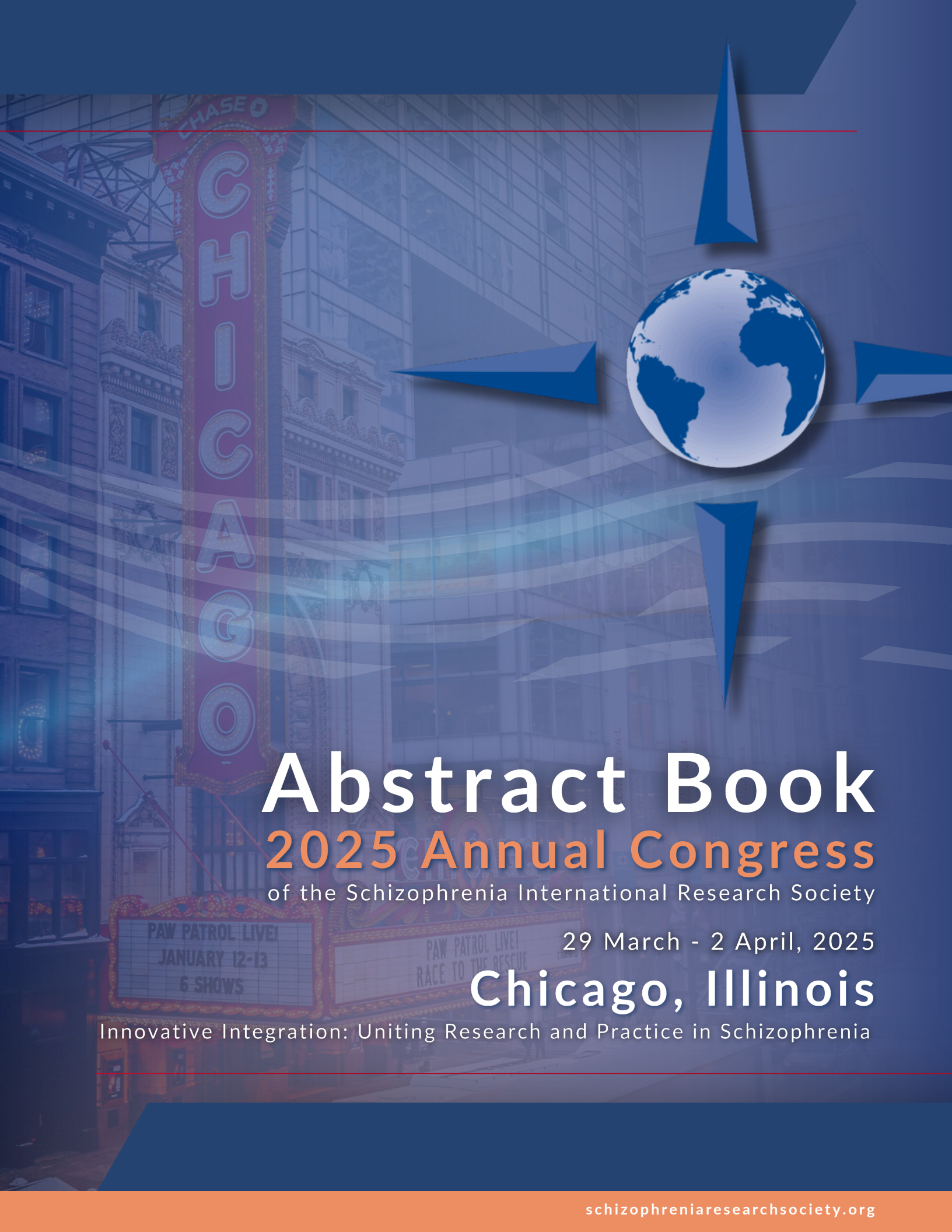


# Abstract Book

## 2025 Annual Congress

of the Schizophrenia International Research Society

29 March - 2 April, 2025

## Chicago, Illinois

Innovative Integration: Uniting Research and Practice in Schizophrenia

**Concurrent Workshops**

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

**1. Faris and Dunham Remembered, Revoked and Reimagined: Chicago's Pioneering Place in Understanding the Social Determinants of Schizophrenia and Other Psychoses**

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

**Overall Abstract:** -

**1.1 Faris & Dunham Remembered, Revoked and Reimagined: Chicago's Pioneering Place in Understanding the Social Determinants of Schizophrenia and Other Psychoses**

James Kirkbride*, University College London*

**Individual Abstract:** One hundred years ago, the sociologists Robert E. L. Faris and H. Warren Dunham embarked on a groundbreaking study of mental disorders in urban areas, focusing on Chicago during the period of the Great Depression, Prohibition and Organized Crime. Their work, published in 1939, laid the foundation for understanding the relationship between urban environments and mental health, most notably schizophrenia. This workshop commemorates the centennial of their pioneering research and explores its lasting impact on our understanding of the social determinants of psychosis.

Faris and Dunham mapped the geographic distribution of the incidence of severe mental illnesses in Chicago using data on first admissions to public and private mental hospitals between 1922 and 1934. Their study revealed a striking pattern: schizophrenia rates were highest in areas of high social disintegration near the city center, decreasingly progressively towards more suburban and affluent residential districts on the periphery. This pattern was similar for substance use disorders. In contrast, bipolar disorders showed a more even distribution throughout the city, with a slight tendency for higher rates in upper-class residential areas. Their research suggested a relationship between the distribution of mental disorders and unfavorable social conditions, particularly for schizophrenia, which inspired numerous studies in various cities across the United States and Europe until the 1960s that largely replicated their findings.

In this workshop, I will explore the lasting relevance of Faris and Dunham's pioneering work a century later. I will reveal how their work initially sparked a new era in psychiatric epidemiology and the pursuit to understand the social etiology of mental disorders until the 1960s. I will show how early concerns over the ecological nature of their studies and causal inference, combined with accelerated interest in biological psychiatry and psychiatric genetics, cast a long shadow over efforts to understand the role of social determinants of schizophrenia and mental health disorders for almost half a century. We will discuss how these challenges have been supplemented by contemporary concerns over the generalizability of these findings to other contexts, most notably in the Global South.

**2. Early Career Researchers Workshop**

Anne Giersch*, INSERM*

**Overall Abstract:** The aim of this workshop is to allow early career MDs and PhDs to meet with members of the society at diverse stages of their career, with different background,

exercising in different countries, working on different topics and in different environments, academic, industry, and or medical.
Presenters will make a short presentation on the topic of risk taking: should a student select a laboratory on the basis of its fame or on the basis of his or her very personal motivations? What about risk-taking in research and what possible consequences does it have on one's own career?

The workshop is meant to be an exchange between the speakers and the attendees, and ample time will be provided for questions from the attendees. The presentations are expected to trigger questions, but any question will be welcome, including those outside the topic of risk taking.

### 2.1 Risk-Taking in Career Decisions as a Non-Clinical Scientist

Gemma Modinos, *King's College London*

**Individual Abstract:** This presentation is aimed at offering mentoring and support to early-career researchers from the perspective of a non-clinical scientist. I will mainly focus on risk-taking (and de-risking) in career decisions related to researcher mobility (e.g., different countries, labs), pursuing a clinical vs non-clinical career (e.g., after training as a clinical neuropsychologist before embarking on a PhD in neuroscience), pursuing the research fellowship vs university lecturer pathway in the UK. The aim is that by sharing personal experiences and through interaction with the audience we can discuss how taking risks, finding and taking up opportunities can shape our careers, and how adaptability, resilience, perseverance, luck, and our personal values and preferences can inform these decisions.

### 2.2 Risk-Taking in Career Decisions as a Physician-Scientist

Halide Bilge Turkozer, *Harvard Medical School McLean Hospital*

**Individual Abstract:** This presentation will explore the concept of risk-taking in career decisions in medicine, focusing on the physician-scientist pathway. Key topics include navigating the challenges of selecting the right psychiatric training program, choosing a mentor, and identifying a research focus. By sharing my personal experiences, I will discuss both the challenges and the potential outcomes of these decisions. These examples will demonstrate how career-defining risks can lead to unexpected opportunities or setbacks, requiring adaptability and persistence. The goal is to offer insights into how thoughtful risk-taking can shape professional growth, while encouraging discussion on how to approach these pivotal choices in academic and clinical careers. The presentation will also highlight the importance of aligning personal aspirations and values with professional decisions.

### 2.3 Risks and Rewards: Working in Industry – Valuable Experience or Career Distraction?

Alexis Cullen, *Karolinska Institutet*

**Individual Abstract:** The expertise and skills that we gain during our academic and clinical careers can provide employment opportunities within the pharmaceutical and healthcare industry. Whilst these roles can provide financial and other benefits, they can also be demanding and time consuming. So, the key question is, do these industry roles provide us with valuable experiences and opportunities that can help enhance our academic careers, or

do they more often divert our attention away from our primary career goals? In this presentation, I will describe my experiences of working as a freelance consultant in market access and health economic and outcome research companies alongside my academic position as a Principal Researcher. My aim is to highlight that non-clinical academics have a range of skills that are highly valuable to these industries and describe some of the advantages that can come with engaging in industry work, whilst also acknowledging the challenges and adaptations that come with these ventures.

### 2.4 Risks and Rewards: Charting an Effective Course Through Your Graduate Experience

Anthony Grace, *University of Pittsburgh*

**Individual Abstract:** How does one go about choosing a graduate program and a mentor? There are many pros and cons to consider; I will present the important factors that you should consider when choosing the direction of your career. I assume that you have chosen your graduate school based on the appropriateness of the program to your goals and interests. But now comes an important decision: with whom should you choose as a mentor? One of the best ways to assess this early on is to perform lab rotations – a short 1-term experience in several laboratories within your sphere of interest. This can expose you not only to new methodologies, but also to see how your prospective mentor runs their laboratory, and if you feel you would be a good fit into that environment. Where you eventually decide to work depends both on your field of interest and what risk you want to take. For example, do you choose a very well-known mentor with a large lab, or a new faculty member that is up-and-coming? While entering a large established lab that has a record of success for their students, one may get lost in the shuffle, and are more likely to work with a postdoc or senior grad student than directly with the mentor. On the other hand, one would likely receive much more hands-on instruction from a newer faculty member; however, this carries the risk of whether the individual receives tenure, or decides to move to another institution? Also, what weight should you put on learning the latest methods versus learning how to design effective experiments? These topics will be explored in our workshop.

### 2.5 The owner-investigator: Why not Start Your Own Site?

John Sonnenberg, *Uptown Research Institute*

**Individual Abstract:** When investigators own their own sites they can functionally align their economic and research goals. Operating free from academia and corporate overlords allows the translational researcher to nimbly explore new research directions, directly pursue and secure funding from pharmaceutical sponsors, and even publish without the corollary of perish. Since starting Uptown Research Institute in 2001 I have served as a Principal Investigator on over 100 schizophrenia trials. I run inpatient and outpatient schizophrenia studies for Phases 1 through 3, examining primary outcomes including psychotic acuity, cognition, inadequate response, negative symptoms, maintenance, methodology, safety, and bioequivalence. By attesting to my path to site ownership, I intend to show early career professionals one additional avenue for the emerging scientist-practitioner. By describing both the challenges and the upsides, I intend to illuminate the factors one should consider before undertaking such an independent pursuit. I will make the argument that we need more investigator-owned sites to serve as a balance to the larger site networks, and to help compensate for the slower pace of trial execution still typical in academia.

## 3. Bridging Perspectives: Insights From Women Across Academia and Industry on Schizophrenia and Other Psychotic Disorders

Kia Crittenden-Ward, *Merck*

**Overall Abstract:** "Bridging Perspectives: Insights from Women Across Academia and Industry on Schizophrenia and Other Psychotic Disorders" brings together leading women scholars, clinicians, and industry experts to explore innovative approaches to psychic disorder research and care. Hosted by the Diversity Task Force of the Schizophrenia International Research Society (SIRS), this symposium underscores the organization's commitment to fostering diversity and inclusivity within the scientific community. By highlighting the contributions of women from various professional backgrounds, the event aims to inspire collaborative efforts and drive advancements in the understanding and treatment of schizophrenia. The symposium will feature comprehensive discussions, culminating in actionable recommendations for SIRS members to facilitate meaningful change within the field. Through diverse, sector-spanning perspectives, this symposium will foster an enriched understanding of schizophrenia, spotlighting the critical contributions of women in advancing research, treatment, and awareness of this complex field.

### 3.1 Schizophrenia Risk Genes in Placentas of Children Prenatally Exposed to COVID-19 and Developmentally Delayed

Danielle Macedo, *Federal University of Ceara*

**Individual Abstract:** This symposium talk will explore how maternal SARS-CoV-2 infections during pregnancy can significantly alter placental gene expression, potentially influencing the neurodevelopmental outcomes of children. The study investigates the molecular pathways involved in this interaction, with a particular focus on those related to neurodevelopmental disorders such as schizophrenia. Using an extensive transcriptomic analysis of placental samples from 30 pregnancies affected by SARS-CoV-2, we integrated RNA sequencing data with neurodevelopmental assessments of the offspring over a two-year period.

Key findings highlighted changes in gene expression related to cognitive development and immune response, as well as genes associated with schizophrenia, such as EGR2, NTRK2, DEFA1, DGCR8, MAPK3, and FURIN. These alterations suggest a strong connection between maternal infection and disruptions in crucial neurodevelopmental processes.

The results provide ground-breaking evidence that maternal COVID-19 infections lead to lasting changes in placental gene expression, impacting pathways critical for neurodevelopment. This consistent upregulation of schizophrenia-related genes highlights a possible mechanism by which prenatal exposure to infections might elevate neuropsychiatric risks. Such insights deepen our understanding of the prenatal impact of viral infections on neurodevelopment and underscore the potential for identifying biomarkers that could guide early interventions to mitigate long-term neuropsychiatric effects.

### 3.2 Migration History and Risk of Psychosis: Results From the Multinational EU-GEI Study and the Recovery College Approach

Ilaria Tarricone, *Bologna University*

**Individual Abstract:** Background: Psychosis rates are higher among some migrant groups. We hypothesized that psychosis in migrants is associated with cumulative social disadvantage during different phases of migration.
Methods: We used data from the EUropean Network of National Schizophrenia Networks studying Gene-Environment Interactions (EU-GEI) case–control study. We defined a set of three indicators of social disadvantage for each phase: pre-migration, migration and post-migration. We examined whether social disadvantages in the pre- and post-migration phases, migration adversities, and mismatch between achievements and expectations differed between first-generation migrants with first-episode psychosis and healthy first-generation migrants and tested whether this accounted for differences in odds of psychosis in multivariable logistic regression models.

Results: In total, 249 cases and 219 controls were assessed. Pre-migration (OR 1.61, 95% CI 1.06–2.44, p = 0.027) and post-migration social disadvantages (OR 1.89, 95% CI 1.02–3.51, p = 0.044), along with expectations/achievements mismatch (OR 1.14, 95% CI 1.03–1.26, p = 0.014) were all significantly associated with psychosis. Migration adversities (OR 1.18, 95% CI 0.672–2.06, p = 0.568) were not significantly related to the outcome. Finally, we found a dose–response effect between the number of adversities across all phases and odds of psychosis (⩾6: OR 14.09, 95% CI 2.06–96.47, p = 0.007).

Conclusions: The cumulative effect of social disadvantages before, during and after migration was associated with increased odds of psychosis in migrants, independently of ethnicity or length of stay in the country of arrival. Public health initiatives that address the social disadvantages that many migrants face during the whole migration process and post-migration psychological support may reduce the excess of psychosis in migrants. In the prospective of the "recoveri college approach", we will discuss evidence based interventions for migrants.

### 3.3 Women in Science: Diversity in Clinical Trials

Yuki Mukai*, Merck Research Laboratories*

**Individual Abstract:** There has been emphasis on the importance of diversity in clinical trials. In schizophrenia clinical trials, there continues to be a need to diversify the participants enrolled in order to understand efficacy and safety across broader patient characteristics. There is continued effort in increasing recruitment in minority populations such as women, Latinos, and Asians. In this presentation, I will talk about the diversity representation in industry sponsored clinical trials and efforts to increase minority representation.

### 3.4 Dynamics of Human Factors in Rater Training/Monitoring: Impacts on Psychosis Clinical Trials

Rachel Berman*, Signant Health*

**Individual Abstract:** Though the intent is to deliver objective feedback to improve rating reliability and validity, human factors such as gender and age may affect communication between parties during vital rater training and data monitoring processes in clinical trials. In this talk, we bring in data and expert report to explore how demographic variables may impact rater/reviewer interactions in clinical trials for schizophrenia and other psychotic disorders.

## 4. Physical Health Side-Effects of Antipsychotics and State-of-the-Art Management Approaches: An Update From the Lancet Psychiatry Physical Health Commission

Toby Pillinger*, King's College London*

**Overall Abstract:** Despite modern medicine's tendency to fragment healthcare into silos, it is critical that people living with psychotic disorders such as schizophrenia have access to holistic treatments that protect both physical and mental health. Antipsychotics, alongside mood stabilisers and antidepressants, are critical components of evidenced-based treatment for people with psychotic disorders. However, the various medications within these classes may lead to a range of important side-effects across multiple organ systems, contributing to morbidity, mortality, and impaired quality of life.

Stemming from Part 3 of 'The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness' from 2019, a 2025 Commission Update has been written which provides an expanded and structured systems-based overview of psychotropic side-effects and their management strategies, relevant to the use of antipsychotics, mood stabilisers, and antidepressants. This Workshop accompanies the publication of the 2025 Commission Update and will provide attendees not only with early access to its guidance, but also an opportunity to discuss its contents with the authors. Gaps in the evidence-base across the various psychotropic classes and side-effect domains will also be considered, and key goals for future research and clinical practice highlighted.

Dr Maria Kapi will provide a lived experience perspective, detailing her own experience of the physical health side-effects of psychotropics and the importance of considering these when treating psychosis. Dustin Graham, Deputy Editor of The Lancet Psychiatry, will provide the Journal's perspective. Dr Sean Halstead will provide an overview of the methodologies used to construct the Commission Update. Professors Dan Siskind and Maggie Hahn will provide summaries of the evidence-based physical health guidance, employing case-based discussion and encouraging audience participation. The session will be chaired by Dr Toby Pillinger and the Discussant will be Professor Rob McCutcheon.

### 4.1 Physical Side-Effects of Antipsychotics: The Lived Experience Perspective

Maria Kapi*, Institute of Psychiatry, King's College*

**Individual Abstract:** I have schizophrenia the last almost 20 years and I am under antipsychotic medication all this time. I did gain weight after prescribed antipsychotics. I developed prediabetes the last 10 years and I am under metformin and that led to type 2 diabetes last year as confirmed by a glucose tolerance test. I believe this is a side effect of the antipsychotic use. After my diagnosis which is likely early enough before diabetes progresses significantly, I wore continuous glucose monitor for several cycles and I have a deep understanding now how nutrition affects my glucose levels, and I am on a strict diet, and I walk a lot daily. Additionally, my prolactin levels are double than the normal values for my age and I privately perform a mammogram every hear, as the UK NHS is really behind screening, and I was called only once for a mammogram three years ago. It is a real worry for me the probability of breast cancer as two of my best friends went through it and I know from

first-hand the level of the battle with the disease. It is already a full-time job to manage schizophrenia, but having other demanding comorbidities as diabetes or elevated prolactin on the top is overwhelming. We need the development of new class of antipsychotics with mild side effects profile.

**4.2 Journal Perspective**
Dustin Graham*, Lancet Psychiatry*

**Individual Abstract:** The goal of this talk will be to provide an overview of the goals of a Lancet Psychiatry Commission and how they apply to this specific topic of physical health and antipsychotics. Discussion will include the importance of multiple perspectives, including those with lived experience.

**4.3 Methodology and Evidence Synthesis Process Underpinning the Commission Update**
Sean Halstead*, The University of Queensland*

**Individual Abstract:** This section of the workshop will discuss the systematic review methodology underlying the Commission Update. As prospectively registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=510496), we undertook an umbrella review of the published literature and international guidelines to survey the evidence base for prevention and intervention strategies for the various domains of physical health side-effects associated with psychotropics, namely antipsychotics, mood stabilisers, and antidepressants.
After screening 6814 titles and abstracts, we identified over 60 systematic reviews and meta-analyses that informed the evidence synthesis of the Commission Update. We also consulted a variety of international guidelines to supplement the above umbrella review search, particularly for side-effects where no meta-analyses for interventions were available. Through this process, we summarised intervention strategies for side-effects for the following domains: cardiometabolic, cardiac conduction, neurological, sexual, endocrinological, gastrointestinal, anticholinergic, sleep-related, renal, haematological, and other organ side-effects.

Of note, there was significant heterogeneity in the literature, and a general imbalance with more meta-analyses and evidence-based interventions researched for antipsychotic related side-effects, particularly cardiometabolic side-effects and extra-pyramidal side-effects, compared to a relatively sparse evidence base for side-effect interventions for antidepressant and mood stabiliser.

This summary of the methodology and key results underpinning the Commission Update will facilitate further case-based discussions by Professors Dan Siskind and Margaret Hahn who will discuss application of the treatment algorithms synthesised in this Commission Update. Key limitations and areas for future research will also be discussed and workshopped with the group.

**4.4 Case Based Discussion on Management Psychotropic Adverse Drug Reactions**
Dan Siskind*, University of Queensland*

**Individual Abstract:** This section of the workshop will involve a case-based discussion highlighting the management of various psychotropic side-effect domains. For the purposes of this presentation, Mr. K is a 25-year-old male living with a diagnosis of schizoaffective disorder.

Neurological side-effects:

Mr. K has been treated for a year with a combination of zuclopenthixol and lithium and presents with concerning abnormal movements and ongoing paranoia. An interactive discussion will be facilitated surrounding the treatment strategies for neurological side-effects, namely tardive dyskinesia, with consideration of the evidence base behind interventions such as psychotropic rationalisation, Vitamin E, Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors.

Sleep-related side-effects:

After being switched from zuclopenthixol to clozapine, Mr. K presents several months latter describing significant fatigue during the day which is interfering with his family responsibilities. Management of sedation, hypersomnolence, and obstructive sleep apnoea as a comorbidity will be discussed.

Gastrointestinal and anticholinergic side-effects:

Mr. K later presents to hospital for severe constipation. His treating team review both the impact of clozapine and possible other agents contributing to anticholinergic burden. The PORIRUA Protocol is followed and prucalopride is utilised. Management of gastrointestinal and anticholinergic side-effects in cases of psychotropic polypharmacy will be workshopped.

Endocrinological and renal side-effects:

After years of symptomatic remission, Mr. K undergoes regular blood tests which indicate hypothyroidism and a decline in renal function (as measured through Glomerular Filtration Rate). Supplementation with thyroxine and management strategies for his emerging chronic kidney disease will be discussed.

Summary:

Throughout this above case-based discussion, treatment algorithms will be presented for management of the various side-effect domains. The aim will be to facilitate an organic open-discussion to highlight areas of consensus and gaps within evidence base.

### 4.5 Case Based Discussion on Management Psychotropic Adverse Drug Reactions

Margaret Hahn, *Center for Addiction and Mental Health*

**Individual Abstract:** Dr. Hahn will present a case highlighting monitoring and management of psychotropic based metabolic and endocrine adverse effects, including considerations of differences between men and women. An interactive discussion will be facilitated surrounding treatment strategies.

## 5. The Future of Open-Access Data Sharing for Psychosis Research: Introducing the Psychosis MRI Shared Data Resource (Psy-ShareD)

Paul Allen, *King's College London*

**Overall Abstract:** Whilst a large number of structural Magnetic Resonance Imaging (MRI) studies have been funded and undertaken, small sample sizes and heterogenous methods: have led to inconsistencies across findings. To tackle this, notable efforts have been made to combine datasets across studies and sites. However, these multi-site initiatives have generally been restricted to MRI scans in one or two illness stages, and often overlooked patient heterogeneity. The Psychosis MRI Shared Data Resource (Psy-ShareD) is a new open access structural MRI data sharing partnership that hosts pre-existing structural T1-weighted MRI data collected across multiple sites worldwide. MRI T1 data included in Psy-ShareD is available in image and feature level formats, having been harmonised using state-of-the-art approaches. All T1 data is linked to demographic and illness-related (diagnosis, symptoms, medication status) measures. Psy-ShareD is free to access for all researchers. Comprehensive data catalogues, scientific support and training resources are available.

### 5.1 Using MRI to Understand Ethnocultural Variance in Psychosis

Neelabja Roy, *National Institute of Mental Health and Neurosciences*

**Individual Abstract:** Although the prevalence of schizophrenia is uniform globally, there are subtle variations in the illness characteristics, including long-term outcomes, across geographies and ethnocultural spaces. Despite this, many brain-based investigations into the pathogenesis of schizophrenia have been conducted in the global North and other developed countries. Recent studies have focused on how ethnicity (encompassing genetic, linguistic, cultural, and environmental factors) can impact brain structure and function. However, this burgeoning research is limited by access to trans-global MRI datasets that allow comparisons between psychosis populations across global regions. We will discuss how Psy-ShareD is attempting to address this issue by including harmonised MRI-T1 datasets from geographical locations beyond Europe and North America.

### 5.2 Data Catalogues and Data Processing Pipelines

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

**Individual Abstract:** This session will cover repository structure and how Psy-ShareD is organised to allow access to MRI T1 datasets and linked clinical and cognitive data. Details on using the Psy-ShareD data catalogue, the central hub for managing and accessing data within the repository, will be provided. The session will also cover harmonisation, validation, quality control and support tools. Governance and data access procedures will also be described including step-by-step instructions on how to request and obtain data from the repository.

### 5.3 Planned Project Using Psy-ShareD Data and Psy-Tool

Jack Rogers, *University of Birmingham*

**Individual Abstract:** Psy-ShareD is applying advanced analytical methods to MRI-T1 data to generate personalised metrics of neuroanatomy. First, using brain-age-gap-estimates (brainAGE) and normative brain modelling indices Psy-ShareD data is being leveraged to provide a personalised framework for the quantification of atypical patterns. We are also using semi-supervised machine learning clustering models to explore heterogeneity within

the neuroanatomical signatures of schizophrenia and psychosis risk. Whilst distinct neuroanatomical subtypes have been identified within schizophrenia, replication and external validation steps remain a critical gap, especially across globally diverse schizophrenia populations. We are also using these advanced analytical approaches to develop pipelines for open access use and research via a Psy-ShareD Toolbox (PSY-TOOL).

**Keynote: A Rights Based Approach to Mental Health Care, Dr. Vikram Patel**

**6:30 p.m. - 7:30 p.m.**

**6. Keynote: A Rights Based Approach to Mental Health Care**

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

**Overall Abstract:** -

**6.1 A Rights Based Approach to Mental Health Care**

Vikram Patel*, Harvard Medical School*

**Individual Abstract:** A rights-based approach to mental health care is a paradigm shift that places human rights at the centre of mental health services and policies. Such an approach is grounded in the values of health equity which embraces the evidence that social determinants are profoundly associated with mental health problems. A rights-based approach recognizes that individuals with mental health conditions are entitled to rights, both which they share with their fellow citizens as well as those which are specific to their mental health condition. This lecture will address, in particular, the right to care which is aligned with the preferences of the person and respects their dignity, autonomy, and freedom while ensuring access to quality care. The lecture will describe the evidence supporting a number of strategies to realize this goal, in particular: addressing the social determinants of mental health problems; strategies to eliminate involuntary treatment and coercion in mental health care; designing programs which address what matters most to persons with mental health problems; shifting the node of care from the hospital to the community through the deployment of community resources as key members of the mental health care team; and the central role of peers in all aspects of the mental health care system.

**Plenary Session I: Adolescent Stress as a Risk Factor for Schizophrenia: Insight from Animal Models - Dr. Anthony Grace**

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

**7. Adolescent Stress as a Risk Factor for Schizophrenia: Insight From Animal Models**

Gemma Modinos*, King's College London*

**Overall Abstract:** -

**7.1 Adolescent Stress as a Risk Factor for Schizophrenia: Insight From Animal Models**
Anthony Grace*, University of Pittsburgh*

**Individual Abstract:** Adolescent stress can have a major impact on the risk and development of pathology in the adult. Moreover, the impact of stress can differ substantially between males and females. We found that the pathological consequences depend on the timing and intensity of the stressors, with parvalbumin (PV) neuron loss in multiple regions a driver of the pathology. Male and female rats were subjected to either daily handling or daily footshock + 3 restraint sessions over 10 days from PD31-40 (prepubertal, PreP) or from PD41-50 (postpubertal, PostP) and tested as adults ( > PD65). Acute stress impacted both males and females across development soon after exposure. Male rats that received combined stressors PreP exhibited hyperdopaminergic state (increased number of DA neurons) in the lateral VTA that projects to the schizophrenia-related associative striatum, as well as anxiety and cognitive deficits in the adult, whereas females were resilient. In contrast, exposure to stress PostP caused female rats to exhibit increased DA population activity primarily in the affect-related medial VTA, whereas the males were resilient. In both sexes, DA neuron overdrive was caused by vHip activation driven by significant vHip PV neuron loss. However, in males vHip activity is associated with PV neuron loss in the BLA leading to BLA activation and vHip PV neuron loss; this appears to be driven by stress-induced precocious maturation of BLA-PFC plasticity. In contrast, PostP stress in females was driven by the thalamic-hippocampal projection. Specifically, we examined the involvement of the nucleus reuniens of thalamus (RE) and thalamic reticular nucleus (TRN), as these regions have been linked to dopaminergic activity and cognitive regulation. PostP stress increased the number of active RE neurons only in females 5-6 weeks after stress, which was associated with a decreased number of PV neurons in the TRN at PD61. Therefore, in females PostP stress affects PV-TRN transmission leading to RE overdrive and hippocampal PV neuron loss, which selectively increased activity in the medial VTA DA neurons. These Results: show that male rats are vulnerable to PreP stress-induced disruption of associative-related DA neuron activity, which is consistent with the increased male susceptibility to schizophrenia and the likelihood that human males are more likely to undergo trauma PeriP in terms of bullying. In contrast, female rats were susceptible only to stress administered PostP, causing vHip PV loss leading to alterations only in the affect-related medial VTA, which is consistent with higher susceptibility to affective disorders and with females more likely to undergo trauma postpubertally in terms of sexual abuse. Therefore, modeling the impact of adolescent stress demonstrates parallels to the human condition, and can suggest mechanisms to circumvent vulnerability at this early stage.

**Concurrent Symposia**

**10:30 a.m. - 12:00 p.m.**

**8. A New Framework for Body and Movement as Foundations to Conceptualization, Early Recognition, Diagnosis, and Treatment in Psychosis**
Alexandra Moussa-Tooks*, Indiana University Bloomington*

**Overall Symposia Abstract:** Early conceptualization of schizophrenia highlighted the importance of bodily and self-disturbance as well as abnormal sensori-/psychomotor function. While work on body and movement/behavior in psychotic disorders has seen a resurgence in interest, there is still much progress to be made in this domain. Recent work is developing more complex understanding of sensori-/psychomotor disturbances in psychosis

phenotypes and ways in which movement and body can be central to therapeutic intervention. In this symposium, we start with a brief introduction to the history that has motivated the field and establish the framework for understanding and examination of both genuine and medication-induced sensorimotor and psychomotor disturbances. We then present ongoing advances in the early identification of psychotic disorders by using motor phenotypes. With this foundation, we move upwards in units of analysis to unpack psychomotor behavior on a broader scale, clarifying the role of neural systems and fundamental sensorimotor processes in psychosis pathology, including work on cerebellar structure. We then discuss the promise of the treatments that centralize the body and movement, while highlighting important distinctions between purely mechanical (exercise) interventions and multi-faceted dance-movement approaches. Finally, we end with lingering questions and challenges in understanding and targeting motor systems in psychosis. We challenge the audience to share their experiences, whether intentional or incidental, questions, and directions they would like to see in this translational pipeline.

### 8.1 Historical Origins and Recent Developments in the Examination of Sensorimotor and Psychomotor Abnormalities in Mental Disorders

Dusan Hirjak*[1]

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

**Background:** Sensorimotor and psychomotor abnormalities encompass a broad range of disturbances in motor, affective, cognitive, and behavioral functions, frequently observed across various mental disorders. These abnormalities, including psychomotor slowing, bradykinesia, neurological soft signs (NSS), abnormal involuntary movements (AIMS), and catatonia, are core clinical features of schizophrenia spectrum (SSD) and mood disorders (MOD). However, the pathomechanisms underlying sensorimotor and psychomotor abnormalities remain unclear, highlighting the need for deep phenotyping studies in patients with SSD and MOD to better understand these dysfunctions.

**Methods** This study employs two primary methods to explore the evolution and current understanding of sensorimotor and psychomotor abnormalities in mental disorders: First, a psychiatric hermeneutics approach is used to trace historical perspectives, focusing on contributions from Krafft-Ebing, Kahlbaum, Kraepelin, and Leonhard, with an emphasis on catatonia as a central psychomotor disorder. The shift in focus following the introduction of antipsychotics in the 1950s, which linked these abnormalities primarily to drug-induced effects, is also analyzed within this framework. Second, we will present data from more than 250 patients with SSD and MOD, assessed using structural and functional neuroimaging techniques along with various sensorimotor and psychomotor evaluation tools. These comprehensive assessments, including advanced neuroimaging and 3D motion capture, aim to identify and analyze dysfunctions in sensorimotor and psychomotor processes.

**Results:** First, the literature from 1800 to 1900 positioned sensorimotor and psychomotor phenomena at the nexus of motor and psychological symptoms, with ongoing debates about their underlying pathophysiological mechanisms. The advent of antipsychotics prompted a paradigm shift, redefining these abnormalities as drug-induced rather than inherently tied to the disorder itself.

Second, there are notable differences in functional connectivity when comparing patients with catatonia, as defined by ICD-11, NCRS, or BFCRS criteria, to age-, sex-, and medication-matched individuals who do not meet the corresponding catatonia criteria. Third,

this talk will demonstrate that corpus callosum alterations are key to the pathophysiology of catatonia, and machine learning models using these changes can significantly enhance diagnostic precision.

**Conclusions:** In conclusion, the understanding of sensori-/psychomotor abnormalities has evolved from early views linking motor and psychological symptoms to recognizing the influence of antipsychotics on sensori-/psychomotor abnormalities abnormalities. Recent studies highlight distinct differences in functional connectivity in catatonic patients and point to corpus callosum alterations as key to its pathophysiology. Machine and deep learning models using these changes show promise in enhancing diagnostic precision.

### 8.2 Early Recognition of Psychosis-Risk Through Motor Phenotypes: A Conceptual Approach

Vijay Mittal*[1]

[1]*Northwestern University*

**Background:** The brain circuits and networks that regulate human movement are the very same that are impacted in psychotic disorders. Motor signs can speak to vulnerability and to disease driving mechanisms. However, to harness the potential of these features for prediction and precision medicine, it is necessary to conceptualize motor signs in the context of early and later neurodevelopmental stages, and to recognize that a wide array of different signs and patterns speak to generalized vulnerability as well as distinct pathogenic processes.
**Methods:** In this presentation I will introduce a theoretical model that suggests general transdiagnostic vulnerability is expressed through one set of motor signs, while other sets reflect basal-ganglia, cerebellar, and cortical pathology. I will support this framework with data from high-risk studies in infancy, early and late childhood, as well as both early and late adolescence. The presentation will include several video examples, conceptual models, and exemplar studies.
**Results:** Evidence suggests that effective assessment and weighing of motor biomarkers is facilitated by the integration of concepts such as heterotypic continuity (i.e., the same vulnerability, such as clumsiness, maybe reflect different motor signs, across different developmental periods) and the distinction between motor and psychomotor processes. Further, distinguishing between movement endophenotypes (reflecting genetic risk, but independent of disease state) and motor biomarkers that are reflective of emerging disease driving mechanisms (e.g., progressive dopamine dysfunction in late adolescence coincides with increasingly strong correlations between dyskinetic movements and positive symptoms in the prodrome) can also add depth and precision to this work. The available evidence also indicates that distinct motor signs (e.g., gesture-speech mismatch, postural sway, hyperkinetic movements, neurological soft sings, spontaneous Parkinsonism's) can reflect unique high-risk subtypes (i.e., unique risk groups distinguished by motor signs that speak more to cerebellar-thalamic, frontal-striatal, and cortico-cortico dysfunction) that may be useful for improving prediction and tailoring treatment.
**Conclusions:** The growing body of literature supports the notion that motor signs have enormous potential for improving understanding, identification, prediction and treatment of early psychosis.

### 8.3 Establishing Mechanistic Models of the Role of Cerebellum in Model Updating Processes to Understand Motor Phenotypes in Psychotic Disorders

Alexandra Moussa-Tooks*[1], Jonathan Tsay[2], Baxter Rogers[3], Richard Ivry[2], Neil Woodward[4], Stephan Heckers[4]

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**Background:** Motor disturbance is a key phenotype in psychotic disorders, with motor signs observed in upwards of 66% of unmedicated, first-episode patients, and before disorder onset. While recent work has linked cerebellum to sensorimotor processing deficits, brain-behavior relationships have been difficult to establish in part due to a muddling of distinct processes in current tasks.
**Methods:** To address these gaps, we present pilot data from a new line of work using a motor learning task not yet utilized in the psychiatry literature. Participants (n=10) completed a computerized reaching task that allows us to capture directly measured (motor speed, implicit learning) and computationally modeled latent constructs (learning rate, motor system noise) with a modified state-space model. Cerebellar volume was calculated with the Spatially Unbiased Infratentorial (SUIT) toolbox. Analyses were performed in R; covariates included intracranial volume, age, sex, and chlorpromazine equivalents.
**Results:** We observed no differences between groups in any metrics of motor speed (initiation or execution of the reach). Psychosis participants did exhibit higher modeled motor noise (d=0.6) and implicit adaptation was positively correlated with cerebellar somatomotor network volume in the psychosis group (d=0.54).
**Conclusions:** Our work provides evidence that the slowing observed in psychosis may not be due to mechanical limitations of the motor system, but noise present in the motor system and an inability to update internal motor models, driven by cerebellum. Continued work will track symptoms and task performance longitudinally.

### 8.4 Dance/Movement Therapy as a Treatment Option for Individuals With Schizophrenia: Addressing Body Dysregulation Through Body-Based Psychotherapy

Jacelyn Biondo*[1]

[1]*Thomas Jefferson University*

**Background:** Dance/movement therapy (DMT) is a trauma-informed, strengths-based approach to psychotherapy that places dance, movement, and the body at the forefront of the therapeutic process. DMT acknowledges and prioritizes dance and the body as relational factors and a primary form of communication. Through DMT, symptomatology associated with schizophrenia are processed on a pre-conscious, pre-verbal level through embodied and relational therapeutic practices.
**Methods:** DMT provides individuals with schizophrenia a treatment option that addresses each component of their symptomatology: physical, mental, cognitive, and social. As individuals with schizophrenia may experience multiple and alternate reality bases, DMT provides a non-verbal approach to psychotherapy that uses the body as a source of entry and processing. This diminishes some of the typical defenses expressed by individuals with schizophrenia that may be prominent in more traditional verbal and behavioral therapies. Moreover, due to the disproportionately high stigmatizing behaviors and barriers to wellness individuals with schizophrenia face, innovative, accessible, and equitable psychosocial treatment options must be prioritized.
**Results:** Engaging through a relational lens, DMT provides individuals with schizophrenia, in both acute and chronic presentations, the potential for: (1) reduction of positive (Biondo et

al., 2021) and negative (Biondo et al., 2021; Bryl et al., 2020; Gökcen et al, 2020; Savill et al., 2017) symptoms; (2) increased self-awareness and mind-body connectivity (Biondo et al., 2021; Bryl et al., 2020); (3) diminished psychological discomfort (Biondo et al., 2021); (4) increased interpersonal skills and sense of belonging (Biondo et al., 2021); and increased self-confidence, self-efficacy, and motivation (Biondo et al., 2021; Bryl et al., 2020).
**Conclusions:** Dance/movement therapists incorporate a multitude of components into their practice in order to attend to the discreet needs of individuals with schizophrenia. Such factors include polyvagal and biochemical regulation, interoception, kinesthetic empathy and attunement, memory and affective systems, and brain lateralization (Homann, 2020). Furthermore, "Movement engages deep systems of biochemical regulations, facilitates arousal and rest, and stimulates the core of self-perception at the neurological intersections of emotional, sensory, and cognitive processes" (Homann, 2020, p. 298).

## 9. Decomposing Early Psychotic and Affective Symptoms With Functional Neuroimaging

Jacqueline Clauss*, Maryland Psychiatric Research Center, University of Maryland School of Medicine*

**Overall Symposia Abstract:** The high-risk and early stages of psychiatric disorders are often characterized by a complex mixture of mood, psychotic, and anxiety symptoms. From a clinical perspective, predicting the longitudinal course of these symptoms remains challenging. Evidence from genetic, neuroimaging, and clinical studies suggests that affective and psychotic symptoms have both shared and unique risk factors. Understanding differences in brain function and connectivity related to these early symptom and risk profiles may provide opportunities for prevention, earlier specialized treatment, and improved prediction of clinical trajectories. Participants in this symposium will present cutting edge behavioral and neuroimaging data supporting both shared and unique mechanisms underlying risk and early disease across the mood-psychosis spectrum. Two presentations will focus on risk states and unique contributions of mood, psychotic, and anxiety symptoms to functional activation and connectivity. The other two presentations will focus on individuals with early established illness, including bipolar disorder (with and without psychotic features), and psychotic disorders (with and without mood features) and connectivity differences based on these profiles. Together, these findings describe altered trajectories of brain function and connectivity as mood and psychotic symptoms emerge. Results: of these studies may inform mechanistic models, diagnostic paradigms, and prediction of clinical trajectories.

### 9.1 Longitudinal Instability of a Mood-Related Resting-State Network in Youth With Bipolar Disorder

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**Background:** Bipolar disorder (BD) is characterized by temporal instability of mood and energy, but the neural correlates of this instability are poorly understood. In previous cross-sectional studies, mania has been correlated with increased functional connectivity (FC) of subcortical regions (i.e., amygdala, ventral striatum, thalamus, and ventral tegmental area) and ventromedial prefrontal cortex. Here, we assess whether BD, with and without history of

psychotic symptoms, is associated with longitudinal instability within this mood-related network of interest (NOI).
**Methods:** Young people with BD-I/II were scanned 4-6 times and age-matched healthy controls (HC) were scanned 4 times over 9 months. Following preprocessing of 20-minute resting-state scans, we extracted time-series data using the Shen parcellation and calculated the mean Pearson "correlational distance" between the functional connectivity (FC) of each scan and all other within-person scans, as a measure of longitudinal instability. We next used linear mixed models, nesting within subject, to assess the relationship between diagnostic group (BD vs. HC) and correlational distance, focusing on edges within an a priori mood-related NOI. We next preliminarily assessed the degree to which findings differed for youth with a lifetime history of psychotic symptoms. All models were adjusted for age, sex, and motion (mean framewise displacement).
**Results:** Our sample consisted of 16 youth (11 BD, 5 HC; 16-25 years old) with 70 scans (50 BD, 20 HC). This included 6 BD youth (26 scans; all BD-I) with a history of psychotic symptoms, primarily during manic episodes, and 5 BD youth (24 scans; all BD-II) without such history. Compared to HC, BD showed greater correlational distance between scans (beta 0.11; p=.0008), distinguishing BD (vs. HC) with excellent accuracy (AUC=0.95). This difference was driven largely by youth without lifetime psychosis (BD-no psychosis vs. HC; beta 0.17; $p < .0001$), who also showed greater correlational distance than BD with lifetime psychosis (BD-no psychosis vs. BD-lifetime psychosis; beta 0.09; $p < .0001$). Youth with a history of psychosis showed greater correlational distance than HC (BD-psychosis vs. HC; beta 0.08; $p < .0001$), but the difference was attenuated compared to those without psychosis. Findings were not explained by medication changes, the amount of time between scans, or time of day differences.
**Conclusions:** Within this pilot sample, we find BD to be characterized by greater correlational distance (i.e., more within-person network instability) within a mood-related NOI. These findings were driven by BD youth without a history of psychotic symptoms, though were also found to a lesser degree in youth with such history. In our small sample, there was complete overlap between BD subtype and history of psychotic symptoms, so the independent contributions of these clinical distinctions cannot be assessed. While preliminary, these results highlight a possible role for precision imaging approaches as a diagnostic marker for BD, particularly for BD-II youth without psychosis.

