p < .01. Likewise, both sleep quality (β = -.30, p = .01) and severity of mood symptoms (β = .34, p < .01) were predictive of self-reported effectiveness in interpersonal interactions on the SFS, R2 = .28, F(2, 64) = 12.33, p < .01. With regard to other aspects of well-being, severity of mood symptoms (β = -.32, p = .01) was the only significant independent predictor of BPNS Competence, R2 = .18, F(2, 64) = 6.99, p < . 01, while sleep quality (β = -.25, p = .05) was the only significant predictor of BPNS Autonomy, R2 = .14, F(2, 64) = 5.34, p = .01. Unexpectedly, sleep quality was not significantly related to MCCB Composite Score, self-reported engagement with leisure activities or activities of daily living on the SFS, or observed performance on the UPSA and SSPA.
Discussion: Findings suggest that sleep quality is a significant contributor to psychological well-being and perception of cognitive functioning. Sleep quality made a contribution to patient functioning in these domains that was independent of the severity of depression and anxiety. Surprisingly, self-reported sleep quality was not related to objectively measured cognitive and social functioning. Our findings indicate that poor sleep quality is prevalent among individuals with schizophrenia and compromises their subjective well-being. Results suggest that treatment of schizophrenia might be improved through routine assessment of sleep quality.

T107. A COMPARATIVE LINGUISTIC ANALYSIS OF NARRATIVES PRODUCED BY INDIVIDUALS AT HIGH- VS. LOW-RISK FOR PSYCHOSIS DURING COVID-19

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Background: COVID-19 has had a drastically negative effect on mental health in the general population. Increased overall levels of depression, anxiety, stress, loneliness, and psychosis-like symptoms have been documented since the start of the pandemic. In order to gain a better understanding of the elevation in psychosis-risk among the general population, we examined narratives written by both high and low psychosis risk individuals reflecting on the pandemic. Linguistic analysis has proven to be an effective method of understanding internal processing and emotions.
Methods: 430 respondents completed an anonymous, online survey evaluating mental, social, and physical wellbeing. Mental health was assessed by the Depression, Anxiety, and Stress Scale (DASS); the UCLA Loneliness Scale, and the Prodromal Questionnaire-16 (PQ-16). Social wellbeing was assessed by the Social Network Index (SNI). Respondents completed a series of questions on demographics, physical health, previous out of body experiences or auditory hallucinations, and past trauma. Participants were asked to write up to 10 lines of text reflecting on how COVID-19 has affected them, their families, friends, and communities. Resulting narratives were analyzed using the Linguistic Inquiry and Word Count Program (LIWC). LIWC generates basic linguistic variables, such as % of “I” words, social words,

positive and negative emotions, and cognitive items. LIWC also generates 4 variables on writing style: analytic, clout (confidence), authenticity, and emotional tone.
Results: Of the total respondents, 18.4% met criteria as being high-risk for psychosis (Ising et al., 2012), while 81.6% were categorized as low-risk. High-risk respondents reported auditory hallucinations and out of body experiences at a significantly higher rate, further validating their elevated risk status. There was no significant difference between groups in total word count, but the two groups differed significantly in LIWC emotional tone and negative emotion scores. High-risk individuals produced more negative emotion words, and negative emotion word frequency was associated with increased PQ distress scores. The mean number of positive emotion words was inversely correlated with increased PQ distress scores. Emotional tone was correlated with increased PQ total scores as well as distress scores. There was a significantly increased report of past history of trauma in high-risk individuals ($p<0.001$). High-risk participants also reported significantly more loneliness and reduced social networks. Finally, high-risk respondents showed increased depression, anxiety, and stress on DASS compared to the low-risk group.
Discussion: Participants at higher risk for psychosis had significantly worse mental health overall. Automated text analysis suggests there are differences in both writing style and content that reflect the inner psychological states of those suffering from symptoms of psychosis or poor mental health. Future research should explore these differences further by comparing other variables (such as word use) between those at high- and low-risk for psychosis. In addition, drawing parallels between high-risk individuals and individuals with diagnosed psychosis may also reveal important information about the relationship between linguistics and psychotic symptomatology.

T108. CLINICIAN-REPORTED PATIENT AWARENESS OF SYMPTOMS AND SEVERITY OF TARDIVE DYSKINESIA IN PATIENTS WITH SCHIZOPHRENIA/SCHIZOAFFECTIVE DISORDER TREATED WITH A VMAT2 INHIBITORS

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Background: Since antipsychotic therapy (often long-term) is an important aspect of schizophrenia management, patients with schizophrenia spectrum diagnoses are at risk for developing drug-induced movement disorders associated with dopamine blockade, including tardive dyskinesia (TD). Vesicular monoamine transporter 2 (VMAT2) inhibitors such as valbenazine (approved for treating TD in adults) are recommended as first-line therapies for TD. Since some patients with schizophrenia or schizoaffective disorder (SZD) may not be aware of their TD symptoms, data from a real-world study of VMAT2-treated patients was performed to assess whether greater symptom severity was associated with patient awareness of TD.
Methods: From July-August 2019, clinicians who prescribed valbenazine within the past 24 months were invited to participate in the study. Clinicians extracted demographic/clinical data from patients' charts and completed a survey for additional data, including treatment outcomes, patient awareness of TD, and location/severity of TD symptoms. Patient awareness of TD (yes/no, per clinician perception or recollection) was analyzed by TD symptom severity