### 9.2 Task-Based Functional MRI Markers of Risk for Psychotic, Mood, and Anxiety Disorders: An Activation Likelihood Estimation Meta-Analysis

Jacqueline Clauss*[1], Zachary Millman[2], Joey Rodriguez[3], Dylan Cugley[4], Katherine Dokholyan[5], Jennifer Blackford[6], Daphne Holt[7]

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**Background:** Identification of functional brain changes present early in at-risk populations represent a first step towards finding treatment and prevention targets. There is evidence for both shared (transdiagnostic) and specific risk factors for psychiatric disorders. Functional neuroimaging is one approach that has aimed to identify changes in brain function associated with such risk. In the current study, our goal was to identify common and specific functional

brain alterations across three known at-risk populations – those at risk for anxiety disorders, mood disorders, and psychosis.
**Methods:** A meta-analysis of functional neuroimaging studies comparing a group at high-risk for developing an anxiety disorder, a mood disorder, or a psychotic disorder, to a control group was performed. Risk was defined based on early or attenuated symptoms, familial risk, or temperament-based risk. The analysis was limited to studies which used task-based functional magnetic resonance imaging MRI (fMRI), whole brain analysis, and with a mean age of < 30 years old. Region-of-interest based analyses were excluded. Studies were identified through a search of manuscripts available on PubMed and Web of Science from January 2000 through December 2022. References from studies and known meta-analyses were examined to identify additional studies for inclusion. 7,103 studies were screened and discrepancies were determined by consensus. Coordinates of the peak voxel of significant between-group whole brain findings were extracted. Coordinates were entered into an activation likelihood meta-analysis using GingerALE software. Contrasts were computed for each high-risk group > control group and control group > high-risk group. Contrasts were thresholded at $p < 0.05$ FWE cluster-corrected using 1000 permutations
**Results:** One hundred and four (104) studies were selected for inclusion, representing 9703 subjects (4794 high-risk and 4909 controls), including 12 studies of anxiety risk, 25 studies of mood disorders risk, and 67 studies of psychosis risk. Compared to controls, participants with risk for anxiety disorders had significantly greater activation in the bilateral rostral and dorsal anterior cingulate cortex. Participants with risk for mood disorders had significantly greater activation in right hemisphere subcortical regions, including the globus pallidus, putamen, and amygdala, as well as the right parahippocampal gyrus and right inferior frontal gyrus. Participants with risk for psychosis had greater activation in areas of the bilateral posterior default mode network, including the posterior cingulate and precuneus, as well as the left dorsolateral prefrontal cortex and insula.
**Conclusions:** Each risk group showed a distinct pattern of brain activation, suggesting some specificity of risk-related brain activation by group. Ongoing analyses include comparisons of risk groups, testing for common patterns across all samples, and testing for differences based on type of experimental task employed.

### 9.3 Value Representation, Working Memory, and Functional Brain Networks in Negative Symptoms of Early Psychosis

Zachary Millman*[1], Daphne Holt[2], Matcheri Keshavan[3], Larry Seidman[4], Alan Breier[5], Martha Shenton[6], Dost Ongur[1]

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**Background:** Negative symptoms of schizophrenia often involve difficulty orienting behavior toward long-term goals. Modern etiological theories suggest that lower levels of working memory impair value representation – the ability to generate, maintain, and use mental abstractions of reward value to guide decision-making – thereby contributing to negative symptoms. People with chronic schizophrenia show alterations on tasks requiring intact value representation, such as delay discounting (DD) paradigms which assess the tendency to favor smaller, more temporally immediate rewards over larger, more distal rewards. These difficulties are in turn associated with more severe negative symptoms, working memory impairments, and functional connectivity reductions within the task-

relevant frontostriatal and frontoparietal networks. Very little is known about the extent to which DD impairments and their links with symptoms and functional network connectivity extend to the early course of illness. Moreover, only one study to our knowledge has compared DD performance between people with early schizophrenia spectrum vs. affective psychosis, despite evidence that these two syndromes may represent distinct neurodevelopmental subtypes.
**Methods:** We will present data from the Human Connectome Project for Early Psychosis: 161 patients with early psychosis and 62 healthy controls ages 18-36. In the DD task, participants chose between smaller and larger hypothetical monetary outcomes that were delivered trial-wise at one of five delay intervals. DD values were calculated as the area under the curve of indifference points; smaller DD values reflect greater discounting. Resting state functional connectivity was acquired on 3T Prisma scanners in four 5-minute runs. Prior findings from this study showed altered structural connectivity of the frontostriatal network; here we will examine functional connectivity of this network and of the frontoparietal network and relate the findings to DD data. We hypothesized that (a) DD impairment is greater in schizophrenia spectrum than affective psychosis patients, and that (b) links between DD and patient status and negative symptoms are accounted for by working memory impairments. We further hypothesize that (c) schizophrenia spectrum patients show the greatest reductions in functional network connectivity and that these differences are related to DD performance.
**Results:** Schizophrenia spectrum patients showed lower DD scores than both controls ($t[173] = 3.181$, $p = .002$) and patients with affective psychosis ($t[160] = 2.502$, $p = .013$), whereas patients with affective psychosis did not differ from controls ($t[105] = 0.320$, $p = .750$). Reduced DD scores were associated with poorer working memory ($r = .224$, $p = .019$) and greater negative symptom severity ($r = -.235$, $p = .014$) in schizophrenia spectrum but not affective psychosis patients ($r = .164$, $p = .289$ and $r = .174$, $p = .258$, respectively). Patient-control differences in DD were eliminated when controlling for working memory performance ($F[1, 209] = 2.177$, $p = .142$) and fully mediated the DD-symptom relation. Functional neuroimaging data will be presented in conjunction with these results.
**Conclusions:** Like chronic schizophrenia, early course of psychosis is associated with reduced DD performance. However, these impairments appear more specific to schizophrenia spectrum vs. affective psychosis. We observed a central role of working memory in linking DD to patient status and negative symptoms, which supports modern theories of negative symptom etiology. Examining the functional network correlates of this critical pattern of findings will inform mechanistic, brain-behavior models of negative symptoms that may inform treatment.

### 9.4 Dissociable Default Mode Network Functional Connectivity Patterns Underlie Affective and Negative Symptoms in Clinical High Risk

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**Background:** Prior to onset, many individuals experience a psychosis-risk, or Clinical High-Risk (CHR) syndrome, which is characterized by subthreshold symptoms of schizophrenia. These syndromes may include negative symptoms (e.g., avolition, alogia, anhedonia), dysphoric mood, impaired self-representation, cognitive decline, and functional deterioration in major life roles, among others. previous studies have reported hyperactivity and hyperconnectivity within the default mode network (DMN), an intrinsic brain network active at rest and during internally focused and self-referential tasks. Furthermore, stronger DMN

functional connectivity was found to be associated with worse psychotic symptoms in patients and in individuals with familial risk. In CHR individuals, there is evidence of increased DMN connectivity, although no association with symptom severity has been reported. The study of DMN hyperconnectivity prior to psychosis onset can provide insight into clinical progression and guide prevention.
**Methods:** To assess intrinsic functional connectivity of the medial prefrontal cortex and associated symptoms in CHR, we analyzed cross-sectional resting-state fMRI data from 158 CHR subjects (age: 18.8±4.9; 78 females) and 93 age-, sex-, and education-matched healthy controls (age: 18.7±4.6; 44 females). DMN functional connectivity was assessed by seeding the medial prefrontal cortex (MPFC). Primary clinical measures were psychosis-risk symptoms assessed via the Structured Interview of Prodromal Syndrome (SIPS) and affective symptoms assessed via the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A).
**Results:** Compared to controls, CHR individuals showed two types of abnormal connectivity patterns: greater functional connectivity (cluster threshold of $p < 0.05$, FDR-corrected; voxel threshold of $p < .001$, uncorrected) between the MPFC seed and 1) other DMN nodes including the posterior cingulate cortex (PCC), angular gyrus, superior frontal gyrus and cerebellum Crus II, as well as 2) the auditory cortices in the superior and middle temporal gyri (STG/MTG). Among CHR subjects, stronger MPFC-PCC connectivity was significantly associated with higher HAM-A scores ($r = 0.23$, $p = 0.006$), and not with the SIPS-N subscale ($r = 0.15$, $p = 0.056$). In contrary, greater MPFC-STG/MTG connectivity was significantly (qFDR < .05) associated with higher total SIPS-N score ($r = 0.26$, $p = 0.001$), but not with HAM-A ($r = 0.09$, $p = 0.286$). Secondary principal component analysis of item-level SIPS scores revealed two principal components (PCs) corresponding to a negative symptoms PC (46.4% of explained variance) and an affective symptoms PC (23.0% of explained variance). A similar dissociation was found where Stronger MPFC-PCC connectivity was significantly associated with higher PC2 scores ($r = 0.27$, $p < 0.001$) but not with PC1 scores ($r = -0.02$, $p = 0.821$); and stronger MPFC-STG/MTG connectivity was significantly associated with PC1 scores ($r = -0.20$, $p = 0.016$) but not with PC2 scores ($r = 0.11$, $p = 0.106$).
**Conclusions:** In conclusion, we found two hyperconnectivity patterns show dissociable associations with two distinct symptom clusters in CHR. These findings suggest that specific hyperconnectivity patterns may underlie distinct dimensions of symptomatology during the prodromal stage, each with transdiagnostic implications.

**10. Prevalence, Prediction and Prevention of Multimorbidity in Psychotic Disorders**
Benjamin Perry*, University of Birmingham, Institute for Mental Health*
**Overall Symposia Abstract:** Individuals with a diagnosis of schizophrenia have a reduced life-expectancy by at least 15 years compared to the non-affected population. A major contributor to this early mortality is cardiovascular and respiratory disorders. This symposium will focus on the early detection of these multimorbidities and most importantly, how they can be prevented or treated.
Mr. Michael Norton will provide a first-person account of his lived experience of psychosis and also how the diagnosis and treatment impacted his physical health. Michael will discuss how the recovery model would be strengthened by further integration of physical health into the paradigm.

Following this, Dr Sean Halstead will present findings from a large meta-analysis that determined the prevalence of multimorbidity in people with severe mental illness, including schizophrenia. This presentation will demonstrate that the health disparity is greater for people under the age of 40 and that at least one-quarter of individuals with severe mental illness have physical multimorbidity.

Mrs. Caroline Hynes will present findings from two reviews. The first will be an umbrella review examining the interventions for dyslipidemia, an important precursor to cardiovascular disease, in people with severe mental health disorders. While there has been a modest amount of research in this area in adults, it is a neglected area in children and adolescents. Therefore, the results of a separate systematic review examining interventions for dyslipidemia in children and adolescents will be presented. This review will demonstrate that this is a neglected area, and there is no clinical guidance for clinicians aiming to prevent the potential sequelae of dyslipidemia in young people. A clinical guideline for the management of antipsychotic-induced dyslipidemia will be presented.

The ultimate goal is for multimorbidity to be prevented, and for this to be achieved, reliable prediction of those at greatest risk needs to be possible. Associate Professor Benjamin Perry will present on the development and inter-continental validation of PsyMetriC, a cardiometabolic risk prediction algorithm that can be used in routine clinical practice to identify individuals at greatest cardiometabolic risk.

Finally, Prof Fiona Gaughran, Professor of Physical Health and Clinical Therapeutics at Kings College London will act as the discussant for this symposium.

## 10.1 Incorporating Physical Health Into the Recovery Paradigm – A Lived Experience Perspective

Michael Norton*[1]

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**Background:** Since it was first defined by William Anthony in 1993, the concept of recovery in mental health has grown in popularity. So much so that it led to the growing recognition of lived experience as a knowledge set that can be used to support traditional services in their approach to care. More recently, a social element to recovery has been adopted which incorporated gaining back social functioning required to contribute meaningfully in society. Part of this new approach focuses on the whole health of an individual, including their physical health. Something which until now, has been a missing factor within the recovery paradigm for many individuals experiencing mental health difficulties.

**Methods:** What follows is an investigation into weight gain that results from the use of a second generation antipsychotic medication: olanzapine. To support this, a qualitative, reflective methodological process: autoethnography will be used. Autoethnography is similar to ethnographic research, but instead of understanding the experiences of other people, autoethnography serves the purpose of gaining first-hand experiences of the presenter in regards to olanzapine intake for psychosis and the impact of the associated weight gain has had on his life to the present day. Additionally, how such lived experiences can become ingrained into the recovery model will also be addressed.

**Results:** Through the process of autoethnography, Michael explores how the decision was made to take olanzapine. Through an honest reflection of his time on this medication, Michael explores how, for him, weight gain was a price he has to pay for living a life relatively free of voices and shadows. However, he also describes in detail the draw that has been so frequently discussed in the literature towards savoury products like high caffeine, high calorie drinks and chocolate for those on this drug and the almost trembling effect this has until these products are consumed. Additionally, Michael explores how weight gain and its physical effects on his physiology has caused self-esteem as well as physical pain and cardiopulmonary issues that still occur to this day.
**Conclusions:** Although antipsychotics are a useful drug in the elimination of the positive symptoms of psychosis, they can have detrimental physical side effects for the person trying to recover. Taking antipsychotics should not be a one-sided decision, rather it should be made in co-production with both sides fully informed on the positive and negative consequences of this action. Additionally, this autoethnographic account highlights the need for more research into the area of physical health when taking antipsychotics so that these physical side effects can be minimised thereby raising compliance levels towards antipsychotic use in mental health care.

### 10.2 Physical and Psychiatric Multimorbidity in People With Schizophrenia: Prevalence and Perspectives

Sean Halstead*[1], Chester Cao[2], Grimur Høgnason Mohr[3], Bjorn Ebdrup[4], Toby Pillinger[5], Robert McCutcheon[6], Joseph Firth[7], Dan Siskind[8], Nicola Warren[1]

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**Background:** People with severe mental illness, such as schizophrenia, face notable disparities in health outcomes, partly due to the simultaneous physical health challenges that often accompany their psychiatric conditions. Multimorbidity, defined as the co-occurrence of two or more chronic conditions, is hypothesised to be a pertinent framework in viewing the cumulative chronic disease burden, both physical and psychiatric, experienced by people with severe mental illness.
This symposium presentation will focus on two research questions (RQ): (RQ 1) How prevalent is multimorbidity among individuals with severe mental illness compared to those without severe mental illness? (RQ 2) Why is multimorbidity an important clinical framework for characterising the health disparities in people with severe mental illness?

**Methods:** RQ 1)
A systematic review and meta-analysis was conducted to estimate the prevalence of physical and psychiatric multimorbidity in people with severe mental illness. We ran a systematic search in CINAHL, EMBASE, PubMed, and PsycINFO from database inception up until February 15, 2024, to identify observational studies that assessed multimorbidity prevalence. Eligible studies needed to contain an observational design, consist of an adult population

(mean age ≥18 years) diagnosed with either schizophrenia-spectrum or bipolar disorder, and measure the prevalence of either physical multimorbidity (≥2 physical health conditions) or psychiatric multimorbidity (≥3 psychiatric conditions, including the severe mental illness). For studies with a control group without severe mental illness, a random-effects meta-analysis was performed to compare the odds of physical multimorbidity between individuals with and without severe mental illness. The absolute prevalence of both physical and psychiatric multimorbidity in those with severe mental illness was also calculated. Sensitivity and meta-regression analyses were conducted to examine various demographic, diagnostic, and methodological factors.

RQ 2)

A narrative synthesis of existing multimorbidity literature was also performed to highlight its clinical significance and identify key challenges for the field in embracing multimorbidity as a public health construct.

**Results:** RQ 1)
From over 10,000 screened abstracts, 82 studies with relevant data were included, comprising a pooled cohort of 1,623,773 individuals with severe mental illness. The odds ratio (OR) for physical multimorbidity between individuals with and without severe mental illness was 2.40 (k=11, 95% CI: 1.57, 3.65), with a greater disparity observed in younger populations under 40 (OR: 3.99, 95% CI: 1.43, 11.10). The absolute prevalence of psychiatric and physical multimorbidity in individuals with severe mental illness was 14% (95% CI: 0.08, 0.23) and 25% (95% CI: 0.19, 0.32) respectively.

RQ 2)

Whilst multimorbidity remains an emerging term in psychiatric literature, it is receiving increased attention as a framework that characterises the complexity of having multiple concurrent physical and psychiatric conditions. We hypothesise that prolonged exposure to cumulative lifetime burden of multimorbidity worsens key health outcomes, summarised as the "three Ds": death, disability, and health-economic deficit.

**Conclusions:** The multimorbidity framework offers a valuable perspective for contextualising the chronic disease burden faced by people with severe mental illness. The findings show that individuals with severe mental illness have over twice the odds of having physical multimorbidity compared to those without. Implementing a multimorbidity-based clinical framework could enhance the prevention and management of complex multiple disease burden in this group, advocating for integrated, multidisciplinary care rather than isolated treatment approaches focused on individual organ systems.
*This Abstract is based upon our published systematic review in The Lancet Psychiatry:

Halstead, S., Cao, C., Høgnason Mohr, G., Ebdrup, B. H., Pillinger, T., McCutcheon, R. A., Firth, J., Siskind, D., and Warren, N. (2024). Prevalence of multimorbidity in people with and without severe mental illness: a systematic review and meta-analysis. The Lancet Psychiatry, 11(6), 431–442. https://doi.org/10.1016/S2215-0366(24)00091-9

### 10.3 Management of Antipsychotic-Induced Dyslipidaemia: Systematic and Umbrella Reviews and Guideline Development

Caroline Hynes-Ryan*[1], Aoife Carolan[1], Faye Carrington[2], David Columb[3], Dolores Keating[1], Brian Odonoghue[3]

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**Background:** Dyslipidaemia is a highly prevalent and important risk factor in the development of atherosclerotic cardiovascular disease. Individuals with severe mental illness have a 2-3 times higher risk of dying from this compared with the general population. Unlike weight gain, dyslipidaemia is asymptomatic which may explain why it hasn't received the attention that it warrants as a modifiable risk factor.
The current focus of assessment/prevention of cardiovascular risk is in adults > 40 which neglects those with severe mental illness taking antipsychotics from adolescence/early adulthood. Clinical complications of cardiovascular disease mainly occur in middle age/later life for the general population. However, for those with severe mental health disorders taking antipsychotics, atherosclerosis has its roots much earlier, therefore, managing antipsychotic-induced dyslipidaemia in children, youth and adults is crucial to optimising their physical health outcomes.

We aimed to evaluate the efficacy of pharmacological interventions for dyslipidaemia in both children and youth taking antipsychotics and in adults with severe mental illness.

**Methods:** We carried out a systematic review in those < 18 years taking antipsychotics (Child/Youth Group) and an umbrella review in adults with severe mental illness (Adult-Group) to identify the evidence for pharmacological interventions to manage dyslipidaemia. For the Child/Youth group, PubMed and Embase were searched from inception to 28/08/24. For the Adult Group, PubMed, Embase and the Cochrane Database of Systematic Reviews were searched from inception to 05/06/24.
**Results:** In the child/youth group, 1530 titles and abstracts were screened and of these, 10 articles were eligible from 9 unique studies. There were no studies that looked exclusively at lipids as primary outcomes. Metformin was the most studied intervention (n=4). In the two RCTs conducted with metformin vs placebo, there was no difference in the lipid outcomes observed. In the two cohort studies, one study found a reduction in triglyceride levels with metformin and no difference was observed between metformin and placebo in the other. Other studies examined psychostimulants (n=1), topiramate (n=2), valproate (n=1), melatonin (n=1) and betahistine (n=1) with only melatonin having a statistically significant impact on lowering total cholesterol and topiramate on lowering LDL.
In the adult group, 1719 titles and abstracts were screened and of these 5 systematic reviews studied lipids as primary outcomes. Pooled meta-analysis of mean difference for endpoint change in lipid parameters showed a statistically significant lowering of total cholesterol and triglycerides for metformin compared to controls. Lipid lowering therapies, omega-3 and statins also demonstrated a statistically significant lowering of total cholesterol but not other lipid parameters.

A clinical guideline is being developed for the management of antipsychotic-induced dyslipidaemia using the GRADE and RIGHT-Ad@pt frameworks and will involve pharmacists, psychiatrists, cardiologists, endocrinologists, general practitioners and people with lived experience.

**Conclusions:** The evidence on the management of antipsychotic-induced dyslipidaemia is incomplete, in particular for those < 18. Licensed treatments for dyslipidaemia (statins) have not been studied in those < 18 and in low numbers in adults. The cardioprotective effect of statins is well studied in the general population and our reviews found no evidence to suggest those with mental illness should be treated differently. While unlicensed for dyslipidaemia, there may be a role for metformin in the management of this side-effect especially for those with comorbid diabetes or antipsychotic-induced weight gain. The results of our reviews will be important in shaping future guidance on the management of antipsychotic-induced dyslipidaemia in children, adolescents and adults.

### 10.4 Psymetric: An Internationally Useful Cardiometabolic Prediction Algorithm for Psychosis Early Intervention

Benjamin Perry*[1], Emanuele Osimo[2], Graham Murray[2], Rachel Upthegrove[3], Golam Khandaker[4]

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**Background:** Cardiometabolic dysfunction such as insulin resistance and dyslipidaemia is commonly detectable from the onset of psychosis-spectrum disorders in some individuals, but there is substantial individual-level variability in the development of adverse cardiometabolic outcomes after a first episode of psychosis.
PsyMetRiC is a cardiometabolic risk prediction algorithm developed and externally validated using electronic health record data from three psychosis early intervention services the UK. PsyMetRiC is able to provide individual-level risk probabilities of developing metabolic syndrome up to six-years later. PsyMetRiC is on course for regulatory approval and implementation in the UK. However, risk prediction algorithms cannot be used in other (i.e., international) populations without confirming they are accurate.

**Methods:** PsyMetRiC has been externally validated using a mixture of cohort and eletronic health record data in seven international settings across four continents (Spain, Switzerland, Netherlands, Finland, Hong Kong, Canada, Australia). Algorithmic accuracy was assessed following best-practice methods, comprising discrimination (area under the curve; C-statistic), calibration (calibration plots), and clinical usefulness (decision curve analysis). In each individual international setting, considerations were made to the benefit/need of recalibration or model revision in order to generate population-specific versions of PsyMetRiC. Each successfully validated and recalibrated/revised algorithm has been added to a freely-available online data visualisation tool, and will be integrated into a clinician-facing web app.
**Results:** To date, PsyMetRiC has been validated in over 3,500 cases of early psychosis across international settings. PsyMetRiC has shown evidence of stable discriminative accuracy (C-statistics ranging between 0.71-0.76). However, calibration plots have mostly revealed minor degrees of miscalibration, necessitating the need for recalibration strategies. Strategies have ranged from recalibrating the intercept to account for differences in baseline risk of metabolic syndrome in different populations, through to the revision and updating of predictors to more closely represent the sociodemographic characteristics of the local population (e.g., race). In all instances, recalibration strategies led to clear improvements in both algorithm calibration accuracy and likely clinical usefulness. In all international

populations, PsyMetRiC is likely to be clinically useful - leading to improved detection (thus early intervention) of future metabolic syndrome cases without increase in false positives. **Conclusions:** PsyMetRiC is a flexible, accurate and clinically-useful cardiometabolic risk prediction algorithm adaptable for the needs and characteristics of different international populations. As well as stakeholder engagement to drive local implementation strategies, more attention on validation in lower and middle income countries is required if PsyMetRiC and the interventions attached to it will make a difference at the global level.

**11. Social and Clinical Determinants of Premature Mortality in Schizophrenia: International Perspectives**

Faith Dickerson*, Sheppard Pratt*

**Overall Symposia Abstract:** Schizophrenia is associated with a reduced lifespan of 10-20 years around the world. This premature mortality is one of the most important adverse outcomes of schizophrenia and deserves the highest priority in efforts to improve the quality of life in persons with schizophrenia. Most data come from North America and Europe. However premature mortality in schizophrenia is a serious problem in other areas of the world, with particularly devastating effects in low- and middle-income countries.
This symposium features researchers from Africa, India, Europe and the United States, consistent with the mission of SIRS to advance international communication and collaboration and the need to include perspectives from underrepresented minorities and countries.

Contributing factors to premature mortality that have been identified include social determinants of health such as limited access to health care, as well as poverty and homelessness. Other contributing factors are tobacco smoking and an increased prevalence of some comorbid medical disorders. While some of the determinants of premature mortality in schizophrenia may be shared across countries, others are specific to individual cultures and geographic areas. Understanding the causes of early death is essential to identify solutions which may be adapted to different settings.

In this symposium we will present data about premature mortality in schizophrenia from around the world, associated social and clinical determinants, and potential remedies.

The first presentation is from Dr. Faith Dickerson reporting on the outcomes of persons with schizophrenia living in Baltimore MD, USA. These individuals received a comprehensive assessment at baseline including variables not typically included in mortality studies. In a follow-up period of up to 24 years, natural cause mortality was associated with lower cognitive functioning, tobacco smoking, obesity, and the presence of co-occurring medical conditions such as autoimmune disorders. Separated/divorced marital status was also significant, underscoring the importance of social support in health outcomes.

The second presentation is from Dr. Smita Deshpande of Bangalore, India who will review the limited available data about premature death from natural causes and suicide in schizophrenia in India, highlighting the issues which contribute to health disparities in a country with life expectancy and health care significantly below that in Western settings.

The third presentation, from Dr. Abebaw Fekadu from Addis Ababa, Ethiopia, will report on a large mortality study conducted in Ethiopia in which the mortality gap was among the highest in the world, > 30 years. The main causes of natural death were infectious conditions such as malaria and tuberculosis which are highly prevalent in many areas of the country.

In the final presentation, Dr. Jayati Das-Munshi from London, UK, will present the results of a study examining the role of social exclusion in all-cause mortality in persons with schizophrenia and bipolar disorder in England. Drawing on census data, the study found that the presence of all social exclusion indicators (e.g. living along, being unmarried, being unemployed) were associated with a higher all-cause mortality risk in the psychiatric group compared to the persons without these disorders in the general population. Some of social exclusions factors such as marital and employment status were particularly implicated in the excess morality in the psychiatric population.

The discussion, led by Dr. Robert Yolken, will engage the presenters and the audience in the consideration of universal strategies to address the mortality gap as well as ones that need to be adapted for the geographic region and income status of individual countries. The discussion will also address ways in which SIRS researchers can contribute to the global reduction of mortality attributed to schizophrenia.

**11.1 Premature Mortality of Persons With Schizophrenia in India- What do we Know?**

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**Background:** India, the most populous country in the world, has a huge mental health treatment gap. For severe mental disorders (SMD) including schizophrenia it is 73.6% and for any psychosis - 75.5% (National Mental Health Survey NMHS, India 2016-17). Disability burden due to schizophrenia is highest among all mental disorders (20.5 -28.2%-NMHS, 2016), but rates of premature mortality in schizophrenia are unknown. Indians with schizophrenia suffer from as many mortality risks as patients in other countries. Up to almost 40% may be affected by metabolic syndrome, one-fifth by hypertension, one-fourth from harmful use of alcohol and tobacco and up to one-fourth may attempt suicide at least once in their lifetime. Surprisingly, Indian mortality data on schizophrenia is sparse.
**Methods:** A review of literature and screening of family history data from research records was conducted.
**Results:** The earliest Indian follow-up from the WHO International Pilot Study of Schizophrenia (IPSS) was of 62/120 schizophrenia patients followed up over 14 years (Dube et al,1984-Agra). Dube reported an elevated standardised mortality ratio (SMR) of 2.3 (males) to 4.5 (females), a sex difference unsupported by recent publications. A subsequent 25-year follow-up at all 4 Indian IPSS sites reported > 1 SMR. i.e. more than the general population, with the highest SMR. of 3 from Chandigarh Rural, Punjab in north India (Harrison et al 2001).
Two Indian studies reported SMR. from rural areas of the South Indian states of Karnataka and Tamil Nadu (TN). In a cohort of 300-odd schizophrenia patients living in Tirthahalli

Karnataka (2009-2011), SMRs were respectively 1.4, 1.8, and 2.2- a far lower rate than in high-income countries (Bagewadi et al 2016). Nevertheless, their patients had a 40-110% greater mortality rate and even higher suicide rate than the general population of that district. The suicide cases had substantially lower socio-economic support. From a rural community in Tamil Nadu, Raghavan et al (2021) reported a 4-year average SMR. (between 2011-2015) of 2.4 with a high suicide rate (12% of the total patients followed). In both these studies, the cause of death was overwhelmingly from 'natural' causes (84% in Tamil Nadu). Formal death certificates were not available in a majority and suicides may have been concealed due to stigma.

Both studies, due to the small number of deaths, reported differences between those who died compared to their living cohort. Neither reported significant sex differentials. Still, compared to those who died, the living cohort in Tamil Nadu was younger and more educated by 2-3 years than those who died.

The worldwide risk factors for premature deaths among schizophrenia patients- physical comorbidities, lack of inappropriate treatment or medication side effects- are uncalculated. Family and cultural biases, the stigma of suicide and the paucity of formal death certificates make analyses difficult. Published morbidity and risk data for schizophrenia is largely from cross-sectional outpatient or inpatient hospital-based surveys. Our research records from the family history of index schizophrenia patients in North India revealed an earlier average age at death for participants with schizophrenia and related disorders versus bipolar disorder (unpublished data).

**Conclusions:** Definite conclusions from currently available Indian schizophrenia data are that mortality among schizophrenia patients is at least double but the suicide rate is far higher than the general population. History of mental illness, a past history of a suicide attempt and low socio-economic status are known risk factors for Indian suicides. Improving the reach of mental health services to detect and treat mental illnesses early may reduce suicides. Innovative research for socially acceptable, easy to administer and effective mental health interventions is required.

### 11.2 Excess Mortality in Severe Mental Illness: 20-Year Population-Based Cohort Study in Rural Ethiopia

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**Background:** Premature mortality is a well-established adverse outcome of severe mental illness (SMI), most notably schizophrenia, bipolar disorder and depressive disorder. However, long-term mortality consequences from population-based cohort studies, especially from low-income countries is scarce. The aim of this study was to describe the long-term mortality outcomes of a well characterised cohort in a LMIC setting.
**Methods:** Following a screening of 68,378 adults aged 15-49, 919 participants were ascertained to have one of the three serious mental disorders; schizophrenia (n=358), bipolar disorder (n=346) and severe depression (n=215). These participants were followed up for 20

years with intensive evaluations in the first 10-years. Verbal autopsy was used to ascertain causes of death.
**Results:** Over a fifth of the participants (n=194/919, 21.11%) had died in the 20-year follow-up; significantly more participants who died had schizophrenia (n=111/ 358, 31.01%) followed by severe depression (n=35/215, 16.28%) and bipolar disorder (n=48/346,13.87%). Although most of the causes were duet to natural causes, mainly infectious conditions, 22.51% (95% CI=16.53, 28.67) had died due to unnatural causes, with 73% dying from suicide. In the first 10-years of follow-up, the standardized mortality ratio in people with SMI was twice the general population, with higher ratios related with schizophrenia. Moreover, patients lost on average, about three decades of their lives due to premature death.
**Conclusions:** Premature mortality remains an important serious consequence of having a SMI, especially schizophrenia. Improving physical health of people with SMI and preventing deaths from unnatural causes should be prioritized. Additional studies of interventions to improve the physical health of people with SMI is warranted.

### 11.3 Natural Cause Mortality in a Cohort of Individuals With Schizophrenia From a US Metropolitan Area

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

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

**Background:** Schizophrenia is associated with premature mortality, mostly due to natural causes. Decreased levels of cognitive functioning have been identified as a determinant of mortality in the general population. However there have been few prospective studies of cognitive functioning and natural cause mortality in schizophrenia. The purpose of our study was to identify the role of cognitive functioning along with clinical and social factors in natural cause mortality in individuals with schizophrenia
**Methods:** We performed a prospective cohort study of persons with schizophrenia or schizoaffective disorder enrolled between February 1, 1999, and December 31, 2022, at a non-profit psychiatric system in Baltimore, Maryland USA, a major metropolitan area. Participants were evaluated with an in-person assessment of their cognitive functioning with the Repeatable Battery of Neuropsychological Status (RBANS) and psychiatric symptom severity with the Positive and Negative Syndrome Scale (PANSS). Information was obtained about demographic variables including maternal education as a proxy for socioeconomic status during upbringing, co-occurring medical conditions from a review of systems, body mass index (BMI), current tobacco smoking, history of substance use or dependence apart from nicotine or caffeine, current medications, and the experience of homelessness within the previous two years.
Natural cause mortality through December 2022 was determined employing data from the National Death Index.

A total of 106 baseline variables including cognitive, demographic, and clinical measures were related to mortality using least absolute shrinkage and selection operators (LASSO). Variables above a threshold value were further analyzed using Cox proportional hazards models.

**Results:** The 844 persons enrolled in the cohort had a mean age of 39.6 □12.1 years; 476 (56.4%) were White; 339 (40.2%) Black; 533 (63.2%) male sex. A total of 158 (18.7%) individuals died of natural causes in up to 23.9 years of follow-up. The most significant correlate of mortality was lower cognitive functioning as measured by the RBANS

(coefficient=-.039, 95% CI -.052, -.025, z=5.72 adjusted P < .001). Additional factors independently associated with mortality included the diagnosis of an autoimmune disorder (HR 2.86, 95% CI 1.83-4.47, z=4.62, adjusted P < .001), tobacco smoking (HR 2.25, 95% CI 1.55-3.30, z=4.23, adjusted P < .001¬), a diagnosis of chronic obstructive pulmonary disease (HR 3.31, 95% CI 1.69-6.50, z=3.48, adjusted P < .0106), Body Mass Index (BMI) (coefficient 1.06, 95% CI 1.02-1.08 z=3.30, adjusted P < .01), a cardiac rhythm disorder (HR 2.56, 95 % CI 1.40-4.69, z=3.06, adjusted P < .02) and being divorced or separated (HR 1.79, 95 % CI 1.22-2.65, z=2.97, adjusted P < .02). An RBANS score < 50th percentile displayed joint effects with being a smoker, having an elevated BMI, or being diagnosed with an autoimmune or cardiac rhythm disorder.
**Conclusions:** In this prospective cohort study of a diverse sample of individuals with schizophrenia from a US metropolitan area, lower cognitive functioning was a strong risk factor for natural mortality. Tobacco smoking, obesity, divorced separated marital status, and some medical conditions also conferred significant risk. Efforts should be directed at methods to improve cognitive functioning, particularly in individuals with additional risk factor for natural cause mortality. The study also points to the need for tobacco cessation treatment, obesity reduction, as well as attention to the social effects of separation and divorce in order to reduce premature mortality in individuals with schizophrenia.

### 11.4 Socioeconomic Inequalities in Excess Mortality in Individuals With Schizophrenia and Other Severe Mental Illnesses

Danni Chen[1], Oleguer Plana-Ripoll[1], Jayati Das-Munshi*[2]

[1]*Aarhus University,* [2]*Institute of Psychiatry, Psychology and Neuroscience, King's College London*

**Background:** Mental disorders are associated with elevated mortality rates and shorter life expectancy. Although low socioeconomic position (SEP) is associated with both mental disorders and excess mortality, it is unknown to what extent SEP explains the elevated excess mortality. Individuals with low SEP may be more often exposed to many risk factors (i.e., smoking, alcohol, drugs, obesity, and social exclusion), and have limited access, continuity, and quality of healthcare; therefore, this population may be more sensitive to the adverse association with mortality. Based on our recent literature review, we observed that relative risks for mortality for people with vs. without mental disorders were similar across SEP levels. However, absolute differences in mortality risks between the two groups might differ by SEP, and this information was rarely reported in previous studies. In addition, evidence on specific types of disorders and cause-specific mortality was scarce. This study aims to investigate the associations between schizophrenia and other types of mental disorders with cause-specific mortality according to individual-level and neighborhood-level SEP.
**Methods:** We designed several cohort studies based on all individuals living in Denmark between January 1, 2000, and December 31, 2020 (N□5.2 million). Information on schizophrenia and other mental disorders was obtained from the Danish Psychiatric Central Research Register, while the date and cause of death were obtained from the Danish Registry of Causes of Death. Individual SEP was defined based on the equated household disposable income as percentile ranks relative to all individuals of the same age and sex, while neighborhood deprivation was defined using a composite measure of aggregated information on income, education, employment status, manual workers, and household crowding and was ranked into percentiles. We used Poisson regression models to estimate mortality rate ratios (MRR) comparing people with and without each diagnosis and stratified by SEP. We compared the average life expectancy between people with SMI and the general population

depending on SEP levels by calculating excess life years lost (LYLs) for all-cause mortality, and for cause-specific deaths. The analysis plan was pre-registered in Open Science Framework (OSF).
**Results:** We observed that people with mental disorders have higher all-cause and cause-specific mortality rates than those without regardless of their income level and neighborhood deprivation. Specifically, in the bottom income quintile, MRR comparing people with and without schizophrenia was 2.33 (95%CI 2.31–2.36) for all-cause mortality, 2.23 (2.20–2.25) for natural causes and 5.08 (4.89–5.29) for external causes, respectively; whilst the corresponding MRRs in the highest SEP quintile were 2.62 (2.58–2.65), 2.51 (2.48–2.55) and 5.99 (5.66–6.33). When looking at specific causes of death, mortality rates for all 11 causes were higher for people with mental disorders compared to those undiagnosed regardless of SEP. For most natural causes and accidents, cause-specific MRRs between people with and without mental disorders were similar across SEP, whilst higher MRRs for alcohol misuses, suicides, and homicides were observed in high-income rather than low-income groups.
**Conclusions:** Schizophrenia and other mental disorders are associated with increased mortality rates as well as shorter life expectancy and the absolute associations were stronger among low SEP strata. This study provides a comprehensive analysis of effect modification by SEP across multiple levels in the associations between specific types of mental disorders and cause-specific mortality. The identified socioeconomic gradients should be prioritized for mortality prevention for people with mental disorders.

**12. Self-Disorders in Schizophrenia and Beyond: Current Findings, New Directions**
Jasper Feyaerts*, Ghent University*
**Overall Symposia Abstract:** Self-disorders are increasingly recognized as core features of the schizophrenia-spectrum. After a period of relative neglect, their importance within various domains of contemporary schizophrenia research-including diagnostic, predictive, etiological and therapeutic-has currently been reestablished. Questions at the forefront of this renewed research attention include: How do self-disorders deviate from normal self-experience? Are self-disorders diagnostically specific to schizophrenia? How do self-disorders develop over time, and what is their relationship to (non-)clinical outcomes? What are underlying mechanisms and how can these be targeted in treatment? To address these topical issues, this symposium engages with novel interdisciplinary work that highlights self-disturbance as a key unifying construct in schizophrenia research that integrates different levels of inquiry—i.e., phenomenological, psychological, neurocognitive, neurobiological and social levels.

The first speaker (Dr. Feyaerts) presents the results of a recent state-of-the-art overview of self-disturbance research, highlighting theoretical challenges, implications for diagnostic assessment, explanatory models, clinical strategies, and new research developments. The primary aim of this overview is to provide the audience with a helpful background for the following three presentations.

The second presentation (Ms Lebovitz and Prof. Park) discusses the results of novel experiments designed to probe bodily self-disorders in schizophrenia-spectrum conditions (SZ) and depersonalization-derealization disorder (DPD). Increased self-disorder levels regardless of diagnosis were related to reduced embodiment of emotions and self-location, increased variability in self-boundary, and altered self-awareness. These findings allow for new insights regarding the phenomenological continuity vs. discontinuity between SZ and

DPD. Results open towards a search for both shared and distinct underlying mechanisms, and attuned therapeutic interventions.

The third presentation (Prof. Giersch) builds on seminal experimental work supporting an intricate link between self-disorders in schizophrenia and disrupted time-expectation. New results of two experimental studies are presented that confirm disrupted time-expectation as a core mechanism underlying self-disorders, while also providing evidence for the benefit of visual cues to improve time-expectation in SZ patients. This last finding suggests new therapeutic prospects for alleviating disturbances of selfhood through visual representation strategies.

The final presentation (Dr. Rosen and Dr. Humpston) presents findings from the Chicago Follow-up Study, a 20-year prospective longitudinal study of depersonalization and derealization. This research examines the longitudinal development of DP and DR as distinct experiences in a clinical sample. The study highlights points of convergence and divergence in DP and DR, offering a nuanced characterization that lays the groundwork for future work to expand the phenomenological understanding of DP and DR particularly in voices, other extreme states, and non-consensus realities.

Dr. Rosen will be co-chair and Prof. Sass-a world-renowned researcher and pioneer in self-disorders-will be discussant for the symposium.

### 12.1 Self-Disorders in Schizophrenia: State-of-the-Art Overview, Challenges and New Directions

Jasper Feyaerts*[1], Louis Sass[2]

[1]*Ghent University,* [2]*Rutgers University*

**Background:** Self-disorders are increasingly recognised as central psychopathological features of the schizophrenia-spectrum. After a period of relative neglect, their importance within various domains of contemporary schizophrenia research--including diagnostic, predictive, etiological, and therapeutic--has currently been reestablished. Despite this renewed research attention, the question of how self-disorders should best be understood and conceptualised continues to present a challenge. Current challenges include not just establishing whether self-disorders truly deviate from ordinary self-experience, but also how they deviate: i.e., (1) what kind or aspect of self is supposedly affected, and (2) just how this particular aspect of selfhood can be considered disturbed. These questions crucially determine how self-disorders should be addressed in research, theory, and clinical practice, yet remain subject to diverging interpretations.
**Methods:** In this presentation, I offer a state-of-the-art overview of diagnostic, etiological and therapeutic research focusing on self-disorders in the schizophrenia-spectrum. The primary aim of this presentation is to offer this comprehensive overview to provide a helpful theoretical and empirical background for the following three presentations.

I first present an overview of current theoretical models of self-disturbance in schizophrenia; clarify the notion of normal selfhood self-disorder implies, its proposed alteration and pathogenic role in schizophrenia, and discuss neurocognitive and clinical implications. Next,

I critically consider the descriptive adequacy of current models with respect to the clinical heterogeneity and variability of the alterations of self -and world-awareness characteristic of schizophrenia. I focus especially on (1) the nature and importance of experiences involving increased sense of self and exaggerated grip/hold in schizophrenia; (2) the need to consider these experiences together with the more commonly recognised instances of diminished sense of self and diminished grip/hold; and (3) the implications of this dual recognition for pathogenic research and neurocognitive modelling.

**Results:** Self-disorders are characterised by substantial heterogeneity and variability which are insufficiently recognised in current research models. Alterations of self-experience can involve not only the oft-noted diminished self-presence in which patients lose the sense of being the subject or agent of their own experiences or actions, but also increased self-presence, as when patients feel they are the central figure or prime target of all that occurs. The lived world of objects, people and situations can similarly show up in opposite ways: either as lacking organisation, fragmented, and uncertain (ie, decreased 'grip/hold'); but also as hyper-organised or hyper-determined, often in a typically grandiose/paranoid manner, such that nothing seems accidental or appears somehow oriented or referring to the patient himself (ie, increased 'grip/hold'). These contradictory aspects may not only succeed each other but can sometimes even co-exist. Such variation may occur across subgroups of patients or phases of illness, but also as more moment-to-moment dynamic shifts at the individual patient level.