(mild/moderate/severe by body region, per clinician assessment) in patients with schizophrenia or SZD.
Results: Data for 601 patients were provided by 163 clinicians (113 psychiatrists; 46 neurologists; 4 primary care physicians). Of these patients, 172 (29%) had schizophrenia and 125 (21%) had SZD. Among the 297 patients with primary schizophrenia/SZD, 274 (92%) were aware of having TD symptoms in at least one body region as reported by the clinician. Positive relationships were seen between clinician-reported patient awareness and clinician-assessed symptom severity in patients with schizophrenia/SZD. In the following body regions, awareness of TD was highest in patients who had severe symptoms (percentage of aware patients by severe, moderate, mild TD symptoms): jaw (94%, 74%, 65%); lips (90%, 83%, 72%); tongue (83%, 75%, 78%); wrists (100%. 73%, 56%); fingers (100%, 78%, 74%); and legs (89%, 57%, 68%). In other regions, awareness was similarly high among patients with severe or moderate TD symptoms: face (82%, 80%, 68%); neck (78%, 76%, 70%). In several regions, awareness was highest among patients with moderate TD symptoms: shoulders (67%, 85%, 52%); hips (40%, 75%, 46%); arms (60%, 68%, 60%); ankles (0%, 57%, 50%).
Discussion: In patients with schizophrenia/SZD who were prescribed a VMAT2 inhibitor for TD, clinicians reported that their patients' awareness of abnormal movements was generally higher in those determined to have moderate-to-severe symptom severity than in those with mild severity. More research is needed to understand how patient awareness is assessed by clinicians, how clinician- versus patient-determined severity contribute to TD burden, and whether different treatment strategies are needed based on these factors.

T109. WHAT'S NEXT FOR TARDIVE DYSKINESIA? EXPERT INSIGHTS FROM A CROSS-DISCIPLINARY VIRTUAL TREATMENT PANEL

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Background: Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents (DRBAs). Despite the availability of approved TD medications (e.g., valbenazine), diagnosis of this disorder remains complex and treatment can be challenging. Here we present findings from panel discussions with healthcare professionals (HCPs) who participated in virtual interviews regarding the diagnosis and treatment of TD.
Methods: In July 2020, 12 HCPs (6 neurologists, 3 psychiatrists, 3 psychiatric nurse practitioners) participated in individual semi-structured qualitative interviews about how TD is diagnosed and treated in real-world clinical settings. Topics included education, screening/diagnosis, and treatment challenges/barriers. No quantitative or statistical methods were applied. The key findings presented at this meeting are intended to be narrative in nature.
Results: The treatment panel generally agreed that any history of DRBA use raises suspicion of potential TD, and that all DRBA-treated patients should be monitored accordingly. More HCP education is needed, particularly with regards to differential diagnosis; this may require more consistency in terminology across medical specialties. Tele-medicine with video can be an effective tool for TD diagnosis/monitoring, but the complexity of the TD patient population may present challenges. First-line treatment with an approved TD medication is recommended; anticholinergics are not appropriate for treating TD. Barriers to treatment include clinicians'

misconceptions (e.g., TD as symptom of underlying disease), patients' lack of awareness, historic lack of approved treatments, and patients' unwillingness to be treated.
Discussion: Despite the availability of FDA-approved TD medications, differential diagnosis and misconception/misinformation about TD are key obstacles to adequate treatment and optimizing patient outcomes. These challenges could be addressed through HCP education on the diagnosis/clinical presentation and treatment of TD, whether virtually or in person. Tele-medicine with video could be used to diagnose TD and assess changes over time.

T110. VIRTUAL INCLUSION OF INDIVIDUALS WITH SERIOUS MENTAL ILLNESS

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Background: Recent studies provide preliminary support for the notion that individuals with mental illness may benefit from mHealth interventions. Still, further research is needed to explore whether and how digital technologies and mHealth interventions can promote the recovery of individuals with mental illness.
The study aimed to: (a) map the prevalence, trends, and experiences related to mHealth and digital technology use among individuals with a mental illness; (b) compare the usage patterns of individuals with a mental illness and individuals from the general population, and (c) examine whether use of mHealth and digital technologies promotes recovery and virtual inclusion among individuals with a mental illness.

Methods: We conducted a web-based survey of technology use and attitudes toward technology among 381 Israeli adults, of which 199 reported having a mental illness.
Results: Our findings indicated significant differences in access to and use of technology among individuals with and without mental illness. Greater experience of emotions, both negative and positive, while using technology and level of community participation and inclusion significantly predicted recovery among the respondents with mental illness.
Discussion: In the virtual era, imposed by the COVID-19 pandemic, there is a growing need to better understand how technology can be used to promote the recovery and inclusion of individuals with serious mental illness. We will discuss our results in the context of virtual inclusion and suggest future directions for research and practice.

T111. REAL-WORLD OUTCOMES OF CLOZAPINE TREATMENT: A MIRROR IMAGE EXAMINATION

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Background: Up to 35% of individuals with schizophrenia (SZ) fail to respond to first-line antipsychotic drugs, resulting in an estimated 11-fold increase in health care utilization and significantly greater morbidity and mortality. Clozapine (CLZ) remains unique relative to other antipsychotic drugs for its superior efficacy and associated 40% lower all-cause mortality. However, CLZ is underutilized in the United States, partly due to non-optimal systems of care supporting its use. Simultaneously, CLZ's real-world outcomes have not been fully characterized across communities. A better understanding of how CLZ influences the demand for services within communities may lead to more optimized and cost-effective treatment delivery for individuals treated with CLZ. Here we examined changes in health care and

municipal claims in Allegheny County, Pennsylvania, before and after the initiation of clozapine.
Methods: Individuals with SZ and health claims for CLZ in Allegheny County were identified between 2008 and 2016. We used a mirror-image study design to examine changes in service utilization before (180 days before first CLZ claim) and after CLZ initiation (180 days after a 6-month initiation period). We also ensured that no claims for CLZ existed in the year prior to treatment initiation and that 80% of days in our initiation period included claims for clozapine. Results were corrected for multiple comparisons. We secondarily used a k-means clustering approach to examine whether clusters of service utilization emerged across our cohort of CLZ-treated individuals.
Results: A total of 163 individuals met the study criteria. We observed a significant decrease in inpatient hospitalization and intensive case management, as well as a significant increase in community residential and social rehabilitative services ($p<0.05$, Bonferroni corrected). In addition, we observed clusters of service utilization that separated individuals by age (below and over 40 years of age), and individuals by change in use of residential facilities or outpatient treatment.
Discussion: Our results support a shift in resource utilization from emergent treatment to services focused on recovery. Exploratory findings also support the existence of several patterns of service utilization within Allegheny County. results from this work may lead to efforts that enhance the adoption of CLZ utilization along with the optimization and personalization of community-based treatment services.

T112. THE EFFECTS OF THE COVID-19 PANDEMIC ON EARLY PSYCHOSIS INTERVENTION PROGRAMS: IMPLICATIONS FOR SERVICE DELIVERY, SERVICE USERS, AND CLINICIANS

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Background: Healthcare service disruptions are widespread amid COVID-19, placing a tremendous burden on clinicians to maintain previous standards of care. The Early Psychosis Intervention Ontario Network (EPION) provides a defined set of fidelity standards to which all Ontario Early Psychosis Intervention (EPI) programs adhere. It is unclear how COVID-19 disruptions are interfering with programs' abilities to meet specific standards, which barriers (e.g., social distancing) are associated with declines in standards, and how these disruptions are affecting service users and their clinicians as a result.
Methods: In an online survey, eighty-six EPION clinicians rated their program's ability to meet fidelity standards after the onset of the COVID-19 pandemic using a 7-point Likert scale (1 = Significantly worsened; 7 = Significantly improved). Participants also rated the degree of change in their patients' symptoms during this period on a 5-point Likert scale (1 = Significantly worsened; 5 = Significantly improved). Lastly, participants indicated their level of work satisfaction across three subscales of the Stanford Professional Fulfillment Index (PFI): Work Exhaustion, Interpersonal Disengagement, and Professional Fulfillment.
Results: Clinicians reported significant decreases in their programs' ability to meet the following EPION standards: Comprehensive Assessment ($t=.2.61$, $p=.011$), Crisis Intervention ($t=-2.21$, $p=.031$), Relapse Prevention ($t=-3.65$, $p=.001$), Psychosocial Support ($t=-4.31$, $p<.001$), Program Graduation ($t=-2.49$ $p=.016$), and Barrier-Free Services ($t=-2.17$, $p<.034$).

Social distancing was the main reason reported for the decrease in standards. Clinicians reported significant worsening of patient symptoms during COVID-19, including hallucinations (t=-3.09, p=.003), delusions (t=-2.42, p=.018), anxiety (t=-8.76, p<.001), low mood (t=-11.34, p<.001), amotivation (t=-2.17, p<.034), social withdrawal (t=-2.17, p<.034), suicidality (t=-8.63, p<.001), substance misuse (t=-4.16, p<.001), and cognitive skills (t=-2.52, p=.014). Symptom ratings were not significantly correlated with adherence to standards. However, decreases in program adherence to fidelity standards were associated with decreases in clinicians' work satisfaction across all three PFI subscales. Work Exhaustion was negatively correlated with ratings on the standards of Comprehensive Assessment (r=-.336, p=.009), Relapse Prevention (r=-.326, p=.012), Psychosocial Support (r=-.350, p=.007), and Professional Training (r=-.257, p=.050). Interpersonal Disengagement was negatively correlated with ratings on the standards of Relapse Prevention (r=-.329, p=.011), Psychosocial Support (r=-.264, p=.043), and Program Evaluation (r=-.306, p=.02). Finally, Professional Fulfillment was positively correlated with ratings on the standard of Crisis Intervention (r=.346, p=.007).

Discussion: In addition to reporting significant declines in EPI programs' adherence to fidelity standards, EPI clinicians are faced with a related worsening in work satisfaction, engagement, and fulfillment. Furthermore, clinicians are recognizing significant worsening in their clients' psychiatric symptoms. Dissemination of these findings will permit programs to enact specific quality improvement strategies and target resource allotment as indicated. Longitudinal data collection will provide further insight into how COVID-19 continues to affect EPI clinics, as well as which areas require further improvements to ensure a proper and effective standard of care and avoid clinician burnout.

T113. PRIORITY SETTING TO UNDERSTAND MULTIPLE STAKEHOLDER PREFERENCES FOR FAMILY INVOLVEMENT IN EARLY INTERVENTION SERVICES FOR PSYCHOSIS IN CANADA - DEVELOPMENT OF A DISCRETE CHOICE EXPERIMENT (DCE) QUESTIONNAIRE

Helen Martin*[1], Srividya N. Iyer[1]

[1]McGill University, Douglas Mental Health University Institute

Background: Family involvement in mental health care services has been a puzzle for several decades' despite of availability of evidence-based family interventions. Providers often ignore involving family caregivers in routine early intervention services for psychosis without considering caregivers' treatment preferences for their ill relative. The primary aim of this study is to describe the development of a discrete choice experiment (DCE) questionnaire designed to identify the attributes and levels of family involvement that are most important to service users, families and service providers.

Methods: We recruited nine participants composed of current and past service users, family members, service providers and administrators who were familiar with early intervention services for psychosis. Through nominal group technique priorities were brainstormed and identified through in-person workshop. Later, participants were asked to rate the importance of selected family involvement attributes through online questionnaire. Key themes were identified by targeted literature review; the questionnaire was developed by the authors iteratively informed by participant ratings. Findings from the group discussion were analysed thematically.

Results: Six key family involvement themes were identified as most important such as type of family involvement, contact frequency, who's responsible for family involvement, kinds of information sharing, how are needs of family members addressed and whose consideration of

needs and preferences result in treatment development. All participants provided their ratings yielding 100% response rate. To our knowledge, this is the first time in the literature of mental health services that all pertinent stakeholders were gathered to elicit priorities for family involvement.
Discussion: Nominal group technique provide valuable insights into consensus building for complex mental health interventions. Family involvement as an evidence-based intervention requires to be recognized for its importance and to understand the underlying reasons for non-compensatory decision-making.