**Conclusions:** Despite significant advances in the assessment, search for underlying mechanisms, and therapeutic strategies for self-disorders, several outstanding issues require to be addressed in future research, including (1) fundamental questions regarding their theoretical conceptualisation (2) increased recognition of their experiential heterogeneity and dynamic variability; (3) implications of this recognition for explanatory models and clinical practice.

### 12.2 Altered Self-Experience in Depersonalization-Derealization and Schizophrenia-Spectrum Conditions

Julia Lebovitz*[1], Sohee Park[1]

[1]*Vanderbilt University*

**Background:** Bodily self-disturbances are central to both depersonalization-derealization disorder (DPD) and schizophrenia-spectrum conditions (SZ; Sass et al., 2013) but they have not been systematically investigated. To elucidate shared and distinct mechanisms that may underlie self-disturbances in DPD and SZ, four core components of the self construct were examined: embodiment, self-location, self-boundary, and self-awareness.

**Methods:** We assessed embodiment, self-location, self-boundary, and self-awareness in individuals diagnosed with DPD, SZ, and the general population (CO). Self-location and embodiment of emotions were assessed with a computerized mapping tool (embody; Nummenmaa et al., 2014). For the self-boundary, we utilized a novel, immersive virtual reality (VR) paradigm to estimate preferred interpersonal distance (IPD). Self-awareness was assessed with self-report measures including Benson Body Disturbances Inventory (B-BODI), Multidimensional Assessment of Interoceptive Awareness (MAIA-2) and Toronto Alexithymia Scale (TAS). In addition, we conducted semi-structured qualitative interviews which focused on self-disturbances. Lastly, Cambridge Depersonalization Scale (CDS) was used to designate participants into high and low depersonalization (DP) groups irrespective of the diagnostic status.

**Results:** Embodiment was reduced in SZ overall, followed by DP and CO groups. High DP group showed weaker embodiment than low DP group for positive emotions (e.g., happiness, pride, love) but increased embodiment for anxiety. Interestingly, high DP group did not embody the self. Self-boundary: There were no group differences in mean IPDs across groups, the S.D. was elevated in the high DP group, indicating greater variability in personal space. Self-Awareness: There were significant group differences in TAS and MAIA-2, with the DPD showing increased alexithymia and reduced interoceptive awareness compared with the SZ and CO. The DP group also reported the highest bodily self-disturbance on the B-BODI. These results were also reflected in the qualitative interviews where DPD participants reported porous self-boundary, feeling disconnected from their physical body and having difficulties experiencing, accessing, and naming emotional experiences.
**Conclusions:** These results demonstrate that both SZ and DPD groups experience altered embodiment, self-location, self-boundary, and self-awareness, suggesting that DP experiences could help explain some of the self-disturbances in SZ. Increased DP levels regardless of diagnostic status were related to reduced embodiment of emotions and self-location, increased variability in self-boundary, and altered self-awareness. These findings highlight the importance of altered self-experience as core to both DPD and SZ, with implications for potential intervention strategies.

### 12.3 Time Expectation in Vision and Sense of Self: Mechanisms and Therapeutic Avenues?

Anne Giersch*[1], Ellen Joos[1], François Foerster[1], Brice Martin[2], Jennifer Coull[3]

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**Background:** Clinically, individuals with schizophrenia (SZ) experience a breakdown of the experience of time continuity, which has been related to disorders of the minimal self by phenomenologists. We used an experimental approach and showed a link between disorders of the minimal self (explored clinically or via the subjective feeling of control) and time expectation (explored experimentally). Experimentally, time expectation is indexed by the ability to benefit from the passage of time. To extract this benefit, we used a variable foreperiod task. Individuals reacted to a visual target appearing at various delays after a cue. Typically expectation increases with time, leading to shorter reaction times when the target occurs after a long than after a short delay. We showed previously this benefit of the passage of time to be impaired in patients with minimal self disorders. We also showed that small, millisecond-level, delays in sensory feedback during an action led to a decrease in the feeling of control. Our results led to the hypothesis that in patients with schizophrenia, the passage of time is disrupted due to a difficulty to integrate millisecond-level disruptions in the time flow. We will show how we explored this hypothesis and how we explored the potential benefit of a starfield, i.e. an optic flow representing the visualization of a continuous passage of time.
**Methods:** A total of 41 outpatients with SZ and 40 neurotypicals were recruited in two different studies. We extracted indexes reflecting the benefit of the passage of time (difference in RT between short long delays/sum of RTs). The sense of self was evaluated with the EASE scale in study 1, and time was manipulated in virtual reality in study 2, by means of the display of synchronous vs. asynchronous distracters in one session, and by adding a starfield in the background in another session. Those manipulations were compared with a condition without distracters and without starfield. The speed of the starfield was selected by the experimenter in one condition, and self-selected in another. In study 2, we

additionally measured the electroencephalographic signals typically accompanying time expectation (e.g. the CNV).
**Results:** We replicated the fragility in time expectation and its link with disorders of the sense of self. Moreover, the presence of an optic flow (only when the speed was self-selected), or of simultaneous (but not asynchronous) distracters, improved the behavioural benefit of the passage of time. There was no effect on the EEG signals, though. The self-selected starfield speed did not differ between groups, and the Results: were not explained by an effect on immersion.
**Conclusions:** The results suggest time expectation and updating can be improved in patients in vision, opening up new therapeutic perspectives. Effects at the clinical level will have to be explored in follow-up studies.

### 12.4 A 20-Year Prospective Study of Depersonalization and Derealization as a Reflection of Alteration in the Sense of Self and Sense of the World

Cherise Rosen*[1], Clara Humpston[2]

[1]*University of Illinois at Chicago,* [2]*University of York*

**Background:** Depersonalization (DP) and derealization (DR) are transdiagnostic symptoms that are more prevalent in individuals diagnosed within the schizophrenia spectrum (Černis et al., 2023; Sierra, 2009). DP and DR are embedded in alterations in the sense of self and sense of the world (Sass et al., 2013; Feyaerts and Sass, 2024). Building on our earlier work, this study introduces a nuanced description of the underlying symptom constructs of DP and DR (Humpston et al., 2020).
**Methods:** The study utilized data from the Chicago Follow-up Study, a longitudinal naturalistic study that recruited individuals at index hospitalization and were reassessed at six time points over 20 years. The study reports findings examining DP and DR in 381 individuals with one or more follow-up evaluation, of which 154 were diagnosed with schizophrenia spectrum, 114 with affective psychosis (62, mania with psychosis; 52, depression with psychosis), and 113 with unipolar depression non-psychosis. The primary clinical indices measured were DP and DR utilizing the Schedule for Affective Disorders and Schizophrenia, Schizophrenia State Inventory, and the Present State Examination. Negative symptoms were assessed using the Behaviour Rating Schedule of the Psychiatric Assessment Interview. We applied a generalized estimation equation (GEE) analysis to examine the trajectory and longitudinal effects of time on DP and DR. We also conducted a linear GEE model, controlling for diagnosis to explore the core longitudinal associations between DP, DR, general symptom categories, symptoms of passivity, and other positive symptoms.
**Results:** GEE results show a significant main effect for diagnostic group differences in both DP and DR, showing that both are more prevalent in individuals with schizophrenia spectrum. The course over 20 years varied, showing that DP increased in individuals with schizophrenia over time, demonstrating a significant effect of diagnosis and follow-up; this interaction was non-significant in DR. The model did not show a main effect of follow-up period over time in either DP or DR. General symptom categories showed that DP was significantly associated with hallucinations, delusions, anxiety, depression, and anhedonia but not negative symptoms. DR was significantly associated with hallucinations, delusions, and negative symptoms. Passivity symptoms in DP were significantly associated with thought withdrawal, thought insertion, and made impulses. In contrast, DR was significantly associated with thought withdrawal, thought broadcasting, made impulses, and made volitional acts. In terms of other positive symptoms, DP was significantly associated with DR, auditory thoughts spoken out loud, auditory hallucinations, voice commenting, delusions

of control, thought dissemination, grandeur, and sexual delusions. DR was significantly associated with DP, somatic hallucinations and delusions, delusions of control, thought control, thought dissemination, persecution, and religious delusions.
**Conclusions:** The present research shows that DP and DR are significantly associated and converge in the expression of thought withdrawal, made volitional acts, delusion of control, and thought dissemination. This research also demonstrates a distinct differential longitudinal trajectory and underlying symptom construct of DP and DR. DP and DR as two aspects of alterations in the sense of self and sense of the world are experienced in the loss of sense of agency and ownership and uniquely for example in increased self-presence in grandiose delusions and the hyperreflexive interpretation in delusions of persecution and in the mystical sense of religious delusions.

## Plenary Session II: Maintenance Treatment Strategies in Psychotic Disorders - Dr. Christy Hui

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

### 13. Maintenance Treatment Strategies in Psychotic Disorders

Dost Ongur, *Mclean Hospital*

**Overall Abstract:** In this plenary lecture, Dr. Hui will discuss maintenance treatment strategies for individuals with psychotic disorders. This talk is of relevance to clinicians and clinical researchers about an area of active investigation. Long term outcomes can vary based on ongoing treatment selections and existing guidelines provide only partial detail about how to handle many common clinical scenarios.

### 13.1 Maintenance Treatment Strategies in Psychotic Disorders

Christy Hui, *University of Hong Kong*

**Individual Abstract:** Deciding whether to continue maintenance medication after achieving full remission from first-episode psychosis is always a complex clinical decision. While some patients choose to endure the side effects and stigma associated with antipsychotic treatment because of its effectiveness in controlling symptoms, it is important to acknowledge that, in real life, many patients desire to stop maintenance medication after achieving full remission. Patients are often more concerned about the prospect of safely discontinuing antipsychotic treatment rather than the actual dosage of the medication. At present, there is no clear-cut guideline outlining which individuals, based on particular characteristics, can safely discontinue antipsychotic treatment, the appropriate timing and schedule of discontinuation, and the duration of medication continuation. Drawing on two decades of clinical data from Chinese-speaking patients in Hong Kong, this talk aims to examine the evidence on outcomes of early maintenance and discontinuation strategies in psychotic disorders. Our goal is to provide valuable insights that will aid patients, caregivers, and clinicians in contemplating and navigating this complex decision-making process. Apart from exploring the clinical recommendations on the duration of maintenance treatment, we examine this clinical evidence regarding patients who either continue or discontinue medication during the early stages of psychosis, and the potential short-term and long-term impacts associated with these decisions. Further insights are provided on the characteristics of patients who are more likely to relapse following medication discontinuation. The talk also considers the important

influence of personal experiences and beliefs of patients and clinicians on their treatment choices and practice. Cultural factors, including family involvement and the perceived status of clinicians, are also crucial in shaping these decisions. The talk concludes by proposing future directions in clinical and research settings to facilitate this decision-making, aiming to identify the strategy best promotes good long-term clinical outcomes in first-episode psychosis.

**Concurrent Symposia**

**3:30 p.m. - 5:00 p.m.**

**14. Intersecting Realities: Understanding Psychosis Through the Lens of Racism**

Hans Oh*, University of Southern California*

**Overall Symposia Abstract:** Leveraging the momentum from last year's symposium on Racism and Psychosis, we continue to build an agenda to explore the vast and multiple ways in which racism impacts psychosis risk. Race is a social construct used to categorize people based on secondary physical characteristics (e.g., skin tone). Historically, the concept of race was erroneously used to infer essential differences across groups; and as such, race has served as the basis of marginalization and oppression. Studies have shown that Black, Latinx, and multiracial individuals have higher risk for psychosis, and much of these disparities can be traced back to racism –the complex system of oppression that operates through multiple pathways, including structures, institutions, culture, and interpersonal interactions to privilege the dominant (White) group while disadvantaging people of color. To advance the research field of psychosis and racism we need to 1) carefully synthesize the literature on this association to evaluate the quality of the evidence and identify research gaps that may inspire future research; 2) include high-quality, epidemiological data to examine whether risk patterns of psychosis across groups align with prevalence patterns of racism; 3) consider multiple descriptors for individuals in addition to ethnicity and race, to improve our understanding of how intersecting characteristics impact psychosis risk. This symposium will address all these knowledge gaps to move the needle on the nature of the association between racism and psychosis. Specifically, India Francis-Crossley will begin by presenting an umbrella review on psychosis and racism. Next, Dr. Deidre Anglin will present findings on the racial and ethnic variation in the prevalence of schizophrenia spectrum disorders and positive psychotic symptoms in a national US-based probability household sample, examining the contribution of neighborhood social determinants of health to these disparities. Then, Dr. Nicole Karcher will examine the intersecting effects of racial/ethnic, gender, and sexual marginalized identities on psychotic experiences, and the extent to which these associations are attenuated when accounting for potential explanatory factors, including experiences of discrimination and state-level laws perpetuating structural inequities. Finally, Oladunni Oluwoye will present on the relationship between discrimination to severity of depression, anxiety, and psychosis symptoms, and the relationship between multiple minoritized statuses and symptom severity among a sample of ethno-racially minoritized individuals with first episode psychosis. Dr. James Kirkbride will synthesize the presentations and share his thoughts on potential avenues toward anti-racism in service delivery, health policies, and larger strategies to reduce disparities. The symposium will set an agenda for addressing racial disparities in psychosis.

## 14.1 Umbrella Review Into the Association Between Racial/Ethnic Discrimination and Psychosis

India Francis-Crossley*[1], Georgie Hudson[1], Lasana Harris[1], Juliana Onwumere[2], James B. Kirkbride[1]

[1]*University College London,* [2]*King's College London*

**Background:** People from racially/ethnically marginalised backgrounds have a consistently elevated risk of developing psychosis compared with people from racial/ethnic majority backgrounds. Estimates of these disparities have demonstrated serious health inequities, especially in people from Black, Latine, Pakistani and Bangladeshi backgrounds; people from Black ethnicities have up to a four-times greater risk of psychosis compared to European Americans (US) and five-times increased risk of psychosis compared to White British people (UK). Proposed explanations, such as migration and clinician bias/misdiagnosis, still leave excess risk unaccounted for, and evidence of social factors suggests a role for racial/ethnic discrimination. Studies have investigated this relationship, but the findings are spread across disparate reviews. We aimed to synthesise the current knowledge on the association between racial/ethnic discrimination and psychosis.

**Methods:** We conducted a systematic search of Medline, Embase, PsycINFO, ProQuest Central and Google Scholar for systematic reviews and meta-analyses, published in peer-reviewed journals, exploring the effect of racial/ethnic discrimination on psychosis (including psychotic disorders, psychotic symptoms, psychotic-like experiences, at-risk mental states and ultra-high risk) with no publication date or language restrictions. Search results were de-duplicated and assessed in duplicate via sequential title, abstract and full text screens, as well as forward/backward citation screening of the included reviews. Data extraction and risk of bias appraisal using the AMSTAR-2 checklist were also conducted in duplicate. Following the pre-registered protocol (CRD42023400656), we performed narrative synthesis of the review findings and reported quantitative data where available from the reviews.

**Results:** The searches identified 2,898 records, 67 of which were screened at full text stage with five eligible for inclusion. An additional two reviews were identified for inclusion via forward/backward screening. The seven included reviews reported 23 primary studies representing 40,146 participants. Five of the reviews explicitly reported on the association between racial/ethnic discrimination and psychosis, all observing evidence of a positive relationship between the two, including meta-analyses for psychotic symptoms (adjusted OR=1.77, 95%CI 1.26, 2.49) and psychotic experiences (pooled OR=1.94, 95%CI 1.42, 2.67). The remaining two reviews did not disaggregate psychosis from non-psychosis outcomes in their analyses, however, both still reported positive associations between racial/ethnic discrimination and their broader mental health categories. Overall, we observed more robust evidence for psychotic symptoms/experiences than psychotic disorder, though the latter remained indicative of an association. However, the findings were hindered by a large majority (87%) of cross-sectional studies preventing investigation of temporality and reverse-causality, and low (n=2) and critically low (n=5) AMSTAR-2 review quality, affecting confidence in the findings.

**Conclusions:** The available review evidence supports a role for racial/ethnic discrimination in developing psychosis, but the evidence base is cross-sectional and of low quality. We require high quality studies to determine the temporal and mechanistic causal pathways through which this occurs. Nevertheless, the results add to current knowledge of the widespread presence of racism and its devastating impacts on health, as well as the importance of public health interventions that reduce exposure to, or the impact of, racial/ethnic discrimination.

## 14.2 Racial Disparities in the Prevalence of Schizophrenia Spectrum Disorders and Psychotic Symptoms in the United States: The Role of Neighborhood-Level Social Vulnerabilities

Deidre Anglin*[1], Mark Olfson[2], Els van der Ven[3], Hans Oh[4], Roberto Lewis-Fernandez[2], Jordan DeVylder[5], Oladunni Oluwoye[6], Lisa Dixon[2], T. Scott Stroup[7], Heidi Guyer[8], Natalie Bareis[7]

[1]*The City College of New York,* [2]*Columbia University and New York State Psychiatric Institute,* [3]*Vrije Universiteit Amsterdam,* [4]*University of Southern California,* [5]*New York University,* [6]*Elson S. Floyd College of Medicine, Washington State University,* [7]*Columbia University* [8]*RTI International*

**Background:** Introduction: Several studies in the United states have found racial differences in the prevalence of schizophrenia spectrum disorders (SSD), but most have sampled from clinical settings which are vulnerable to well documented racial biases in routine clinical practice, especially among Black individuals. Social determinants of health (SDoH) have been postulated as explanations of racial differences in psychosis outcomes, but no studies in the US have examined the contribution of SDoH experienced and assessed at the neighborhood/structural level using zip code data. The present study aimed to re-examine racial and ethnic variation in the prevalence of SSD and positive psychotic symptoms (PS) in a national probability household sample, and examine the contribution of neighborhood SDoH to these disparities.
**Methods:** The national household sample (n=4,764) of the Mental and Substance Use Disorder Prevalence Study (MDPS) was used for the present study. Non-elderly adults were assessed by clinicians with the Structured Clinical Interview for DSM-5 (SCID-5) for SSD (past year and lifetime), including schizophrenia, schizoaffective disorder, and schizophreniform disorder, and positive psychotic symptoms (PS). Clinicians received extensive training and supervision in the administration of the SCID-5 prior to and during data collection that included intermittent calibration exercises to ensure consistency. Weighted logistic regression models estimated ethnoracial differences in the prevalence of SSD and PS in unadjusted models, age- and sex-adjusted models, and models further adjusted for a neighborhood social vulnerability metric (SVM) score, a composite index of five major social determinants of health (SDoH) domains.
**Results:** Of the 4,764 individuals clinically interviewed, 114 (weighted prevalence estimate of 1.8%) had SSD and 461 (5.4%) experienced at least one positive psychotic symptom. Compared to Non-Hispanic White (NHW) individuals, Non-Hispanic (NH)-Black individuals had significantly higher weighted prevalence of SSD (4.1% vs. 1.2%; adjusted odds ratio [aOR], 3.49 [95%CI:1.37-8.91]) and PS (9.3% vs. 4.9%; (aOR, 2.04 [95%CI:1.15-3.63]). NH-multiracial individuals had significantly higher prevalence of SSD (5.6%; aOR, 4.59 [95%CI:1.53-13.76]) but not of PS. NH-American Indian/Alaskan Native (NH-AI/AN) individuals had significantly higher prevalence of PS (21.4%; aOR, 5.45 [95%CI:1.63-18.28]). Adjusting for SVM reduced ethnoracial differences in psychosis-outcome prevalence. The change in estimate (CIE) was highest for the NH Black-White group difference (37%), reducing statistical significance for both SSD: CIE=37.3; aOR, 2.49 (95%CI:0.63-9.90) and PS: CIE=18.9; aOR, 1.69 (95%CI:0.83-3.44). Adjusting for SVM attenuated the NH multiracial-White group difference in SSD (CIE=22.0; aOR, 3.95, 95%CI:1.30-12.00), but the difference remained significant. Adjusting for SVM did not

reduce the significant NHAI/ AN-NHW group difference in prevalence of PS (CIE=11.8; aOR, 4.76 [95%CI:1.35-16.87]).
**Conclusions:** Conclusion: This national US-based household study found racial differences in the prevalence of clinician-assessed SCID-based schizophrenia-spectrum disorders and positive psychotic symptoms. The higher prevalence particularly among Black individuals, was connected to social inequities and community-level vulnerabilities embedded in neighborhoods and associated with structural racism. Decades of research has focused on individual risk factors. Modifying social determinants of poor health in neighborhoods will require implementing policies that counter inequities across multiple levels of societal functioning.

### 14.3 An Intersectional Lens on Associations Between Marginalized Identities and Psychotic-Like Experiences

Nicole Karcher*[1], Hans Oh[2]

[1]*Washington University School of Medicine,* [2]*University of Southern California*

**Background:** Psychotic-like experiences (PLEs), including perceptual abnormalities and mild delusional thoughts, are relatively common in school-age children. While research has found associations between PLEs with racial and ethnic marginalized identities, as well as between PLEs with sexual and gender marginalized identities, research as rarely taken an intersectional lens towards these associations. In addition to examining the intersecting effects of racial/ethnic, gender, and sexual marginalized identities with PLEs, the present work also examines the extent to which these associations are attenuated when accounting for potential explanatory factors, including experiences of discrimination and state-level laws perpetuating structural inequities.
**Methods:** Using the unique longitudinal Adolescent Brain Cognitive Development Study data (ages 9-14), mixed effect models examined the associations between marginalized racial/ethnic identity (n=5234), marginalized sexual identity (n=1443), and marginalized gender identity (n=326) with distressing PLEs. Models also examined the extent to which associations between marginalized identity with distressing PLEs were attenuated when accounting for experiences of discrimination, levels of immigration/ethnic density, and geo-coded indices of state-level indicators of bias (i.e., based on sex, sexual orientation, race, immigration status).
**Results:** indicate that marginalized racial/ethnic (95%CI: 0.213,0.272), sexual orientation (95%CI: 0.352,0.433), and gender (95%CI: 0.286,0.459) identities were all associated with greater mean-level distressing PLEs. There was evidence was interactions of racial/ethnic and sexual orientation marginalized identities, with individuals with both racial/ethnic and sexual orientation marginalized identities showing the highest distressing PLEs. Including experiences of discrimination and geo-coded indices of state-level indicators of racism attenuated associations between marginalized identity status with distressing PLEs (e.g., up to 55.87% attenuation of the association between racial/ethnic marginalized identity with distressing PLEs).
**Conclusions:** Findings show evidence that marginalized identity status is a strong predictor of distressing PLEs in adolescence. Further, the findings provide insights into the role of intersecting identities on early psychosis spectrum symptoms, finding that endorsing both marginalized racial/ethnic and sexual orientation identities is associated with greater distressing psychotic-like experiences. Analyses indicate that while systemic inequity-related indicators such as experiences of discrimination and biased state-level laws attenuate these links, associations between marginalized identity and PLEs remained. These analyses point to

potential etiological pathways for PLEs and identify potential clinical and public policy initiatives to improve youth mental health.

### 14.4 The Relationship Between Discrimination, Multiple Minoritized Statuses, and Symptom Severity at Intake Among Ethnoracially Diverse Individuals With Early Psychosis

Oladunni Oluwoye*[1], Bryony Stokes[1], Megan Puzia[1]

[1]*Elson S. Floyd College of Medicine, Washington State University*

**Background:** Disparities exist across the continuum of care for early psychosis that impact ethnoracial minorities. We aimed to better understand the relationship of discrimination to severity of depression, anxiety, and psychosis symptoms at intake and the relationship between multiple minoritized statuses and symptom severity among a sample of ethnoracially minoritized individuals with FEP enrolled in CSC.
**Methods:** Overall, 129 ethnoracially minoritized individuals enrolled in CSC completed the Experiences of Discrimination measure, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder (GAD-7), and the Community Assessment of Psychic Experiences (CAPE-P15) as part of the New Journeys Network Measurement Battery at intake. Generalized linear mixed models (GLMM) were used to investigate the effects of gender, sexual orientation, ethnoracial group, and lifetime and daily discrimination on severity of self-reported symptoms. Ethnoracial groups included Black/African American, American Indian/Alaska Native, Asian/Pacific Islander, Multiracial, and Hispanic/Latino (ref). Sexual orientation was dichotomized to sexual minority (LGBTQ+) and heterosexual (ref). Gender was dichotomized to gender minority (female, transgender, and gender diverse) and male (ref).
**Results:** In this sample 17% (n=22) of clients were sexual minorities and 33% (n=43) were gender minorities. Approx. 7% (n=9) identified as AI/AN, 9% (n=11) identified as Asian/Pacific Islander, 14% identified as Black/African American, 13% (n=17) as Multiracial, and 57% as Hispanic/Latino. Individuals who reported more instances of daily discrimination had significantly higher scores on the CAPE-P15 (β=0.33, CI: 0.03, 0.04, $p < .001$), GAD-7 (β=0.33, CI: 0.30, 0.37, $p < .001$), and PHQ-9 (β=0.43, CI: 0.39, 0.47, $p < .001$) when holding all other variables constant. Individuals who reported more instances of lifetime discrimination had significantly lower scores on the CAPE-P15 (β=-0.54, CI: -0.08, -0.03, $p < .001$) and GAD-7 (β=-0.40, CI: -0.67, -0.14, $p = .003$), and higher scores on the PHQ-9 (β=1.39, CI: 0.97 – 1.81, $p < .001$). There were significant differences in self-reported symptoms of psychosis and anxiety by ethnoracial group. Black/African American clients reported significantly higher scores on the CAPE-P15 (β=0.33, CI: 0.30, 0.37, $p < .001$) and GAD-7 (β=7.21, CI: 4.60, 9.82, $p < .001$) compared to Hispanic individuals. Asian clients reported significantly higher scores on the CAPE-P15 (β=0.28, CI: 0.26, 0.31, $p < .001$) and significantly lower scores on the GAD-7 (β=-5.06, CI: -7.00, -3.13, $p < .001$) compared to Hispanic individuals. Alaska Native/American Indian individuals reported significantly lower scores on the GAD-7 (β=-1.15, CI: -2.16, -0.14, $p = .026$). Sexual minorities had significantly lower scores on the CAPE-P15 (β=-0.10, CI: -0.17, -0.04, $p = .003$), GAD-7 (β=-2.42, CI: -3.81, -1.03, $p < .001$), and PHQ-9 (β=-1.74, CI: -2.811, -0.664, $p = .002$) compared to clients who identified as heterosexual. Gender minorities reported significantly lower scores on the CAPE-P15 (β=-0.13, CI: -0.21, -0.06, $p < .001$) compared to males.
**Conclusions:** This study contributes to the existing body of literature on experiences of discrimination and disparities among ethnoracial groups with FEP. Our findings underscore the need for improving pathways to CSC for minoritized populations with specific attention to individuals with multiple minoritized statuses. Additional research with a larger sample of

individuals with multiple minoritized statuses is needed to comprehensively explore intersecting marginalized identities

**15. Immune-Metabolic Biomarkers in Psychosis: Translational Ex-Vivo to In-Vivo Approaches**

Paolo Brambilla*, University of Milan*

**Overall Symposia Abstract:** This symposium convenes an international panel of experts to explore the role of immune-metabolic biomarkers in psychosis, encompassing ex-vivo analyses, in-vivo studies, and clinical trials. By integrating diverse methodologies, the session offers a comprehensive view of the molecular, immune, and metabolic underpinnings of psychosis and their translational potential.

Dr. Paolo Enrico will kick off the symposium with research using MALDI Imaging Mass Spectrometry (IMS) to map lipid compositions in ex-vivo human brain samples. This innovative approach allows for the localization of specific fatty acids at the microstructural level, illuminating the lipid landscape in brain tissues and paving the way for enhanced diagnostic and therapeutic strategies in schizophrenia through label-free imaging techniques.

Following this, Dr. Alex Dickens will delve into the significance of circulating lipids as biomarkers for early psychosis and related metabolic conditions. His advanced lipidomic analyses reveal that specific lipid profiles can serve as both prognostic and diagnostic tools in high-risk populations and first-episode psychosis (FEP) patients. Additionally, his exploration of the endocannabinoid system's role in lipid alterations provides valuable insights into the mechanisms linking brain function with peripheral biomarkers, potentially guiding early intervention strategies.

Dr. Fabiana Corsi-Zuelli will then extend the discussion to the immune system's influence on psychosis, presenting findings from the Psychosis Immune Mechanism Stratified Medicine Study. This study investigates the therapeutic potential of inhibiting IL-6 signaling with tocilizumab in psychosis patients exhibiting low-grade inflammation. By examining immune cell responses and their modulation through targeted therapy, Dr. Corsi-Zuelli's research highlights the promise of immune stratification in enhancing treatment precision and effectiveness.

Finally, Dr. Alessandro Pigoni will provide a clinical perspective with preliminary results from the PHLAMES study, which examines the presence and impact of neuronal surface autoantibodies (NSAbs) in FEP patients. This research explores the clinical and neurobiological differences between NSAbs-positive and NSAbs-negative patients, suggesting that these autoantibodies may help identify distinct subgroups within psychosis and guide more targeted treatments.

Overall, this symposium underscores the importance of integrating diverse methodologies to advance our understanding of psychosis. From molecular imaging and lipidomic profiling to immune modulation and clinical biomarkers, the research presented highlights the transformative potential of immune-metabolic biomarkers in refining diagnostic and therapeutic approaches. The panel's international and multidisciplinary expertise exemplifies

the collaborative effort needed to tackle the complexities of psychosis, ultimately aiming to improve patient outcomes through innovative scientific strategies.

### 15.1 Identifying Lipidic Signatures in Schizophrenia by Using Lipidomic Techniques in Ex-Vivo Brain Samples

Paolo Enrico*[1], Cecilia Cabasino[2], Giuseppe Delvecchio[2], Paolo Brambilla[1], Yvan Torrente[1], Italia Bongarzone[3]

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**Background:** Schizophrenia (SCZ) is a complex psychiatric disorder with an unclear etiology, requiring exploration of various biological mechanisms. The impaired glial-neuronal interactions model highlights changes in glial cells as central to SCZ pathophysiology. Conventional imaging methods often rely on labeling, necessitating cost-effective alternatives. Matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) provides a label-free approach that generates 2D ion density maps to visualize analyte distribution in tissue sections, enabling the assessment of molecular signatures in health and disease and aiding in lipidomic-based clinical diagnostics.
**Methods:** Our study utilized MALDI-IMS on ex vivo human brain slices obtained from the NIMH biobank. We scanned brain sections to create digital whole slide images (WSIs) and evaluated them using QuPath. Lipid homogenates were obtained and profiled using MALDI MS. Lipid suspension was deposited on slides with a matrix for spectra acquisition. Data were analyzed using SCiLS lab software to visualize and characterize lipid distributions.
**Results:** Our preliminary results demonstrate that MALDI-IMS effectively segments tissue features and identifies lipid composition variations across distinct brain regions. We obtained high-quality images and, for the first time, localized specific fatty acid types at the microstructural level in the human brain. This groundbreaking localization provides a new understanding of the lipid landscape in brain tissues.
**Conclusions:** MALDI-IMS is a powerful, label-free imaging technique capable of providing detailed spatial lipidomic profiles in brain tissues. Our findings highlight its potential to enhance the understanding of SCZ at the molecular level and contribute to the development of personalized diagnostic and therapeutic approaches. The translational impact of this research is significant, as it aims to leverage clinical and post-mortem samples to identify prognostic and stratification biomarkers. This can ultimately advance personalized care for individuals with affective and psychotic disorders. Our work underscores the critical role of lipidomics in psychiatric research, paving the way for future advancements in personalized medicine.

### 15.2 Circulating Lipids as a Source of Biomarkers for Early Psychosis

Alex Dickens*[1], Partho Sen[2], Matthew Kempton[3], Neus Barrantes-Vidal[4], Conrad Iyegbe, Merete Nordentoft[5], Thomas Pollak[3], Anita Riecher-Rössler[6], Stephan Ruhrmann[7], Gabriele Sachs[8], Rodrigo Bressan[9], Marie-Odile Krebs, G. Paul Amminger[10], Lieuwe de Haan[11], Mark Van der Gaag[12], Lucia Valmaggia[3], Tuulia Hyötyläinen[13], . EU-GEI At Risk Study[3], Matej Oresic[13], Philip McGuire[14]

[1]*University of Turku/Turku Centre for Biotechnology,* [2]*Turku Bioscience Center, University of Turku and Åbo Akademi University, Turku, Finland,* [3]*Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK,* [4]*Universitat Autònoma De Barcelona,* [5]*Mental Health Centre Copenhagen,* [6]*University of Basel Psychiatric Clinics,* [7]*University of Cologne, Germany,* [8]*Medical University of Vienna, Vienna, Austria,* [9]*Universidade Federal de Sao Paulo - UNIFESP,* [10]*Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Australia,* [11]*AMC, Arkin,* [12]*VU University Amsterdam Clinical Psychology,* [13]*Örebro University,* [14]*University of Oxford*

**Background:** Circulating metabolites and especially lipids have been a rich source of potential biomarkers for neurological diseases. Early work in psychosis has demonstrated that circulating lipids can predict weight gain in first episode patients. The mechanism by which the brain alters the circulating lipidome remains a key question and the endocannabinoid system has been hypothesised to be one key link. This is because of the off-target activities of the endocannabinoid lipids and related structures such as the ability of PEA to regulate PPAR-alpha a known regulator of lipolysis. Our studies have focused on measuring the lipidome in early psychosis and those at high risk to explore how the blood lipidome can be utilised as prognostic or diagnostic biomarkers. We have also explored how the endocannabinoid system is altered in early psychosis to explore if this has a role in why the circulating lipids change.

**Methods:** We have utilised two liquid chromatography mass spectrometry-based assays to assess the untargeted serum lipidome and a targeted endocannabinoid assay to explore how these molecules change in early psychosis. These assays have been deployed in a range of clinical samples from the high-risk populations (EU-GEI,) and first episode cohorts (METSY). Regional brain cannabinoid receptor type 1 (CB1R) availability was quantified in two, independent samples of patients with FEP (n = 20 and n = 8) and HC (n = 20 and n = 10), by applying three-dimensional positron emission tomography, using two radiotracers, [11C]MePPEP and [18F]FMPEP-d2.

**Results:** Rapid weight gain within the first year of a first episode can be predicted by an increase in the short chain saturated triacylglycerols. This finding was discovered in a cohort from the Helsinki and then validated in an independent cohort from Turku and London. We found that several phosphatidylcholines (PC), sphingomyelins (SM), and triacylglycerols (TG) remained elevated specifically in FEP patients compared to controls. We identified four circulating lipids PC (40:5), SM d (36:1), TG (18:1/18:2/18:2), and TG (18:1/22:5/16:0), which were dysregulated in FEP patients compared to CTR in at least three cohorts. At baseline, compared with control subjects, CHR subjects had higher levels of triacylglycerols with a low acyl carbon number and a double bond count, as well as higher levels of lipids in general. CHR subjects who subsequently developed psychosis (n = 50) were distinguished from those that did not (n = 213) on the basis of lipid profile at baseline using a model with an AUC of 0.81. CHR subjects who became psychotic had lower levels of ether phospholipids than CHR individuals who did not.

When exploring how the endocannabinoid systems is regulated in early psychosis we have observed that in HC, there was an inverse association between levels of circulating arachidonoyl glycerol, anandamide, oleoylethanolamide, and palmitoyl ethanolamide, and CB1R availability in the posterior cingulate cortex. This phenomenon was, however, not observed in FEP patients. These same endocannabinoids should a loss of association with the circulating lipids in the EU-GEI cohort.

**Conclusions:** There is a set of biomarkers which can predict the transition to psychosis from high-risk individuals. There is also a set of consistent lipids which predict the onset of first-episode psychosis. Furthermore, aspects of the disease such as metabolic co-morbidities can also be predicted by the measurement of circulating lipids. Taken together lipids can be used both as a prognostic and diagnostic biomarkers in early psychosis and those at high risk of developing psychosis.

### 15.3 The Interleukin-6 Pathway Unveiled by Multi-Colour Flow Cytometry and Functional Analysis: Implications to Psychosis

Fabiana Corsi-Zuelli*[1], Zhi Li[2], Ashley Pegg[2], Cristina Matas de las Heras[3], Elizabeth Jinks[3], Jamie Cowley[2], Ines M Morano[3], Cristina Marta Del-Ben[4], Golam Khandaker[5], John Suckling[6], Bill Deakin[7], Jack Rogers[8], Sian Lowri Griffiths[9], Ella Warwick[9], Omar Qureshi[3], Rachel Upthegrove[10], Nicholas M Barnes[9]

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**Background:** Evidence indicates that interleukin 6 (IL-6) may play a causal role in psychosis. However, no studies have yet tested the therapeutic potential of targeting IL-6 in psychosis by stratifying patients based on inflammatory markers and symptoms. IL-6 activates cells through the phosphorylation of STAT3 (pSTAT3), which can be antagonised by tocilizumab, an anti-IL-6 receptor monoclonal antibody. PIMS (Psychosis Immune Mechanism Stratified Medicine Study) is a proof-of-concept trial designed to assess IL-6 signalling inhibition on anhedonia in psychosis. Approximately 60 patients with psychosis (ICD-10 F20, F22, F25, F28, F29) with evidence of low-grade inflammation (IL-6≥0.7 pg/mL) and anhedonia are receiving intravenously either a single dose of tocilizumab or saline. An additional 30 patients without inflammation and 30 healthy controls are undergoing baseline assessments for comparison. The primary aim of PIMS is to examine the potential effect of IL-6 inhibition on anhedonia, psychotic symptoms and cognition, with further investigation into the cellular immunological mechanisms using deep immunophenotyping of peripheral blood mononuclear cell subsets (PBMCs).
**Methods:** We optimised a multi-colour flow cytometry assay to characterise the absolute number, frequency, and function of various PBMC subsets isolated from peripheral human blood samples. This optimised protocol includes a phosflow assay to quantify STAT3 phosphorylation (pSTAT3) in PBMCs after exogenous IL-6 exposure. Briefly, PBMCs (1x106 cells/well) isolated from human peripheral blood were stimulated with exogenous recombinant human IL-6 (0.1 - 100 ng/mL) after incubation with tocilizumab (20 µg/mL) or vehicle. The geometric mean of fluorescence intensity (MFI) of total PBMCs was evaluated to select the optimal concentration of exogenous IL-6. Levels of pSTAT3 within different PBMC subsets were quantified by multi-colour flow cytometry after fixation, permeabilization and staining procedures. All experiments were performed in triplicates.
**Results:** Exogenous IL-6 evoked a concentration-dependent increase in intracellular pSTAT3 (MFI pSTAT3, IL-6 (ng/mL): 0.1: 505.6±1.1; 1.0: 587.2±1.1; 10: 622.2±1.0; 100: 629.7±1.1, which was inhibited by pre-incubating cells with tocilizumab (geometric mean±SD, minimum 358.3±1.0; maximum: 611±1.12). Our preliminary results showed that adaptive immune cells, particularly CD4+ T cells, were the most responsive cells to exogenous IL-6

(10 ng/mL), demonstrated by increased pSTAT3 levels (60.4%), followed by hypofunctional (32.8%) and functional Tregs CD4+CD25+CD127- (26.7%), CD8+ T cytotoxic (23.9%), and CD3+CD56+ natural killer T cells (17.5%). Less responsive cells were gamma-delta T cells CD3+CD4-CD8- (8.9%), classical monocytes (8.9%), B cells CD22+ (3.6%), and CD56+ NK cells (0.9%). Pre-treatment with tocilizumab reduced the IL-6-induced pSTAT3 levels among CD4+ T cells (54.4% reduction), hypofunctional Tregs (30.8%), functional Tregs (21.8%), CD8+ T cells (18.6%), and NK T cells (10.78%).
**Conclusions:** Our findings suggest that adaptive immune cells, particularly CD4+ T and hypofunctional Tregs, are the most responsive cellular populations to exogenous IL-6 stimulation in vitro. Although preliminary, our results will aid to the identification of immune cell dysfunction in psychosis, which remains largely unknown. Our next step is to assess the impact of intravenous infusion of tocilizumab on PBMCs profiled in immune-active psychosis patients. We will also compare the cellular immune profile of immune-active psychosis at baseline with those of non-immune active psychosis and healthy controls. Functional assessment of IL-6/STAT3 signalling in immune cell subsets and their response to exogenous IL-6 stimulation will inform abnormal immune response in psychosis and allow measurement of response to tocilizumab at the cellular level.

### 15.4 Clinical and Neurobiological Differences Between First-Episode Psychosis With and Without Circulating Auto-Antibodies: Preliminary Findings From the Phlames Study

Alessandro Pigoni*[1], Giuseppe Delvecchio[2], Matteo Rocchetti[3], Letizia Squarcina[4], Alice Mandrini[5], Adele Ferro[6], Marcella Bellanii[7], Matteo Gastaldi[5], Paolo Brambilla[8]

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**Background:** In recent years, we have witnessed increased knowledge and awareness of autoimmune encephalitis (AE). These autoimmune entities often present with mixed psychiatric and neurologic features but in up to 4% of the cases the presentation is purely psychiatric. AEs are characterized by autoimmune Neuronal Surface Autoantibodies (NSAbs), found in the Cerebro Spinal Fluid that are considered pathognomonic. The definitive diagnosis can be made only through NSAbs in the Cerebro Spinal Fluid, but symptoms and signs of possible and probable diagnosis have been described (Pollack et al., 2020). However, NSAbs can also be found in peripheral blood in various percentages of patients, even without the clinical syndrome of AE. The role of these antibodies in psychiatric patients is yet not known.
On these bases, the PHLAMES study aims at evaluating patients experiencing first episode psychosis (FEP) for signs and symptoms of AE in a psychiatric setting, with the double objective of assessing the diagnosis of AE and the role of circulating NSAbs in psychiatric patients, by means of clinical evaluation, biological samples, and neuroimaging.

**Methods:** Here, we present the preliminary results of the PHLAMES study. 55 patients with FEP ( < 6 months from the onset) were enrolled. A complete psychiatric and neurologic assessment was performed; cognitive tests were administered, including Ray Auditory Verbal Learning Test (RAVLT), Raven's Coloured Progressive Matrices, and Trial Making test A

(TMT-A). All patients underwent blood samples to test for circulating auto-antibodies against SNC structures.
A smaller subsample also underwent structural magnetic resonance imaging (sMRI).

Analyses compared patients testing positive for serum NSAbs (NSAbs-POS) to those testing negative (NSAbs-Neg). For clinical and cognitive variables, ANOVA was applied, with correction for multiple testing. For sMRI, the two groups were compared using sex and age as covariates.

**Results:** 12.8% of the patients tested positive for serum NSAbs (NSAbs-POS). No difference in terms of age, sex, BMI, years of education, and ethnicity was found between patients positive and negative for NSAbs.
Regarding the neurologic variables, NSAbs-POS significantly showed more memory deficits, parkinsonism signs, and speech disorders ($p < 0.001$), compared to NSAbs-NEG patients. Similarly, NSAbs-POS patients presented a significant in TMT-A, Raven, and RAVLT scores ($p < 0.05$) compared to NSAbs-NEG. Finally, NSAbs-POS patients presented an increased score at PANSS "Somatic implication" item and a reduced score at PANSS "Insight" ($p < 0.05$) items, suggesting a higher concern of these patients regarding their help and a greater awareness of their condition.

Regarding sMRI, NSAbs-POS showed an increase in grey matter compared to NSAbs-POS, in several areas, including right superior frontal gyrus, left middle temporal gyrus, left paracentral lobule, right supramarginal gyrus, right inferior parietal gyrus, and right lingual gyrus.

**Conclusions:** Our preliminary findings suggest the possibility that NSAbs-POS patients might represent a subpopulation of FEP with specific characteristics. Specifically, in our sample, NSAbs-POS showed a higher presence of neurological and cognitive alterations, coupled with an increased insight. Such alterations are similar to those present in AE, although to a lesser extent. Moreover, differences in grey matter were present, suggesting that this subgroup may have a different neurobiological underpinning. These results are preliminary and need confirmation in bigger samples, but they might represent a step towards the identification of clinically meaningful subgroups in FEP defined through an easy and not invasive test, helping to dissect the heterogeneity of psychiatric disorders and moving towards precision psychiatry.