T114. THE EFFECT OF NEGATIVE EMOTION ON PROACTIVE AND REACTIVE RESPONSE INHIBITION IN INDIVIDUAL WITH SCHIZOTYPY: AN ERP STUDY

Lu-xia Jia*[1], Jun-yan Ye[1], Xiao-jing Qin[1], Ya Wang[1]

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Background: Negative emotion has been shown to interfere with the efficacy of response inhibition. According to the Dual Mechanisms of Control theory, response inhibition includes proactive inhibition (preparation for stopping) and reactive inhibition (outright stopping). It remains unclear whether negative emotion such as angry affects proactive and reactive response inhibition in individuals with schizotypy, a subclinical group at risk for schizophrenia, and what are the neural mechanisms underlying these processes.
Methods: Fifteen individuals with schizotypy and 15 matched controls (HC) performed a modified emotional stop-signal task with electroencephalographic (EEG) data recorded. Participants were required to judge the emotion (neutral or angry) of faces while withhold their responses when the border of the photo becomes red. There were two levels of stop signal probability: 0% (no stop trials) and 25% (25% stop trials). Analyses on the go trials indicate proactive control, and analyses on the stop trials indicate reactive control.
Results: At the behavioural level, no effect of emotion or group was found on go trials, while angry faces elicited longer stop signal reaction time (SSRT) compared to neutral faces in both groups with no group difference. At the neural level, for go trials, both groups exhibited significantly increased N2 and decreased P3 amplitude at 25% stop condition compared with 0% stop condition, indicating proactive inhibition for neutral faces; while these effects did not exist in angry faces. No group difference was found. For stop trials, schizotypy exhibited significantly smaller N2 and P3 amplitude compared with HC in both angry and neutral faces. Moreover, schizotypy individuals showed smaller P3 amplitude in angry faces compared to neutral faces while HC did not show such difference.
Discussion: The current findings suggest that schizotypy individuals might be as effective as HC in recruiting proactive inhibition both for angry and neutral faces. However, angry faces impaired reactive inhibition compared to neutral faces in both schizotypy and HC groups at the behavior level, this effect existed in schizotypy individuals at the neural level. These results contribute to our more precise understanding of how negative emotion affect proactive and reactive inhibition in individuals with schizotypy.

T115. N-ACETYL CYSTEINE AS A TREATMENT FOR NEGATIVE AND COGNITIVE SYMPTOMS FOR TREATMENT RESISTANT SCHIZOPHRENIA

Erica Neill*[1], Susan Rossell[1], Dan Siskind[2], Cherrie Galletly[3], Anthony Harris[4], Caitlin Yolland[1], Olivia Dean[5], Michael Berk[6], Jerome Sarris[7], Frances Dark[8], Dennis Liu[9], Paul Francis[5], Kiymet Bozaoglu[10], Denny Meyer[1], Andrea Phillipou[1], David J. Castle[11]

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Background: Negative and cognitive symptoms of schizophrenia are the greatest contributors to poor quality of life and are generally poorly managed by current antipsychotic treatments. Research suggests that this treatment resistance (TR) affects some 20-30% of patients. Those who fail to respond to first line antipsychotic treatments and are labelled as TR, are prescribed Clozapine. Unfortunately, of these patients, 40-60% remain symptomatic. As such, there are a significant number of Clozapine resistant patients who experience residual symptoms on an ongoing basis. Agents which offer symptom relief to Clozapine resistant patients are desperately needed. One such potential agent is N-acetyl cysteine (NAC) which is a precursor to glutathione (GSH), and is of particular interest due to its ability to modulate both glutamate and dopamine and its role in reducing oxidative stress and inflammation. Pilot data showed that NAC improved negative symptoms in a subgroup of Clozapine resistant patients suggesting its utility for this group. Given the relationship between cognition and negative symptoms and the impact of oxidative stress and inflammation on cognition, it was hypothesised that both negative and cognitive symptoms will be improved after 52 weeks of NAC treatment.

Methods: This was a phase III, randomised, double-blind, placebo-controlled trial of 2g of NAC per day with outcomes points at 8, 24 and 52-weeks. All participants were taking Clozapine and demonstrating ongoing TR. At baseline, there were 42 patients in the NAC and 43 in the placebo condition. At the final 52 week time point, there were 21 patients on NAC and 22 on placebo.

The groups were matched across symptom severity and cognitive function at baseline. Expectation-maximisation algorithm was used to impute missing items. A mixed model repeated measures (MMRM) analysis was conducted to determine time by group interactions.

Results: After controlling for positive and general symptoms along with affect, there were no significant group by time interactions at 52 weeks for negative or cognitive symptoms. There were significant group by time interactions for PANSS depression and PANSS excitement with the NAC group demonstrating a decrease in depression and an increase in excitement at 52 weeks.

Discussion: Neither negative symptoms nor cognitive symptoms were significantly improved by 52 weeks treatment of 2g of NAC daily for TR Clozapine patients. The failure of NAC to improve these areas may be as a result of the chronicity and severity of the illness in our Clozapine resistant group. This sample were more symptomatic (PANSS total ~73) with a longer illness history (~18 years) than those in the pilot study reported. As such, while NAC may be helpful in TR patients, there are likely still limits. It is interesting that there was a finding of decreased PANSS depression and increased PANSS excitement in the NAC group at 52 weeks supporting bipolar study findings that NAC may improve mood symptoms. Future

studies may consider enrolling a less chronic and severely treatment resistant group to better understand the potential of NAC as an adjunct treatment for TR patients.

T116. THE ROLE OF COPING IN DETERMINING NEED FOR CARE IN PSYCHOSIS: FINDINGS FROM THE UNIQUE STUDY

Zera Brittenden[1], Thomas Ward[1], Emmanuelle Peters*[1]

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Background: Previous research indicates an important role for cognitive and behavioural responses to psychotic experiences (PEs) in determining need-for-care in psychosis. Identifying differences in responses between individuals with persistent PEs with and without need-for-care can help to elucidate risk and protective factors in psychosis.
Methods: A comprehensive and reliable coping styles framework was developed to categorise the coping styles section of the AANEX (Appraisals of Anomalous Experiences) Interview (Brett et al., 2007). The response styles of clinical (n=73) and non-clinical (n=92) individuals with persistent PEs from the UNIQUE Study (Peters et al., 2016) were compared. We also predicted that threat appraisals would mediate the relationship between maladaptive responding and distress.
Results: Clinical individuals were significantly more likely to endorse maladaptive and less likely to endorse adaptive response styles than nonclinical individuals. Group membership explained almost double the variance in maladaptive compared to adaptive responding. Cognitive-attentional experiences were more common in the clinical group and also predicted maladaptive responding. Lastly, the relationship between maladaptive responding and distress was partially mediated by threat appraisals of PEs.
Discussion: Response styles to PEs are likely to play a role in need-for-care status, with maladaptive coping potentially being related to diminished cognitive resources. There was a joint role for threat appraisals and maladaptive responding in maintaining distress, in line with cognitive behavioural approaches to psychosis aiming to address appraisals and responses to PEs.

Sunday Poster Session

1. The Link Between Cognitive Impairment and Diabetes in a Tunisian Sample of Patients with Schizophrenia

Hanen Ben Ammar*[1], Ghada Hamdi[2], Dhouha Falfel[2], Amal Arous[2], Rania Felhi[2], Leila M'nif[2]

[1]University of Tunis El Manar, [2]psychiatric hospital, Tunis

2. Computational Model for the Simulation of the Prepulse Inhibition Test - Interfaces with Schizophrenia

Thiago Bezerra*[1], Cristiane Salum[2]

[1]MSc Student, [2]Universidade Federal do ABC

3. Attitude and Perception of a Tunisian Sample of Patients with Schizophrenia and Bipolar Disorder Towards COVID-19 Vaccine

Dhouha Falfel*[1], Hanène Ben Ammar[2], Ghada Hamdi[2], Meha Ben Miled[2], Emira Khelifa[2], Leila M'nif[2]

[1]Psychiatric Hospital, Tunis, [2]psychiatric hospital , Tunis

4. Towards a Bio-Behavioral Model of Social Functioning Outcomes: A Machine Learning Approach

Kathleen Miley*[1], Martin Michalowski[1], Sophia Vinogradov[2]

[1]University of Minnesota, School of Nursing, [2]University of Minnesota Medical School

5. How We Assess Metacognition in Psychosis?

Luciana Diaz-Cutraro*[1], Helena García-Mieres[1], Raquel López-Carrilero[2], Marta Ferrer-Quintero[2], Marina Verdaguer-Rodríguez[1], Roger Montserrat[2], Steffen Moritz[3], Paul Lysaker[4], Giancarlo DiMaggio[5], Carolina Palma-Sevillano[6], Susana Ochoa[2]

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6. Longitudinal Hippocampal Subregion Development in Young People with Psychotic Experiences

Aisling O'Neill*[1], Erik O'Hanlon[1], Niamh Dooley[1], Eleanor Carey[1], Helen Coughlan[1], Thomas Frodl[2], Mary Cannon[1]

[1]Royal College of Surgeons in Ireland, [2]Department of Psychiatry, Trinity College Dublin, Ireland

7. Thalamic Connectivity System Across Psychiatric Illnesses: A Review

Wu Jeong Hwang*[1], Yoo Bin Kwak[2], Kevin Kang Ik Cho[3], Tae Young Lee[4], Minji Ha[5], MINAH KIM[6], JUN SOO KWON[7]

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8. Aberrant Triple Network Connectivity in First Episode Psychosis and High-Risk Individuals

Ah Ra Kim*[1], Minah Kim[2], Jun Soo Kwon[3]

[1]Seoul National University College of Natural Sciences, [2]Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Republic of Korea, Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Seoul, Republic of Korea, Department of Neuropsychiatry, Seoul National University Hospital, Republic of Korea, Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea, Institute of Human Behavioral Medicine, SNU-MRC, Seoul, Republic of Korea

9. Clarifying the Relationship Between Loneliness and Positive Schizotypal Traits: Social Vs. Emotional Loneliness

Taylor Johnson*[1], Sarah Hope Lincoln[2]

[1]Case Western Reserve University, [2]Dept of Psychological Sciences, Case Western Reserve University

10. Examining the Functional Benefit of Normal-Range Verbal Memory in First-Episode Psychosis: A Longitudinal Study

Gabrielle Pochiet*[1], Delphine Raucher-Chéné[2], Katie Lavigne[1], Ridha Joober[2], Ashok Malla[2], Martin Lepage[2]

[1]McGill University, [2]Douglas Mental Health University Institute

11. Treatment Seeking Attitudes, Stigma, and Defeatist Beliefs among Those at Risk for Psychosis

Ruth Firmin[1], Lauren Luther[2], Madeline Ward*[1], Kelsey Bonfils[3], Michelle Salyers[4]

[1]Rhode Island Hospital/Alpert Medical School of Brown University, [2]Massachusetts General Hospital/Harvard Medical School Department of Psychiatry, [3]The University of Southern Mississippi, School of Psychology, [4]Indiana University-Purdue University Indianapolis

12. Altered Effective Connectivity within an Oculomotor Control Network in Individuals with Schizophrenia

Matthew Lehet*[1], Ivy Tso[2], Bas Neggers[3], Ilse Thompson[4], Beier Yao[1], Rene Khan[5], Katharine Thakkar[1]

[1]Michigan State University, [2]University of Michigan Medical School, [3]Rudolf Magnus Institute for Neuroscience, [4]University Medical Center Groningen, [5]Icahn School of Medicine at Mount Sinai

13. Abnormal Pupil Light Reflex Relates to Negative Symptom Severity and Working Memory in Schizophrenia

Jessica Fattal*[1], Jan W. Brascamp[1], Rachael Slate[1], Matthew Lehet[1], Eric D. Achtyes[2], Katharine N. Thakkar[1]

[1]Michigan State University, [2]Cherry Health

14. Volume Deficit in Hippocampal CA Subfield in Subjects with High Genetic Loading for Schizophrenia

Sunah Choi*[1], Taekwan Kim[1], Minah Kim[2], Jun Soo Kwon[3]

[1]Seoul National University College of Natural Sciences, [2]Seoul National University Hospital; Seoul National University College of Medicine, [3]Seoul National University College of Natural Sciences; Seoul National University Hospital; Seoul National University College of Medicine