### 16. The Neuroscience of Language in Psychosis: A Diverse Global Perspective From the Discourse Consortium

Maria Francisca Alonso, *Universidad de Valparaíso*

**Overall Symposia Abstract:** Language disturbances are a central feature of schizophrenia, often leading to difficulties in communication and social interaction. As a result, many patients face challenges in education and employment. The connection between formal thought disorder and the brain's language network sugests that the disorganized thoughts and speech observed in individuals with psychosis may arise from neural dysfunctions in language-related brain regions. This symposium will explore cutting-edge research on the neurocognitive mechanisms behind language abnormalities in schizophrenia and psychosis. Gaining insight into these mechanisms could help identify brain targets for stimulation, enhancing the effectiveness of language impairment rehabilitation.

Dr. Tugce Cabuk will examine the abnormalities in white matter tracts, particularly the inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF), in both FEP patients and their unaffected siblings. She will discuss how these tracts are vital components of the extended language/semantic network, involved in lexical retrieval, semantic mapping, and the socio-emotional aspects of communication.

Dr. Maria Alonso will present evidence of disrupted excitatory–inhibitory balance within the semantic network, which affects semantic control and contributes to disorganized speech in psychosis.

Rui He will enhance the current understanding by discussing how this disorganization is linked to whole-brain connectivity patterns, challenging prevailing assumptions about coherence in patients with schizophrenia speech and the significance of semantic similarity metrics.

Dr. Frederike Stein will explore the correlation between three robust linguistic dimensions—complexity, cohesion, and richness—and brain structure across diagnostic categories. She will delve into how language richness negatively correlates with grey matter volume in the right posterior insula, while cohesion is negatively associated with white matter integrity in language-related tracts.

Finally, Dr. Lena Palaniyapan will lead a discussion on the potential, limitations, and future research directions in this area.

**16.1 Analyzing Language Ability in First-Episode Psychosis and Their Unaffected Siblings: A Diffusion Tensor Imaging Tract-Based Spatial Statistics Analysis Study**

Tugce Cabuk*[1], Didenur Şahin Çevik[1], Işık Batuhan Çakmak[2], Helin Yılmaz Kafalı[3], Bedirhan Şenol[2], Hanife Avcı[4], Kader Karlı Oğuz[5], Timothea Toulopoulou[1]

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**Background:** Schizophrenia (SZ) is a highly heritable mental disorder, and language dysfunctions play a crucial role in diagnosing it. It is well known that these dysfunctions have been linked to white matter (WM) abnormalities in language-related brain regions. Due to the disorder's strong hereditary nature, it could be expected that first-degree family members might display similar structural brain abnormalities detected in the patients. Although language-related symptoms such as disorganized speech were predicted by the polygenic risk for SZ which emphasized the common genetic liability for the disease, few studies investigated possible WM integrity abnormalities in the language-related tracts in those at familial high-risk for SZ. Also, their results are not consistent.
**Methods:** In this current study, we examined possible aberrations in language-related white matter tracts in patients with first-episode psychosis (FEP, N = 20), their siblings (SIB, N = 20), and healthy controls (CON, N = 20) by applying whole-brain Tract-Based Spatial Statistics (TBSS) and region-of-interest (ROI) analyses. We also assessed language ability by Thought and Language Index (TLI) using Thematic Apperception Test (TAT) pictures and

verbal fluency to see whether the scores of these language tests would predict the differences in these tracts.
**Results:** We found significant alterations in language-related tracts in the whole brain TBSS analyses such as inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) among three groups ($p < 0.05$, FWE corrected) and between SIB and CON. In ROI analyses, we found significant differences in Fractional Anisotropy (FA, KW = 6.16, p = 0.046) and Radial Diffusivity (RD, KW = 6.33, p = 0.042) across the 3 groups in the right UF. Among 3 groups, the reason for the alteration in the right UF (FA) (p = 0.039) and (RD) (p = 0.036) is the difference between SIB and CON. We also proved partly their relationship with the language test as indicated by the significant correlation detected between TLI Impoverished thought/language sub-scale and ILF (rho = 0.28, $p < 0.05$). We could not find any difference between FEP and CON.
**Conclusions:** These results showed that the abnormalities, especially in the ILF and UF, could be important pathophysiological vulnerability indexes of schizophrenia. Previous studies showed that ILF and UF are in the extended language/semantic network and have related language functions. More linguistically, they are responsible for involving lexical retrieval/selection or lexical-to-semantic mapping (i.e. comprehension) and semantic-to-lexical mapping (i.e. production), semantic association, and naming. However, it could be said that all these linguistic functions in these WM tracts, especially in the UF, are within the domain of the socio-emotional aspect of life in the extended semantic network. Language is intrinsically social. Conveying our conceptual knowledge or ideas with words to others is affected by our emotional history. Besides, in our sample, the TLI Impoverished thought/language subscale score is relatively high. This subscale represents the features of the negative syndrome of schizophrenia and the linguistic functions of the negative symptoms are mostly reduced verbal fluency, lack of spontaneity and diminished expression of ideas during interpersonal interactions. Based on our results, it could be said that not only FEP patients but also their healthy siblings are not able to talk much (e.g., socio-emotional aspect), so they produce fewer words and sentences compared to healthy controls. Further studies are required to understand better the role of language as a possible endophenotype in schizophrenia with larger samples.

### 16.2 Decoding Brain-Language Relationships Across Psychiatric Disorders: A Transdiagnostic Study Using Natural Language Processing and Neuroimaging Techniques

Frederike Stein*[1], Svenja Seuffert[1], Rieke Mülfarth[1], Tilo Kircher[1]

[1]*University of Marburg*

**Background:** Psychiatric disorders are often characterized by shared language and cognitive impairments that transcend traditional diagnostic categories. Natural language processing (NLP) offers a powerful tool for detecting subtle linguistic deviations reflective of cognitive and emotional processes. However, the neurobiological underpinnings of these linguistic patterns remain poorly understood. Using data from the FOR2107 cohort, we adopt a transdiagnostic approach to explore the relationship between NLP-derived linguistic features and brain structure across affective and psychotic disorders.
**Methods:** A total of 364 participants were included (n=118 major depressive disorder, n=26 bipolar disorder, n=48 schizophrenia-spectrum disorders, and n=172 healthy controls). Spontaneous speech was elicited using four pictures from the Thematic Apperception Test, yielding approximately 12 minutes of speech per participant. NLP models were applied to extract various linguistic features, including lexical (e.g., type-token-ratio, lexical diversity),

syntactic (e.g., length, complexity, diversity), and semantic (e.g., similarity, coherence, density) domains. Bootstrapped factor analysis was used to identify latent linguistic dimensions. Brain imaging data included both T1-weighted and diffusion-weighted MRI to assess gray matter volume (GMV), white matter fractional anisotropy (FA), and brain networks. Correlations between NLP-derived linguistic dimensions and brain structural measures were examined.
**Results:** We identified three robust linguistic dimensions (i.e., complexity, cohesion, richness) that were associated with brain structure. For example, richness was negatively correlated with the GMV of the right posterior insula. Additionally, cohesion showed significant negative associations with the FA of language-related fiber tracts, such as the uncinate, superior and inferior longitudinal fascicles. These correlations were observed across diagnostic categories, indicating that certain brain-linguistic relationships may be transdiagnostic in nature.
**Conclusions:** Our results provide a refined mapping of cross-disorder NLP dimensions, highlighting their neuroanatomical signatures linked to language-related local and global brain structural measures. Our findings open a promising avenue for transdiagnostic, dimensional studies in pathogenetic research.

### 16.3 Perplexity of Utterances in Untreated First-Episode Psychosis: An Ultra–High Field MRI Dynamic Causal Modelling Study of the Semantic Network

Maria Francisca Alonso*[1], Wolfram Hinzen[2], Rui He[3], Joseph Gati[4], Lena Palaniyappan[5]

[1]*Universidad de Valparaíso,* [2]*Universitat Pompeu Fabra; Catalan Institute for Advanced Studies and Research (ICREA),* [3]*Universitat Pompeu Fabra,* [4]*Western University,* [5]*Douglas Mental Health University Institute*

**Background:** Psychosis involves a distortion of thought content, which is partly reflected in anomalous ways in which words are semantically connected into utterances in speech. We sought to explore how these linguistic anomalies are realized through putative circuit-level abnormalities in the brain's semantic network.
**Methods:** Using a computational large-language model, Bidirectional Encoder Representations from Transformers (BERT), we quantified the contextual expectedness of a given word sequence (perplexity) across 180 samples obtained from descriptions of 3 pictures by patients with first-episode schizophrenia (FES) and controls matched for age, parental social status, and sex, scanned with 7 T ultra–high field functional magnetic resonance imaging (fMRI). Subsequently, perplexity was used to parametrize a spectral dynamic causal model (DCM) of the effective connectivity within (intrinsic) and between (extrinsic) 4 key regions of the semantic network at rest, namely the anterior temporal lobe, the inferior frontal gyrus (IFG), the posterior middle temporal gyrus (MTG), and the angular gyrus.
**Results:** We included 60 participants, including 30 patients with FES and 30 controls. We observed higher perplexity in the FES group, indicating that speech was less predictable by the preceding context among patients. Results of Bayesian model comparisons showed that a DCM including the group by perplexity interaction best explained the underlying patterns of neural activity. We observed an increase of self-inhibitory effective connectivity within the IFG, as well as reduced self-inhibitory tone within the pMTG, in the FES group. An increase in self-inhibitory tone in the IFG correlated strongly and positively with inter-regional excitation between the IFG and posterior MTG, while self-inhibition of the posterior MTG was negatively correlated with this interregional excitation

**Conclusions:** As an explanation for peculiar speech in psychosis, these results index a shift in the excitatory–inhibitory balance regulating information flow across the semantic network, confined to 2 regions that were previously linked specifically to the executive control of meaning. Based on our approach of combining a large language model with causal connectivity estimates, we propose loss in semantic control as a potential neurocognitive mechanism contributing to disorganization in psychosis.

### 16.4 Semantic and Neural Metrics of (In)Coherence

Rui He*[1], Maria Francisca Alonso[2], Iris Sommer[3], Philipp Homan[4], Lena Palaniyappan[5], Wolfram Hinzen[1]

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**Background:** Atypical forms of discourse in psychosis were conceptualized early on as revealing 'loosening of associations', which has been quantified for two decades as the decrease in semantic similarity between consecutive word pairs using embeddings from large language models. This assumption, however, lacks empirical support and is facing challenges. In this presentation, we comprehensively investigated the correlation between discourse coherence and semantic and probability metrics derived from large language models, followed by the correlations with neuroactivity as obtained with 7T resting-state fMRI.
**Methods:** We test this assumption in three extensive datasets from the general population in three languages, English, Danish, and Chinese, with a comprehensive set of 131 computational semantic and probabilistic metrics. Analyses were also performed on picture descriptions from 94 individuals across subsections of schizophrenia spectrum disorders (SSD) and controls for semantic correlates of incoherent speech in SSD. Finally, we reconstructed the cortical hierarchy in a subset of the 94 individuals where resting-state fMRI images were available, including twenty-nine untreated first-episodic psychosis (FEP) patients, matched to twenty-nine healthy controls (HC) on age, gender, and education. The cortical hierarchy in question consists of a gradient of functional connectivity values ranging from lower-order cognitive networks (visual and somatomotor) to higher-order networks (default mode). The dispersions between the lower-order and higher-order networks were related to human coherence.
**Results:** In the three datasets from the general population, only 6 out of the 131 variables showed weak but significant correlations with human-rated coherence. Incoherence speech in SSD, specifically in the first episode of schizophrenia, could be measured mainly with the skewness of the distribution of sentence-level semantic similarity scores and the perplexity of the discourse. Furthermore, coherence in this clinical sample positively correlated with the dispersion of a whole-cortical gradient of intrinsic functional connectivity as measured with resting-state fMRI.
**Conclusions:** Together these findings confirm the widely held assumption that speech in schizophrenia across different symptom profiles is less coherent, with an associated neural correlate in a whole-cortex intrinsic connectivity pattern, while disconfirming the widely held assumption that semantic similarity metrics measure such coherence.

## 17. Second to None: Advocating and Expanding the Enduring Unique Relevance of Clozapine for Schizophrenia

Robert Bittner*, Goethe University Frankfurt, University Hospital*

**Overall Symposia Abstract:** Treatment resistance manifests in about thirty percent of all patients with schizophrenia, in the majority of cases during the first psychotic episode. More than 65 years after its synthesis clozapine remains the only effective antipsychotic drug for patients with treatment-resistant schizophrenia. Furthermore, a growing body of evidence indicates that the benefits of clozapine extend considerably beyond narrowly defined treatment resistance, including but not limited to the largest reduction in all-cause mortality among all antipsychotic compounds. Although these findings are reflected in all major national and international treatment guidelines, converging evidence from developed countries clearly indicates that clozapine remains substantially underused. The considerable decline in response rates associated with its delayed initiation underscores the need for concerted efforts to identify and reduce prescription barriers to make clozapine the routine early treatment offer it unequivocally needs to be. To achieve this goal, the identification of better predictors of both treatment resistance and adverse drug reactions as well as the development of more effective augmentation strategies for patients which do not show a sufficient response to clozapine are of equal importance. This symposium will highlight findings from a variety of large-scale studies and data sets, which can facilitate a more timely, widespread, safe and effective use of clozapine. Furthermore, the data we discuss will add to the case of clozapine as the most effective treatment option for many of the most vulnerable patients.

Heidi Taipale will present two studies based on the Finnish and Swedish nationwide registers. In patients experiencing their first psychotic relapse despite the use of non-clozapine oral antipsychotics, clozapine was significantly more effective in preventing a second relapse than any other oral antipsychotic. Among antidepressants and mood stabilizers augmentation with sertraline and valproate led to a significant decrease in relapse rates and somatic hospitalization.

Dan Siskind will report interim results from an ongoing 12-week randomised, placebo-controlled, double-blind, parallel-group clozapine augmentation trial comparing 1000mg of cannabidiol daily with placebo with PANSS positive scores as the primary outcome measure. Secondary outcomes include total and negative PANSS, sleep quality, anxiety, neurocognitive measures, depression scores, metabolic syndrome components, and alcohol consumption.

Marte van der Horst will discuss data from the CLOZIN study demonstrating high patient satisfaction primarily due to its efficacy. Hypersalivation, weight gain, and increased sleep were the most common side effects, with younger patients being particularly affected. A lower baseline BMI was associated with weight gain. Moreover, a high genetic load for schizophrenia increased the risk for treatment resistance but also predicted a good response to clozapine.

Robert Bittner will present an analysis of German health insurance data investigating changes in clozapine prescription patterns between 2010 and 2021. Here, the standardized prescription prevalence for clozapine decreased steadily, particularly among younger men in metropolitan areas. Moreover, an online survey of psychiatrists working in a hospital setting revealed that

the handling of clozapine was regarded as the most important prescription barrier. Clinicians regarded blood dyscrasia and weight gain as the most problematic side effects.

### 17.1 Real-World Update: Benefits of Switching Early to Clozapine, and Clozapine Augmentation With Antidepressants and Mood Stabilizers

Heidi Taipale*[1], Jari Tiihonen[2], Antti Tanskanen[2]

[1]*Niuvanniemi Hospital, University of Eastern Finland,* [2]*Karolinska Institutet*

**Background:** Delay in clozapine initiation is a wide-spread clinical problem. Another important dilemma is the lack of treatment options beyond clozapine and lack of evidence on effectiveness and safety of potential clozapine augmentation strategies. The results from two register-based studies are presented, first investigating switching to clozapine in first-episode schizophrenia (FES) after the first relapse, and second investigating real-world effectiveness of clozapine augmentation with antidepressants or mood stabilizers in two nationwide cohorts.

**Methods:** First study included all persons aged ≤45 years with FES during 1996–2014 (N=3000) from Finland who experienced their first psychosis relapse within five years of first schizophrenia diagnosis. Treatment strategies were assessed during 30 days before hospitalization for the first relapse, and 30 days after discharge, categorized as long-acting injectable (LAI), clozapine, non-clozapine oral antipsychotic (OAP) monotherapy, OAP polypharmacy, and antipsychotic non-use. Adjusted hazard ratios (aHRs) of the risk of second relapse were analyzed with Cox regression models during 2 years post first relapse. Second study included all patients with schizophrenia using clozapine, identified from Finnish (years 1996-2017) and Swedish (years 2006-2023) nationwide registers. The main outcome was psychosis relapse, associated with periods of augmentation vs. clozapine in a within-individual design, using each individual as his/her own control and analyzed with stratified Cox models. The two national cohorts were analyzed separately, and the results were combined with random-effects meta-analysis.

**Results:** In the first study, most persons were without antipsychotics (45.5%) or using OAP-monotherapy (32.4%) before first relapse. Of them, 71.7% experienced a second relapse. Compared to continuing the same treatment strategy used before the first relapse (aHR=1.00), switch to clozapine was always associated with the lowest risk of second relapse (aHR for switch from OAP-monotherapy to clozapine 0.66, 95%CI 0.49-0.89, relapse rate OAP-monotherapy continuation=73.2% vs. switch to clozapine=57.1%). Switch to another OAP-monotherapy (aHR 0.99, 0.76-1.28) was not associated with decreased risk.
The analysis of the augmentation study included 23,206 clozapine users; 14,053 in the Finnish cohort and 9,153 in the Swedish cohort. Regarding antidepressant augmentations, the lowest risk of relapse was observed for sertraline (meta-analysis aHR 0.76, 95%CI 0.69-0.83) and duloxetine (0.78, 0.68-0.89). Concerning mood stabilizers, a decreased risk of relapse was observed for valproate (0.86, 0.82-0.90). These results were consistent between the cohorts. Sertraline and valproate showed decreased risk also for a composite outcome of relapse/ somatic hospitalization, indicating overall effectiveness and safety combined.

**Conclusions:** In patients with FES experiencing their first psychosis relapse despite use of non-clozapine oral antipsychotics, continuation with the same antipsychotic modality or

switch to another non-clozapine OAP is not beneficial in relapse prevention, suggesting that clozapine should be started instead. This finding challenges current treatment guidelines recommending clozapine as a third-line treatment, resulting in treatment practices characterized by long delays to clozapine initiation. Regarding clozapine augmentation strategies, meta-analysis from two nationwide cohorts supported the use of sertraline and valproate as potential augmentation strategies to clozapine.

### 17.2 CANCLOZ: Cannabidiol for Clozapine Resistant Schizophrenia

Dan Siskind*[1], Nicola Warren[2], Andrea Baker[3], Claudia Bull[2], Mike Trott[2], Urska Arnautovska[2]

[1]*University of Queensland,* [2]*Faculty of Medicine, The University of Queensland,* [3]*Queensland Centre for Mental Health Research*

**Background:** Schizophrenia affects approximately 1% of the global population, with about a third of these individuals having treatment-resistant schizophrenia (TRS). Clozapine is the most effective known antipsychotic for TRS, yet only 40% of TRS patients show adequate response to clozapine. Existing augmentation strategies for clozapine are limited in effectiveness. Cannabidiol (CBD) has shown promise in reducing positive psychotic symptoms in schizophrenia but has not been tested specifically among people with clozapine-resistant schizophrenia.
**Methods:** This study is a 12-week randomised, placebo-controlled, double-blind, parallel-group trial. 88 individuals with clozapine-resistant schizophrenia are being randomly assigned (1:1) to receive either 1,000mg of CBD daily or a placebo. Participants will be aged 18-64, meet DSM-IV criteria for schizophrenia or schizoaffective disorder, have a PANSS score ≥60, and be on a stable dose of clozapine for at least 18 weeks with a blood level of > 350ng/ml. Interim analyses will be conducted at 25%, 50%, and 75% recruitment, and interim analyses will also provide an opportunity to reallocate participants dependent on conditional power. The primary endpoint is the change in positive PANSS scores at 12 weeks. Secondary endpoints include measures of total and negative PANSS, depression, anxiety, sleep quality, quality of life, alcohol consumption, weight change, metabolic syndrome components, neurocognitive functions, and safety and tolerability of the treatment.
**Results:** We will present interim results, discussing any potential difference in positive PANSS scores in the CBD group compared to the placebo group at week 12. Secondary outcomes will be presented on changes in total and negative PANSS, sleep quality, anxiety, neurocognitive measures, depression scores, metabolic syndrome components, or alcohol consumption between the CBD and control group. Tolerability of CBD will be reported.
**Conclusions:** Novel treatments for clozapine-resistant schizophrenia are urgently needed. If found to be effective in improving positive psychotic symptoms, CBD may have a role as a safe augmentation agent for people with clozapine resistant schizophrenia.

### 17.3 Results From the CLOZIN STUDY: From Side Effects and Genetic Liability to Patient Satisfaction and Beyond

Marte van der Horst*[1], Jurjen Luykx[2], Cynthia Okhuijsen-Pfeifer[1]

[1]*UMC Utrecht,* [2]*Amsterdam UMC, GGz InGeest*

**Background:** Despite its proven effectiveness in reducing symptoms, hospitalizations, and mortality, clozapine remains underused in many countries due to a range of patient- and

clinician-related barriers. The CLOZIN study aims to identify clinical and genetic factors associated with treatment outcomes in clozapine therapy, aiming to gain insights into indicators of successful treatment and potentially reduce barriers to its use.
**Methods:** The CLOZIN study is an ongoing, multi-country, observational cohort involving individuals aged 18 and older diagnosed with psychosis spectrum disorders who are receiving clozapine. Designed to minimize exclusions, the study ensures a diverse and representative real-world population. A broad range of data is collected, with study visits lasting approximately 30 minutes. Several sub-studies have already been completed and published. This presentation provides an overview of findings, beginning with an analysis of clozapine users' satisfaction with their treatment, alongside the demographic and clinical variables associated with it. Additionally, we mapped the prevalence of common clozapine-associated adverse drug reactions (ADRs) and identified factors linked to their occurrence. We also explored the comedication profiles of clozapine users, assessing cross-country differences and the impact of ADRs in relation to concomitant medication use, including antipsychotic polytherapy. Finally, genome-wide association studies (GWAS) and polygenic scores (PGS) for schizophrenia were used to examine associations between genotype and symptom severity, as well as the varying liability to schizophrenia across different patient groups.
**Results:** To date, over 1,000 clozapine users from nine countries have been enrolled. Patient satisfaction averaged 7.4/10 and was primarily linked to treatment effectiveness, followed by symptom severity and adverse drug reactions (ADRs). The most frequent ADRs were hypersalivation, weight gain, and increased sleep, particularly in younger patients. Weight gain was more common among those with a lower baseline BMI, while constipation was associated with higher clozapine levels. No differences in ADR rates were observed between antipsychotic monotherapy and polytherapy users. Regarding comedication profiles, we found that 46% of participants were on polypharmacy, with lorazepam, vitamin D, and aripiprazole being the most frequently prescribed medications. There were significant differences in prescribing habits across countries, especially in the management of clozapine-associated ADRs, where treatment approaches varied considerably. In terms of genetics, we observed that polygenic scores (PGS) for schizophrenia progressively increased from healthy controls to clozapine users, with the latter showing the highest risk. Additionally, higher PGS-schizophrenia scores and predicted CYP2C19 enzyme activity were associated with lower symptom severity.
**Conclusions:** We identified several factors associated with vulnerability to therapy resistance, ADRs, patient satisfaction, and therapy compliance in patients treated with clozapine. These insights can be used to personalize clozapine treatment and reduce prescription barriers, thereby enabling more effective treatment for these patients.

### 17.4 In Search of the Causes for Clozapine Underutilization: Analysis of Clozapine Prescription Patterns and Prescriber Attitudes in Germany

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**Background:** Clozapine remains the most effective antipsychotic, and the only drug approved for treatment-resistant schizophrenia (TRS). Clozapine is the single most effective drug for reducing all-cause mortality in TRS. Consequently, clozapine should be widely used for TRS but also for certain non-TRS patients. Yet only a fraction of suitable patients actually receives clozapine – often years after treatment resistance becomes evident and despite the

fact that a delayed initiation of clozapine has a clear negative effect on its efficacy. The majority of patients consistently reports a high degree of satisfaction with clozapine. Conversely, there is increasing evidence that clozapine underutilization is attributable to a considerable degree to prescriber concerns regarding the feasibility of clozapine treatment. Overall, there is a clear need for transnational efforts to improve clozapine utilization. Yet, the substantial differences between different health care systems necessitate a clear understanding of country-specific causes including clozapine prescription patterns and prescriber attitudes.
**Methods:** We conducted annual cross-sectional studies from 2010 to 2021, based on the Pharmacoepidemiological Research Database (GePaRD), which contains data from 20% of the German population. We included all individuals aged 0–64 years with continuous insurance coverage, as well as those who were born or died in the respective year and identified all outpatient prescriptions of clozapine for individuals with a diagnosis of schizophrenia in the same year. Next, we calculated the prescription prevalence (number of people with ≥1 prescription per 100,000 individuals) overall and stratified by sex and residential area (urban-rural). All estimates were directly age- and/or sex-standardized to the German general population. Additionally, we conducted an anonymized online survey among psychiatric residents and specialists working in a hospital setting regarding their attitude toward and knowledge about clozapine use in schizophrenia.
**Results:** Overall, the standardized prescription prevalence steadily decreased from 61.2/100,000 in 2010 to 53.5/100,000 in 2021. This trend was observed for both sexes, with men having higher prevalence rates than women (men: from 73.3 to 65.7/100,000; women: from 48.7 to 40.9/100,000). Regarding regional differences in prescription prevalence, declines were observed between 2010 and 2021 in major cities (78.1 to 60.6/100,000) and urban districts (58.6 to 50.4/100,000), while prevalence increased in rural districts with urban tendencies and sparsely populated rural districts during this period (47.2 to 52.1/100,000 and 48.8 to 51.7/100,000, respectively). Among the 80 prescribers, who completed our online survey, handling of clozapine as well as its monitoring requirements were considered to be the most important prescription barrier. Clinicians regarded blood dyscrasia and weight gain as the most problematic side effects. Most participants reported not having received any formalized clozapine-related training.
**Conclusions:** The alarming observation of a decline in clozapine prescription rates in Germany particularly in metropolitan areas, where patients with TRS are likely overrepresented, contrasts with trends in other Western countries, e.g. Finland and the UK, where clozapine prescriptions have increased in recent years. Systematically instituting dedicated TRS teams appears to be an important first step to reverse this concerning trend. Moreover, our findings constitute a call for action on the national and European level to ease blood monitoring requirements. Additionally, instituting obligatory systematic training in clozapine use for psychiatric residents appears to be essential.

### 18. Expanding the Frontiers of CHR Research – Baseline Analyses From the Accelerating Medicines Partnership® – Schizophrenia Consortium

Michael Sand, *S2 Consulting*

**Overall Symposia Abstract:** The clinical high risk for psychosis (CHR) paradigm offers a platform for efforts to develop medications to prevent schizophrenia and other psychoses. Nearly one in five young people presenting for psychiatric care meet criteria for CHR, and those meeting criteria are at roughly 20% risk of converting to overt psychosis within in a few years. Moreover, all CHR patients experience attenuated psychotic symptoms, most

experience negative or affective or anxiety symptoms and a degree of functional impairment, and many experience cognitive impairment. No medication treatment is specifically indicated for CHR in any country. The Foundation for the National Institutes of Health (FNIH) Accelerated Medicines Partnership® (AMP®) program was established in 2014 and aims to accelerate the treatment of 10 diseases or disorders where a greater understanding is needed. FNIH established the AMP – Schizophrenia program in 2019. Its first project, the largest longitudinal observational study for CHR to date, comprises grants to two international research networks totaling 43 sites and a data center and will enroll nearly 2000 CHR participants and more than 500 community controls (CC) with follow-up over two years. Its second project will conduct 1 or 2 proof of principle clinical trials in CHR participants of compounds selected by the AMP SCZ Compound Selection Subcommittee. The second public data release from the Observational Study to the NIMH Data Archive in May 2024 included data for 807 CHR and 213 CC. It is expected that findings shown at the meeting will derive from the larger 3rd release. In the first talk, Dr. John Torous from Beth Israel Deaconess Medical Center and Harvard Medical School will present baseline ecological momentary assessment findings from cell-phone app surveys, audio diaries, and passive measures (GPS and phone usage) and wrist actigraphy, including derived measures of environmental exposures and sleep pattern. In the second presentation, Dr. Jean Addington from the University of Calgary will present baseline CHR vs CC and correlation findings for attenuated positive, negative, affective, and anxiety symptoms and functioning and compare the AMP SCZ sample to those from previous observational studies. In the third presentation, Dr. Phillip Wolff from Emory University will discuss how language features extracted from clinical and open-ended interviews using AI methods can differentiate CHR and CC participants. He will also present findings showing how these language features cluster into distinct patterns, offering insights into potential subtypes within the CHR population. In the fourth talk, Dr. Eve Lewandowski from McLean Hospital and Harvard Medical School will present CHR vs CC and clustering analyses of the baseline AMP SCZ cognitive data from the PennCNB battery to identify possible cognitively impaired and other CHR subgroups. Mr. Carlos Larrauri, patient advocate and Co-Chair of the AMP SCZ Steering Committee, will provide insights into these findings through the lens of his lived experience.

### 18.1 Exploring Digital Phenotyping Data in AMP SCZ

John Torous*[1], Carrie Bearden[2], John Kane[3], Justin Baker[4], Dominic Dwyer[5], Barnaby Nelson[6], Patrick McGorry[7], Scott Woods[8], AMP SCZ[9]

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**Background:** This talk outlines the design of the digital component of the Accelerating Medicines Partnership® Schizophrenia (AMP SCZ) project, a large international collaborative project that follows individuals at CHR for psychosis over two years. The digital component comprises one-year smartphone-based digital phenotyping and actigraphy. Smartphone-based digital phenotyping includes 30-item short daily self-report surveys, voice diaries, and passive data capture (geolocation, on/off screen state, and accelerometer). Actigraphy data are collected via an Axivity wristwatch.
**Methods:** The mindLAMP app has been built iteratively over the last five years with continual feedback from patients, clinicians, family members, and researchers. In this study

the use of mindLAMP is focused on the assessment of diverse data streams that are divided into active (surveys and voice diaries) and passive (sensors) and voice diaries. mindLAMP is deployed in a decentralized manner. Full details are offered at the website: docs.lamp.digital Participants are also asked to wear the Axivity wristband (on their non-dominant hand) for the 1 year duration of the digital component of the study.

Surveys: The daily surveys are intended to capture self-reported emotions, thoughts, and behaviors of the past day as daily assessments.

Passive Data: The GPS sensor measures the longitude and latitude of a user at a designated frequency. The triaxial accelerometer measures acceleration applied to the device. Each measurement is measured in acceleration due to gravity (Gs) and is taken relative to the coordinate plane of the device. The screen state sensor records when the screen is turned on or off, when the device is locked or unlocked, and any changes in battery level from charging or discharging the device.

Voice Diaries: The voice diaries offer participants the possibility of recording up to 2 minutes of free speech to talk about any topic they wish.

**Results:** Pilot data has shown how geolocation data can be used to quantity environmental exposures in patients with schizophrenia, accelerometer to quantify sleep duration and patterns, screen state to quantify screen exposure and its impact on mental health, EMA surveys to correlate with in-person clinical assessments, voice samples to inform severity scores, and metadata to inform suicide risk. These myriad functional measures can be quantified longitudinally throughout the study to serve as metrics of target engagement and clinical outcomes to complement more traditional measures. Utilizing machine learning and statistical tools, we can transform this multivariate, heterogeneous, and longitudinal data into digital phenotypes of illness that may guide individual-level prediction of risk. Methods including but not limited to anomaly detection-based risk models can be deployed to explore the clinical value of this data.
**Conclusions:** Having a comprehensive understanding of a patient's unique journey is of significant value to patients, their families, and their clinical teams. The digital phenotyping and actigraphy arms of AMP SCZ present one the largest and most transparent data sets designed to enable clinical discovery today and future research breakthroughs for years to come.

### 18.2 Clinical Characteristics of Youth at Risk for Developing Psychosis in AMP-SCHZ

Jean Addington*[1], Lu Liu[2], Monica Chu[1]

[1]*University of Calgary,* [2] *Mathison Centre for Mental Health Research and Education, University of Calgary*

**Background:** The Accelerating Medicines Partnership Schizophrenia (AMP-SCHZ) consists of two large clinical networks, ProNET and PRESCIENT, with over 40 sites in North America, Australia, Europe, and Asia currently enrolling participants. Together these two networks propose to study a wide range of clinical variables in 1977 participants who are at clinical high risk for developing psychosis (CHR). Comprehensive details of baseline clinical data as described below will be presented for the complete sample.
**Methods:** Ascertainment methods and demographics will be described. Analysis of the newly developed PSYCHS (Positive Symptoms and Diagnostic Criteria for the CAARMS

Harmonized with the SIPS) will operationalize CHR criteria and demonstrate the different CHR syndromes plus the range and severity of the 15 attenuated psychotic symptoms (APS) of the PSYCHS. Depression is a major concern with CHR youth and severity of depression will be examined and presented with results from the SCID for DSM-5, the Calgary Depression Scale for Schizophrenia and the Columbia Suicide Severity Rating Scale. Negative symptoms, an important feature of CHR, will be reported with results from the Negative Symptom Inventory-Psychosis Risk (NSI-PR), a scale specifically developed for the assessment of negative symptoms in CHR. Impaired functioning, in particular social functioning, has been linked to the later development of psychosis in CHR. Using the Global Functioning: Social and Role Scales baseline ratings on social and role functioning using these specifically designed for CHR scales will be examined. Finally, recent work has suggested the importance of patient reported outcomes (PROs) in youth and several such measures (The Overall Anxiety Severity and Impairment Scale, Patient Global Impression of Severity, Patient-Reported Outcomes Measurement Information System-Sleep Disturbance, Perceived Stress Scale, Perceived Discrimination) were used in SCHZ-AMP.
In addition to describing ratings on these scales, there will be a focus on the PSYCHS to compare APS between the networks and sites. Likewise, an examination of APS in conjunction with referral sources will determine if there are APS differences relative to different ascertainment methods. Finally, similarities or differences in the SCH-AMP sample relative to other large consortia will be discussed. Preliminary data suggests that results similar to those in other samples are being observed.

Data analyses will include descriptive statistics, t-tests and correlations.

**Results:** Complete baseline data from this large multi-site, multi network project will be available by early 2025 and will be analyzed as described.
**Conclusions:** This data analyses of the demographic and clinical features of this large international sample is a necessary prerequisite for understanding the nature of the sample and its relevance for other comprehensive project assessments to be presented including cognition, natural speech/language, passive/ecological momentary digital phenotyping and multi-modal biomarkers.

### 18.3 Utilizing Generative AI for Early Detection of Psychosis: Linguistic Feature Clustering and Risk Differentiation in CHR Populations

Phillip Wolff*[1], Zarina Bilgrami[1], Martha Shenton[2], Barnaby Nelson[3], Scott Woods[4], Guillermo Cecchi[5], Cheryl Corcoran[6]

[1]*Emory University,* [2]*Brigham and Women's Hospital, Harvard Medical School,* [3]*Orygen,* [4]*Yale University,* [5]*IBM Research,* [6]*Icahn School of Medicine at Mount Sinai*

**Background:** Psychosis and its risk syndromes are frequently marked by disruptions in spoken language, indicating illogical thought patterns, disjointed associations, and limited content (Andreasen, 1979a, 1979b; Bearden et al., 2011). Recent research has found that linguistic traits associated with the onset of psychosis can be identified in transcripts through manually designed algorithms, focusing on aspects like discourse coherence, syntactic complexity (Corcoran et al., 2018; Bedi et al., 2015), semantic richness and content (Rezaii et al., 2019), and speech connectedness (Spencer et al., 2021). With the rise of Generative AI, a new assessment method has emerged, leveraging abstract features for machine learning classification without reliance on specific theories, offering the potential for more accurate and unbiased evaluations.

**Methods:** Language samples were gathered from 286 individuals identified as being at Clinical High Risk (CHR) for psychosis and 65 Community Control (CC) participants as part of the Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) project (Release 2.0). These samples were drawn from PSYCHS clinical assessments and open-ended interviews. The PSYCHS interviews followed a semi-structured format, focusing on 15 positive symptom categories, while the open-ended interviews were more participant-led, allowing for natural and open discussions.

We used Meta's LLaMA 3 Large Language Model (LLM) with 70 billion parameters, asking it to assess the normality of interview responses. Because normality is not tied to any specific mental health condition, this method enables unbiased feature extraction. For example, in response to the PSYCHS question, "Have you ever felt that some person or force has been controlling your thoughts?" a participant might answer, "Sometimes if I'm on a strange train of thought, I hear ringing in my ear." LLaMA 3 would evaluate if the response was normal and, if it wasn't, describe why. In this case, LLaMA 3 might conclude, "No, the response is not normal. The interviewee describes experiencing physical sensations (ringing in the ear) linked to specific thoughts." When asked to clarify further, LLaMA 3 might explain, "The response is abnormal because it indicates an unusual connection between physical sensations and thought processes."

**Results:** A Naïve Bayes (NB) classifier, trained on the words and phrases generated by LLaMA 3's initial and follow-up responses, successfully differentiated between Clinical High Risk (CHR) individuals and Community Control (CC) participants across 10 test sets. For the PSYCHS interviews, the classifier achieved an Area Under the Curve (AUC) of 0.682, a precision of 0.603, and a recall (sensitivity) of 0.680. In contrast, during the open-ended interviews, the classifier performed with an AUC of 0.585, a precision of 0.581, and a recall of 0.585. This discrepancy between speech elicitation methods is expected, as the PSYCHS interviews are designed to directly assess symptoms. In a follow-up analysis, we examined the range of features generated by LLaMA 3. To assess the similarities between these features, we asked LLaMA 3 to rate the semantic similarity of all pairwise feature combinations on a scale from 0 to 9. We then reduced the dimensionality of the resulting similarity matrix using Principal Component Analysis (PCA) to 15 dimensions. The reduced matrix was subsequently analyzed using hierarchical clustering. Silhouette coefficients indicated that the features grouped into three main clusters, which further divided into eight sub-clusters. The first group of sub-clusters included features related to unconventional beliefs, working memory, logical reasoning, and unhealthy preoccupations or intrusive thoughts. The second group focused on features involving lack of insight, disorganized thinking, and difficulties with expression, including uncertainty. The final sub-cluster centered on the use of filler words, reality testing, and abrupt topic shifts.

**Conclusions:** AI-generated features can effectively differentiate individuals at Clinical High Risk from Community Controls. Notably, these features form distinct clusters, potentially providing valuable insights into subtypes within the CHR population. These findings underscore the advantages of incorporating advanced AI methods into clinical data analysis, offering a deeper understanding of psychotic disorders and enhancing early detection strategies.

## 18.4 CHARACTERIZING COGNITION IN CLINICAL HIGH RISK

Kathryn Lewandowski*[1], Kelly Allott[2], William Stone[3]

[1]*Harvard Medical School/McLean Hospital,* [2]*Orygen and Centre for Youth Mental Health, The University of Melbourne,* [3]*Harvard Medical School / Beth Israel Deaconess Medical Center*

**Background:** Cognitive impairment is a core feature of psychotic disorders. Impaired cognitive performance is present prior to illness onset at the group level, and findings show that cognitive impairments in people identified as being at clinical high risk (CHR) for the development of psychosis are often more pronounced in those who go on to develop a psychotic disorder. Conversion risk calculators developed in the context of longitudinal studies of CHR include cognitive measures as key predictors, and cognition is among the biomarkers used to identify distinct biotypes in psychosis. The Accelerating Medicines Partnership Schizophrenia (AMP® SCZ) is the largest project of its kind, collecting clinical, cognitive, and other biomarker data in young people at CHR and healthy controls across two large data collection networks with 43 sites worldwide, and a data processing, analysis, and coordination center. These data will include 1977 participants classified as CHR and over 600 community controls (CC). Here we aim to describe cognitive characteristics in the CHR and control groups, and associations with clinical and functional measures at baseline.
**Methods:** Cognitive data are collected using the PennCNB. Eight subtests are administered including: the Short Penn List Learning Test; Motor Praxis Test 2; Short Penn Continuous Performance Test; Penn Emotion Recognition Test; Short Fractal N-Back Test; Digit-Symbol Test; Short Visual Object Learning Test; and the Short Computerized Finger-Tapping Test. Estimated IQ is collected using the two-subtest version of the WASI-II, the WRAT-5 word reading test, or a word reading task available in a site's primary language. Cognitive assessment is collected at multiple timepoints; here we will present the baseline data. T-tests will be used to compare CHR and CC groups, and correlations will be run examining the associations between cognitive measures and clinical and functional variables in the CHR group. Lastly, we will apply clustering algorithms to identify possible cognitive subgroups of patients who share similar cognitive profiles and compare clusters on cognitive and functional measures. These clusters may also be used in our predictive models of primary (conversion) and secondary outcomes.
**Results:** Complete baseline data from this large multi-site, multi network project will be available by the end of 2024 and will be analyzed as described above
**Conclusions:** These data examine baseline cognitive characteristics in CHR and CC, and associations between cognitive biomarker measures and clinical and functional variables. Additionally, we will explore the possibility that cognitive heterogeneity can be characterized using data driven analyses, identifying distinct cognitive subtypes that may provide important prognostic information that will be included in future longitudinal analyses and predictive modeling.

## 19. Social and Economic Interventions for People Living With Psychosis

Helen Baldwin*, King's College London*

**Overall Symposia Abstract:** There is substantial evidence that those with a psychotic disorder, compared with the general population, are much more socially disadvantaged across domains such as education, employment, housing, income, social security, and social isolation. These social adversities are more pronounced for people from marginalised communities. Not only do social adversities form part of the aetiology of psychosis onset, they also exacerbate mental distress in those already experiencing psychosis.

Current provision does not adequately address these social and economic adversities; in fact, services often contribute to systemic inequalities which people with psychosis face. For example, as more people from Black minoritised groups who present to services have greater social needs, and these needs limit the effectiveness of care, the failure of services to address these disproportionately disadvantages those in Black minority groups. This failure to address the problems which are often most fundamental to wellbeing may go some way to explain the lack of trust in services we currently see.

This highlights an urgent need to address social needs as a foundation for further intervention. There are several existing interventions in this area which aim to improve the social circumstances of people with psychosis. However, there are many issues with the current evidence base. Firstly, research efforts have been focussed on certain areas (e.g. employment) more than others (e.g. income). Secondly, these interventions are often tested in isolation from one another, overlooking the extent to which these needs are interconnected. Thirdly, the extent to which marginalised groups have been included in this research, as well as what works for whom, has been overlooked. Nevertheless, there is reason for much optimism, particularly given the promising body of research testing targeted intervention to address social exclusion of vulnerable groups.

Our symposium comprises presentations from leading researchers in the field of social psychiatry and psychology. Our symposium will begin with an overview of the current evidence of social and economic interventions for people living with psychosis, including evidence of what works for whom, based on two recent systematic reviews by researchers at King's College London (Dr Helen Baldwin and Dr Anna Greenburgh).

Exploring targeted intervention in more depth, our next speaker has played a key role in design and research of innovative targeted social interventions for people with psychosis from marginalised groups. Professor Dawn Edge (University of Manchester) will present recent evidence on the feasibility and acceptability of the Culturally-adapted Family Intervention (CaFI) for African-Caribbean people diagnosed with schizophrenia and their families.

Finally, Onaiza Qureshi (Interactive Research and Development (IRD), Pakistan) and Dr Lakshmi Venkatraman (Schizophrenia Research Foundation (SCARF), India), will each offer recent findings from the 'Improving outcomes for people with psychosis in Pakistan and India - enhancing the Effectiveness of Community-based care' (PIECEs) research programme. This symposium will close with a discussion of these research findings within the wider context of social inclusion for people living with psychosis from Professor Craig Morgan.