15. Cerebellar Dysconnectivity in Drug-Naïve First-Episode Schizophrenia

Hengyi Cao*[1], Xia Wei[1], Wenjing Zhang[1], Yuan Xiao[1], Jiaxing Zeng[1], John Sweeney[2], Qiyong Gong[1], Su Lui[1]

[1]West China Hospital of Sichuan University, [2]University of Cincinnati

16. Stigma Towards Individuals with Schizophrenia: Examining the Effects of Negative Symptoms and Diagnosis Awareness on Preference for Social Distance

Aqsa Zahid*[1], Michael Best[1]

[1]University of Toronto Scarborough

17. Locus of Control Mediates the Relationship between Schizotypy and Feelings of Defeat

Jill Laquidara*[1], Laura Cameron[2], Taylor Johnson[2], Sarah Hope Lincoln[2]

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18. Second-Generation Antipsychotics and Medical Comorbidity: A Retrospective, Cross-Sectional Exploratory Study in an Urban Outpatient Psychiatry Clinic

Catherine Bennett*[1], David Goldsmith[1]

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19. An Occupational Therapy Intervention to Enhance Social and Physical Well-Being in Young Adults with First Episode Psychosis

Sarah Zagorac*[1], Caitlin Taylor[1], Nuriya Neumann[2], Tina DeAngelis[1]

[1]Thomas Jefferson University, [2]Horizon House Inc.

20. Disentangling Recovery in First Episode Psychosis (FEP)

Gloria Morello-Torrellas*[1], Regina Vila-Badia[2], Nuria Del Cacho[3], Anna Butjosa[4], Marina Esteban-SanJusto[2], Clara Serra-Arumí[2], Georgina Vallejo-Rius[3], Daniel Muñoz[4], Group PROFEP[3], Judith Usall[2]

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Monday Poster Session

1. Prevalence and Consequences of Metabolic Syndrome in Patients with Schizophrenia in Tunisia

Hanen Ben Ammar*[1], Ghada Hamdi[2], Dhouha Falfel[2], Amal Arous[2], Rania Felhi[2], Leila M'nif[2]

[1]University of Tunis El Manar, [2]psychiatric hospital , Tunis

2. Limbic Morphometry in Individuals with Schizophrenia and Their Nonpsychotic Siblings

Rachael Slate*[1], Derin Cobia[1], Kaitlyn Greer[1], Matthew Smith[2], John Csernansky[3], Lei Wang[4]

[1]Brigham Young University, [2]University of Michigan, [3]Northwestern University Feinberg School of Medicine, [4]The Ohio State University Wexner Medical Center

3. Impaired Face Emotion Recognition in schizophrenia: Task Performance, Eye-Tracking and Neurophysiological Analyses and Comparison to Autism Spectrum Disorder

Elisa Dias*[1], Pamela Butler[1], Abraham VanVoorhis[1], Stephanie Wolfer[1], Gail Silipo[1], Russell Tobe[1], Daniel Javitt[2]

[1]Nathan Kline Institute for Psychiatric Research, [2]Nathan S. Kline Institute for Psychiatric Research

4. Dysmorphophobia and Aesthetical Rhinoplasty: Case Report

Dhouha Falfel*[1], Hanène Ben Ammar[2], Meha Ben Miled[2], Emira Khelifa[2], Leila Mnif[2]

[1]Psychiatric Hospital, Tunis, [2]psychiatric hospital , Tunis

5. Polygenic Risk Score Distributions Suggest that Treatment Resistance in Schizophrenia is Unlikely to Be Driven by Schizophrenia - Associated Common Variations

Rose Mary Xavier*[1], Brian Britt[1], Martilias Farrell[2], Mathew Harner[3], Tyler Diettrich[3], Dawn Filmyer[3], Lisa Bruno[3], Raquel Gur[4], Laura Almasy[4], Patrick Sullivan[5], Richard Josiassen[6]

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6. Worry, but Not Too Much: Clozapine Induced Myocarditis - An Electronic Health Register Analysis of Timing, Clinical Markers and Diagnostic Accuracy

Aviv Segev*[1], Ehtesham Iqbal[2], Theresa McDonagh[2], Cecilia Casetta[2], Ebenezer Oloyede[2], Susan Piper[2], Carla Plymen[2], James MacCabe[2]

[1]Tel-Aviv University, Sackler Faculty of Medicine, [2]King's College London

7. Thalamocortical Dysrhythmia in Patients with Schizophrenia Spectrum Disorder and Individuals at Clinical High Risk for Psychosis

Minah Kim*[1], Tak Hyung Lee[2], Jun Soo Kwon[3]

[1]Seoul National University Hospital, [2]Samsung Electronics Co. Ltd, [3]Seoul National University College of Medicine

8. Neural Correlates of Impaired Cognitive Reappraisal in Early Psychosis

Silvia Lho*[1], Minah Kim[2], Taekwan Kim[3], Jun Soo Kwon[4]

[1]Seoul National University College of Medicine, [2]Seoul National University College of Medicine; Department of Psychiatry, Seoul National University College of Medicine, [3]Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, [4]Seoul National University College of Medicine; Department of Psychiatry, Seoul National University College of Medicine; Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences; Institute of Human Behavioral Medicine, SNU-MRC

9. Exploring the Relationship between N-Acetylaspartate and White Matter Integrity in Individuals with Schizophrenia and Unaffected Relatives: A Combined 1H MRS-DTI Approach

Dominic Roberts*[1], Lara Rösler[2], Jannie P. Wijnen[3], Vincent O. Boer[4], Dennis W.J. Klomp[3], Wiepke Cahn[5], René S. Kahn[6], Sebastiaan F.W. Neggers[5], Katharine N. Thakkar[1]

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Magnetic Resonance, [5]Department of Psychiatry, University Medical Center Utrecht, the Netherlands, [6]Icahn School of Medicine at Mount Sinai

10. Differential Patterns of Change in Texture Measures of Prodromal and First-Episode Psychosis Patients

Sun-Young Moon*[1], Hyungyou Park[2], Minah Kim[3], Subin Lee[2], Jun Soo Kwon[3]

[1]Seoul National University Hospital, [2]Seoul National University, [3]Seoul National University College of Medicine

11. Exploration of the Contribution of Individual Positive and Negative Symptoms to Theory of Mind in Schizophrenia and Related Psychotic Disorders

Élisabeth Thibaudeau*[1], Jesse Rae[1], Delphine Raucher-Chéné[1], Martin Lepage[1]

[1]McGill University, Douglas Mental Health University Institute

12. Understanding Preferences of People Living with Schizophrenia in Australia

Simon Fifer[1], Brittany Keen[1], Richard Newton[2], Andrea Puig*[3], Marija McGeachie[3]

[1]Community and Patient Preference Research, [2]Peninsula Mental Health Service, [3]Janssen

13. Athens Multifamily Therapy after a First Psychotic Episode

Mirjana Selakovic*[1], Valeria Pomini[2], Afrodite Zatraloudi[3], Dimitris Galanis[4], Afrodite Feretzaki[5]

[1]GH, [2]1st Department of Psychiatry, National & Kapodistrian University of Athens and University Mental Health Research Institute "Costas Stefanis", [3]4Assistant professor in Mental Health Nursing Department of Nursing University of West Attica, [4]2Social Worker, Family Therapist, EPAPSY, [5]Social Worker, Family Therapist, Department of Psychiatry - "Sismanoglio" General Hospital

14. Influence of Migration on the Thought Process of Individuals at Ultra-High Risk for Psychosis

Arthur Suman Nogueira*[1], Julio C. Andrade[1], Mauricio H. Serpa[2], Tania M. Alves[3], Elder L. Freitas[3], Lucas Hortêncio[3], Martinus T. van de Bilt[3], Wagner F. Gattaz[3], Wulf Rössler[4], Alexandre A. Loch[3]

[1]University of Sao Paulo, [2]University of São Paulo, [3]University of Sao paulo, [4]University of Zurich

15. Suicidality and Posttraumatic Stress Disorder Elevated in Patients with Comorbid Psychosis and Borderline Personality Disorder

Madeline Ward*[1], Ruth Firmin[1], Mark Zimmerman[1]

[1]Rhode Island Hospital/Alpert Medical School of Brown University

16. Childhood Trauma is Associated with Increased Extracellular Freewater and Localised Reductions in White-Matter Microstructural Organisation in Individuals with and without Schizophrenia

Laura Costello*[1], Giulia Tronchin[2], Laurena Holleran[2], Maria Dauvermann[3], David Mothersill[4], Karolina I. Rokita[2], Ruan Kane[2], Brian Hallahan[2], Aiden Corvin[5], Derek Morris[2], Declan McKernan[2], John Kelly[2], Colm McDonald[2], Gary Donohoe[2], Dara M. Cannon[2]

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17. Oculomotor Corollary Discharge Abnormalities: A Trans-Diagnostic Marker of Psychosis?

Beier Yao*[1], Martin Rolfs[2], Rachael Slate[1], Dalia Fragoso[1], Eric Achtyes[1], Ivy Tso[3], Vaibhav Diwadkar[4], Deborah Kashy[1], Katharine Thakkar[1]

[1]Michigan State University, [2]Humboldt University, [3]University of Michigan Medical School, [4]Wayne State University

18. Heterogeneity of Recent Onset Depression and Recent Onset Psychosis: A Semi-Supervised Machine Learning Neurobiological Based Approach

Paris Alexandros Lalousis*[1], Stephen Wood[2], Renate Reniers[1], Lianne Schmaal[2], Raimo Salokangas[3], Christos Pantelis[4], Eva Meisenzahl[5], Paolo Brambilla[6], Stefan Borgwardt[7], Rebekka Lencer[8], Nikolaos Koutsouleris[9], Rachel Upthegrove[1], Dominic Dwyer[10]

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19. Tapered Discontinuation versus Maintenance Therapy with Antipsychotic Medication in Patients with First-Episode Schizophrenia: Results and Obstacles in the Randomized Clinical Trial Tailor

Anne Emilie Stürup*[1], Carsten Hjorthøj[2], Nikolai Albert[2], Signe Dolmer[3], Merete Birk[3], Bjørn H. Ebdrup[4], Lene Eplov[2], Heidi Dorthe Jensen[2], Ditte Lammers Vernal[5], Helene Speyer[2], Ole Mors[3], Merete Nordentoft[2]

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Tuesday Poster Session

1. Fregoli Delusion and Serial Killing

Hanen Ben Ammar*[1], Ghada Hamdi[2], Dhouha Falfel[2], Naouel Mhadhbi[2], Rania Felhi[2], Rym Ridha[2]

[1]University of Tunis El Manar, [2]psychiatric hospital ,Tunis

2. Identifying Distinct Trajectories of Negative Symptoms Following First-Episode Psychosis: A Two-Year Study of Patients Admitted to an Early Intervention Service

Joshua Unrau*[1], Olivier Percie du Sert[2], Delphine Raucher-Chéné[2], Ridha Joober[2], Ashok Malla[2], Martin Lepage[2]

[1]Douglas Mental Health University Institute, McGill University, [2]Douglas Mental Health University Institute, McGill University, Montreal, Canada

3. Patterns of Cultural Variations in Panss Symptom Ratings

Martina Micaletto*[1], Prateek Verma[1], Zinan Chen-Tackett[1], Rebecca Laird[1], Wei Zhou[1], H. Todd Feaster[1]

[1]Signant Health

4. Dexmedetomidine Reduce Stress-Related Behaviors and Improves Sleep Parameters in Rodent Models

Michael De Vivo*[1], Subhendu Seth[2], Dinesh Dhull[2], Friso Postma[3], Frank Yocca[2]

[1]BioXCel Therapeutics, [2]BioXcel Therapeutics, [3]BioxCel Therapeutics

5. Patients' Trust in Institutions and Doctors in Early Interventions Services in Psychosis: A Cross-Cultural Study in India and Canada