### 19.1 Interventions to Improve the Social and Economic Circumstances of People Living With Psychosis

Anna Greenburgh*[1], Helen Baldwin[1], Hannah Weir[1], Zara Asif[1], Dionne Laporte[1], Jayati Das-Munshi[1], Craig Morgan[1]

[1]*King's College London*

**Background:** People with psychosis are much more social disadvantaged across multiple domains. The role of these social adversities in the onset and persistence of psychosis is clear however current services fail to address these fundamental social and economic needs, contributing to cycles of worsening mental health, social exclusion and loss of trust in services. Little is known about what populations have been recruited to research thus far meaning that we do not know whether existing interventions are effective for the most marginalised and vulnerable groups. Indeed, there has been no attempt to understand what social interventions work for whom and whether targeted intervention exists for specific sociodemographic and socioeconomic groups. Anna Greenburgh and Helen Baldwin will present two systematic reviews which comprise the first attempts in the field to answer these questions.

**Methods:** We conducted a systematic literature review, updated from two recent systematic reviews of interventions to improve the social and economic outcomes of people with a mental health problem (Barnett et al., 2022; Killaspy et al., 2022). Despite the broader focus of this review, in this symposium we will solely present the synthesised results of the studies pertaining to psychosis spectrum disorders only.

**Results:** We included 72 studies investigating interventions to improve the social and economic conditions of people with psychosis. These studies were conducted across 19 different countries, many of which (n=20) were conducted in the USA. The life domains that interventions addressed included the domains of Community Support (n=11), Education (n=4), Employment (n=19), Family relationships (n=5), Housing (n=3), Offending (n=2), Social Connectedness and social skills (n=33), and Trauma/Victimisation (n=2), where some studies were relevant to more than one domain.

We identified a consistent lack of reporting of adequate race and/or ethnicity data and a distinct lack of inclusion of people from racialised groups. There was a paucity of research examining if effectiveness varied according to ethnicity and/or race, gender or socioeconomic status (n=7) and only one study reported sufficient data to allow interpretation of results, where these stratified analyses pertained to gender and socioeconomic status. All the interventions which had been designed bespoke or adapted for marginalised groups demonstrated acceptability or effectiveness on at least one social and/or economic outcome measure, highlighting the potential utility of targeted interventions for specific sociodemographic groups.

**Conclusions:** These findings highlight the wide range of existing interventions which aim to improve the social and/or economic circumstances of people living with psychosis. However, the findings also highlight the inadequate reporting and representation of some sociodemographic communities, in particular racialised groups, and thus, a lack of understanding of what works for whom. Targeted intervention may go some way to addressing this imbalance and getting support to those who need it most.

### 19.2 A Culturally Adapted Family Intervention (CAFI) for People of African-Caribbean Origin Diagnosed With Schizophrenia and Their Families

Dawnette Edge*[1], Amy Degnan[1], Sarah Cotteril[1], Katherine Berry[1], John Baker[2], Richard Drake[1], Kathryn Abel[1]

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

-**Background:** African and Caribbean descended people in the UK experience the highest incidence of schizophrenia and the greatest inequity in related mental health care. There is an urgent need to improve their access to evidence-based psychological therapy and outcomes. Family intervention (FI) is a National Institute for Health and Care Excellence-approved psychosocial intervention. Despite strong evidence of its clinical- and cost-effectiveness for schizophrenia, FI is rarely offered, and evidence its acceptability and utility is lacking for people from minority ethnic communities. Culturally-adapted Family Intervention (CaFI), co-created with people from African-Caribbean and Mixed Heritage backgrounds has previously been found to be acceptable and its delivery feasible (Edge et al., 2018). We are now conducting a large-scale, multi-site randomised controlled trial (RCT to test the effectiveness of CaFI in a larger sample of Sub-Saharan African and Caribbean heritage people living with schizophrenia, and their families.

**Methods:** Community Partnered Participatory Research (CPPR) approaches (including community engagement, focus groups, individual interviews, and expert consensus conference) were used to culturally-adapt an extant model of FI with the study population, family and community members, advocates, and healthcare professionals. Our approach to cultural adaptation also involved developing bespoke therapy manual, resources and culturally-informed training for therapists.

The resultant CaFI therapy was evaluated via a study with a convenience sample of 31 African-Caribbean family units [service users, relatives/family support members (FSMs)] to assess the feasibility of implementing CaFI and its acceptability with key individuals. Service users (patients) were recruited from clinical and community settings across mental health services in the north of England. FSMs enabled patients without access to their families (e.g., people seeking asylum) to participate.

**Results:** Twenty-four family units (92%) completed therapy with 77.42% (24/31) completing all 10 x 1-hour CaFI therapy sessions. The mean number of sessions attended was 7.90. It also proved feasible to implement CaFI with a population known to be mistrustful of mental health services and under-represented both in psychological therapies and clinical research. The study also demonstrated the feasibility of collecting a range of outcome data at baseline, post- intervention and at the 3-month follow-up. The rating of sessions (satisfaction ratings exceeding 80%) and the qualitative findings indicated that CaFI was acceptable for service users, families, FSMs and health-care professionals.

I will also present some preliminary observations from the RCT which emanated from this study.

In this presentation, I will also aim to present some preliminary observations from our subsequent multi-site RCT.

**Conclusions:** The CaFI intervention yielded high rates of recruitment, attendance, retention and data completion, and proved to be both acceptable and feasible for a range of key stakeholders. CaFI offers culturally-appropriate targeted care for people with schizophrenia from underserved and marginalised racial and ethnic backgrounds. As such, CaFI also has the potential to be modified for and delivered to other underserved groups in society whose needs are not currently being met by existing service provision.

### 19.3 Integrating Social Support Into Routine Psychiatric Care for People With Psychosis

Onaiza Qureshi*[1], Syjo Davis[2], Lakshmi Venkatraman[2], Padmavati Ramachandran[2], Sana Zehra Sajun[3], Maryam Younus[1], Aneeta Pasha[1], Victoria Bird[3]

[1]*IRD Pakistan,* [2]*Schizophrenia Research Foundation, India,* [3]*Unit for Social and Community Psychiatry, QMUL UK*

**Background:** Psychiatric care in low-resource settings within South Asia are often limited by resource constraints, high caseloads, and a predominantly biomedical focus, which can neglect critical social determinants of mental health important for recovery. Research shows that social support plays a significant role in recovery, improving quality of life (QoL), social functioning, and overall well-being for people with psychosis. While efforts have been made to enhance family support as part of the recovery process for people with SMI, there still exists a gap around incorporating social support as part of routine psychiatric care e.g. through therapeutic alliance between clinical providers and patients. Existing psychiatric practices in low-resource settings therefore need effective, appropriate and low-cost forms of care that utilise and strengthen existing personal and social resources available to individuals, their families and communities. The NIHR-funded project "Improving outcomes for people with psychosis in Pakistan and India – enhancing the Effectiveness of Community-based care" (PIECEs) aimed to redress this gap by adapting and evaluating DIALOG+, an evidence-based, low-cost, and structured communication tool, to enhance routine psychiatric consultations and therapeutic alliance between service users and clinical providers. By emphasizing patient-centred care across eight holistic life and three treatment domains, DIALOG+ promotes a comprehensive approach that aligns with service user needs for more holistic care and social support in routine settings.

**Methods:** DIALOG+ is a patient-centred digital tool incorporating targeted support for patient-reported satisfaction across eight holistic life domains (including relationships, employment) and three treatment domains (including medication, practical support and meetings with provider), all grounded in a solution-focused approach. It emphasizes the development of a strong therapeutic alliance between healthcare providers and service users. The intervention was evaluated through a cluster randomized controlled trial (RCT) with 29 clinicians and 441 people with psychosis in three psychiatric facilities (2 private and 1 public) across India and Pakistan, informed by patient-reported satisfaction across the intervention domains. Interviews with 14 clinicians and 40 patients were conducted to get an in-depth understanding of how DIALOG+ influenced their therapeutic alliance and perception of social support.

**Results:** Preliminary findings from the RCT in low resource settings indicate that DIALOG+ positively impacts patients' quality of life (QoL) and social functioning (results from RCT in India and Pakistan in progress and due in February 2025). Qualitative evidence suggests that DIALOG+ enhances therapeutic alliances, particularly with traditionally biomedical practitioners like psychiatrists. While some clinicians expressed resistance toward integrating psychosocial elements into routine consultations, not seeing it as their primary responsibility, many appreciated the structure it provided, as well as the opportunity to better understand patients' broader needs. Clinicians reported feeling motivated by seeing improvement in their patients' overall well-being and felt the intervention supported with clinical assessments.

**Conclusions:** Despite its potential, implementing DIALOG+ in busy public healthcare settings remains challenging, especially where continuity of care is often disrupted due to overloaded outpatient departments (OPDs) and short consultation times. To improve the sustainability of approaches like DIALOG+ in routine practice we can incorporate Quality Improvement workshops in psychiatric settings and identify community-led and user-led participatory approaches. These community-led solutions can address identified barriers and support the scaling of DIALOG+ to make psychiatric care more holistic in low-resource settings.

## 19.4 From Participants to Partners: User-Led Empowerment and Social Inclusion in Mental Health

Lakshmi Venkatraman*[1], Onaiza Qureshi[2], Syjo Davis[1], Renata Peppl[3], Padmavati Ramachandran[1], Aneeta Pasha[2], Victoria Bird[3], Paul Heritage[3]

[1]*SCARF India,* [2]*IRD Pakistan,* [3]*QMUL UK*

**Background:** In South Asia (SA), research traditionally frames people with lived experience (PWLE) of mental health conditions, such as psychosis, as participants or subjects rather than as active collaborators thus underutilizing the PWLE insights as experts by experience.
In contrast, there is a growing global movement advocating for the active involvement of PWLE as essential collaborators in all stages of research and service delivery. The participatory approach enhances quality of research. The participatory approach fosters social inclusion, empowers PWLE and reduces the stigma they face.

The NIHR funded PIECEs project aimed to improve the quality of community-based care for psychosis in India and Pakistan by upscaling the use of participatory arts methodologies and community engagement for psychosis. The initiative employs participatory arts and theatre to actively engage service users not just as participants but as co-creators and leaders in the development and dissemination of interventions for psychosis care.

Social inclusion in psychosis care within South Asia remains limited, with mental health services often neglecting the broader social and cultural aspects that contribute to the well-being of service users. The PIECEs project is an example of how participatory arts methodologies can transform the role of PWLE in mental health care by centering their participation.

**Methods:** SCARF (Schizophrenia Research Foundation) in India and IRD (Interactive Research and Development) in Pakistan, adopted innovative methods to ensure that PWLE are not just participants but essential collaborators in their mental health work.
The methods used:

1. The Lived Experience Advisory Panel (LEAP) is a structured initiative that facilitates the meaningful inclusion of PWLE in research and service development. Through regular meetings with researchers, LEAP ensured that the project remained grounded in real-world experiences. LEAP members offered insights on culturally relevant practices, barriers to access, and effective forms of community-based support.

2. Participatory and user led performances: Both SCARF and IRD have used theatre as a means to promote mental health awareness, reduce stigma, and give PWLE a voice in public spaces. Through theatre the PWLE expressed their stories in a creative non clinical format providing the audience a deeper understanding of the challenges and resilience of individuals living with psychosis. In addition to educating the public, the performances also empowered the performers who took ownership of their stories and led the mental health advocacy.

3. Namma Area (meaning “Our Space” in Tamil), a social hangout space was created as a dedicated social space at SCARF to foster community, belonging, and social inclusion for service users. This informal, peer-driven environment allow PWLE to engage in social activities, form friendships, and participate in community life, outside of the clinical setting.

4. Service User-Led Academic Dissemination of PIECEs Research: In a significant shift from traditional models of academic research dissemination, SCARF and IRD have prioritized service-user-led dissemination of PIECEs research findings. PWLE played an active role in presenting and communicating research outcomes to various stakeholders, including the academic community and the public.

**Results:** The project attempted to identify culturally relevant ways to facilitate service use empowerment and found it reduced self-stigma. The participatory approaches improved self-efficacy, social inclusion and was found to be a great tool to destigmatize psychosis in communities. The different stakeholders including the researchers, PWLE, arts organisations and the public recognised the importance of the participatory approaches.
**Conclusions:** The shift from viewing people with lived experience (PWLE) of psychosis merely as participants in research to embracing them as essential collaborators marks a significant transformation in mental health care in South Asia.
By involving PWLE from the outset and giving them leadership roles, these initiatives provide a model for rethinking mental health research and care, ensuring that the voices of those with lived experience are at the center of shaping the future of mental health in South Asia. This approach not only enhances the relevance of research but also fosters more inclusive, humane, and effective mental health systems.

## Plenary Session III: From Lab to Life: Bridging Evidence and Real-World Impact at Scale in Digital Interventions for Psychosis - Dr. Mario Alvarez-Jiminez

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

### 20. From Lab to Life: Bridging Evidence and Real-World Impact at Scale in Digital Interventions for Psychosis

Keith Nuechterlein*, UCLA Semel Institute for Neuroscience and Human Behavior*

**Overall Abstract:**

### 20.1 From Lab to Life: Bridging Evidence and Real-World Impact at Scale in Digital Interventions for Psychosis

Mario Alvarez-Jimenez*, Orygen Digital*

**Individual Abstract:** Digital interventions hold significant potential to transform psychosis care by offering scalable, engaging, effective and time-unlimited solutions. Yet, this promise remains largely unrealized, with evidence-based innovations failing to translate into real-world practice at scale.
This presentation will address this critical gap by reviewing the latest evidence in digital interventions for psychosis, including insights from our research on the MOST digital platform, which demonstrates engagement, acceptance, and clinical efficacy. Despite these advancements, real-world implementation studies reveal significant barriers to adoption, including limited integration with mental health services, workforce readiness challenges, and misalignment with service user needs. Moreover, efficacious, evidence-based digital mental health interventions lose much of their effectiveness in the real world. On the other hand, a

proliferation of mental health apps with little evidence risks undermining trust and efficacy in the field.

Using the MOST platform as a case study, the presentation will explore strategies for addressing these challenges. It will highlight the role of implementation science, user-centred design, and new translational research frameworks, complex interventions, trans-diagnostic frameworks and AI in developing scalable, sustainable, evidence-based interventions. This keynote will provide actionable insights for transforming digital psychosis care, bridging the gap from promise to practice, and to bring about real-world impact at scale.

**Concurrent Symposia**

**10:30 a.m. - 12:00 p.m.**

**21. Looking Psychosis in the Eye? Retinal Biomarkers of Disease Risk, Pathophysiology, and Progression**

Florian Raabe*, Max-Planck Institute of Psychiatry*

**Overall Symposia Abstract:** As part of the central nervous system (CNS), the retina shares many anatomical and physiological similarities with the brain due to its common embryonic origin. In this context, studying the retina as an accessible "window to the brain" offers a unique possibility to investigate non-invasively the CNS of patients with neuropsychiatric diseases. Retinal imaging and electrophysiological biomarkers can be obtained rapidly and non-invasively and are emerging as tools for assessment of the integrity of the CNS in both research and clinical practice. Moreover, retinal imaging methods provide higher resolution than standard brain imaging techniques and allow for the investigation and tracking of underlying pathophysiological mechanisms, including neuroprogression, hypoperfusion, and weakened and delayed neural firing. An increasing body of data indicate that microstructural [assessed via optical coherence tomography (OCT)] and functional alterations [assessed via electroretinography (ERG)] of the retina relate to volume changes of the brain, cognitive impairment, functional decline and disease progression in multiple neurodevelopmental and neurodegenerative disorders. In schizophrenia (SZ), data indicate retinal alterations such as neural layer thinning, microvascular network atrophy, and reduced and delayed neural firing. These retinal features of SZ are related to polygenic risk score for the disorder, duration of illness, and brain volumes. However, important questions remain about diagnostic specificity and transdiagnostic symptom relationships, prediction of cognitive and functional impairment, relationships with specific genetic and pathophysiological mechanisms (e.g., neuroinflammation), and the developmental course of retinal changes in SZ. This symposium will provide an overview of the developments of the last decade of this dynamic field.
Silverstein et al. present data indicating greater severity of retinal neuroprogression in SZ relative to mood disorders and the lack of a transdiagnostic relationship with psychosis across these disorders, in addition to findings suggesting that retinal neural layer thinning in SZ reflects an accelerated aging process.

Lizano et al. discuss findings indicating that there are inner and outer retinal layer differences in psychosis, which may inform the processes taking place in the central nervous system, which may also serve as an index for clinical and cognitive outcomes.

Maziade et al. show that retinal neural layer thinning measured by OCT, as was reported for reduced strength of neural firing [ERG)], are detectable in unaffected young offspring of parents affected by SZ or BP suggesting an early developmental origin of these anomalies also found in adult patients.

Raabe et al. present data revealing a polygenic contribution to retinal alterations in SZ and will highlight the retina's potential to dissect cellular disease mechanisms in SZ. In sum, this symposium will highlight how retinal imaging and electrophysiological measurements could serve as clinical biomarkers in the treatment of people with SZ. We will illustrate the potential of these methods for use in everyday clinical practice, given the potential for portable, rapid, non-invasive data acquisition. Finally, we will emphasize how retinal investigations could help to dissect neuropathophysiological mechanisms in SZ.

## 21.1 Retinal Neuroprogression in Schizophrenia is More Severe Than in Mood Disorders and Reflects Accelerated Aging

Steven Silverstein*[1], Kaitlyn Kaiser[1], Brittany Blose[2], Iwona Juskiewicz[1], Adam Kierzstyn[3], Pawel Krukow[4]

[1]*University of Rochester Medical Center,* [2]*University of Rochester,* [3]*Lublin University of Technology,* [4]*Medical University of Lublin*

**Background:** Retinal neural layer thinning and microvascular density reduction have been demonstrated in schizophrenia (SZ) in several studies, supporting the view emerging from literature reviews and meta-analyses that the retina, as part of the central nervous system (CNS), offers a useful window into CNS pathology in schizophrenia, including neurodegeneration and hypoperfusion. Here, we report data from two ongoing studies that focus on questions of diagnostic specificity and the extent to which retinal changes in SZ reflect an accelerated aging process.

**Methods:** In the first, ongoing, study, we have thus far collected retinal imaging [optical coherence tomography (OCT) and OCT angiography (OCTA)] data on 25 patients with psychotic disorders, 27 patients with mood disorders (BP or MDD) and 20 age-matched healthy control subjects. In the second study, we used machine learning (ML) analyses [Simple Regression Tree (SRT), Gradient Boosted Tree (GBT), Random Forest (RF) and Tree Ensemble (TE)] to derive retinal age metrics in a sample of healthy controls and these models were then applied to a sample of 108 SZ patients.

**Results:** In Study 1, we are observing significant group differences in macula central subfield neural layer thickness in the right and left eye ($F=5.63$ $p=.006$ and $F=6.43$, $p=.003$). Post-hoc tests indicate thinner maculae in the psychotic disorders group compared to both the control ($d=1.11$) and mood disorders ($d=.65$) groups ($ps < .05$), with the latter not differing from the other groups. Means for BP (n=12) and MDD patients (n=15) do not differ significantly and are nearly identical. On OCTA, the three groups also differ in left eye foveal avascular zone (FAZ; the center of the macula that is normally without blood vessels, and that can enlarge with loss of surrounding vasculature) area ($F=3.59$, $p=.033$), with post-hoc tests showing significant differences between the control and psychotic disorders groups only. A priori polynomial contrasts indicate significant linear trends for FAZ area and macula thickness in which controls had the most normal values, followed by mood disorder patients, then psychotic disorder patients. Mood disorder patients with a history of psychotic features

(n=13) do not, at this point, differ from those without a history of psychotic features (n=14) (p=.99). We also observe relationships between macula thickness/volume and IQ, as estimated by the Shipley-2 Vocabulary subtest. Among mood disorders patients, IQ is significantly correlated with macula thickness and perfusion (r=.45, p=.023 and r=.46, p=.02; due to group sizes, only right eye measures were tested). Trend-level findings reflecting medium effect sizes are observed in the psychotic disorder group (r=.43, p=.053 and r=.35, p=.116, respectively). Updated findings from larger samples will be reported at SIRS. In Study 2, all four ML methods produced similar findings, indicating a significant positive retinal age gap in SZ that can be observed as early as the late teenage years and is most pronounced in the earliest decades of illness. Most patients under age 30 had retinal age estimates older than their chronological ages.
**Conclusions:** Taken together, these two data sets suggest that retinal neuroprogression in schizophrenia reflects an accelerated aging process, that this process is more related to schizophrenia than to bipolar disorder or major depressive disorder, and that it is not a general correlate of psychosis trandiagnostlcally. Implications of these findings for screening and monitoring patients for further neuroprogression and cognitive and functional decline will be discussed.

## 21.2 Neuroretinal and Retinal Vascular Alterations in Psychosis and Their Clinical and Brain Correlates

Erik Velez-Perez[1], Willa Molho[1], Parduman Dhunna[1], Chelsea Kiely[1], Nora Sheehan[1], Nicolas Raymond[1], Rebekah Trotti[1], Tunde Aideyan[1], Paulo Lizano*[2], Brendan Stiltner[1], Victor Zeng[1], Cemal Demirlek[1]

[1]*Beth Israel Deaconess Medical Center.,* [2]*Beth Israel Deaconess Medical Center, Harvard Medical School*

**Background:** Psychotic spectrum disorders (PSD), including individuals with early course psychosis (ECP), are characterized by symptomatic, cognitive, and neuroanatomical changes. Recently, the retina has been considered a window to understanding the changes taking place in the brain in individuals with PSD and ECP. Recent studies have used optical coherence tomography (OCT), OCT angiography (OCTA), and electroretinography (ERG) to investigate retinal changes in PSD and ECP. In this study, we provide an overview of the meta-analytic alterations observed in PSD, as well as evidence from studies examining retinal alterations and clinical/brain correlates in PSD and/or ECP.
**Methods:** Data from meta-analyses of OCT, OCTA, and ERG data will be summarized and presented comparing PSD, schizophrenia, or bipolar disorder with healthy controls (HC). Moderators of retinal imaging measures, such as age, smoking, device type, etc., will be considered. Case-control data from the UK Biobank, a pilot study in PSD, and a longitudinal ECP study will be used to report on the relationship between retinal phenotypes, clinical measures, cognition, and neuroanatomical changes (structural, microstructural, and functional imaging).
**Results:** The OCT meta-analysis identified thinning of the pRNFL, m-Retina, mGCL-IPL, mIPL, and mRPE in schizophrenia patients. Bipolar disorder showed thinning of the pRNFL, pGCC, and macular Retina. Moderating effects of age, illness duration, and smoking on retinal structures were identified. The OCTA meta-analysis, showed no differences in the foveal avascular zone and superficial layer foveal vessel density in PSD. The ERG meta-analysis showed reduced amplitude of both a- and b-waves under photopic and scotopic

conditions in PSD. OCT measures correlated with symptoms, cognition, and brain structure, while OCTA and ERG measures primarily correlated with cognition.
**Conclusions:** Meta-analytic evidence demonstrated that structural, vascular, and functional abnormalities exist in people with PSD. The greatest evidence exists for OCT measures, but few studies have examined expanded areas or layers of the retina. OCTA studies are rapidly growing which should shed lit on the retinal vascular alterations identified in PSD and ECP, but few studies have examined the choriocapillaris and choroidal vasculature. ERG studies are also growing and provide a physiological representation of alterations in the retina that may inform the changes taking place in the brain. There are few studies examining the relationship between retinal phenotypes and clinical, cognitive, or neuroanatomical measures in PSD and ECP. The evidence thus far suggests that retinal imaging may be a proxy of brain alterations that can be used as predictors of neuroprogression in psychosis.

### 21.3 Children at Genetic Risk for Schizophrenia, Bipolar Disorder and Major Depressive Disorder Show Oct Retinal Layer Thinning as Seen in Adult Patients Suggesting an Early Developmental Endophenotype

Michel Maziade*[1], Eric Arsenault[2], Jasmin Ricard[2], Marie-Claude Boisvert[2], Énora Fortin-Fabbro[2], Alexandre Bureau[3]

[1]*Laval University, Quebec, Canada,* [2]*Centre de recherche CIUSSS de la Capitale-Nationale,* [3]*Université Laval, Département de Médecine Sociale et Préventive*

**Background:** The neurodevelopmental model is now documented in schizophrenia (SZ), bipolar disorder (BP) and major depressive disorder (MDD). The study of genetically high-risk children (GHRs) born to a parent with SZ, BP or MDD is a powerful approach to understanding the developmental origins of disorders (Maziade 2017 New England J Medicine). The retina shares structural and functional similarities with the brain and offers non-invasive probes of human neural tissue to study neurodevelopment for future translation to early detection and prevention.
We previously reported abnormal electroretinographic (ERG) retinal function both in GHRs and in adult patients, e.g., reduced rod and cone response amplitudes and prolonged implicit times. It is therefore a logical next step to investigate the relevance of retinal structural (anatomical) properties in GHRs using a powerful retinal imaging technique (optical coherence tomography, OCT). In addition, previous studies and meta-analyses in adult SZ and BP patients strongly suggest that layer thinning, especially of the retinal ganglion cell body and axon layers (e.g., mGCL-IPL and pRNFL), may be an additional neural risk endophenotype that could be added to the ERG as a developmental marker to better define the early risk state.

Objective: To investigate whether GHRs show similar retinal cell layer thinning as observed in adult patients and to test the relationship between OCT layer thickness and ERG amplitudes and implicit times.

**Methods:** The sample consisted of 196 subjects who had both eyes scanned with OCT and recorded with ERG: 76 adult SZ, BP or MDD patients (47% males) aged 18-55 years ($\bar{x}$= 40.4; sd = 9.2 yo) paired with 50 healthy controls balanced for age and sex, and 47 healthy GHR children (50% males) aged 6-17 years ($\bar{x}$= 11.6; sd = 2.9 yo) paired with 23 controls.
**Results:** Among other findings, the mean macular thickness in adult patients was, as expected, significantly thinner compared to controls ($\bar{x}$= 282.0µm, ES: 0.40, p = .025).

Similarly, the mGCL-IPL was found to be thinner in patients ($\bar{x}$ = 85.3µm) than in controls ($\bar{x}$ = 88.9µm, ES: 0.47, p = .016). Notably, we also observed in GHRs a significant thinning of the macular mGCL-IPL ($\bar{x}$ = 89.9µm) compared to controls ($\bar{x}$ = 92.9µm, ES: 0.51, p = .034) with similar findings for the superior and inferior quadrants.
Furthermore in GHRs, thinning of the mGCL-IPL superior quadrant correlated (r = 0.24, p = 0.036) with reduced cone a-wave amplitude (cone ERG). Thinning of the inferior quadrant of the mGCL-IPL correlated with prolonged rod b-wave implicit times (rod ERG) (r = -.26, p = .023) and with decreased rod and cone a-wave amplitudes (r = .27, p = .019; r = .24, p = .033).

**Conclusions:** The results support a developmental origin of the OCT abnormalities, as GHR children would show the same GCL structural abnormalities as adult patients, as we had incidentally reported for ERG. The data suggest an association between functional and structural retinal abnormalities and, as with the ERG, early OCT abnormalities were shared by offspring of SZ, BP or MDD parents, a commonality consistent with other common features of the three disorders.

### 21.4 Genetic Investigation of Retinal Cell Types Reveals Synaptic Pathology in Schizophrenia

Emanuel Boudriot[1], Marius Stephan[1], Finn Rabe[2], Lukasz Smigielski[2], Elias Wagner[3], Daniel Keeser[1], Philipp Homan[2], Sergi Papiol[4], Florian Raabe*[4]

[1]*LMU University Hospital, LMU Munich, Munich, Germany,* [2]*University of Zurich, Switzerland,* [3]*Augsburg University,* [4]*Max-Planck Institute of Psychiatry*

**Background:** The retina, as an accessible part of the central nervous system, offers a window into the pathophysiology of brain disorders. Recent studies employing optical coherence tomography (OCT) and electroretinography (ERG) have identified both structural and functional retinal alterations in schizophrenia (SZ). However, it remains unclear which specific retinal layers are affected, how retinal changes relate to clinical symptomatology, and how alterations in the visual system are linked to genetic disease risk. Additionally, it is uncertain whether these retinal alterations result from primary disease mechanisms within the retina itself, and which specific retinal cell types and biological processes are involved.
**Methods:** Associations between clinical disease phenotype and biological alterations of the visual system was applied to comprehensively investigate the visual system in a cohort of 103 patients with schizophrenia spectrum disorders (SSDs) and 130 healthy control individuals. Moreover, findings from genome-wide association studies in schizophrenia, bipolar disorder, major depressive disorder, multiple sclerosis, Parkinson disease, Alzheimer disease, and stroke were combined with retinal single-cell transcriptomic data sets and translated in the population-based UK Biobank cohort (UKBB).
**Results:** Sparse partial least squares analysis revealed a “phenotype-eye-brain” signature linking higher disease severity including longer illness duration, and cognitive deficits with structural thinning of retinal layers and altered electrophysiological responses (Spearman’s r = 0.60; p < 0.001). This signature correlated with higher polygenic risk scores for SZ, suggesting that these retinal changes might be influenced by genetic factors (p < 0.001). MAGMA cell type enrichment analyses identified that Amacrine cells (interneurons within the retina) were robustly enriched in SZ genetic risk across mammalian species and in different developmental stages. This enrichment was primarily driven by genes involved in synapse biology. Within 36.349 individuals of the UKBB without SZ, higher polygenic risk for SZ was associated with thinning of the ganglion cell–inner plexiform layer, which

contains dendrites and synaptic connections of amacrine cells (b = −0.09; 95% CI, −0.16 to −0.03; P = .007).
**Conclusions:** These studies provide a deeper understanding of the complex interplay between retinal alterations, brain changes, and genetic risk in SZ. Structural and functional alterations of the retina in SZ may reflect broader pathophysiological neuronal processes including synaptic disturbances. This research underscores the potential of retinal investigations to advance our understanding of SZ and opening new avenues for non-invasive diagnostic and therapeutic approaches.

## 22. Advancing the Understanding and Treatment of Psychosis Spectrum Disorders Through Novel Anti-Inflammatory Approaches

Nusrat Husain, *University of Manchester*

**Overall Symposia Abstract:** Advancing the Understanding and Treatment of Psychosis Spectrum Disorders through Novel Anti-inflammatory Approaches
Session 1: Prof. IBC will present six randomised control trial findings of minocycline, methotrexate, simvastatin, ondansetron and omega-3 fatty acids in treating early-stage schizophrenia, multi-episode schizophrenia and ARMS.

Session 2: Dr. IH will discuss the link between peripheral inflammation and depressive symptoms in Pakistani bipolar disorder patients, suggesting the potential for anti-inflammatory treatments in LMICs.

Session 3: Dr OH will talk about the inflammatory profiles in the schizophrenia spectrum, which suggests inflammation increases with disease progression, highlighting the need for targeting inflammation across the schizophrenia spectrum.

Session 4: Dr. MS will present a systematic umbrella review of adjunctive therapies, including amino acids, hormonal therapies, and N-acetylcysteine, and offer provisional recommendations for improving symptoms in chronic schizophrenia.

The symposium highlights the growing evidence supporting anti-inflammatory agents in managing psychosis spectrum disorders, especially in LMICs like Pakistan. It emphasises the need for personalised treatments and future research for improved long-term outcomes.

## 22.1 Advancing the Understanding and Treatment of Psychosis Spectrum Disorders: Evidence of Integrating Novel Anti-Inflammatory Agents From Pakistan

Imran Chaudhry*[1], Omair Husain[2], Ishrat Husain[2], Nasim Chaudhry[3], Nusrat Husain[4]

[1]*Ziauddin University and University of Manchester,* [2]*Centre for Addiction and Mental Health, Toronto, Canada,* [3]*Pakistan Institute of Living and Learning,* [4]*University of Manchester*

**Background:** At-risk mental state (ARMS) and psychosis are psychiatric conditions with complex symptomatology, including distressing symptoms, cognitive impairments, and functional deficit. Schizophrenia spectrum disorders severely affect social, occupational and interpersonal functioning, making early intervention interventions a clinical priority.

Emerging evidence highlights the importance of targeting neuroinflammation, oxidative stress, and neurodegeneration, which are thought to contribute to the development and progression of psychosis. Our recent clinical trials have explored novel pharmacological treatments targeting at-risk mental states, early psychosis, multi-episode schizophrenia focusing on anti-inflammatory agents, neuroprotective compounds, and adjunctive treatments.
Objectives:

To synthesize findings from the recently completed clinical trials investigating effectiveness of novel anti-inflammatory agents added to treatment as usual in treating schizophrenia spectrum disorders. The trials evaluated the efficacy in reducing negative symptoms, general psychopathology, preventing the onset of full-blown psychosis and improving overall functioning.

**Methods:** Six randomised double-blind placebo-controlled trials explored the efficacy of various anti-inflammatory agents. Minocycline as an add-on treatment (n=144) investigated the benefits of negative symptoms in Brazil and Pakistan. A 12-week trial (N = 92), carried out in Karachi, Pakistan, evaluated the safety, tolerability, and preliminary efficacy of low-dose methotrexate in individuals with early schizophrenia within the first 5 years of diagnosis. A 12-week, multicenter trial (N = 68) assessed sodium benzoate (NaB) and N-acetylcysteine (NAC) for their feasibility and preliminary clinical efficacy in treating early-stage schizophrenia. A multicentre double-blind trial of Minocycline and Omega-3 fatty acid aimed to prevent and/or delay the onset of psychosis in individuals with ARMS. Two studies involving (N=303) and (N=36) patients with schizophrenia within five years of diagnosis, investigated the adjunctive effects of simvastatin and ondansetron on positive, negative, and general psychopathology.
**Results:** Minocycline significantly reduced negative symptoms in early schizophrenia (PANSS adjusted difference 3.53, $p < 0.001$). Methotrexate improved positive symptoms ($\beta = -2.5$; [95% CI -4.7 to -0.4]) but did not affect negative symptoms. Side effects were non-severe, though one case of leukopenia occurred. In individuals with ARMS, The risk of transition was greater in those randomised to omega-3 alone or in combination with minocycline (17.3.%), compared to 10.4 % in those not exposed to omega-3; a risk-ratio (RR) of 1.67, 95 % CI [0.95, 2.92] $p = 0.07$. Sodium Benzoate and N-acetylcysteine demonstrated feasibility, though clinical effects on psychosis symptoms were minimal. Simvastatin and ondansetron when given alone reduced negative symptoms compared to placebo. Individual treatment effects versus placebo were −1.9 points (95%CIs −3.23, −0.49; $p = 0.01$) for simvastatin and −1.6 points for ondansetron (95%CIs −3.00, −0.14; $p = 0.03$). Their combination was ineffective and increased depression and side effects.
**Conclusions:** Findings from these trials highlight the potential of individual pharmacological treatments, such as minocycline, ondansetron, and methotrexate, in reducing positive and negative symptoms in early schizophrenia. However, the combination of treatments, such as simvastatin and ondansetron, proved less effective. Sodium benzoate and N-acetylcysteine were feasible but yielded minimal clinical effects. These results suggest that while targeting neuroinflammation and oxidative stress holds promise, careful identification of individuals who would benefit from immune-modulating treatments before these interventions translates to clinical practice.

### 22.2 Associations Between Peripheral Inflammation and Clinical Phenotypes of Bipolar Depression in a Lower-Middle Income Country

Ishrat Husain*[1], Brett Jones[2], Urbee Mahmood[2], Imran Chaudhry[3], Ameer Khoso[4], Omair Husain[1], Abigail Ortiz[2], Nusrat Husain[3], Benoit H. Mulsant[5], Allan Young[6]

[1] *Centre for Addiction and Mental Health,* [2]*University of Toronto, Toronto, ON, Canada.,* [3]*University of Manchester,* [4]*Pakistan Institute of Living and Learning,*[5]*Centre for Addiction and Mental Health, University of Toronto,* [86]*King's College, London*

**Background:** There has been increased interest in repurposing anti-inflammatories for the treatment of bipolar depression. Evidence from high-income countries suggests that these agents may work best for specific depressive symptoms in a subset of patients with biochemical evidence of inflammation but data from lower-middle income countries (LMICs) is scarce. This secondary analysis explored the relationship between pretreatment inflammatory markers and specific depressive symptoms, clinical measures, and demographic variables in participants with bipolar depression in Pakistan.
**Methods:** The current study is a cross-sectional secondary analysis of a randomized controlled trial of two anti-inflammatory medications (minocycline and celecoxib) for bipolar depression (n = 266). A series of logistic and linear regression models were completed to assess the relationship between C-reactive protein (CRP) (CRP > or < 3 mg/L and log10CRP) and clinical and demographic features of interest and symptoms of depression. Baseline clinical trial data was used to extract clinical and demographic features and symptoms of depression were assessed using the 24-item Hamilton Depression Rating Scale.
**Results:** The prevalence of low-grade inflammation (CRP > 3 mg/L) in the sample was 70.9%. After adjusting for baseline body mass index, socioeconomic status, age, gender, symptoms related to anhedonia, fatigue, and motor retardation were most associated with low-grade inflammation.
**Conclusions:** Bipolar disorder (BD) patients from LMICs may experience higher rates of peripheral inflammation than have been reported in Western populations with BD. Future trials of repurposed anti-inflammatory agents that enrich for participants with these symptom profiles may inform the development of personalized treatment for bipolar depression in LMICs.

## 22.3 Non-Specific Markers of Inflammation and the Association With Psychopathology and Functioning Across the Schizophrenia-Spectrum: Findings From a Lower-Middle Income Country

Muhammad Husain*[1], Ameer Khoso[2], Suleman Shakoor[2], Brett Jones[1], Inti Qurashi[3], Nusrat Husain[4], George Foussias[5], Imran Chaudhry[4]

[1]*University of Toronto,* [2]*Pakistan Institute of Living and Learning,* [3]*Institute of Population and Mental Health, University of Liverpool, Liverpool, United Kingdom,* [4]*University of Manchester,* [5]*Centre for Addiction and Mental Health*

**Background:** Inflammatory mechanisms are thought to contribute to the pathophysiology of schizophrenia spectrum disorders (SSD). We investigated the differences in non-specific markers of inflammation between individuals with at-risk mental state (ARMS), first episode psychosis (FEP) and multi-episode schizophrenia. We also examined the associations between markers of inflammation, psychopathology and functioning within these three groups.
**Methods:** This study is a cross-sectional secondary analysis of pooled data gathered from five clinical trials evaluating novel anti-inflammatory treatments as adjuncts to standard care

for individuals with SSD. The primary studies study took place in Pakistan between 2010 to 2022. For the purposes of this study we analysed demographic, clinical, functional and complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) data from three groups: ARMS, FEP, and multi-episode schizophrenia. Neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), ESR and CRP were compared between ARMS, FEP and multi-episode schizophrenia. Associations between markers of inflammation and psychotic symptoms and functioning were also evaluated. Analysis of variance (ANOVA) was used to examine the differences between groups with continuous variables when data was normally distributed, and group differences were analysed using post hoc tests to identify significant differences between the groups.
**Results:** A total of 921 participants, comprising 550 males and 371 females, were included in this analysis (ARMS: n=326; FEP: n=274; multi-episode schizophrenia: n =321). Significant mean differences ($p < 0.001$) were found between NLR and CRP between the three groups, with multi-episode schizophrenia having higher levels (NLR: Mean ± SD = 2.55 ± 0.98; CRP: Mean ± SD = 6.43 ± 2.06), followed by FEP (NLR: Mean ± SD = 2.27 ± 0.92; CRP: Mean ± SD = 5.23 ± 1.50) and lowest levels were observed in the ARMS group (NLR: Mean ± SD = 1.78 ± 0.72; CRP: Mean ± SD = 4.57 ± 1.15). A statistically significant difference ($p < 0.05$) in ESR was observed between ARMS (ESR: Mean ± SD = 24.53 ± 17.62) and chronic schizophrenia (ESR: Mean ± SD = 28.53 ± 20.60), while no significant differences were found between ARMS and FEP or between FEP and multi-episode schizophrenia. No statistically significant differences were found in PLR between the three groups. MLR values were also significantly different ($P < 0.001$) between the three groups with multi-episode schizophrenia having lowest levels (MLR: Mean ± SD = 0.82 ± 0.48), followed by FEP (MLR: Mean ± SD = 0.91 ± 0.68) and highest levels were observed in the ARMS group (MLR: Mean ± SD = 1.06 ± 0.72). We found weak correlations between markers of inflammation, psychopathology and functioning.
**Conclusions:** We found evidence that non-specific markers of inflammation differ between individuals across SSD from a lower middle-income country. NLR and CRP may increase with disease progression and higher levels were observed in individuals with multi-episode schizophrenia compared to individuals with ARMS and FEP. We acknowledge that the observed differences in inflammatory markers may have been driven by other factors including iatrogenic (e.g., pharmacotherapy, psychotherapy, neurostimulation), lifestyle (e.g., smoking, exercise, diet) or other environmental factors (e.g., stress, medical co-morbidity). Nonetheless, the Results: suggest that inflammatory mechanisms may contribute to the causation and persistence of psychosis and/or its association with medical comorbidity and shortened life span.

### 22.4 Adjunctive Agents to Antipsychotics in Schizophrenia: A Systematic Umbrella Review and Recommendations for Amino Acids, Hormonal Therapies and Anti-Inflammatory Drugs

Marco Solmi*[1], Guillaume Fond[2], Jasmina Mallet[3], Mathieu Urbach[4], Michael Eriksen Benros[5], Michael Berk[6], Martina Billeci[7], Laurent Boyer[8], Christoph U Correll[9], Michele Fornaro[7], Jayashri Kulkarni[10], Marion Leboyer[11], Pierre-Michel Llorca[12], David Misdrahi[13], Romain Rey[14], Franck Schürhoff[15], Iris E. C. Sommer[16], Stephen Stahl[17], Baptiste Pignon[18], Fabrice Berna[19]

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**Background:** This umbrella review and guidelines aimed to provide evidence to support the rational choice of selected adjunctive therapies for schizophrenia.
**Methods:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and World Federation of Societies of Biological Psychiatry (WFSBP)-grading recommendations, 63 randomised control trials (RCTs) (of which 4219 unique participants have completed the RCTs) and 29 meta-analyses were analysed.
**Results:** Provisional recommendations (WFSBP-grade 1) could be made for two molecules in augmentation to antipsychotics: (1) N-acetyl-cysteine (NAC, 1200-3600 mg/day, for > 12 consecutive weeks) in improving negative symptoms, general psychopathology (positive and negative syndrome scale for schizophrenia (PANSS) general psychopathology factor (G)-G subscale), with the RCTs with the longer duration showing the most robust findings; (2) polyunsaturated fatty acids (3000 mg/day of eicosapentaenoic acid, for > 12 weeks) in improving general psychopathology. Weaker recommendations (ie, WFSBP-grade 2) could be drawn for sarcosine (2 g/day) and minocycline (200-300 mg/day) for improving negative symptoms in chronic schizophrenia (not early schizophrenia), and NAC for improving positive symptoms and cognition. Weak recommendations are not ready for clinical practice. There is provisional evidence that oestrogens and raloxifene are effective in some patients, but further research is needed to determine their benefit/risk ratio.
**Conclusions:** The results of this umbrella review should be interpreted with caution as the number of RCTs included in the meta-analyses was generally small and the effect sizes were weak or medium. For NAC, two RCTs with low risk of bias have provided conflicting results and the WFSBP-grade recommendation included also the results of meta-analyses. These drugs could be provisionally prescribed for patients for whom no other treatments have been effective, but they should be discontinued if they prove ineffective.