Salome Xavier*[1], Aarati Taksal[2], Greeshma Mohan[3], Thara Rangaswamy[3], Padmavati Ramachandran[3], Norbert Schmitz[4], Howard Margolese[5], Ridha Joober[2], Ashok Malla[2], Srividya Iyer[2]

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University Department of Psychiatry, [5]Prevention and Early Intervention Program for Psychosis- McGill University Health Centre (PEPP-MUHC)

6. The Effects of Cannabis and Methamphetamine Use on Cognitive Performance Over the First Two Years of Treatment in First-Episode Schizophrenia

Frederika Scheffler*[1], Lebogang Phahladira[1], Chanelle Buckle[1], Stéfan Du Plessis[2], Laila Asmal[2], Hilmar Luckhoff[3], Retha Smit[1], Riaan Olivier[2], Robin Emsley[2]

[1]Stellenbosch University, [2]University of Stellenbosch, [3]Stellenbosch University, Department of Psychiatry

7. Characterising Neural Heterogeneity in Psychiatric Disorders Using Normative Models

Ashlea Segal*[1], Linden Parkes[2], Kevin Aquino[3], Seyed M. Kia[4], Thomas Wolfers[5], Barbara Franke[4], Martine Hoogman[4], Christian F. Beckmann[6], Lars Westlye[7], Ole A. Andreassen[8], Andrew Zalesky[9], Ben Harrison[9], Christopher Davey[9], Carles Soriano-Mas[10], Jeggan Tiego[1], Murat Yücel[1], Leah Braganza[1], Chao Suo[1], Michael Berk[11], Sue Cotton[12], Mark Bellgrove[1], Andre F. Marquand[13], Alex Fornito[1]

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8. Immuno-Metabolic Profile of Psychotic Patients with Metabolic Syndrome: Results from the Face-Sz Cohort

Marianne Foiselle*[1], Susana Barbosa[2], Ophelia Godin[3], Nicolas Glaichenhaus[2], Leboyer Marion[4], Ryad Tamouza[5]

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9. Using Exploratory Graph Analysis to Understand Anxiety Comorbidity in Serious Mental Illness

Natasha Tonge*[1], Clayton H. Brown[2], Amy Drapalski[1], Alicia Lucksted[2]

[1]VISN 5 MIRECC, [2]University of Maryland School of Medicine

10. Impaired Migration of Autologous Induced Neural Stem Cells from Patients with Schizophrenia and Implications for Genetic Risk for Psychosis

Junhee Lee*[1], Sehyeon Song[2], Juhee Lee[2], Soobean Choe[2], Eun Kyung Choe[3], Tae Young Lee[4], Myong-Wuk Chon[5], Seong Who Kim[6], Myung-Suk Chun[7], Mi-Sook Chang[2], Jun Soo Kwon[1]

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11. Cellular White Matter but Not Extracellular Free Water Alterations in Schizotypal Personality Disorder

Yoo Bin Kwak*[1], Kevin Kang Ik Cho[2], Minah Kim[3], Tae Young Lee[4], Ji-Won Hur[5], Ofer Pasternak[6], Jun Soo Kwon[7]

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12. Enhanced Dopamine in Prodromal Schizophrenia (EDiPS): A Novel Model of the Prodrome of Schizophrenia

Alice Petty*[1], Xiaoying Cui[2], Deniz Kirik[3], Oliver Howes[4], Darryl Eyles[2]

[1]Neuroscience Research Australia, [2]Queensland Brain Institute, [3]Lund University, [4]Imperial College London

13. Insight in Schizophrenia is Not Associated with Awareness of Antipsychotic Induced Movements

Rose Mary Xavier*[1], Benjamin Cherian[1], Wales George[2]

[1]The University of North Carolina at Chapel Hill, [2]Southern Virginia Mental Health Institute

14. The Impact of Environmental Risk Factors on Brain Structure in Subjects with Psychotic Experiences

Kate Merritt*[1], Pedro Luque Laguna[2], Michael Bloomfield[3], Sarah Ashley[1], Mark Drakesmith[4], Leon Fonville[5], Stanley Zammit[6], Abraham Reichenberg[7], John Evans[8], Glyn Lewis[3], Matthew Kempton[9], David E. J. Linden[10], Derek Jones[4], Anthony David[11]

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15. Impact of Family History of Psychosis on Symptoms and Social Behavior: A Family Case Report

Maha Ben Miled*[1], Hanen BEN AMMAR[2], Dhouha Falfel[3], Emira Khelifa[4], Leila Mnif[3]

[1]Faculty of Medecine Tunis Tunisia, [2]Faculty of medicine of Tunis, [3]Faculty of medecine of Tunis, [4]Hospital Al Razi, Manouba, Tunisia

16. Stressful Life Events and Cannabis Consumption in First Episode of Psychosis

Marina Esteban-Sanjusto*[1], Clara Serra-Arumí[2], Regina Vila-Badia[2], Anna Butjosa[3], Nuria Del Cacho[2], Gloria Morello-Torrellas[2], Jose Luis Bogas[2], Marta Pardo[3], Group PROFEP[2], Judith Usall[2]

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17. Does Trauma-Related Distress Predict Control over Voice-Hearing Experiences?

Hatice Eken*[1], Brittany Quagan[2], Alyson Negreira[3], Alison Branitsky[4], Catalina Mourgues[2], Albert Powers[2]

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18. 4D Quantification Tool for High Density EEG Biomarker

Prasanta Pal*[1], Remko Van Lutterveld[2], Alexandra Roy[1], Judson Brewer[1]

[1]Brown University, [2]University Medical Center Utrecht

19. Examining Mental Health Engagement among Veterans Diagnosed with Serious Mental Illness

Holly McKinley*[1], Annika Duryea[2], Tasha Nienow[1]

[1]Minneapolis VA Health Care System, [2]University of Minnesota

20. Cumulative Environmental Risk for Schizotypy across the Psychosis Spectrum

Emiliana Tonini*[1], Yann Quidé[2], Thomas Whitford[3], Melissa Green[2]

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