## 23. Beyond the Résumé: The Thought and Communication Factor Behind Unemployment in Psychosis

Lena Palaniyappan, *Douglas Mental Health University Institute*

**Overall Symposia Abstract:** We join forces from researchers across Europe, Canada, Australia and US, to shed light on one of the most under researched set of symptoms - communication disturbances - that is emerging as a critical determinant of personal recovery. This symposium will be co-chaired by professors Palaniyappan (Montreal, Canada) and Sommer (Groningen, Netherlands), who study language in schizophrenia from different angles, including neuroimaging and computational approaches across different stages of schizophrenia.

- From a unique long-term cohort, Prof. Kircher (Marburg, Germany) will show that thought, language and communication disorder is a frequent observation in affective disorders even in the absence of mania/psychosis.
- Prof. Sommer will provide a comparison between clinician-rated and NLP quantified thought disorder. Even when the clinician uses the abbreviated version, the scoring of the thought and language index is time consuming. A replacement with rapid automated NLP software is efficient and may detect cases that were not yet diagnoses.
- Prof. Bosia (Milan, Italy) will draw on her background in rehabilitation and highlight the defining role played by pragmatic communication in the neurophysiological aberrations in psychosis and highlight the therapeutic potential of communication-based interventions for patients with thought disorder.
- Prof. Rossell (Melbourne, Australia) will show the prognosis of patients with and without thought disorder in terms of psychosocial outcomes including employment, disability pension, education and relationships.
- Finally, Prof. Kuperberg (discussant; Boston, US) will discuss the emerging issues of language in schizophrenia, embedding the novel findings in the context of her long career combining both clinical experience as a psychiatrist with pioneering expertise in psycholinguistics.

## 23.1 Formal Thought Disorder Beyond Psychosis: Prevalence, Brain Structural and Functional Correlates in Schizophrenia and Major Depression

Tilo Kircher*[1]

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**Background:** Formal thought disorder (FTD) involves impairments in language production and thought processes. While commonly studied in schizophrenia-spectrum disorders (SSD), FTD is also significantly prevalent in Bipolar (BD) and Major Depressive Disorder (MDD). Despite this, comprehensive studies characterizing FTD in MDD and BD using both operationalized rating scales and particularly neurobiological measures are surprisingly scarce.

**Methods:** This study assessed the prevalence and severity of FTD in n=758 acute MDD patients compared to age, sex, and education-matched healthy controls (HC) and n=160 SSD patients. Whole-brain MRI analyses were employed to explore associations between FTD and

MRI derived gray (GMV) and white matter brain structure, as well as functional resting-state connectivity in acute MDD using SPM, FSL, and CONN toolboxes. We hypothesized that FTD would be prevalent in acute MDD, though at lower rates than in SSD. Associations with brain structure and functional connectivity were anticipated in regions previously identified in SSD studies.
**Results:** 37.5% of acute MDD patients presented with any FTD symptom compared to 69.4% of SSD patients and 11.1% of HC. Negative FTD were present in 29% of MDD patients, while positive FTD were present in 14.5%. 6.1% of MDD patients presented with both negative and positive FTD at the same time. Increased latency of response was the most frequently observed FTD symptom. FTD prevalence was not related to sex or comorbidity. The total amount of FTD was negatively correlated with the GMV of the right posterior cingulate gyrus and with white matter fractional anisotropy of the right corticospinal tract. Functional resting state seed-to-voxel analyses showed total, positive, and negative FTD to be positively correlated with functional connectivity between the Amygdala-Hippocampus complex and the right pre- and postcentral gyri. Positive FTD was negatively associated with the functional connectivity of the orbito-frontal cortex and left lateral occipital gyrus as well as the superior temporal gyri and the subgenual cingulate cortex. All identified brain structural and functional correlates of FTD were not correlated with age of onset, current depression severity, lifetime number and duration of depressive episodes and hospitalizations, the duration of the current episode, and current medication.
**Conclusions:** This presentation will review past studies on FTD in different diagnoses. The current results highlight the transdiagnostic prevalence of FTD in acute MDD, with neurobiological correlates surprisingly similar to SSD. Results open a new avenue for diagnosis independent pathogenetic and etiological studies focusing on transdiagnostic syndromes.

### 23.2 Comparison of Human Versus Computer-Rated Thought Disorder in Patients With Schizophrenia

Iris Sommer*[1], Bodyl Brand[1], Alban Voppel[1], Sanne Koops[1], Janna de Boer[1]

[1]*University Medical Center Groningen*

**Background:** Thought disorder (TD) is a classic yet often overlooked symptom commonly affecting people with psychotic and affective disorders. Detailed investigation using structured rating scales can provide quantification of TD, also in mild cases, but this assessment takes up a lot of time. Several Natural Language Processing Methods: have been suggested to provide an alternative quantification of TD, which can save time and increase detection rate of this symptom.
We here compared clinician-rated TD to NLP-rated TD to investigate if NLP can be an adequate replacement of structured rating scales.

**Methods:** The study involved a total sample of 56 participants, 41 of whom were male. The mean age of the participants was 41.9 years (SD = 12.0), and the mean Positive and Negative Syndrome Scale (PANSS) total score was 56.3 (SD = 12.9). Baseline scores for the Thought And Language Disorder (TALD) measures were 10.2 (SD = 5.1) for the negative subscale and 8.6 (SD = 7.3) for the positive subscale.
Speech was recorded using a digital TASCAM DR-40 recording device using head-worn AKG-C544l

cardioid microphones, with separate recording channels for participant and interviewer with a

sampling rate of 44.1 kHz. The semi-structured interview was performed by trained interviewers; for

an elaborate description of the interview methodology, see previous reports from our group. Topics discussed in the interview were neutral, avoiding specific illness related topics, and participants

could skip questions if they wanted.

Audio files were automatically converted to text using Whisper automatic speech recognition (ASR). Manual transcriptions were used to verify ASR accuracy. he audio files were transcribed manually. Resulting text files were analyzed with a sentence BERT model for Dutch (BERTje) to obtain semantic similarity measures per audio file.

**Results:** Analyses of semantic space measures revealed a significant baseline positive association with TALD positive scores (mean similarity r = .390, minimum similarity r = .324). Item-specific analyses suggest that this effect is primarily driven by the constructs of derailment, pressure of thought, and thought interference.
**Conclusions:** Significant correlations are demonstrated between TALD positive scores and NLP analyses based on Bert models. Recordings could be made during clinical interviews and automated analyses could provide an extra quantified measure of TD valuable for clinicians. As not all professionals are used to scoring the different categories of TD, this may lead to large differences in clinician-rated TD. Automated scoring of TD can provide reliable quantification of this important symptom. When more therapeutic options, including speech therapy, become available, a standardized TD assessment can improve detection rate in clinical practice.

### 23.3 Why Language is Key to Predict Symptoms Severity in Schizophrenia: A Machine-Learning, Communication-Oriented Approach

Marta Bosia*[1], Biagio Scalingi[2], Giulia Agostoni[1], Federico Pacchioni[3], Chiara Barattieri di San Pietro[2], Paolo Canal[2], Michele Francesco D'Incalci[3], Jacopo Sapienza[3], Margherita Bechi[3], Federica Repaci[3], Guglielmino Carmelo[3], Roberto Cavallaro[1], Nevio Dubbini[4], Valentina Bambini[2]

[1]*Università Vita-Salute San Raffaele,* [2]*University School for Advanced Studies- IUSS ,Pavia, Italy,* [3]*IRCCS San Raffaele Scientific Institute, Milan, Italy,* [4]*Miningful SRLS, Pisa, Italy*

**Background:** Formal Thought Disorder (FTD) is a core feature of schizophrenia, often preceding the onset of psychotic symptoms and with major impact on the global outcome. FTD is strongly intertwined with linguistic processes, especially at the level of pragmatics, i.e., the use of language in communication, with significant overlaps between the two in neurobiological and neurocognitive substrates. Indeed, the analysis of patients' pragmatic phenotype allows for a fine-grained detection and characterization of FTD and, more importantly, rehabilitative programs addressing pragmatics can improve FTD. In this study, we tested the hypothesis that linguistic and pragmatic measures, combined with EEG derived indexes, can improve accuracy in detecting symptoms severity via machine learning (ML) models.
**Methods:** Forty-one individuals with a diagnosis of schizophrenia underwent a 5-minute resting state EEG recording and were assessed for pragmatic abilities and psychopathology. Their speech during the pragmatic tasks was further analyzed via Natural Language Processing to extract a set of lexical and semantic variables. A Least Absolute Shrinkage and

Selection Operator (LASSO) regression was employed to perform feature selection and identify the most important EEG and language predictors for total symptoms' severity. Then, two LASSO models were built to predict symptoms severity, one (M1) including selected EEG features and the other (M2) including also selected language features, and compared using Mean Squared Error (MSE), adjusted R2, Diebold-Mariano (DM) test, and the Bayesian Information Criterion (BIC).
**Results:** Feature selection led to the identification of the following main predictors: transition from microstate A to C ($\beta = -0.474$), transition from microstate C to A ($\beta = 0.401$), the variance explained by all microstates ($\beta = 0.280$) and the level of aperiodic activity ($\beta = -0.154$) for EEG; expressive pragmatics score ($\beta = -0.351$), mean level of lexicalized emotions ($\beta = -0.158$), mean word frequency ($\beta = 0.189$) and mean word imageability ($\beta = 0.184$) for language features. Both models reached an acceptable performance in predicting psychopathology (M1: MSE = 0.590, adjusted $R^2 = 0.344$, BIC = -3.03; M2: MSE = 0.334, adjusted $R^2 = 0.582$, BIC = -11.53), yet the performance significantly increased when adding language and pragmatic features (DM stat= -1.79, $p < 0.05$).
**Conclusions:** These results suggest that global psychopathological severity can be best predicted through a combination of EEG and linguistic variables, highlighting the key role of language as well as its neurobiological roots. Specifically, data support the predictive value of microstates dynamics and aperiodic activity as global measures of the brain functioning, and pragmatic processes, especially in the expressive domains, which may be strictly related to FTD. On the clinical side, the ML extracted selection of feature highlights relevant linguistic and neurophysiological treatment targets that could be addressed via remediation programs and neuromodulatory techniques, respectively. Moreover, these results pave the way to develop and implement new, feasible, fast and cost-effective tools to characterize the patients' phenotype and discriminate clinical outcomes in psychotic disorders.

### 23.4 Is There an Employment Gap: Do Individuals With Formal Thought Disorder Face Greater Difficulties Gaining Work?

Susan Rossell*[1], Philip Sumner[2], Sean Carruthers[1], Wei Lin Toh[2]

[1]*Swinburne University,* [2]*Swinburne University of Technology*

**Background:** Formal thought disorder (FTD) is recognised as a central feature of psychosis and is associated with poorer prognostic outcomes, including diminished social functioning and quality of life. While some literature suggests that individuals with FTD may experience reduced occupational functioning, this area remains underexplored. Given the lack of psychosocial interventions targeted at FTD and the recovery-focused approach to helping individuals with psychosis return to work, it is crucial to investigate the relationship between FTD and employment outcomes.
**Methods:** This study examined employment characteristics—including current and optimal employment status—in three cohorts of patients with psychosis: 1) 62 inpatients with schizophrenia or current bipolar mania, 2) 118 outpatients with schizophrenia or bipolar I, and 3) 142 individuals from a mixed psychiatric inpatient and outpatient cohort, all with a history of hallucinations. Cohort 1 provided lifetime status of FTD, while cohorts 2 and 3 reported on current FTD status.
**Results:** In cohort 1, all individuals with a lifetime history of FTD were on a disability pension, with 34.1% never having been employed, a significant difference compared to those without a lifetime history of FTD, where 19% were on a disability pension and 9.5% never employed. In cohort 2, those currently experiencing FTD had a greater likelihood of being on a disability pension than those without current FTD (91% vs. 60%). There were no significant

education or IQ differences between FTD and no FTD patients in cohorts 1 and 2. In cohort 3, individuals with current FTD were similarly more likely to be unemployed than those without FTD (61% vs. 38%). Further, the type of usual employment was different, with those with FTD more likely to have never been employed or working in unskilled occupations (34% and 10%) compared with those without current FTD (12% and 2%). Those with FTD in cohort 3 also had significantly lower IQ and educational achievements. In the combined dataset (N=322) a stepwise linear regression established that current employment status was significantly explained by a combination of current FTD severity ($t=-4.99$ $p < .001$) and number of years in education ($t=4.13$ $p < .001$), and not current age or IQ.
**Conclusions:** The findings underscore that individuals experiencing FTD are at a significant disadvantage concerning employment compared to those with similar diagnostic conditions but without thought disorder. Enhanced psychosocial interventions that facilitate effective communication and expression for those with FTD are essential for mitigating this disadvantage and supporting their recovery journey.

### 24. The Cerebellar Mechanisms in Psychosis: Recent Advances in Animal And Human Studies

Hengyi Cao, *Feinstein Institute for Medical Research and Zucker Hillside Hospital*

**Overall Symposia Abstract:** The cerebellum plays a key role in synchronizing neural computations in the brain to generate orderly and meaningful thoughts and behaviors. Cerebellar dysfunction has increasingly been recognized as a critical contributor to cognitive impairments and psychopathology in psychosis. Dysfunction in the cerebellar-cortical circuitry leads to “cognitive dysmetria”, which has been proposed as a fundamental neurobiological change underlying the pathogenesis of schizophrenia. However, it remains poorly understood how the structure and function of the cerebellar-cortical circuitry are altered and how they contribute to nuanced cognitive functions and clinical behaviors in schizophrenia.

This symposium aims to assemble the most recent findings highlighting the cerebellar mechanisms in cognition and psychopathology in psychosis. We will start with a brief introduction to the historical work that have motivated the field, and then present four studies covering research from both animals and humans. In the first study, Dr. Parker will present an animal work deciphering cerebellar neuronal signals in relation to the encoding of time intervals, a key cognitive process pertinent to thought and behavioral coordination in humans that is disrupted in schizophrenia. She will show that inhibition of cerebellar neuronal activity is required to precisely encode suprasecond intervals of time in rats. Translating to humans, Dr. Rokem will interrogate white matter integrity of the cerebellar peduncles, which are key fiber tracts facilitating the communications between the cerebellum and cerebral cortex. He will show evidence for altered myelination that is specifically present in the superior cerebellar peduncle in patients with schizophrenia, implying bottom-up structural dysconnectivity from the cerebellum to the thalamus and midbrain. In line with this finding, Dr. Begue will highlight the function of the cerebellum-midbrain loop, a key circuitry for dopaminergic signaling and reward processing in humans. She will unveil a stably diminished anti-coactivation pattern of cerebellum-ventral tegmental area (VTA) that predicts the severity of apathy in schizophrenia. Lastly, Dr. Cao will present a machine learning-based analysis to identify the left cerebellar crus 1 and 2 area as a cognitive “epicenter” that

consistently predicts various cognitive functions in schizophrenia. Stimulating this area via transcranial magnetic stimulation (TMS) significantly improves cognitive composite scores in patients, suggesting a novel treatment target in the cerebellum for potential clinical translation.

At the end of the symposium, the chair will summarize these findings and lead the discussion on the promises and challenges of cerebellar studies in psychosis, where the panel will discuss the current consensuses, potential caveats, and future directions in the field. We encourage the audience to raise questions and share their opinions to help advance the understanding of current findings and translating these findings to future patient care.

### 24.1 Cerebellar Inhibitory Control During Supra Second Time Estimation

Krystal Parker*[1], John Freeman[1], Hunter Halverson[1], Jangjin Kim[1], Ainsley Rothgeb[1]

[1]*University of Iowa*

**Background:** A myriad of neuropsychiatric disorders involve cognitive dysfunction due to abnormalities in thalamocortical circuitry, yet the specific role of cerebellar input remains unknown. Filling this gap in knowledge is essential as there are no current treatments that effectively target cognitive dysfunction such as working memory, attention, reasoning, and timing. We study the underlying neural mechanisms for how cerebellar activity is relayed to the thalamus, what computations or integrations take place within the thalamus, and how this activity influences the frontal cortex and cognitive function.
**Methods:** We use a peak-interval timing task that relies on cognitive processes such as working memory and attention and is known to be abnormal in schizophrenia. Rats are trained to associate specific stimuli (light/tone) with temporal durations (4 and 12s) for water rewards. Using a triple-stie tetrode hyperdrive we record the neural activity in the lateral cerebellar nuclei, medial dorsal thalamic nuclei, and medial frontal cortex in rats well trained in the interval timing task. We present data from 6 rats – 862 neurons from the medial frontal cortex, 1545 medial dorsal thalamus nuclei, and 800 lateral cerebellar nuclei neurons. Data are analyzed for modulation around the cue and reward, and for ramping or increasing or decreasing activity over the interval. Further, we divide trials into good timing, poor timing, and non-response trials to define the functional significance of this activity as related to temporal processing. Analyses are underway to define the influence of the cerebellar inhibition on thalamic and frontal neurons using more advanced neurophysiological analyses including spike-spike and spike-field coherence.
**Results:** Our preliminary analyses identified that a large portion of the neurons in the lateral cerebellar nuclei are inhibited in a ramping down pattern to the time of the trained interval. Interestingly, single neurons maintained the nadir of their activity to the time of the trained interval with altered slopes dependent on the interval on good timing trials. This pattern of activity was less precise on poor timing trials, and there was no clear modulation on non-response trials.
**Conclusions:** The cerebellum is necessary to precisely encode the trained temporal duration in the interval timing task given loss of duration encoding precision on poor and non-response trials. How this inhibitory cerebellar output influences downstream timing circuitry is unknown but continued analyses in this current dataset will further define this relationship and shed light on the role of the cerebellum in timing in the range of seconds to minutes.

## 24.2 Tissue Properties of the Cerebello-Thalamic-Cortical Network in Schizophrenia: Support for the Cognitive Dysmetria Theory

Ariel Rokem*[1], Teresa Gomez[1], Halil Velioglu[2], John Kruper[1], Adam Richie-Halford[3], Sivan Jossinger[4], Michal Ben-Shachar[4], Jason Yeatman[3], Hengyi Cao[2]

[1]*University of Washington,* [2]*Feinstein Institutes for Medical Research and Zucker Hillside Hospital,* [3]*Stanford University,* [4]*Gonda Multidisciplinary Brain Research Center, Bar-Ilan University*

**Background:** The cognitive dysmetria theory of schizophrenia (SZ) posits that the core cognitive deficits arise from dysfunctions of cortical-thalamic-cerebellar (CTC) circuits. This theory has received empirical support from fMRI studies, which found increased connectivity in CTC in individuals with SZ. In the present study, we focused on properties of the white matter tissue of the superior cerebellar peduncles (SCPs), a key component of the CTC circuit.

**Methods:** We analyzed diffusion MRI (dMRI) data from two separate datasets: 1) UCLA Consortium for Neuropsychiatric Phenomics LA5c Study (CNP). This sample includes 272 subjects (ages: 21-50): 49 with SZ, 49 with bipolar disorder, 41 with ADHD, and 123 healthy controls (HC). DMRI data were collected with 2 mm isotropic resolution and 1,000 s/mm2 b-value in 64 directions. 2) A second dataset was collected at the Feinstein Institute for Medical Research (FE). This sample included 63 subjects (ages: 17-39): 31 with SZ and 32 HC. DMRI data were collected with 1.4mmx1.4mmx1.3mm resolution and 3,000 s/mm2 b-value in 98 directions. Both datasets were processed using the same pipeline: We used QSIPrep for preprocessing, which includes denoising and corrections for motion and eddy currents. The SCPs were identified in each individual using the pyAFQ software (https://tractometry.org/pyAFQ/) and anatomical criteria that capture the known decussation of this bundle. Because the sample contains data of varying quality and the cerebellum was not always covered, visual QC of each subject's SCP was conducted by two observers (TG and AR, blind to group). A subject's data were included only if both observers considered SCP delineation to be in the correct anatomical location and with the expected decussation. In CNP, this included 46 SZ, 39 bipolar, 35 ADHD, and 94 HC. In FE, this included 26 SZ and 26 controls. In CNP, samples of matched case/control were constructed from by simultaneously matching on age, sex and data quality (quantified as raw neighbor correlations). We focused on tract profiles of the mean diffusivity (MD) and fractional anisotropy (FA) calculated with DTI. Statistical differences were evaluated using tractable (https://tractometry.org/tractable/), which models the tract profiles using generalized additive models (GAMs), accounting for the shape of the tract profiles along with variability among participants5. Model covariates included age, sex, and raw neighbor correlations.

**Results:** In CNP, statistically significant differences were found in MD tract profiles of the left SCP, where individuals with SZ had lower MD than the matched controls. No other significant differences were found. Individuals with ADHD and bipolar were no different from matched controls in SCP tissue properties. Replicating and extending these results, in the FE dataset we found both a significant difference in left SCP, as well as right SCP in both FA and MD, with SZ having higher FA and lower MD in both tracts.

**Conclusions:** Previous literature has associated schizophrenia with global abnormalities in diffusion measures, primarily measured as a reduction in FA6. Here, we found relatively lower MD and higher FA in the SCP, a component of the CTC. Lower MD could indicate increased myelination in SZ and therefore increased connectivity. increased density and directional coherence (but not axonal diameter) may also have similar effects on MD. Increase FA is associated with increased myelination in SZ in this tract but could also be

associated with reduced crossing fibers. Thus, these results may be in line with previous fMRI results that found increased functional connectivity in the CTC in individuals with SZ, and further supports the cognitive dysmetria theory of SZ.

### 24.3 A Reproducible Anti-Coactivation Pattern Between the Cerebellum and Ventral Tegmental Area Relates to Negative Symptoms in Schizophrenia: Implications for Mechanism-Informed Therapy

Farnaz Delavari[1], Jade Awada[2], Dimitri Van de Ville[3], Thomas Bolton[4], Mariia Kaliuzhna[4], Fabien Carruzzo[4], Noemie Kuentzi[5], Fares Alouf[2], Florian Schlagenhauf[6], Stephan Eliez[7], Stefan Kaiser[8], Indrit Bègue*[2]

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**Background:** Negative symptoms in schizophrenia are debilitating and lack effective treatments. Reward system dysfunction and cerebellum anomalies have been linked to negative symptoms. The cerebellum modulates the reward system through the ventral tegmental area (VTA), though the role of cerebellum-VTA connectivity in these symptoms remains unclear.

**Methods:** We conducted interviews and acquired resting-state functional magnetic resonance imaging in 146 individuals, including patients with schizophrenia (SZ) and healthy controls (HC). After strict quality check, the final sample included 105 individuals (58 SZ) at baseline (T1), 41 individuals (22 SZ) at 3-month follow-up (T2), and 21 patients at 9-month follow-up (T3; interviews only). We analyzed the dynamic functional connectivity of cerebellum and VTA activity using Co-Activation Patterns analysis

**Results:** We identified a reproducible anti-coactivation pattern cerebellum-VTA pattern across distinct recordings at T1 and T2 ($r = 0.98$) encompassing bilateral paravermal regions of Crus I and II. This pattern's duration was significantly reduced in SZ in T1 and in T2, indicating an enduring deficiency in cerebellar inhibition of the VTA. Lower emergence of this pattern at T1 and lower persistence at T2 were associated with more severe apathy, but not diminished expression. Lower persistence at T2 related to more severe apathy but not diminished expression at T3.

**Conclusions:** Reproducible longitudinal evidence of the cerebellum's'dysmetric' regulation of reward circuitry opens a new therapeutic avenue for targeted cerebellar non-invasive brain stimulation to alleviate negative symptoms in schizophrenia. Our ongoing randomized clinical trial testing a CB-VTA anti-coactivation-guided stimulation will provide crucial evidence on its efficacy as novel intervention for treatment-resistant negative symptoms.

**24.4 Down to the Nitty-Gritty of "Cognitive Dysmetria": Mapping Cerebellar Connectivity to Cognition in Psychosis**

Hengyi Cao*[1], Miklos Argyelan[1], Joanna Yan[1], Halil Aziz Velioglu[1], Franky Fang[1], Andrea Joanlanne[1], Simran Kang[1], Lara Prizgint[1], Jenna Schugart[1], Kadeem Brown[1], John Cholewa[1], Philip Watson[1], Sunny Tang[1], Ricardo Carrion[1], Jose Rubio[1], Moein Foroughi[2], Todd Lencz[1], Anil Malhotra[1]

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**Background:** Cerebellar dysfunction has been strongly implicated in both cognition and psychosis, and the "cognitive dysmetria" hypothesis posits that cognition is the intermediary in the pathway from cerebellar dysfunction to psychopathology. However, the nuanced pattern linking cerebellum-behavior relationships in patients remains unclear. Establishing such link is important to understand cerebellar mechanisms and to identify neural targets for treatment of cognitive deficits in psychosis.

**Methods:** In the first study, we investigated a total of 100 patients with early-stage psychosis from the Human Connectome Project Early Psychosis (HCP-EP) study (mean age 22.8 years, 64 males). The entire cerebellum was parcellated into 125 fine-grained functional parcels, and the cerebellar functional connectome measuring connectivity between each cerebellar parcel and the whole brain was computed from the resting-state data. Cognitive functions were assessed using the NIH toolbox including six distinct domains (working memory, episodic memory, attention, executive function, verbal processing, and processing speed). We used connectome-based predictive modeling to probe cognitive functions most predicted by cerebellar connectivity. Mediation analysis was subsequently conducted linking cerebellar connectivity to PANSS symptoms, with cognitive scores as mediator.

In the second study, 12 patients with a schizophrenia spectrum disorder were recruited for a randomized, sham-controlled cerebellar TMS treatment trial (6 active TMS, 6 sham). Each patient was treated for two weeks with an iTBS protocol, targeting the posteriormost part of the cerebellum left to the midline under neuronavigation (corresponding to the left crus 1 and 2 area). Cognitive evaluations were performed using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline and end of the 2nd week.

**Results:** In the HCP-EP sample, the cerebellar connectome significantly predicted three cognitive functions in patients, namely, verbal ability (r [predicted vs observed] = 0.47, $p < 0.001$), working memory (r [predicted vs observed] = 0.42, $p = 0.002$), and cognitive flexibility (r [predicted vs observed] = 0.33, $p = 0.01$). While each cognitive domain was predicted by a distinct cerebellar connectivity pattern, the left crus 1 and 2 area turned out to be a common region whose connectivity consistently predicted all three functions. The mediation analysis further unveiled that verbal ability score was a significant mediator that fully mediated the relationship between cerebellar connectivity and negative symptoms ($p < 0.001$).

In the TMS sample, stimulation of the left crus 1 and 2 area showed a significant group by time interaction effect on overall cognitive composite score ($p = 0.02$, Cohen's $d = 1.52$), with score improvement in the active TMS group ($p = 0.04$) but not sham group. Domain-specific analysis revealed large interaction effect on working memory (Cohen's $d = 1.51$) and medium-to-large interaction effects on verbal memory (Cohen's $d = 0.76$) and executive function (Cohen's $d = 0.73$), remarkably consistent with the domains identified in the HCP-EP sample.

**Conclusions:** These findings suggest a potential causal pathway from cerebellar connectivity to domain-specific cognitive deficits and psychopathology in schizophrenia. Moreover, they also point to the cerebellum as a potential neural target for treatment of cognitive dysfunction in patients with psychotic disorders.

## 25. Understanding and Treating Social Disconnection in Schizophrenia

Stephen Marder, *University of California, Los Angeles, Semel Institute for Neuroscience*

**Overall Symposia Abstract:** Impairments in the ability of some patients with schizophrenia to form social connections with others have a large impact on their ability to function. This session will focus on recent research that has characterized these impairments and studies that are exploring psychological and pharmacological approaches to improving social connectedness. Sanja Killian from Stellenbosch University will focus on the themes of social disconnection and isolation in the experiences of both schizophrenia patients and their family members in middle income and impoverished areas of South Africa. Using qualitative research methods, her findings explored how social disconnectedness is related to how patients are seen and understood in their communities. Lauren McBride from UC San Diego will present data from a study that used ecological momentary assessment and a loneliness scale to study the link between trait loneliness and structural social behavior indicators in schizophrenia. Findings from the study suggest that differences in social activity (such as time spent alone) varies across subgroups of psychosis patients and may inform targeted interventions. L. Felice Reddy from the University of North Carolina will present results from a novel recovery-oriented psychosocial intervention aimed at reducing motivational negative symptoms and improving community functioning. In two randomized controlled trials. The studies found that the intervention resulted in improvements in social motivation and social functioning among those with schizophrenia and other severe psychiatric illnesses and a history of homelessness. Anya Bershad from UCLA will present results from studies of pharmacological agents that promoted prosocial behavior including a clinical trial assessing the acute effects of a low dose of the mu-opioid agonist/kappa antagonist buprenorphine on social motivation in socially disconnected patients with schizophrenia. Michael Green will serve as the session discussant.

### 25.1 Social Disconnection, Isolation and Stigma From a Lived Experience Approach

Sanja Kilian*[1], Laila Asmal[1], Hilmar Luckhoff[1], Lebogang Phahladira[1], Retha Smit[1], Robin Emsley[2]

[1]*Stellenbosch University,* [2]*Faculty of Medicine and Health Sciences, Stellenbosch University*

**Background:** The move towards deinstitutionalisation has shifted the care of persons living with schizophrenia (PLWS) to families and communities. In low- and middle-income countries such as South Africa with limited resources, families and communities generally have limited access to support and psychoeducational programs. As a result, there tend to be misconceptions regarding the nature of the illness and the needs of PLWS, which may impact social disconnection in schizophrenia.

**Methods:** We explored the lived experiences of PLWS as well as the lived experiences of family members caring for PLWS using a qualitative exploratory approach. We interviewed 25 participants and used thematic analysis to analyse the data.

**Results:** Isolation was a common theme that emerged from the data. PLWS had very few or no friends. The majority of participants thought that the community and extended family were uninformed about schizophrenia and that the PLWS is not seen and understood by people outside of the immediate family. Participants reported that people outside the immediate family discriminated against PLWS. This made families feel it was their responsibility to shield the family members living with schizophrenia and protect them for the community.
**Conclusions:** The themes of social disconnection and isolation were interconnected with themes around stigma and discrimination. Social disconnectedness seems, to some extent, shaped by how persons living with schizophrenia are seen and understood by their communities. Social isolation and disconnection are central to the narratives of PLWS and their families.

### 25.2 Home Alone Matters for Whom? Sociodemographic and Diagnostic Differences in the Link Between EMA-Derived Social Behavior and Loneliness

Lauren McBride*[1], Miya Gentry[1], Amy Pinkham[2], Barton Palmer[3], Ellen Lee[3], Eric Granholm[3], Philip Harvey[4], Colin Depp[3]

[1]*San Diego State University, University of California, San Diego Joint Doctoral Program in Clinical Psychology,* [2]*The University of Texas at Dallas,* [3] *University of California, San Diego* [4]*University of Miami Miller School of Medicine*

**Background:** Ecological momentary assessment (EMA) has revealed strong links between loneliness and negative experiences in psychosis, but few associations between loneliness and structural measures of social activity (e.g., time spent alone). It may be, however, that the link between loneliness and social activity varies across subgroups of people with psychosis, which could inform more targeted interventions. We evaluate sociodemographic and diagnostic moderators of the link between loneliness and EMA social activity in a comparatively large sample of people with psychosis.
**Methods:** N=264 participants with schizophrenia or bipolar disorder with psychotic features were assessed for loneliness using the UCLA Loneliness Scale. Participants completed ecological momentary assessment (EMA) surveys on their smartphones (3x per day for 10 days) regarding social behavior (i.e., time spent alone, time spent at home, social interaction frequency). Associations between social behavior variables and loneliness were assessed. We then examined differences in social behavioral correlates with loneliness across sociodemographic context and diagnostic groups.
**Results:** Consistent with prior research, there was no association between time spent alone and loneliness. Significant but small correlations were evident between loneliness and not interacting with others and more time spent at home. No sociodemographic and diagnostic variables were associated greater levels of loneliness. Time spent alone and reduced interactions were associated with diagnosis of schizophrenia, identifying as non-white, identifying as not Hispanic or Latino/a/x, being single, and living alone. In addition, there were significantly stronger correlations between loneliness and social behavior variables among older, unemployed, financially dependent, and single participants. Notably, time spent with friends was associated with lower levels of loneliness in all groups.
**Conclusions:** Although past literature has found generally weak associations between loneliness and the quantity of social behavior (e.g., time spent alone) in schizophrenia and in the general population, we found that stronger links were evident for participants with higher disability. These findings suggest that loneliness could be improved by addressing social

activity and fostering friendships in more vulnerable subgroups of people with psychotic disorders.

### 25.3 A Novel Psychosocial Intervention for Social Motivation Deficits

Felice Reddy*[1], Shirley Glynn[2], Michael Green[3]

[1]*University of North Carolina at Chapel Hill,* [2] *University of California, Los Angeles /VA Greater Los Angeles Healthcare System,* [3]*University of California, Los Angeles*

**Background:** Negative symptoms significantly interfere with daily functioning among individuals with schizophrenia and are considered an unmet treatment need. Among the types of negative symptoms, experiential negative symptoms (amotivation and anhedonia) are the primary determinants of impaired functioning. Social motivation deficits contribute to impairments in social and interpersonal functioning in a wide range of disorders. We developed a novel recovery-oriented psychosocial intervention aimed at reducing motivational negative symptoms and improving social connection and community functioning in individuals with negative symptoms. The intervention combines two evidence-based practices, Motivational Interviewing and Cognitive Behavior Therapy (MI-CBT) and was originally delivered in 12 group sessions. In recent years we have expanded the protocol to directly focus on social motivation and community integration, in a variety of psychiatric conditions that are characterized by motivation deficits. This talk will present Results: from two randomized controlled trials that used MI-CBT to address social motivational deficits. The first study applied MI-CBT to people with schizophrenia who had at least moderate levels of negative symptoms. The second study implemented MI-CBT in an RCT to improve social motivation and functioning in homeless-experienced Veterans with a range of diagnoses including schizophrenia, PTSD, depression, and substance abuse.
**Methods:** The original study included 79 participants with schizophrenia and moderate to severe negative symptoms in an RCT comparing the 12-session MI-CBT treatment with a control condition. Participants were assessed at three time points through the study period, which included a 3-month follow-up. In the second study, 60 homeless-experienced Veterans with a range of psychiatric diagnoses were randomly assigned to 12 weeks of the intervention plus 3 monthly booster sessions or a control condition. Both groups were assessed 4 times over 9 months. In both studies, motivational negative symptoms and social functioning were the primary outcome measures. In the second study we also examined social motivation using the University of Rhode Island Change Assessment Scale (URICA) which measures an individual's stage of change.
**Results:** In the original study, compared with the control group, participants in the MI-CBT group showed significantly greater improvements in motivational negative symptoms over the acute treatment period ($F=10.50$, $df=1,111$, $p=.0016$). Their gains relative to baseline were maintained at follow-up ($F=15.02$, $df=1,111$, $p=.0002$). There were nonsignificant effects toward improvements in community functioning. In the second study, there was a significant between group treatment effect ($F=5.20$, $df=2,92$, $p=.007$). On the social functioning measure, there was a significant treatment effect for the group by time interaction ($F=3.6$, $df=2,87$, $p=.03$). The motivational stage of change measure also showed a significant group by time interaction ($F=5.60$, $df=2,94$, $p=.005$), indicating the MI-CBT condition improved in terms of readiness to take action toward social goals and the control group did not.
**Conclusions:** The results suggest a novel combined psychosocial intervention yields improvements in social motivation and social functioning among those with schizophrenia and other severe psychiatric illnesses and a history of homelessness. These findings indicate

that social motivation deficits and accompanying social functioning deficits are responsive to a psychosocial intervention in adults with a variety of severe psychiatric diagnoses.

### 25.4 Effects of Buprenorphine on Social Motivation in Schizophrenia

Anya Bershad*[1], Michael Green[2], Stephen Marder[3], Eric Reavis[4]

[1]*David Geffen School of Medicine at UCLA,* [2]*University of California, Los Angeles; VA Greater Los Angeles,* [3]*UCLA Semel Institute for Neuroscience and Human Behavior; VISN 22 MIRECC, VA Greater Los Angeles Healthcare System,* [4]*Semel Institute for Neuroscience and Human Behavior at UCLA*

**Background:** Impaired social motivation is a negative symptom of schizophrenia and a major cause of disability and suffering for many patients struggling with the illness. Despite the enormous burden on patients, there are no efficacious pharmacologic treatments of this symptom for those suffering from the illness. One potential target for treatment of impaired social motivation is the opioid system. Both the mu-opioid system and the kappa-opioid system have been shown to mediate social behavior. Buprenorphine is a unique opioid drug that acts as a mu partial agonist and kappa antagonist, and thus has the potential to target deficits in social motivation. Despite this promise, its effects on social motivation have not been tested in patients with schizophrenia.
**Methods:** Here we report the preliminary results of an ongoing study testing the effects of a low dose of buprenorphine on social motivation in socially disconnected patients with schizophrenia. In this double-blind, cross-over, placebo-controlled trial, participants attended two laboratory sessions, receiving either placebo or 0.15mg buprenorphine. During expected peak drug effect they completed self-report questionnaires and behavioral tasks assessing social motivation.
**Results:** Low-dose buprenorphine was well-tolerated by the participants, and for in several cases, indistinguishable from placebo. The study is ongoing, though preliminary analysis suggests buprenorphine increased ratings of sociability.
**Conclusions:** The results of this study suggest a role for the opioid system in mediating social motivation and lay the foundation for larger-scale clinical trials investigating buprenorphine as a treatment for social deficits in schizophrenia.

## 26. Contributions to Psychosis Risk in Women Across the Lifespan

Albert Powers*, Yale University School of Medicine*

**Overall Symposia Abstract:** Women experience multiple unique life stages that are characterized by hormonal shifts and increased psychosis vulnerability. These include menarche, the postpartum period, and menopause. Despite well-established relationships between these critical time points and psychosis emergence, the factors that contribute to risk remain understudied.

To highlight the unique needs of women in these life stages, this symposium will explore emerging data on symptom evolution and genetic risk as they relate to sex hormones and polypeptides in women, aiming to highlight the importance of tailored approaches to their diagnosis and care. First, Dr. Katherine Damme will present evidence that estradiol availability at menarche influences neuromaturation (structure and connectivity) and psychosis risk. Dr. Paola Dazzan will then discuss factors predisposing to post-partum

psychosis. Following this, Dr. Megan Kelley will review evidence of the psychosis prodrome as it manifests during perimenopause. The symposium will end with a presentation by Dr. Bodyl Brand on strategies for personalizing treatment for women with psychosis, addressing both pre- and post-menopausal stages across the female reproductive lifespan.

By merging evidence from life stages that confer unique risk for psychosis in women, we aim to identify commonalities, differences, and opportunities for risk stratification, prevention, and adequate treatment.

**26.1 Rising Estrogen and Mechanisms of Psychotic-Like Experiences in the Transition to Adolescence**

Katherine Damme*[1], Vijay Mittal[2]

[1]*University of Texas Dallas,* [2]*Northwestern University*

**Background:** Despite a growing focus on the adolescent prodromal phase, little attention has been given to understanding early mechanisms during the premorbid stage. This premorbid stages occurs in the transition from childhood to adolescence, at a time when liability for psychosis interacts with both normative and abnormal developmental changes, marked by the emergence of subtle psychosis symptoms (i.e., psychotic-like experiences (PLEs)- unusual perceptions, thoughts, and behaviors) and cognitive decline. This period is also marked by initiation and rising estrogen levels in biological females, which has a powerful impact on the neuromaturation, connectivity, and cognitive function, particularly in regions dense in estrogen receptors like the hippocampus. Effects of estrogen on the normative neurodevelopment may act on mechanism of psychosis onset and provide resiliency that underlay the characteristic sex differences in the timing of onset, course, and phenomenology of psychosis. The following analyses leverage normative changes in late childhood and early adolescent development provides a natural experiment to understanding the neurodevelopmental interactions estrogen has with vulnerability to psychosis.
**Methods:** The Adolescent Brain and Cognitive Development (ABCD) Study is a landmark multisite, large-scale, longitudinal investigation of individuals in late childhood and early adolescence that provides a unique opportunity for addressing this gap in the literature. The study includes pubertal scales, neuroimaging sessions, cognitive assessments, and hormone assays on large groups of individuals with a baseline scan prior to menarche and the follow-up scan after menarche (n=716), examining hippocampal connectivity. While individuals differ in their sensitivity to estrogen levels, menarche reflects that the individual has reached a sufficient saturation of estrogen during this initial rise to trigger downstream biological processes, and is used here as a broad marker of hormonal development. Additional analyses centered around other estrogen receptive areas (e.g., cerebellum) and examining relative timing of menarche are in progress.
**Results:** Menarche related to reduced PLE-Severity ($t=4.18$, $p=3.29e-05$), increased whole hippocampal volume ($t=12.8$, $p < 2e-16$), increased hippocampus-DMN connectivity ($t=3.15$, $p=0.0017$), reduced Hippocampus-ECN connectivity ($t=5.59$, $p=3.11e-08$), and reduced Hippocampus-visual network connectivity ($t=4.34$, $p=1.66e-05$), but not Hippocampus-SAL network connectivity ($t=1.17$, $p=0.24$).

Follow-up analyses demonstrated that menarche status moderated the relationship between hippocampal disconnectivity and PLE Severity; ($t = 1.99$; $p = 0.04$, $\eta 2$partial=.0008), such that decreased hippocampal-visual connectivity was related to increased symptoms in the pre-menarche group ($r = 0.06$, $p < 0.0001$) but not in the post-menarche group ($r = 0.03$, $p = 0.98$).

**Conclusions:** Menarche status was related to PLE severity, hippocampal volume, and hippocampal disconnectivity relavant to emergence of psychosis. Although hippocampal-visual network dysconnectivity related to PLE severity, this effect was moderated by menarche status; before the availability of estradiol (pre-menarche), lower hippocampal connectivity significantly contributed to the PLE severity, but when estradiol was available (post-menarche) hippocampal dysconnectivity did not account for PLE severity. This moderation suggests that the estrodiol's influence on hippocampal plasticity also reduced the mechanistic role of the hippocampus on PLE severity, and emphasizes the importance considering estrogen's role during this critical developmental period role for understanding psychosis lability factors.

## 26.2 How Biology and the Environment Interact to Increase Risk of Postpartum Psychosis

Paola Dazzan*[1]

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

**Background:** Puerperal or Postpartum Psychosis (PP) is the most severe psychiatric disorder associated with childbirth. Although PP occurs in concomitance with the biological changes of childbirth, and is very frequent in women with specific risk factors, its neurobiological basis is still poorly understood.
**Methods:** We recruited 56 women at-risk of developing PP (26 became unwell and 30 remained well in the postpartum), and 47 control women, evaluated in pregnancy and in the postpartum. We acquired stress markers and brain structural and functional MRIs in a 3T scanner.
**Results:** Women at-risk who became unwell had smaller anterior cingulate, postcentral and parahippocampal gyri than those who remained well (all $p < 0.05$). They also showed reduced resting connectivity within an executive network compared to controls. At rest, women at-risk also showed decreased connectivity in the executive network, and altered emotional load-dependent connectivity between executive, salience, and default-mode networks. AR-unwell women particularly showed increased salience network-dependent modulation of the default-mode and executive network. Women at-risk were more likely to have experienced childhood adversity, and to show an abnormal stress response, with higher daily cortisol levels compared to women at risk who remained well ($t(65)=-2.8$, $p < .01$) and higher inflammatory markers (C-Reactive protein, Interleukin L-6 and TNF-A).
**Conclusions:** Women at risk of PP who develop an episode share some risk factors with psychoses unrelated to the puerperium. Evidence that an episode of PP is associated with stress response alterations provides a target for pharmacological and psychological interventions (such as stress management) to the most vulnerable women.

## 26.3 Characterization of the Prodrome in Menopause Associated Psychosis (MAP)

Megan Kelley*[1], Albert Powers[2]

[1]*Yale University,* [2]*Yale University School of Medicine*

**Background:** Psychosis frequently emerges in adolescence early adulthood, often preceded by a prodrome of attenuated, subclinical symptoms. Characterizing this prodrome has led to large-scale efforts in biomarker identification and early intervention. However, it remains unclear whether similar prodromal phases occur at other high-risk time points. Women face unique periods of heightened psychosis risk, such as postpartum and during the menopause transition, which have long been acknowledged but are still under-recognized clinically. Menopause-associated psychosis (MAP) accounts for a substantial portion of cases in women, and these women often experience worse outcomes compared to those with early-onset psychosis or men with late-onset psychosis. Characterizing the MAP prodrome could help mitigate this gender and age disparity and improve early intervention strategies for this high-risk group. This study presents preliminary findings from the Yale Predictors and Risk Evaluation of Menopause-Associated Psychosis (PREMAP) study, which aims to identify biomarkers and prodromal characteristics in MAP.
**Methods:** Fourteen women diagnosed with a psychotic -spectrum disorders after age 35 with onset coinciding with perimenopause participated in structured interviews, including the Structured Interview for Psychosis-Risk Syndromes (SIPS), the Structured Clinical Interview for DSM-V (SCID-V), and the Interview for Retrospective Assessment of Onset and Course of Schizophrenia and Other Psychoses (IRAOS). Subclinical symptom onset and worsening were assessed through SIPS and verified by IRAOS, with SCID used to confirm the psychosis diagnosis.
**Results:** 50% of MAP subjects reported lifelong subclinical symptoms, which intensified during perimenopause. The remaining participants developed entirely new subclinical symptoms prior to conversion. In both cases, the appearance or worsening of symptoms occurred on average, three years before conversion. Additionally, 62% of MAP cases evolved from pre-existing bipolar disorder or depression without psychotic features.
**Conclusions:** These findings suggest the existence of a prodromal phase in MAP, lasting about three years before full psychosis onset. Two distinct prodromal trajectories are suggested: one involving lifetime subclinical symptoms and another with newly emerging symptoms during perimenopause. Furthermore, individuals with pre-existing mood disorders appear to be at heightened risk for MAP conversion.

## 26.4 Pharmacological Treatment Strategies for Schizophrenia Spectrum Disorders Across the Reproductive Lifespan

Bodyl Brand*[1], Janna de Boer[2], Iris Sommer[2]

[1]*University of Oxford,* [2]*University Medical Center Groningen*

**Background:** The role of estrogen in the pathophysiology of Schizophrenia Spectrum Disorders (SSD) has been well-documented over the past three decades. However, clinical practice still largely applies a unisex approach to treatment, which may not adequately address the unique needs of female patients. This review critically evaluates whether this approach is insufficient and explores strategies for better tailoring pharmacological treatment to the female body.
**Methods:** This review synthesizes existing literature on the effects of hormonal changes throughout the reproductive lifespan and their impact on psychotic vulnerability in female SSD patients. We focus on how current antipsychotic treatments impact endogenous estrogen levels and examine the role of both endogenous and exogenous estrogens (e.g., contraceptives, hormonal replacement therapy, HRT) in modulating psychotic vulnerability.

**Results:** Before menopause, female patients benefit from endogenous estrogen production, making it particularly important to avoid antipsychotics that raise prolactin levels, as they can induce estrogen deficiency, which in turn increases vulnerability to psychosis. An understudied area is the impact of contraceptive on disease severity in premenopausal patients. Reaching menopausal age is associated with an increased susceptibility to psychosis. While some of the neurobiological effects of menopausal estrogen decline are linked to increased susceptibility to psychosis, there is a notable lack of studies directly linking these two factors. Furthermore, there is a significant gap in research on the menopause transition, which is crucial to determine whether it is solely menopause itself or the transition leading up to it that contributes to this increased psychotic vulnerability. After menopause, female patients could benefit from augmentation with raloxifene or HRT. Multiple studies have shown raloxifene's potential to improve symptoms in postmenopausal women. While there is a lack of clinical trials on the effects of HRT on psychosis, our Finnish cohort study suggests that its use indeed reduces the risk of psychosis when started before the age of 55. Further clinical studies are needed to determine the efficacy and optimal timing for starting these therapies.
**Conclusions:** This review underscores the need for further research on the impact of hormonal changes on psychotic vulnerability in women with SSD, particularly regarding the effects of exogenous estrogens (i.e. contraceptives and HRT). Although estrogen decline during the menopause transition is likely linked to increased vulnerability to psychosis, there is a lack of direct studies on this relationship. Additionally, while HRT and raloxifene may benefit postmenopausal women, the optimal timing for initiating these treatments remains unclear. Overall, more targeted research is essential to fully understand how hormonal fluctuations throughout the reproductive lifespan influence psychotic vulnerability and to refine treatment strategies accordingly.

**Plenary Session IV: Cannabis Use and Psychosis: From Risk to Treatment - Dr. Marta di Forti**

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

**27. Cannabis use and Psychosis: From Risk to Treatment**
Celso Arango*, Hospital General Universitario Gregorio Marañon*
**Overall Abstract:** -

**27.1 Cannabis use and Psychosis: From Risk to Treatment**
Marta Di Forti*, SGDP, Institute of Psychiatry*

**Individual Abstract:** My group has provided the first evidence showing the impact of frequent use of high potent strains of cannabis on risk for psychotic disorder and its earlier age of onset, as well as contributed to show its impact on the illness outcome.
This work has led to the development of the Cannabis Clinic for Psychosis (CCP). The CCP, is the first and only UK NHS service that offers adults with psychotic disorders who use cannabis a flexible intervention to cannabis use reduction/cessation.

Methods:

The CCP model of care includes: 1) one-to-one sessions using evidence-based Addiction psychosocial interventions tailored to each patient's needs whilst considering their psychosis

co-morbidity, 2) a weekly online PEER group, which offers to the patients attending, the opportunity to hear from world leading expert on cannabis use and psychosis, and/or cannabis dependence and ask questions and share experience.

We recently completed a proof of concept review of the outcome data from the first 46 patients who completed their intervention with the CCP.

Results:

74% of the patients stopped using cannabis and the remaining 26% reduced their frequency of use and the potency of the type used. These changes explained a significant proportion of improvements in all clinical and functional outcomes measured, and lead to 90% of the patients returning work or education.

Conclusions: These data support the feasibility of tailoring existing Addiction tools to the needs of adults suffering from a psychotic disorder with co-morbid cannabis use. Therefore, it is important to implement the existing research and clinical knowledge, to develop services like the CCP that offer an important tertiary prevention strategy providing young adults with psychosis the knowledge and support needed to prevent and/or reverse the negative impact that cannabis use can have on their illness course and family, as well as mental health services.

**Plenary Session V: Psychosis research in Mexico: Insights from Neuroimaging Studies - Dr. Camilo de la Fuente-Sandoval**

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

**28. Psychosis Research in Mexico: Insights From Neuroimaging Studies**

Kate Merritt*, University College London*

**Overall Abstract:** Mexico City comprises a large metropolitan area with a population of 22 million but with limited mental health resources. The Instituto Nacional de Neurología y Neurocirugía is the main referral service in the city, where secondary causes of psychosis are ruled out.

In this context, the first-episode psychosis clinics and the Adolescent Program of Neuropsychiatric and Imaging Study (PIENSA) programs were founded in 2006, with the opportunity of studying these early diagnosed, unexposed-to-medications populations. Our laboratory has been focused on the NMDA receptor hypofunction hypothesis of schizophrenia, which involves the study of glutamate and γ-aminobutyric acid (GABA) using proton magnetic resonance spectroscopy.

This presentation will focus on the findings of our laboratory, the agreements and differences within the nuances of the findings and the available data of other groups, and the future directions and opportunities in the study of early psychosis.

**28.1 Psychosis Research in Mexico: Insights From Neuroimaging Studies**
Camilo de la Fuente-Sandoval*, Instituto Nacional de Neurologia y Neurocirugia*

**Individual Abstract:** Mexico City comprises a large metropolitan area with a population of 22 million but with limited mental health resources. The Instituto Nacional de Neurología y Neurocirugía is the main referral service in the city, where secondary causes of psychosis are ruled out.
In this context, the first-episode psychosis clinics and the Adolescent Program of Neuropsychiatric and Imaging Study (PIENSA) programs were founded in 2006, with the opportunity of studying these early diagnosed, unexposed-to-medications populations. Our laboratory has been focused on the NMDA receptor hypofunction hypothesis of schizophrenia, which involves the study of glutamate and γ-aminobutyric acid (GABA) using proton magnetic resonance spectroscopy.

This presentation will focus on the findings of our laboratory, the agreements and differences within the nuances of the findings and the available data of other groups, and the future directions and opportunities in the study of early psychosis.

**Concurrent Symposia**

**10:30 a.m. - 12:00 p.m.**

**29. Syndemics and Psychosis: New Theory, New Research**
Jeremy Coid*, Queen Mary University of London*

**Overall Symposia Abstract:** The aims of the symposium are to:
Understand the importance of syndemic theory for psychosis research.

Understand the three tenets of research using syndemic approaches - social determinants, disease clustering, and disease interaction.

Recognise strengths and weaknesses of existing syndemic psychosis research.

Consider the public health implications of syndemic theory for future interventions.

Background:

Syndemics are highly important in mental health because they propose causal models for psychotic spectrum disorders based on social determinants. Syndemics are new in psychiatry, with only two published studies with psychosis as an outcome. However, Syndemics were first defined 30 years ago. There is extensive literature in other fields, primarily AIDS/HIV, and The Lancet commissioned a series of reviews in 2017. But this has primarily by-passed mental health until now.

A syndemic was defined by Singer (1996) as an aggregation of two or more epidemics or diseases or other health conditions in a population whereby there is some level of deleterious biological or behavioural interface that exacerbates adverse health effects of any or all of the diseases involved. Syndemics involve adverse interaction between epidemics of all types. They are most likely to emerge under conditions of health inequality caused by poverty, stigmatisation, stress, or structural violence, and where cultural and historical factors may

have an effect. Studies of Syndemics should demonstrate (I) disease clustering, (II) synergistic interactions between health conditions leading to psychosis, and (III) the social determinants or contextual factors for the identified syndemic. Tsai has pointed out that few published studies demonstrate synergistic interactions, and the term can, unfortunately, be used loosely. However, there is a pressing need to develop a new syndemic theory, and there may be more than one syndemic model.

More recently, child adversity was identified as key in determining later synergy between psychopathology and health-related behaviours, which are specific along pathways to psychosis. These pathways may be independent of, or only partially dependent on, gene-environment interaction. The key notion is that the environmental risk factors in a syndemic are of sufficient impact to cause psychosis through their multiplicative synergistic effects. This differs considerably from studies using sum score effects of individual risk factors. These are insufficient and non-specific for psychosis as outcome.

### 29.1 The Effect of the Genetic Susceptibility for Schizophrenia and the use of Cannabis on Dimensions of Psychosis Symptoms, Aggression, and Violence

Diego Quattrone*[1]

[1]*King's College London*

**Background:** The syndemic theory assumes that physical and/or mental health conditions cluster with social determinants and correlate at a population level. In South London, the most preventable risk factor for psychotic disorders is cannabis use, which is associated with a specific symptom dimension phenotype (e.g., more positive and less negative symptoms at the subclinical level and the first episode of psychosis [FEP]) and violence and aggression outcomes. Population genetics allow us to estimate a polygenic score (PGS) due to common risk variants and rank individuals based on their susceptibility to developing a condition. However, it is unclear the effect of schizophrenia PGS on positive psychotic symptoms and violence and aggression in cannabis-associated psychosis.
**Methods:** We analysed data from two incidence studies. In the multinational 'European Network of National Schizophrenia Networks Studying Gene-Environment Interactions' study we estimated transdiagnostic dimensions of psychotic symptoms (N=617 FEP patients) and experiences (N=979 controls) using item response bi-factor modelling in FEP and population controls and built individuals' schizophrenia PGS across 16 urban and non-urban setting across 6 countries. We used linear regression to compute the combined effect of PGS and cannabis use on the dimensions of positive psychotic symptoms and experiences.
In the 'Changes in psychosis incidence in South London' study (N=3,500 FEP patients), we used logistic regression to estimate the effect of different socio environmental predictors on the likelihood of being admitted to a psychiatric intensive care unit (PICU) at First-Episode of Psychosis and of having an episode of seclusion (supervised confinement) due to violence and aggression during the PICU admission.

**Results:** The EU-GEI study showed associations between SZ-PRS and the positive symptom dimension in FEP patients (B = 0.19; 95%CI 0.03 to 0.35) and controls (B = 0.14; 95%CI 0.03 to 0.26). Daily and current cannabis use was associated with the positive dimensions in FEP (B = 0.31; 95%CI 0.11–0.52) and controls (B = 0.26; 95%CI 0.06–0.46), over and above

SZ-PRS. There was no interaction between these two terms in the model. The 'Changes in psychosis incidence in South London' study showed that the use of cannabis was the stronger predictor for being admitted to PICU at FEP (OR=2.87; 95%CI 2.08 to 3.96). We further found that cannabis use was associated with a higher likelihood of having an episode of seclusion during admission (OR=2.51; 95%CI 1.59 to 4.56).
**Conclusions:** Our studies suggest that cannabis use correlated with more severe psychosis presentation, conferring risk to positive symptomatology beyond the genetic liability to schizophrenia and conferring risk to having a PICU admission and spending time in seclusion. Our findings further support that cannabis use is associated with psychotic experiences in the general population, and these experiences have similar genetic substrates as clinical disorders. Overall, our findings highlight the utility of population genetics for examining gene-environment interaction. It finally demonstrates that exposure to one factor may add complexity to presentations so that positive symptoms and aggressivity cluster in the context of cannabis use at FEP.

### 29.2 Childhood Adversity and Syndemic Effects on Psychosis

Yamin Zhang*[1], Jeremy Coid[2]

[1]*Affiliated Mental Health Center, Zhejiang University School of Medicine,* [2]*Queen Mary University of London*

**Background:** Psychosis and other mental disorders are more common among populations experiencing social inequalities and exclusion. These populations experience more child adversity which is thought to impact brain development. It is unclear why some exposed individuals experience psychotic symptoms and others do not. The study investigated whether a syndemic explained a psychotic outcome, determined by child adversity.
**Methods:** Self-reported cross-sectional surveys in different sites and populations of 7,461 British men. Latent class (LC) analysis to identify categorical psychopathological outcomes. LCs were then tested by interaction analysis between syndemic factors of substance misuse (SM), violence/criminality (VC), and risky sexual behavior (SH) derived from confirmatory factor analysis according to childhood adversity. Pathways analysis using partial least squares path modeling.
**Results:** A 4-class model with excellent fit identified an LC with both psychotic and anxiety symptoms. A syndemic model of joint effects adducing a three-component latent variable of SM, SH, and VC showed synergy between these components and explained the psychotic outcome, differentiating it from other, common mental disorders. There were significant interactions on the multiplicative scale specific to the psychosis outcome: SM X SH, SH X VC, SM X VC; and on the additive scale SM X SH.
**Conclusions:** Multiplicative synergistic interactions between SM, SH, and VC were a mechanism that determined a psychotic outcome, but not for other common mental disorders This was specific to men who had experienced childhood adversity along indirect pathways involving the syndemic. A small subgroup also showed a direct pathway. Population interventions should target SM and VC in adulthood, but preventing child adversity should be the primary public health strategy.

### 29.3 Syndemic Localization: Psychosis and Geo-Demographic Classification in Hackney, East London

Jeremy Coid*[1]

[1]*Queen Mary University of London*

**Background:** Singer argued that Syndemics are localised in areas where large-scale social forces beyond the control of the local population give rise to co-occurring epidemics that synergistically interact to adversely affect health. This preliminary study in the London Borough of Hackney, UK, questioned whether housing policy constituted one key social determinant. It tested whether the incidence of psychosis among men and women measured at a small area level was associated with self-reported psychotic symptoms among young men a decade later.
**Methods:** 147 First episode cases in Hackney over 2 years, 1996-98; 115 (78.2%) non-affective, 32 (21.8%) affective psychosis. Young men's Health and Modern Lifestyles survey, random location sampling, 822 men 18-34 years, self-reported psychotic symptoms using PSQ, sampled in 2011. Measures: Index of multiple deprivations, income, employment, health deprivation education, skills training, crime, and living environment. ACORN classification of residential neighbourhoods. Adjusted multivariate associations to investigate independent relationships between psychotic disorders and reported psychotic symptoms a decade later, at small area level and according to housing type.
**Results:** The same neighbourhood areas with a high incidence of psychosis in 1996-1998 generated a higher prevalence of psychotic symptoms reported by male residents in 2011. Of 56 potential ACORN types, psychosis measures were higher among persons renting types specifically designated: multi-ethnic, young, converted flats; multi-ethnic, purpose-built estates; multi-ethnic, crowded flats. Social deprivation was not associated with psychosis after adjustment.
**Conclusions:** Persons with multiple social and health problems were concentrated into a small range of housing types rented from private landlords but mainly from the local government authority. These are characterised by overcrowding, dampness, and lack of repairs. Residents are insecure with little or no choice in their housing. Syndemic factors include concentrated childhood disadvantage, relationship breakdowns, criminality, and substance misuse. A substantial number move home each year.

## 29.4 The Association Between Drug Use and Violence and Aggression in Psychiatric Intensive Care

Giovanni Martinotti*[1], Diego Quattrone[2]

[1]*University "G.d'Annunzio" of Chieti-Pescara,* [2]*MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London*

**Background:** The use of drugs is associated with violence and aggression in both the general population and individuals with a psychiatric disorder. In the United Kingdom, a high acute risk of violence and aggression in psychiatric patients is managed in Psychiatric Intensive Care Units (PICUs). There is scarce evidence on the extent to which the different type of drugs are associated with the level of violence in PICU as well as their psychoplastic effects.
**Methods:** We screened clinical records of all individuals living in the London boroughs of Southwark, Lambeth, Lewisham, and Croydon who were admitted to Psychiatric Intensive Care Units (PICUs) between 2018 and 2024. We collected data on their pattern of drug use and psychopathology at and during the admission using the Operational Criteria Checklist for Psychotic Illness (OPCRIT) and pattern of violence and aggression using the Modified Overt Aggression Scale (MOAS). We used regression modelling to examine the association

between the different types of drugs and psychopathology and violence and aggression outcomes.
**Results:** N=1,200 individuals had at least one admission to PICU within the time frame, and the boroughs under investigation. There was a positive association between the overall use of drugs and the score at the MOAS, with amphetamines accounting for the strongest effect size. Moreover, specific type of drugs were correlated with one particular psychopathology pattern and its variation during the admission.
**Conclusions:** The use of drugs is a predictor of violence and aggression during PICU admission and account for different patterns of psychopathology.

**30. From Evidence to Practice: Schizophrenia as a Model for Knowledge Translation in Medicine**

Heidi Taipale*, Niuvanniemi Hospital, University of Eastern Finland*

**Overall Symposia Abstract:** From evidence to practice: schizophrenia as a model for knowledge translation in medicine.

Background:

Schizophrenia presents significant challenges to both patients and healthcare systems, and the process of translating scientific evidence into effective clinical practice remains a critical area of focus. Knowledge translation (KT) provides the framework for ensuring that research findings are effectively applied in clinical settings, addressing gaps between evidence and everyday care. This symposium, "From Evidence to Practice: Schizophrenia as a Model for Knowledge Translation in Medicine," will explore the cycle of KT in schizophrenia, featuring four presentations that span from experimental research to real-world applications.

The symposium will focus on the cycle of evidence from key KT challenges and strategies, including the role of platform randomized controlled trials (RCTs), comprehensive reviews of schizophrenia treatments, the importance of lived experience in shaping care, and the development and implementation of treatment guidelines. By examining schizophrenia as a case study for KT, this symposium offers valuable insights into the broader application of KT frameworks in medicine.

Method:

The symposium will address key KT challenges and strategies, including the role of randomized controlled trials (RCTs) platform, a living systematic literature review framework with associated online tools to fill the gap between evidence and clinical care and inform evidence-based treatment of schizophrenia, the integration of lived and living experiences into research, knowledge translation, and clinical guideline making with also digital tools associated with guidelines. By examining these elements, the presentations will illustrate how evidence can be effectively generated, synthesized, and translated into clinical

practice, ultimately aiming to improve treatment personalization and efficacy for individuals with schizophrenia.

Conclusion:

This symposium will provide a multi-phase view of translational medicine and KT in schizophrenia care, covering the journey from generating high-quality evidence through platform RCTs, to synthesizing and updating this evidence with umbrella reviews, to integrating patient perspectives and ensuring that guidelines are effectively evidence-based and co-designed with persons with living experience. By showcasing the complexities and opportunities within the KT process, these presentations will offer attendees practical strategies to enhance the translation of evidence into practice, ultimately improving outcomes for individuals with schizophrenia.

**30.1 Evidence-Based Interventions for Schizophrenia (EBI-SCZ): A Novel Living Umbrella Review, Evaluation, Analysis and Communication Hub (U-Reach) Approach**

Marco Solmi*[1], Ana Catalan[2]

[1]*University of Ottawa,* [2]*Basurto University Hospital*

**Background:** Schizophrenia is often a severe and chronic mental disorder that is associated with high rates of health service use, hospitalization, homelessness, unemployment, morbidity and mortality. Evidence from population-based data is crucial to improving clinical care and outcomes. Several (network) meta-analyses ((N)MAs) of randomized controlled trials (RCTs) are published every year on the treatment of schizophrenia (SCZ). However, policymakers, clinicians, and persons with lived experience often lack the resources, time, or expertise to systematically review the literature, making it challenging to inform evidence-based clinical care and guidelines and improve outcomes for people with schizophrenia.
**Methods:** We are conducting a living umbrella review (UR) following the Umbrella Review, Evaluation, Analysis, and Communication Hub (U-REACH) framework. This involves systematically searching multiple databases, along with a manual search, to identify pairwise and network meta-analyses of randomized controlled trials (RCTs) focused on schizophrenia treatment, or on treatment of schizophrenia side effects. Two reviewers are independently screening the literature and extracting data in duplicate, capturing key variables such as age group, schizophrenia phase, interventions, controls, and outcomes. We are assessing the quality of the NMAs using the AMSTAR 2 tool and evaluating the credibility of the evidence with the GRADE approach. To ensure transparency and collaboration, we are developing an online platform in partnership with various stakeholders, following open science principles.
**Results:** We will present results: from the living umbrella review, and the associated online platform, Evidence-Based Interventions - Schizophrenia (EBI-SCZ), which will provide links to psychoeducation material on schizophrenia and make all MA evidence on schizophrenia freely available to various stakeholders. EBI-SCZ is offering a filtering panel that allows users to distill only the evidence of interest from the vast amount of data, and it includes visualization tools to help translate data into actionable information for clinical practice. A clinician-facing preference tool will also be presented, and its features compared with other

existing tools will be discussed. EBI-SCZ will inform regular updated of international guidelines for the treatment of schizophrenia.
**Conclusions:** EBI-SCZ will make all meta-analytic evidence on the treatment of SCZ and its treatment side effects publicly available, and is collaborating with international guideline makers to complement guidelines and associated digital tools with a transparent evidence repository following open science principles. U-REACH is a unique platform aiming to become the global reference hub for updated evidence synthesis, with EBI-SCZ being the first focused on the evidence on schizophrenia treatment. Several other U-REACH platforms across different conditions are already available, and more transdiagnostic platforms are currently being developed and expanded with a variety of digital tools designed to meet interest-holders needs on a disease-by-disease fashion.

### 30.2 Schizophrenia Platform for Improving Recovery With Integrated Trials (S.P.I.R.I.T.)

Dan Siskind*[1]

[1]*University of Queensland*

**Background:** Adaptive platform trials, demonstrated extremely successfully in other health domains like COVID-19, streamline evidence generation by addressing multiple questions rapidly and much more efficiently. Platform trials offer an efficient approach, by using one standardised control arm, while comparing outcomes across multiple parallel treatment arms. Throughout the trial, predefined interim analyses assess the viability of treatment arms, informing whether treatment arms should be terminated early and facilitating enrolment of participants to more promising treatment arms, or to newly added treatment arms. This optimised use of control data reduces the overall sample size required, minimising recruitment time and resource expenditure compared to traditional individual RCTs. This design has promise for trials among people with schizophrenia.
**Methods:** Rather than 'intervention focused', our platform is 'schizophrenia focused' and uses adaptive randomisation techniques to simultaneously evaluate multiple interventions, generate separate effects across subgroups, and minimise trial downtime. A Master Protocol has been established to guide all trial operations, focusing on four core health domains identified through consumer consultation for treating schizophrenia. Domain-specific primary outcomes are defined: Cardiometabolic (weight), Psychotic symptoms (PANSS), Cognition (BACS), and Social functioning (SF-36). An integrated, cloud-based data management system will be implemented for secure, standardized data collection and automated quality control. A Bayesian statistical framework will be used for data analysis, incorporating prior knowledge for a comprehensive assessment of treatment efficacy. Interim analyses will allow for modifications such as dropping or introducing treatment arms based on predefined criteria.
**Results:** Our first SPIRIT platform trial randomisation is SWIFT (Schizophrenia Weight Improvement From Tirzepatide). This trial will compare tirzepatide (10mg subcutaneous, weekly) to placebo injections over 24 weeks among 108 people with schizophrenia on antipsychotic medications and obesity. The primary outcome will be change in body weight (percent). Secondary outcomes include changes in metabolic syndrome components, proportion of participants with > 5%, > 10% and > 15% loss of body weight, visceral/hepatic adiposity, cognition, quality of life and psychosis from baseline to 24 weeks. Early stopping will be non-binding, considered only once sufficient data has been accrued, and in consultation with the trial steering committee. Sufficient data will be defined as occurring

once 50% of participants have completed the trial. If future funding becomes available, we can add a new treatment arm, such as retatrutide.
**Conclusions:** Through the creation of world's first schizophrenia platform trial, we will improve the efficiency of clinical trials, with multiple interventions tested simultaneously against a single control group. As ineffective treatments within schizophrenia domains are identified, they can be dropped, and new interventions added without needing to start a new trial. This will lead to immediate consumer benefit, with a higher probability of receiving an effective treatment since there are multiple active treatment arms. Moreover, as ineffective treatments are dropped and effective ones are identified more quickly, patients benefit from better treatments sooner and more efficient treatment can be more rapidly translated into better health care for this population group.

### 30.3 Translating Research Into Practice in People With Psychosis: The Importance of the Lived Experience Voice

Asa Konradsson-Geuken*[1]

[1]*Uppsala Universitet*

**Background:** The integration of lived experience into psychosis research is vital for bridging the gap between research and effective clinical practice. Drawing from personal experience as a close relative to someone with psychosis, we emphasize the unique insights gained through the emotional and practical challenges of caregiving. These insights highlight the need for a more person-centered approach in mental health care.
**Methods:** In Sweden, the progressive inclusion of individuals with lived experience, both patients and relatives, in research and policy development sets a leading example. This model ensures that research outcomes are not only clinically valid but also resonate with the real-world experiences of those affected by psychosis. On a national level, the Swedish approach promotes a collaborative framework where patient voices help shape care systems, ultimately improving treatment outcomes and patient satisfaction.
**Results:** The result of integrating the experiences of patients and caregivers in psychosis research could lead to improved quality of care and more person-centered treatment. By elevating these voices in research, interventions can become more relevant to the real needs faced by patients and their families. At the national level, as seen in Sweden, this can foster more collaborative care systems with better treatment outcomes and patient satisfaction. Internationally, this model could inspire other countries to adopt similar approaches, enhancing global mental health care practices and ensuring that they are more empathetic and effective.
**Conclusions:** From an international perspective, this model serves as a blueprint for other nations aiming to enhance their mental health systems. Countries that actively incorporate lived experience into research, policy-making, and clinical practice are better equipped to address the complex needs of individuals with psychosis. By broadening the involvement of patients and relatives, the global mental health community can foster more inclusive and effective interventions, pushing the boundaries of traditional research frameworks and improving quality of care on a worldwide scale. By listening to and learning from those who live through these experiences, we can develop more empathetic, effective, and sustainable mental health care systems, both nationally and internationally.

### 30.4 Integrate: Developing an Algorithmic Global Guideline for Schizophrenia

Toby Pillinger*[1], Dan Siskind[2], Rob McCutcheon[3]

[1]*King's College London,* [2]*School of Medicine, The University of Queensland, Brisbane, MIRT, Woolloongabba Community Health Centre, Addiction and Mental Health Services and MIRT,* [3]*University of Oxford*

**Background:** Schizophrenia affects approximately 0.7% of the global population during their lifetime and imposes a significant healthcare burden worldwide. Effective treatments exist; however, pharmacological treatments are often associated with significant side-effect burden and delays in providing optimal treatment are common. Numerous guidelines exist regarding the treatment of schizophrenia. However, existing guidelines are typically lengthy, country-specific, and often lack an evidence-based algorithmic approach, which limits their use in clinical settings. A recent review highlighted these shortcomings, and also noted inadequate guidance on maintenance treatment duration and management of negative symptoms.
**Methods:** From May 2023, INTEGRATE (INTErnational Guidelines foR Algorithmic Treatment) authors from all United Nations regions collaborated to develop a consensus guideline for the pharmacological treatment of schizophrenia. Following an umbrella review of the literature, input from expert workshops, consensus survey, and lived experience focus groups, a consensus algorithmic guideline and associated digital tool were developed.
**Results:** Key recommendations include a focus on metabolic health from treatment initiation, timely assessment and management of non-response, symptom domain-specific interventions, mitigation of side-effects, and the prompt use of clozapine in cases of treatment resistance. Further details will be provided in the talk.
**Conclusions:** The treatment of individuals with schizophrenia is a central component of general psychiatric practice. Effective treatments exist, but maximising therapeutic effects requires a dynamic and flexible approach involving patients in decision-making.

## 31. Novel Approaches to Addressing Relapse in Psychosis: Combining Language Analysis and Neuroimaging to Identify Clinically Actionable Biomarkers

Jose Rubio*, Northwell Health*

**Overall Symposia Abstract:** Most patients with psychotic disorders relapse multiple times over the course of their illness. With each relapse, individuals may see their future response to treatment decrease, may be less likely to achieve recovery, and could put themselves or others at risk. Given the global trend towards less common use of maintenance treatment, mitigating the frequency and intensity of relapses becomes essential to improve long-term morbidity and mortality of psychotic disorders, a condition characterized by recovery rates of < 15% and about 15 years of shorter life expectancy. Most often relapses could have been easily avoided by continuing antipsychotic treatment, while in other cases deterioration may occur despite guaranteed treatment and early introduction of clozapine may be necessary. Additionally, other factors such as co-occurring substance use, psychosocial stressors, symptoms and function between episodes, and possibly brain response to chronic antipsychotic exposure may influence the risk of relapse. If such risk can be quantified for a given individual at any given moment, it might be possible to modify the course of illness through personalized secondary prevention. Indeed, there might be cognitive and neurophysiological signals that precede relapse and that could be used accordingly. Specifically, in this panel we will present novel data on how cognitive and neurophysiological information can be captured through natural language processing and neuroimaging techniques to develop clinically actionable biomarkers. Rubio will present unpublished data on the use of fMRI to predict symptom trajectory during guaranteed antipsychotic treatment with long acting injectables. Dazzan… . Homan will report on novel

and unpublished data showing baseline neurocomputational modeling of goal-directed and habitual decision making and its association with psychotic relapse. Sommer will share novel data on the predictive potential of quantitative speech and language markers recorded in a large cohort of FEP patients who discontinue medication. These talks highlight both unifying principles, and newly-discovered complexities on the identification of potentially clinically actionable biomarkers related to the risk of relapse. Conclusions: are relevant for both researchers and clinicians, as preventing relapse psychosis is an acute clinical priority for which we will provide new leads. The panel is 50% women, includes LGTBI representation, and participants from the US and abroad. It includes a range of experience, from Assistant to Full Professor, and includes the seating and elected President of the Schizophrenia International Research Society (SIRS). Methodologically, it spans from neuroimaging to natural language processing. We bring complementary sets of expertise contributing to advancing the field of clinically actionable biomarkers in relapse prediction and prevention.

## 31.1 Predictive Capacity of Functional Connectivity for Symptom Trajectories During Guaranteed Relapse-Prevention Treatment

Jose Rubio*[1]

[1]*Northwell Health*

**Background:** After initial treatment response, individuals with schizophrenia move to the relapse-prevention (or maintenance) phase of treatment with antipsychotic drugs. A major challenge to study this phase of treatment is that adherence with antipsychotic maintenance is very common yet uncertain at the individual level. Therefore, symptom trajectories during this phase are often confounded by non-adherence. To address this limitation, we study prospectively individuals who start relapse-prevention treatment with long-acting injectable (LAI) antipsychotics, for whom continuous treatment delivery is guaranteed.
**Methods:** 183 individuals with schizophrenia or schizoaffective disorder were recruited within 6 months of having started LAI treatment between 2017 and 2023. They were followed-up monthly and if still on LAI treatment after 12 weeks (n=54), they were scanned, and continued to be followed-up for one more year with monthly psychopathology assessments. Baseline scans (i.e., 12 weeks after study) included two 590 volume (TR=0.72) runs of resting state fMRI, which were used to generate functional connectivity matrices after a 300 x 300 parcellation of the brain. Scans underwent quality assurance (QA), with minimal QA thresholds for motion and artifacts. Individual symptom trajectories were calculated using a mixed model for repeated measures, in which random intercept and slopes were fitted for symptom ~ time, where symptoms were total psychopathology (BPRS), psychosis (BPRS psychosis subscore), negative symptoms (NSA), drug attitudes (DAI). Using this model, we predicted the individual symptom severity at one year after scan. Also, we used time to LAI discontinuation as an outcome. We applied linear ridge regression using k-fold cross validation to predict symptom trajectory and symptoms at one year after baseline scan using the connectivity matrices as predictive features with accuracy defined as correlation between predicted and observed scores in the k folds not used for model development.
**Results:** n=45 participants fulfilled QA criteria and were entered in the analyses. N=29 (64%) of participants were men, mean age 29.88 (9.56), n=10 (22.2%) were white race. At the time of the scan, mean BPRS was 32.95 (9.60), psychosis subscore was 8.30 (4.63), NSA was 3.03 (1.46), DAI was 2.51 (2.47); and at one year the change was for BPRS .97 (8.03), for psychosis subscore .44 (3.61), for NSA .58 (0.67), and for DAI -.34 (0.39). Median time

to LAI discontinuation was 250 days. Our predictive model model using features from the connectome had accuracy of r=.16 for the random slope of negative symptoms and r=.25 for predicted scores at one year, r=.14 for the random slope of DAI scores and r=.15 for predicted DAI scores at one year, and r=.12 for time to treatment discontinuation. Prediction of total and positive symptom trajectory was not significant.
**Conclusions:** Using a paradigm that removes the confounder of non-adherence during the relapse-prevention phase of treatment, resting state functional connectivity shows promise in predicting the trajectory of symptoms that are relevant for the course of illness. While positive and total symptom trajectories were not directly predicted by baseline scans, relevant phenomena such as time to treatment discontinuation and attitudes towards antipsychotic treatment were. Future studies should examine the ability of cognitive, in addition to neuroimaging features, in predicting treatment discontinuation and attitudes towards antipsychotics, which account for most of the variance in relapse in schizophrenia.

## 31.2 The Neuromorphological Correlates of Treatment Response Following the First Psychotic Episode: The Need for new Approaches

Paola Dazzan*[1]

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

**Background:** Over the last 40 years hundreds of neuroimaging studies have investigated the brain morphological and functional correlates of psychosis risk and outcome. Unfortunately, these studies have not contributed to the development of a personalized medicine approach for those individuals with a diagnosis of schizophrenia.
**Methods:** We used a semi-supervised method to replicate two neuromorphological subtypes previously identified in chronic schizophrenia in 572 individuals with first episode psychosis. We used a multi-group machine learning analysis with nested cross-validation design to investigate baseline clinical signatures separating the subtypes. In a second study, we applied cortical thickness normative modelling to 320 first-episode psychosis individuals, to quantify heterogeneity and to predict symptoms and response to antipsychotic medication using cortical atypicality from baseline up to 95 weeks (median follow-ups = 4).
**Results:** Clinical multivariate signatures separated two morphological subgroups (balanced accuracy = 64%; $p < 0.0001$), and the group with only higher striatal volume was more likely to show symptom remission at 1- and 5-year. Two dominant patterns of 'lower brain volume' and 'higher striatal volume' (with otherwise normal neuromorphology) were already present at first episode psychosis. Individuals with only higher striatal volume showed higher education and higher likelihood of symptom remission at 1-year and 5-year.

No more than 6.4% of patients had extreme deviations in a single brain region, and linear mixed-effects modelling showed that negative deviations in cortical thickness in parietal and temporal regions at baseline were related to more severe negative symptoms at follow up.

**Conclusions:** Moving from traditional correlational or cross-sectional analytical approaches to new analytical pipelines could help disentangle this heterogeneity. Moving the field forward, the findings of these studies have shown that different neuromorphological subtypes of psychosis associated with specific outcome profiles can be identified, and that neuroimaging normative models can be applied to psychosis to make individualized predictions of outcome.

**31.3 Shifts in Reinforcement Learning and Their Association With Psychotic Relapse**

Wolfgang Omlor[1], Giacomo Cecere[1], Philipp Homan*[2]

[1]*University Hospital of Psychiatry/University of Zurich,* [2]*University of Zurich*

**Background:** The early phase is critical in the trajectory of psychotic disorders, with frequent relapses contributing to worse long-term outcomes. We focused on neurocognitive deficits in reinforcement learning, and hypothesized that individuals with psychotic disorders would show lower rates of goal-directed vs. habitual learning, and dorsal cognitive striatal connectivity compared to neurotypical individuals. We further hypothesized that these neurocognitive effects would be associated with higher rates of psychotic relapse.
**Methods:** The STRICON study involved 50 medicated individuals (mean age = 26.9 years; 24% females) during the early phase (defined as a maximum cumulative exposure to antipsychotics of < 2 years) of psychotic disorders (defined as schizophrenia, schizophreniform disorder, psychotic disorder not otherwise specified, and schizoaffective disorder) and 50 age- and sex-matched neurotypical individuals. All individuals underwent a two-step reinforcement learning task during fMRI, and patients were followed-up for a year. Relapse was defined as re-hospitalization during follow-up.
**Results:** We found a shift towards more habitual vs. goal-directed learning in individuals with psychotic disorders compared to neurotypical individuals (difference = 0.41; t (98) t = 11.84; P < 0.001) and lower functional connectivity between the dorsolateral caudate and the dorsolateral prefrontal cortex (pFWE < 0.05). Surprisingly, individuals with and without relapse did not show marked differences in reinforcement learning (difference = 0.02; t (48) = 0.56; P = 0.58), but did show a positive association between higher rates of model-free reinforcement learning with time to relapse (r = 0.34; P < 0.05), suggesting that individuals with psychotic disorder with higher rates of model-free learning relapsed later than those with lower rates of model-free learning.
**Conclusions:** This study found a marked shift from goal-directed towards habitual reinforcement learning in early phase psychosis that was accompanied by lower functional connectivity in the dorsal cognitive circuit. Surprisingly, this shift was predictive of longer time until relapse during a one-year follow up, suggesting that habitual learning may have protective effects during remission.

**31.4 Risk of Relapse During Tapering of Antipsychotic Medication: The Effect of Tapering Speed and Dopamine D2 Affinity**

Shiral Gangadin[1], Franciska de Beer[1], Ben Wijnen[2], Marieke Begemann[3], Nico J. van Beveren[4], Nynke Boonstra[5], Lieuwe de Haan[6], Martijn Kikkert[7], Wim Veling[2], Sanne Schuite-Koops[1], Iris Sommer*[1]

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**Background:** While antipsychotic maintenance treatment effectively prevents psychotic relapse after a first episode psychosis (FEP), many remitted antipsychotic users wish to taper their medication due to side-effects, long-term health concerns, stigma, or the desire to regain autonomy. Current guidelines for safe tapering of antipsychotics emphasize that discontinuation should be gradual and with decreasing dose-reduction steps as the dosage approaches zero (i.e. hyperbolic dose reduction). It is not clear exactly how slow the tapering

speed should be, especially in first episode patients who have used medication for < a year. Furthermore, to prevent dopamine supersensitivity, dopamine D2 affinity of the antipsychotic drug is also an important factor, which has hardly been studied. To better understand the effects of both tapering speed and dopamine affinity, this study examines relapse risk and time to relapse in 228 persons with FEP who taper antipsychotic medication over an 18-month period after remission.
**Methods:** Relapse was defined using consensus criteria on basis of the Positive and Negative Syndrome Scale, including hospitalization for psychosis and explicit clinical judgement of the treating clinician. Antipsychotic use was based on data from the Dutch Foundation for Pharmaceutical Statistics (SFK) and self-reports. Tapering speed (in daily olanzapine equivalents/day) was calculated as the difference of antipsychotic dose at the start and end of tapering, divided by the number of days in between. Clinicians were provided with tapering schedules facilitating hyperbolic dose reduction over 3-6 months, but the actual tapering speed and the final dose varied as a result of participants and clinician preferences. Antipsychotics were categorized into partial agonists (e.g. aripiprazole), or antagonists with high (e.g. risperidone) or low D2 affinity (e.g. olanzapine). Logistic and Cox proportional hazards regression analyses were controlled for age, sex, cannabis use and duration of FEP, and for differences in clinical and sociodemographic characteristics between dopamine affinity groups using inverse probability of treatment weighting.
**Results:** Within 18 months, 45.6% (n=104) experienced a relapse after antipsychotic dose reduction or complete discontinuation. The average tapering speed was 10 mg/day olanzapine over 75 days, with an average tapering duration of 124 days, ranging from 7 to 312 days. Logistic regression analysis showed that the tapering speed did not predict the risk of relapse (p=0.323). Users of high D2 affinity antagonists (n=57) had a higher risk of relapse compared to those using low D2 affinity antagonists (n=117) (p=0.035) and compared to partial agonists users (n=54) (p=0.023). Users of high D2 affinity antagonists had a shorter time between the end of tapering and relapse than low affinity antagonist users (p=0.026) and partial agonist users (p=0.036).
**Conclusions:** In this group of relatively well-functioning and closely monitored individuals in remission from a FEP, dopamine D2 affinity of the antipsychotic was more important in predicting psychotic relapse risk than tapering speed. Users of high D2 affinity antipsychotics were at higher risk of relapse compared to those using other types of medication. This higher risk for relapse after tapering can be a relevant factor when selecting an antipsychotic drug for people with a first psychosis. For FEP patients already stabilized with strong D2 antagonists, extra monitoring during tapering is warranted.

### 32. Psychedelics and Psychosis: Ethical, Research and Clinical Implications of a Complex Relationship

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

**Overall Symposia Abstract:** This is the official symposium submission of the SIRS Ethics Committee. The symposium examines the ethical, research and clinical dimensions of the complex relationship between psychedelics and psychosis. Psychedelics, such as psilocybin, LSD, and DMT, have shown promise in treating various mental health conditions, including depression and PTSD. However, their impact on psychosis remains a critical area of concern. From an ethical perspective, the use of psychedelics in research and clinical settings raises questions about safety, informed consent, and the potential for inducing or exacerbating psychotic episodes, especially in vulnerable populations. It is crucial to establish stringent protocols to protect individuals predisposed to psychosis, as these substances can trigger

psychotic symptoms in those with genetic or environmental risk factors. Research-wise, studies indicate that while psychedelics can modulate brain networks involved in perception, mood, and cognition, their effect on individuals with or at risk of psychosis is unpredictable. The therapeutic potential of psychedelics in psychosis treatment, such as addressing negative symptoms of schizophrenia, remains largely unexplored due to these risks. Clinically, careful patient selection, thorough screening, and close monitoring are essential when considering psychedelics as part of therapy, given the potential for severe and lasting adverse effects. The proposed symposium includes 4 experts on the topics that will present the outline of an ethically-informed approach in research and clinical application, balancing the potential benefits against the risks to ensure patient safety and well-being.

**32.1 Psychedelic use in Individuals With Psychotic Experiences**

Joseph La Torre[1], Jade Gallo*[2]

[1]*University of Washington School of Medicine,* [2]*Columbia University*

**Background:** Historically, individuals with psychotic disorders have been excluded from psychedelic-assisted therapy (PAT) research, largely due to concerns about potential adverse effects. This study explores psychedelic use among individuals with psychotic experiences or diagnoses (n = 100) to assess the benefits and risks. Participants completed a retrospective survey detailing their mental health, psychedelic use, and the impact of a memorable psychedelic experience on well-being, relationships, and spirituality. Thematic analysis revealed that most participants (88%) reported personal growth, improved insight, mystical experiences, and enhanced emotional well-being. However, 11% reported negative outcomes, including symptom exacerbation and dysphoria. These findings suggest a spectrum of experiences in this population, raising important questions about the exclusion of psychotic individuals from PAT research and the potential benefits with proper protocols. Further research is needed to determine the benefit-to-risk ratio of psychedelics for this group.
**Methods:** This study employed a mixed-method, cross-sectional, retrospective survey design to explore the effects of psychedelic use in individuals with psychotic experiences or diagnoses. Participants (n = 100) were recruited through online platforms, including Reddit, and completed a comprehensive survey via Qualtrics. The survey collected demographic data, mental health histories, details of psychedelic use (such as substance type, dose, and set and setting), and the impact of a specific memorable psychedelic experience. Qualitative data were analyzed using inductive thematic analysis to identify recurring themes, while supplemental quantitative data provided insights into patterns of personal growth, mystical experiences, and psychological changes. The study aimed to assess both positive and negative outcomes to better understand the risks and potential benefits of psychedelic use for this population.
**Results:** The study revealed a wide range of outcomes from psychedelic use in individuals with psychotic experiences or diagnoses. A majority (88%) of participants reported positive effects, including personal growth, enhanced insight, mystical experiences, improved emotional well-being, and increased spiritual contemplation. Specifically, 67% noted a deepening of spirituality, while 51% reported better understanding of past traumas. Additionally, 60% reported experiencing increased appreciation for life and relationships.

However, 11% of participants described negative outcomes, such as exacerbation of symptoms, dysphoria, and terror. A small portion also reported mixed experiences, featuring both positive and distressing elements. These findings suggest that while most individuals experienced beneficial effects, a subset faced challenges, highlighting the complexity of psychedelic use in this population and the need for further research to assess risks and optimize treatment protocols.

**Conclusions:** This study offers important insights into the experiences of individuals with psychotic disorders or symptoms using psychedelics, a population typically excluded from clinical research. The findings suggest that, under certain conditions, many individuals with psychotic experiences report personal growth, improved mental health, and enhanced spirituality following psychedelic use. These positive outcomes challenge the blanket exclusion of this group from psychedelic-assisted therapy (PAT) research, suggesting that certain individuals may benefit when appropriate safeguards and therapeutic frameworks are in place.

Results: The results suggest that, while there may be a potential for therapeutic benefit in individuals with psychotic conditions, these treatments should be approached with caution. More controlled research is needed to fully assess the safety, efficacy, and long-term impacts of psychedelic use in this group, with a focus on developing protocols that mitigate risks and enhance positive outcomes. This study also raises important ethical considerations around the exclusion of vulnerable populations from emerging psychedelic therapies, particularly as it affects marginalized groups disproportionately diagnosed with psychotic disorders.

### 32.2 Safety Considerations for Psychedelic Assisted Psychotherapy (PAP)

Susan Rossell*[1]

[1]*Swinburne University*

**Background:** There has been a recent surge of interest in the field of psychedelic research, especially with regards to the therapeutic properties of these compounds. This has led to the emergence of psychedelic assisted psychotherapy (PAP). PAP has begun to show promise for a range of mental health conditions, including major depressive disorder and PTSD, leading to (perhaps premature) international changes in scheduling and regulatory policies in relation to psychedelics. This presentation will present the specific safely and ethical factors that need to be considered when engaging in either PAP research, or its implementation into clinical practice.
**Methods:** A review of relevant literature will be presented. This will be supplemented with specific case-examples and evidence from my own extensive experience conducting clinical trials with a range of psychedelic compounds (psilocybin, methylone, DMT).
**Results:** We currently have a state of play where researchers and clinicians alike have been raising ethical concerns with regards to PAP. The specific issues that will be discussed will include: I) the key challenge of heightened expectations regarding the supposed transformative effects of these drugs, II) the unescapable unblinding in clinical trials, III) the challenges of informed consent, IV) minimising conflicts of interest and grandiosity, V) risks of problematic interpersonal dynamics, and vi) the complexities of the underground movement in this space. A final critical issue that will be given careful consideration is the

processes that are involved in screening and eligibility when reviewing who is or is not suitable for PAP.
**Conclusions:** To assure the safe and ethically responsible clinical administration of psychedelics, we need to develop, obtain consensus for, and disseminate rigorous ethical and practice standards. There are not yet globally endorsed standards, but there is initial work in this space that has highlighted important factors that we need to pay attention to. Further research, and continued conversation, are required to refine our best practices with this regard.

### 32.3 Psychedelics as Models for Psychosis

Philip Corlett*[1]

[1]*Yale University*

**Background:** Since 2016, psychedelic science – particularly with human participants – has undergone a rambunctious revival. Studies administering psilocybin and lysergic-acid-diethlyemide (LSD) to healthy volunteers undergoing functional magnetic resonance imaging promised insights into the mechanisms of consciousness. Psychedelic psychotherapy studies have shown promise in people with affective and addictive disorders. It seems prudent to take stock of the current status of psychedelic research, its past, and its possible futures. We focus here on the impact of psychedelics on beliefs, since this work encapsulates many of the challenges and promises of psychedelic science. I will consider whether and how psychedelics change human beliefs, with a particular focus on how these compounds induce experiences and beliefs that are redolent of hallucinations and delusions.
**Methods:** I will review studies of the phenomenology, psychology, and underlying neurobiology of the acute and persistent effects of these psychotomimetic drugs.
**Results:** Acute intoxication with psychedelics induces simple and complex visual hallucinations. The longer-term effects of these mystical psychedelic experiences on beliefs remain unclear. These possible long-lasting effects – beyond acute intoxication – have long been the subject of a moral panic. Do psychedelics induce a persistent psychotic state, characterized by uninvited and frightening flashbacks? The answer is certainly not uniformly. Although in some individuals (typically not those who volunteer for controlled clinical studies, who are pre-screened for safety, but rather those using recreationally) a persistent hallucinatory persistent perceptual disorder (HPPD) does occur. It comprises simple, often geometric, visual hallucinations (Type I), sometimes with accompanying distress (Type II). These persistent visual hallucinations suggest that new perceptual prior beliefs are created by the psychedelic experience and sustained outside of the acute drug context. Since they do not typically invite narrative Conclusions: about alternate realities or alien agents, HPPD experiences do not appear to alter propositional beliefs. Indeed, much like the hallucinations that occur in neurological illnesses, most people with HPPD retain insight into the unreality of their hallucinations. That being said, many people who self-administer, or who experience psychedelics in a clinical research context, do consider their experiences intensely spiritual and/or mystical. It appears that sense of spirituality transcends the acute drug experience for many (although not all) participants, for at least a number of months after the index experience.
**Conclusions:** Baseline beliefs and expectations color the psychedelic experience - to the point where no drug exposure may even be necessary to induce them. Given that people with a history of psychosis have been excluded from contemporary clinical trials, I suggest caution regarding proposals to explore psychedelic therapy for psychotic disorders. However, I also acknowledge that placebo and suggestion effects appear attenuated in participants with

schizophrenia, there may be grounds to explore the possibilities further. That being said, the psychedelic renaissance is recent and marred by poor quality studies and hype. Much more basic science is warranted with these compounds before the risks and benefits can be accurately assessed.

### 32.4 Can Computational Modeling Help Identifying Patients With Psychotic Spectrum Disorders who Could Benefit From Serotonergic Agonist add-on Therapy?

Renaud Jardri*[1], Pantelis Leptourgos[2]

[1]*Lille University Medical Centre,* [2]*Group for Neural Theory, DEC, ENS, Paris, France*

**Background:** In this presentation, we will introduce a hierarchical Bayesian model (i.e. circular inference) that has been proposed to account for aberrant percepts or beliefs in a variety of contexts, ranging from hallucinations in schizophrenia to distorted perceptions under the influence of psychedelics.
**Methods:** In particular, we will present a theoretical canonical microcircuit implementing Circular Inference. We will argue that different perceptual aberrant phenomena can emerge from at least two different types of inference loops.
**Results:** Based on simulations, we argue that control of these loops relies on inhibitory neurons located in different cortical layers that interact differently with dopaminergic and serotonergic pathways.
**Conclusions:** We will discuss the possibility of using this framework to further develop computational assays capable of identifying candidates with psychotic manifestations who could benefit from 5HT2a-R agonist therapies.

### 33. Environmental Risk Factors in Early Psychosis: Investigating Divergent and Convergent Psychosocial Pathways

Benson Ku*, Emory University School of Medicine*

**Overall Symposia Abstract:** Schizophrenia spectrum disorder is impacted by various environmental factors early in development, which are quantifiable with subjective (i.e., self-report) and objective (area-level estimates from living addresses) methods. However, these methods are often investigated in isolation, and the mechanisms of these associations are often unclear. Therefore, it is important to investigate how these environmental factors may interact (e.g., social stressors and air pollutants) and lead to specific symptoms. However, there are challenges to investigating these complex environmental risk factors: longitudinal assessments of environmental exposure and phenotype are often lacking, highly correlated exposures are difficult to tease apart, and mechanisms underlying environmental risk factors for psychosis are often unexplored. Our symposium will address these challenges and feature novel— yet-to-be-published—studies with novel methods and study designs applied to diverse datasets across different counties.

Benson Ku will discuss long-term trajectories of distressing psychotic-like experiences (PLE) and their associations with the neighborhood exposome. He will present unpublished findings from a large cohort, age-range of 9-10 years, the Adolescent Brain Cognitive Development. He used machine learning methods to cluster neighborhoods and found that neighborhoods characterized by rural areas with low walkability and urban areas with high socioeconomic deprivation, air pollutants, and crime were associated with PLE with different psychosocial pathways.

Lan Zhou will present on the complex interrelationships between childhood trauma, psychosocial factors, premorbid functioning, and clinical symptoms using a network analysis approach from the HAMLETT study, a large Dutch cohort clinical trial focused on first-episode psychosis (FEP). Her findings reveal that different types of childhood trauma, such as neglect and abuse, have distinct connections with psychosocial functioning. These insights suggest potential targets for early intervention strategies to promote recovery in FEP patients.

Giuseppe D'Andrea will present data from the EU-GEI study showing the intertwining of a measure of subclinical psychosis in the general population and the incidence of clinical-threshold psychotic disorders within the same time span and geographic areas. Furthermore, by providing evidence of similar effects of urbanicity on subclinical psychosis and full-blown psychotic disorders, he will reinforce the hypothesis of shared effects of contextual factors on phenotypes of psychosis spectrum disorders among the population, from subthreshold symptoms to threshold disorders.

Edoardo Spinazzola will discuss the association between heavy cannabis use and subthreshold paranoia, anxiety, and depression in a general population sample, using data from the Cannabis and Me (CAMe) online survey—the largest independent study in the UK on the effects of cannabis use. He found that greater frequency of cannabis use is associated with higher levels of psychotic symptoms (ideas of persecution > ideas of reference), anxiety, and depression. His findings also suggest the lasting mental health effects in people with former cannabis use, even after cessation.

Prof. Murray will summarize and discuss the key findings, and implications of these findings for clinical translation and future studies of environmental risk factors for psychosis.

**33.1 Neighborhood Exposome and Persistent Distressing Psychotic-Like Experiences Across Four Years Among Young Adolescents in the US**

Benson Ku[1], Emerald Yuan[2], Grace Christensen[2], Lina Dimitrov[2], Benjamin Risk[2], Anke Huels[2], Qingyue Yuan*[2]

[1]*Emory University School of Medicine,* [2]*Emory University*

**Background:** Recent research has demonstrated that domains of social determinants of health (SDOH) (e.g., air pollution and social context) are associated with psychosis. However, SDOHs have often been studied in isolation. This study investigated distinct exposure profiles, estimated their associations with persistent distressing psychotic-like experiences (PLE), and evaluated whether involvement with physical activities partially explains this association.
**Methods:** Analyses included 8,145 young adolescents from the Adolescent Brain and Cognitive Development Study. Data from baseline and three follow-ups were included. Area-level geocoded variables spanning various domains of SDOH, including socioeconomic

status, education, crime, built environment, social context, and crime, were clustered using a self-organizing map method to identify exposure profiles. Generalized linear mixed modeling tested the association between exposure profiles and persistent distressing PLE and physical activities (i.e., team and individual sports), adjusting for individual-level covariates including age, sex, race/ethnicity, highest level of parent education, family-relatedness, and study sites.
**Results:** Five exposure profiles were identified. Compared to the reference Profile 1 (suburban affluent areas), Profile 3 (rural areas with low walkability and high ozone) and Profile 4 (urban areas with high SES deprivation, high crime, and high pollution) were associated with persistent distressing PLE. Team sports mediated 6.14% of the association for Profile 3.
**Conclusions:** This study found that neighborhoods characterized by rural areas with low walkability and urban areas with high socioeconomic deprivation, air pollutants, and crime were associated with persistent distressing PLE. Findings suggest that various social-environmental factors may impact the development of psychosis through different psychosocial pathways.

### 33.2 Geographic Variation of Subclinical Psychosis and its Relationship With Incidence of Threshold Clinical Psychotic Disorders

Giuseppe D'Andrea*[1], Ilaria Tarricone[2], Diego Quattrone[3], Marta Di Forti[4], Robin Murray[4]

[1]*McGill University,* [2]*Bologna University,* [3]*MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, ,* [4]*Institute of Psychiatry, King's College, London*

**Background:** Incidence of psychotic disorders varies widely by geographic regions, encouraging research on environmental factors which might explain such spatial variation. Over the last decades, the traditional concept of psychosis as a dichotomic entity has been questioned by multiple lines of evidence, leading to the affirmation of the psychosis continuum model. According to the latter, subthreshold psychotic symptoms are normally distributed in the general population and have a shared aetiology with threshold-clinical disorders. We therefore sought to examine patterns of variation of subclinical psychosis across multiple sites while accounting for the incidence of clinical psychotic disorders over the same time-span and catchment areas.
**Methods:** We will present data from two studies from the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) study. Between May 2010-April 2015, three groups of people were recruited across 17 centres in 6 different countries (Brazil, England, France, Italy, the Netherlands, and Spain): (1) first-episode psychosis patients aged 18-64; (2) population-based healthy controls within the same age-span and catchment areas; (3) siblings of FEP participants. We only used data from population-based controls. The recruitment process followed specific measures to maximize representativeness of the local population-at-risk. Controls were administered the Structured Interview for Schizotypy-Revised (SIS-R) and the Community Assessment of Psychic Experiences (CAPE) to measure, respectively, schizotypal traits and psychotic-like experiences (PLEs). In Study 1, we used multi-level regression models to examine variation of subclinical psychosis phenotypes across EU-GEI sites and its relation with local FEP incidence. In Study 2, we restricted the analyses to 14 European sites examined the association between subclinical psychosis and urbanicity and tested whether the association differed significantly comparing Northern- and Southern-European countries using multi-level regression with the interaction term of population density x recruitment region.

**Results:** A total of 1,497 population-based controls were recruited. In Study 1, we found that schizotypal traits varied largely between-sites, with up to 15% variation attributable to site-level characteristics. Most of the between-sites variance of schizotypy was explained adjusting for local incidence of FEP. PLEs showed a more uniform distribution across the study sites. In Study 2, we found that schizotypy was significantly associated with urbanicity (β=0.248,95%CI=0.122-0.375;p < 0.001). The association was substantially stronger in Northern Europe (β=0.620,95%CI=0.362-0.877;p < 0.001) compared with Southern Europe (β=0.190,95%CI=0.083-0.297;p=0.001).
**Conclusions:** Schizotypal traits varied robustly by study site, being prominent where incidence of FEP was also higher. This supports the hypothesis that shared contextual factors influence the between-sites variation of psychosis, including subclinical forms. The association between urbanicity and subclinical psychosis was much stronger in North European countries, in accordance with the EU-GEI incidence study. Overall, schizotypy proved to be an optimal candidate for assessing variation of psychosis spectrum. Further advantages encompass the fact that can be measured on a dimensional, continuous scale, and that, unlike threshold-clinical disorders, it is not affected by the reverse causation bias.

### 33.3 Relationship Between Childhood Trauma, Psychosocial Factors, Psychopathology and Current Functioning in First-Episode Psychosis: Insights From Network Analysis

Lan Zhou*[1], Roberto Doornebal-Bakker[1]

[1]*University Medical Center of Groningen*

**Background:** Childhood trauma is associated with an increased risk of psychopathology, accelerated brain aging, and abnormal psychosocial development later in life. A better understanding of the interplay between childhood trauma, psychosocial factors, clinical symptoms, and current functioning in first-episode psychosis (FEP) is crucial for promoting functional recovery and developing targeted intervention strategies. Network analysis, a data-driven approach, is well-suited for unraveling the complex interactions between these variables. However, the relationship between childhood trauma and psychopathology in FEP has been understudied. This study aimed to explore these associations and use network analysis to identify potential pathways of interaction.
**Methods:** This study applied network analysis to examine the interrelationships among childhood trauma, psychosocial factors, premorbid functioning, psychopathology, and current functioning in 283 adult FEP patients. The network was constructed using the Graphical Least Absolute Shrinkage and Selection Operator (LASSO) combined with an extended Bayesian information criterion (BIC) model. Centrality analyses quantified the importance of individual nodes, and bridge analyses investigated how psychosocial factors link childhood trauma to schizophrenia symptomatology.
**Results:** Preliminary results revealed distinct associations between specific dimensions of childhood trauma, psychopathology, and current functioning. Childhood deprivation, such as neglect, was linked exclusively to lower social support and a higher avoidant attachment style. Conversely, experiences of childhood threat (e.g., abuse) were specifically associated with higher levels of anxious attachment. Centrality analysis highlighted self-esteem and avoidant attachment as pivotal within the network, while anxious attachment played a bridging role between childhood abuse and general symptoms. Additionally, current global functioning bridged the relationship between childhood neglect and schizophrenia symptomatology (positive, negative, and general symptoms).
**Conclusions:** These findings underscore the distinct contributions of different childhood trauma dimensions to the psychopathology network in FEP, with critical associations

observed between trauma and psychosocial functioning. This highlights the potential for targeted interventions addressing specific psychosocial pathways to improve outcomes for individuals with FEP.

### 33.4 Patterns of Past and Current Cannabis use and Levels of Subclinical Paranoia, Anxiety and Depression: Results From the Cannabis & Me (CAMe) London Population Online Survey

Edoardo Spinazzola*[1], Giulia Trotta[1], Isabelle Austin-Zimmerman[2], Zhikun Li[2], Diego Quattrone[2], Robin Murray[1], Marta Di Forti[1]

[1]*King's College London, IoPPN,* [2]*King's College London,*

**Background:** Paranoia is the unfounded and irrational fear that others hold harmful intentions towards the individual. The association between heavy cannabis use and paranoia is well established, and it has been replicated both in epidemiological and experimental settings. Interestingly, heavy cannabis use appears to be more strongly associated with the persecutory dimension of paranoia, while its link to ideas of reference is less pronounced. However, little is known about whether cannabis use can increase the risk of developing subthreshold paranoia in the general population, and if this effect is reversible once cannabis use is stopped. Similarly, we are also interested in the effects of heavy cannabis use on the levels of subthreshold anxiety and depressive symptoms; this could suggest that anxiety and depression may be mediating factors in the pathway from cannabis use to psychosis (i.e. the affective pathway to psychosis). Therefore, we aim to explore whether the frequency of cannabis use influences the risk of developing subthreshold a) paranoia, b) anxiety, and c) depression, and whether these effects differ between people with current and past cannabis use, including those who have stopped using cannabis for at least one year.
**Methods:** Using the Cannabis and Me (CAMe) study online platform, we analysed data from 4,858 individuals from the general population who had either never used, were currently using, or had used cannabis in the past. Recruitment and data collection began in 2022 and continue to date. Data on cannabis use were obtained from the Cannabis Experience Questionnaire modified version. Linear regressions were used to test if frequency of use predicted GPTS (Green et al paranoia score), GAD (Generalised Anxiety Disorder), and PHQ-9 (Patient Health Questionnaire) scores.
**Results:** We included 1,356 people who never used cannabis, 820 people who stopped more than one year before, and 2,682 people who were currently using cannabis from the CAMe online survey. Firstly, we conducted general sociodemographic analyses to study our sample. Our linear regression models, adjusted for age, sex, ethnicity, employment status, and years of education showed that cannabis use is associated with higher levels of subthreshold paranoia, anxiety, and depression scores. This association is consistent across different levels of use, and findings were replicated even when focusing only on past users compared to never users.
**Conclusions:** In the general population, the frequency of cannabis use was positively correlated with higher levels of subclinical paranoia (GPTS), anxiety (GAD), and depression (PHQ-9). Although the sample size for past daily and frequent users was small (35 and 60, respectively), the data suggests that even after cessation, cannabis may exert lasting effects on mental health, warranting mental health interventions for both current and former users. Lastly, consistently with previous evidence, we found that ideas of persecution were more strongly linked to cannabis use, while ideas of reference also showed a significant, though smaller, association.

**34. Decoding Psychosis Risk: Global Perspectives on Clinical and Molecular Predictors**

Kim Do*, Lausanne University*

**Overall Symposia Abstract:** Innovative approaches spanning clinical assessments to molecular biomarkers are transforming our understanding of clinical high-risk (CHR) states for psychosis. This symposium showcases unpublished research from diverse global perspectives.

Majda Cheour will present findings on CHR individuals in Tunisia, focusing on suicide risk and impulsivity. A 12-month study revealed that suicidal ideation decreased over time among those at ultra-high risk (UHR) for psychosis, with no initial differences compared to first episode psychosis patients. Impulsivity was associated with poorer clinical outcomes, including increased psychological distress and severe psychotic symptoms. Key findings highlight psychosocial factors influencing CHR status and the effectiveness of structured assessments like CAARMS and SCID.

Ines Khadimallah will present novel findings on brain-derived extracellular-vesicle (EV) microRNAs (miRNAs) as blood-based biomarkers for predicting psychosis transition in CHR individuals. In a multicentre study involving 325 participants from 10 international centres, Khadimallah's team quantified circulating EV-miRNAs associated with redox regulation, neuroinflammation, NMDAR hypofunction, and blood-brain-barrier integrity. Four miRNAs - mir-132, miR-9, miR-34a, and mir-941 - demonstrated high accuracy in distinguishing between CHR individuals who transitioned to psychosis (CHR-T) and those who did not (CHR-NT), with an area under the curve (AUC) of 0.97. These results suggest that brain-derived exosomal miRNAs hold promise as biomarkers for predicting psychosis transition.

Diana Perkins will describe recent findings from the North American Prodrome Longitudinal Study (NAPLS2-3) on youth at CHR for psychosis. She will discuss a blood diagnostic incorporating markers of inflammation, oxidative stress, and hypothalamic-pituitary dysregulation that distinguished CHR individuals who developed psychosis with 91% accuracy. Perkins will also present a risk calculator combining clinical and neurocognitive variables that predicted psychosis onset with 71% accuracy when applied to an independent cohort. Finally, she will report on an external validation study using the novel blood assay of brain-derived EV miRNAs (described by Khadimallah) to predict psychosis conversion in the NAPLS3 cohort. This assay showed excellent predictive utility with an AUC of 0.96 in distinguishing CHR-T from CHR-NT individuals.

Philip McGuire will review the current status of candidate blood biomarkers for psychosis onset, focusing on data from a prospective follow-up study of the EU-GEI cohort. Blood samples were collected at baseline from 344 CHR participants and analysed for inflammatory, lipidomic, and redox markers. During the five-year follow-up, 19% of the cohort developed a psychotic disorder. McGuire will present findings on the predictive value of various markers, including VEGF, the IL-10:IL-6 ratio, ether phospholipids, and miRNAs

34a and 941. Models using the four miRNAs discovered by Khadimallah showed excellent performance in discriminating between CHR-T and CHR-NT individuals (C=0.96, 95% CIs:0.87-1.00). These findings across different modalities may all relate to the central role of redox dysregulation / oxidative stress in psychosis pathophysiology.

This symposium presents innovative approaches in CHR prediction, from clinical assessments to advanced molecular biomarkers. It highlights the importance of culturally adapted early intervention programs, the potential of brain-derived EV miRNAs as biomarkers, the combination of clinical, neurocognitive, and biological markers for accurate risk prediction, and the central role of redox dysregulation/ oxidative stress in psychosis development. These studies pave the way for more personalized strategies in psychosis prevention and early intervention.

### 34.1 Clinical and Psychological Predictors in a Tunisian Chr Cohort: Insights and Implications

Majda Cheour*[1], Feten Fekih-Romdhane[1], Bouthaina Abbassi[1], Farah Ghrissi[1], Rahma Damak[1], Nouha Ben Hamed[1]

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**Background:** Clinical high-risk (CHR) individuals for psychosis are a critical focus in mental health research due to their increased vulnerability to developing full-threshold psychotic disorders. Understanding the CHR status is crucial, especially in regions like Tunisia, where cultural and socioeconomic factors may influence mental health outcomes. This study focuses on impulsivity and suicide risk among individuals at ultra-high risk (UHR) for psychosis, comparing them with first episode psychosis (FEP) patients. The research aims to provide insights into the psychosocial factors affecting CHR status and evaluate the effectiveness of structured assessments such as the Comprehensive Assessment of At-Risk Mental States (CAARMS).
**Methods:** Two separate cohorts were studied over a 12-month period. The first cohort included UHR individuals assessed for impulsivity using the Barratt Impulsiveness Scale (BIS-11) and the Wisconsin Card Sorting Test (WCST). The second cohort focused on suicide risk among UHR individuals compared to FEP patients, utilizing CAARMS and other psychological assessments. Participants were evaluated at baseline, 6 months, and 12 months.
**Results:** In the impulsivity cohort, higher motor impulsivity at baseline predicted more severe positive psychotic symptoms at 12 months. Impulsivity was linked to lower quality of life and increased psychological distress. In the suicide risk cohort, no significant differences in baseline suicidal ideation were found between UHR and FEP groups. However, suicidal ideation decreased significantly over time in UHR participants. Increased PANSS scores at one year were associated with higher suicidal ideation scores.
**Conclusions:** Impulsivity is a significant predictor of poor clinical outcomes in UHR individuals, indicating a need for targeted interventions to improve quality of life and reduce psychological distress. The decrease in suicidal ideation over time among UHR individuals suggests that early intervention programs can be effective. These findings underscore the importance of culturally adapted mental health strategies in middle-income countries like

Tunisia and highlight the need for tailored approaches to address impulsivity and suicide risk in CHR populations.

### 34.2 Circulating Exosomal Micrornas as Biomarkers for Predicting Psychosis Transition in Clinical High-Risk Individuals

Ines Khadimallah*[1], Kim Do[2], Matthew J. Kempton[3], Margot Fournier[1], Andrea-Giorgia Piotti[1], Michel Cuenod[1], EU-GEI High Risk Study Group, Philip McGuire[4]

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**Background:** Identification of biomarkers for transition to psychosis in clinical high-risk (CHR) individuals is crucial for targeted preventive interventions. Previous research has implicated redox dysregulation, neuroinflammation, NMDAR hypofunction, and blood-brain barrier (BBB) disruption in the pathophysiology of psychosis. This study investigated the potential of circulating brain-derived extracellular vesicle (EV) microRNAs (miRNAs) associated with these pathways as blood-based biomarkers for predicting psychosis transition in CHR individuals.
**Methods:** In a multicenter study (EUGEI cohort), 268 CHR individuals and 57 healthy controls were recruited from 10 centres in Europe, South America and Australia. Clinical assessments were conducted at baseline and at 12 and 24 months. Blood was collected at baseline for the measurement of four exosomal miRNAs and their putative target proteins. Plasma levels of four exosomal miRNAs (miR-132, miR-9, miR-941, and miR-34a) implicated in redox regulation, neuroinflammation, NMDAR function, and BBB integrity were quantified. Target proteins (MMP9, TIMP1, VCAM1, and SERPINE1) were also measured to validate the biological relevance of miRNA alterations.
**Results:** CHR individuals who transitioned to psychosis during follow-up (CHR-T) had significantly lower levels of miR-9 and higher levels of miR-34a compared to both CHR individuals who did not become psychotic (CHR-NT) and healthy controls. Conversely, CHR-NT individuals showed elevated levels of miR-132 and miR-941 compared to CHR-T and healthy control groups. Significant differences were observed in the levels of target proteins SERPINE1, VCAM1, and MMP9 activity between the groups. CHR-T individuals exhibited higher levels of these proteins compared to CHR-NT and healthy controls. A four-miRNA panel (miR-132, miR-9, miR-941, and miR-34a) demonstrated high accuracy in distinguishing between CHR-T and CHR-NT individuals, with an area under the curve (AUC) of 0.97.
**Conclusions:** Our findings suggest that circulating brain-derived exosomal miRNAs associated with redox regulation, neuroinflammation, NMDAR function, and BBB integrity, with their protective or vulnerability-increasing effects, hold promise as biomarkers for predicting psychosis transition in CHR individuals. The high accuracy of the four-miRNA panel in differentiating CHR-T from CHR-NT individuals highlights its potential clinical utility. These results provide a basis for the development of Extracellular-vesicles-microRNAs as blood biomarkers to guide early intervention strategies in at-risk individuals.

### 34.3 Recent Clinical and Biological Findings in NAPLS Cohort

Diana Perkins*[1], Clark Jeffries[2], Jean Addington[3], Carrie Beardon[4], Kristen Cadenhead[5], Tyrone Cannon[6], Barbara Cornblatt[7], Matcheri Keshavan[8], Daniel Mathalon[5], William S Stone[9], Elaine Walker[10], Scott Woods[6], Ines Khadimallah[11], Kim Do[12]

[1]*University of North Carolina,* [2]*University of North Carolina at Chapel Hill,* [3]*University of Calgary,* [4]*University of California, Los Angeles,* [5]*University of California, San Diego,* [6]*Yale University,* [7]*The Zucker Hillside Hospital,* [8]*Harvard University,* [9]*Beth Israel Deaconess Medical Center; Harvard Medical School,* [10]*Emory University,* [11]*Center for Psychiatric Neuroscience, Lausanne University Hospital, Switzerland,* [12]*Lausanne University*

**Background:** Clinical diagnostic criteria for the psychosis prodrome identify persons with a 10%-20% two-year psychosis risk. While much higher than the general population risk, this relatively low conversion rate hampers the development and implementation of preventative interventions. Thus, a biomarker assay that improves psychosis risk prediction would be of high value. In addition, biomarkers may illuminate mechanisms involved in the emergence of schizophrenia and potentially point towards new therapeutic targets. Previous studies find evidence for alterations in blood molecules related to redox status and immune system function. Blood also contains exosomes that are secreted by cells from all organs. Exosomes contain proteins, lipids, and nucleic acids that are enveloped by the cell's own plasma membrane. Exosomes thus contain molecules reflecting the source cell leading to the development of novel methods to isolate brain-derived exosomes. In this presentation we report on findings from the NAPLS3 study, comparing persons at clinical high risk for psychosis who converted to psychosis with nonconverters and unaffected controls. Results include levels of brain-exosomal-derived regulatory nucleic acids (miRNAs) involved in inflammatory pathways (miR-132, miR-34, miR-9) and redox/mitochondrial pathways (miR137, miR941, miR132, COX6A2) as well as plasma levels of blood analytes involves in immune system function.

**Methods:** The North American Longitudinal Study (NAPLS3) includes 710 subjects meeting COPS criteria for psychosis clinical high-risk criteria and 96 unaffected controls. Baseline plasma samples from 49 converters, 55 nonconverters (all followed for at least two years) and 46 unaffected controls were analyzed in the lab of Professor Kim Do for levels of exosomal microRNAs, and COX6A2 using previously described methods. Baseline plasma from an overlapping group of subjects (converter n=58, nonconverter n=58, control n=33 ) was analyzed using the Lumina platform by Rules Based Medicine for levels of 70 analytes related to immune system function.

**Results:** Combining levels of mir-9, miR-34, miR-94, and miR-132 discriminated psychosis converters from nonconverters with and area under the receiver operating curve (AUC) of 0.92. Combining the two strongest predictors, miR-132 and miR-941 produced and AUC of 0.92. Levels of miR-941 and miR-9 were lower and miR-34 higher in converters compared to nonconverters and to controls ($p < 0.01$). Levels of miR-132 were lower in converters compared to nonconverters ($p < 0.01$) but did not differ from controls. Levels of COX6A2 were lower in converters compared nonconverters and to controls and levels of mir-137 were higher in converters compared to controls. The Lumina platform failed to detect many of the low abundant analytes (including the majority of cytokines) leaving only 42 for analyses. There were no differences in the expression of blood analytes between groups. Efforts to build a risk calculator based on these analytes was not successful.

**Conclusions:** In this subgroup of the NAPLS3 cohort a biomarker including the levels of four exosomal microRNAs is highly predictive of conversion to psychosis in persons at clinical high risk. These findings replicate findings from other clinical high-risk cohorts. The microRNAs included in the risk-predictor support the potential roles of mitochondrial

dysfunction, redox dysregulation and neuroinflammation in the development of psychotic disorders.

### 34.4 Candidate Blood Biomarkers for Psychosis Onset

Philip McGuire*[1], Matej Oresic[2], Alex Dickens[3], Kim Q Do[4], Valeria Mondelli[5], Ines Khadimallah[4], Nikolaos Koutsouleris[6], Graham Blackman[1], David Mongan[7], David Cotter[8], Thomas Pollak[5], Matthew Kempton[5], Lucia Valmaggia[9], EU-GEI High Risk Study Group

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**Background:** A key goal for research on psychosis is to identify biomarkers that can be used to predict the onset of illness. In people at Clinical High Risk (CHR) for psychosis, candidate biomarkers have been examined across a range of different data modalities, including psychopathology, cognition, and imaging. Here we report on data relating to putative biomarkers measured in peripheral blood samples collected from a large prospective study of a cohort of people at CHR for psychosis.
**Methods:** 344 people at CHR for psychosis were recruited to the EU-GEI High Risk study from 11 sites in Europe, Australia and South America. Blood samples were collected at baseline. Participants were then monitored clinically for up to 5 years. 19% of the cohort developed a psychotic disorder subsequent to baseline. Blood samples were analysed for lipidomic, redox, inflammatory, and proteomic markers in laboratories in Turku, Lausanne, London and Dublin, respectively. We compared the levels of putative biomarkers between the subgroups of CHR participants who had or had not developed psychosis. Machine learning models were then used to assess prediction accuracy (in terms of Area Under the Curve; AUC) for each type of blood measure.
**Results:** Transition to psychosis was associated with lower levels of ether phospholipids, higher levels of microRNA 34a, and lower levels of microRNA 941. Transition was also linked to higher levels of VEGF and a higher IL-10:IL-6 ratio, and with differences in the concentrations of proteins in the complement and coagulation pathways. Predictive accuracy for was 0.81 for the ether phospholipids, 0.97 for the microRNAs, 0.57 for the inflammatory markers, and 0.95 for the proteomic markers.
**Conclusions:** These data suggest that a number of different types of blood measure have the potential to serve as biomarkers for the onset of psychosis in people at clinical high risk. The positive findings for the lipidomic, inflammatory and redox markers may be inter-related through their common involvement in a pathophysiological pathway that involves oxidative stress. Critical next steps are to test whether these measures can be individually validated as biomarkers for psychosis in independent CHR cohorts, and to investigate whether predictive accuracy can be enhanced by combining data from different types of blood markers, and by incorporating data from other modalities.

## Plenary Session VI: Predicting Risk, Identifying Precursors, and Characterizing Course: Pathways of Inquiry - Dr. Diane Gooding

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

**35. Predicting Risk, Identifying Precursors, and Characterizing Course: Pathways of Inquiry**

Robin Murray*, Institute of Psychiatry, King's College, London*

**Overall Abstract:** As I asserted recently (Gooding, 2022, Schizophrenia Research), schizophrenia may be characterized by different etiological pathways as well as by various combinations of symptoms. Although there is some consensus about the nature of schizophrenia, we still don't know how to prevent or cure it. Most of my research has focused on predicting risk for schizophrenia and schizophrenia-spectrum disorders, identifying precursors of the later manifestation of schizophrenia and other psychoses, and characterizing differing trajectories of course and outcome. This talk will feature several methods (e.g., psychophysiological, cognitive) and data types (e.g., phenomenological, self-report, experimental psychopathology). After summarizing my research, I will suggest ways to "carve nature at its joints."

**35.1 Predicting Risk, Identifying Precursors, and Characterizing Course: Pathways of Inquiry**

Diane Carol Gooding*, UW-Madison College of Letters and Sciences*

**Individual Abstract:** In a recent paper (Gooding, 2022, Schizophrenia Research), I asserted that schizophrenia may be characterized by different etiological pathways as well as different combinations of symptoms. Most of my research has focused on predicting risk for schizophrenia and schizophrenia-spectrum disorders, identifying precursors of the later manifestation of schizophrenia and other nonaffective psychoses, and characterizing differing trajectories of course and outcome.

This talk will feature several methods (e.g., genetic high-risk, psychophysiology, experimental psychopathology) and data types (e.g., self-report, behavioral) as we examine the risk indicators and endophenotypes of schizophrenia and schizophrenia-spectrum disorders. After summarizing my work, I will suggest ways to further "carve nature at its joints."

**Concurrent Symposia**

**3:00 p.m. - 4:30 p.m.**

**36. Implementing Cognitive Remediation in the Real World**

Mahesh Menon*, University of British Columbia*

**Overall Symposia Abstract:** Cognitive impairments in schizophrenia spectrum disorders (SSD) have been shown to be pervasive, persistent across the course of illness, not improved by medications, and predict the level of functional disability a person with psychosis might experience. Over 130 clinical trials and multiple meta-analyses have demonstrated that Cognitive remediation (CR) is an efficacious intervention that improves cognition and functioning in SSD. However, CR has not yet been routinely implemented in most clinical programs. In this symposium, we will bring together a group of experts who have all been leading large scale implementation initiatives of CR in the US, UK, and Canada, demonstrating its effectiveness and value, as well as providing helpful tips and tools to help sustain the longevity of the program across different health systems in Europe and North America.

Professor Til Wykes will present information from a large adaptive trial and a programme of implementation of cognitive remediation in the UK that examines the barriers and potential facilitators.

Dr. Alice Saperstein will present on the process of engaging stakeholders, adapting material and rolling out CR across New York state, highlighting the ways to increase engagement and completion rates in an early intervention program.

Dr. Mahesh Menon will present the results of a provincial pilot project offering CR to adults connected to the mental health teams in British Columbia, Canada- demonstrating improvements in subjective and objective cognition, reduced disability and improved functioning.

Given the impact that the pandemic has had on staff turnover in public health, and the limited access that clinicians have to training, providing ongoing training programs for CR is a priority. Prof. Martin Lepage will describe the development of E-cog, an online learning platform which trains clinicians to provide virtual CR groups.

Prof. Antonio Vita will be the discussant. His recent meta-analyses have identified some of the predictors of outcome in CR, and he will summarize the results highlighting ways that programs in routine clinical practice can maximize benefits to patients.

### 36.1 Wide Scale Implementation Does not Just Rely on Good Evidence of Efficacy – Beyond the Randomised Control Trial to Implementation

Til Wykes*[1]

[1]*Institute of Psychiatry, Psychology and Neuroscience*

**Background:** Despite rigorous evidence of the benefits, costs and savings and mentions in treatment guidance, cognitive remediation access is still sparse. Providers are often confused by disagreements about the strength of the benefits evidence, some think it is a game not a treatment and others do not consider that cognition should be a treatment target. These are all issues that were present in the literature at least ten years ago.
**Methods:** Drawing on the literature and data from a large UK adaptive randomised control trial, we will draw out key issues for: (I) understanding the barriers and facilitators for the implementation into first episode services through a set of qualitative studies, (II) evaluating different modes of therapy provision in terms of cost effectiveness and (III) developing and evaluating online training and competency tests.
**Results:** (I) Clinicians need to understand the relevance of cognition and be aware of effective interventions, (II) Despite evidence of efficacy a therapist seems important for engagement and leads to cost effective therapy and (III) online therapy can improve competencies for delivering cognitive therapy and differences in the time to complete and success in competencies seems to be related to management commitment.
**Conclusions:** All the implementation issues can be overcome but we still need to understand the non-specific effects of cognitive remediation as well as the specific if we are to provide a formulation-based approach. Clinicians need to know that cognitive remediation is not “brain training” but is a holistic therapy that involves an active therapist providing motivation

support, and who helps to mitigate the impact of cognitive difficulties through metacognition to develop awareness of cognitive approaches to problems.

### 36.2 Cognitive Remediation Implementation: Referral, Engagement, and Completion Within Early Intervention Services

Alice Saperstein*[1], Alice Medalia[2]

[1]*Columbia University,* [2]*Columbia University and New York State Psychiatric Institute*

**Background:** Cognition is a valued target of treatment identified by participants and providers of early intervention services, yet large systems of care in the U.S., including those that specialize in early intervention, are not universally equipped to implement Cognitive Remediation (CR) as an evidence-based practice. This study reports on the implementation of CR at OnTrackNY (OTNY), a nationally recognized model for providing public access to early intervention to individuals ages 16-32 with non-affective psychosis.
**Methods:** New York State's Cognitive Remediation to Promote Recovery service was adapted with stakeholder input to be programmatically and developmentally appropriate, while retaining the key evidence-based treatment elements: active trained clinicians, repeated practice of cognitive skills, strategy coaching, and discussion groups to facilitate transfer to daily life. Cognitive health needs assessments generated CR referrals and facilitated shared decision-making during treatment planning. Two OTNY teams first piloted "Brain Gym" as a 12-week curriculum, delivered as either 24 twice-weekly clinician-led sessions or 12 once-weekly clinician-led sessions with 12 hours independent cognitive exercise practice. Feedback informed refinements to the cognitive exercise menu and discussion manual to improve feasibility and acceptability. Second, 11 OTNY teams implemented the refined Brain Gym curricula with clinic-level randomization to a once- or twice-weekly delivery approach. Program evaluation supported de-identified data analyses to evaluate feasibility and acceptability. Process evaluation indicated implementation facilitators and barriers. Considered all together, data indicated overall and relative "fit" of Brain Gym approaches with the model of early intervention service delivery.
**Results:** From 2019-2023, 1,193 young people were enrolled in the 11 OTNY clinics offering Brain Gym, of whom 77% were screened for cognitive health needs. Clinicians identified cognitive difficulties in 53.9% of those screened and referred 27% to Brain Gym. Once referred, 77.6% initiated treatment though fewer than 40% completed the full intervention. Comparing delivery methods, referral rates were nearly double, and treatment initiation was significantly higher at programs delivering once-weekly (84.3%) versus twice-weekly (64.4%) treatment. The difference in rate of treatment completion was statistically nonsignificant and satisfaction among all treatment completers was high. Participants who engaged in once-weekly sessions and independent practice rated group-based work as more acceptable than working independently, with varied rates of computer access and homework completion reported.

Resources afforded by a Cognitive Health Toolkit facilitated systematic assessment of cognitive health needs and CR service provision. Multi-team and interdisciplinary supervision meetings provided opportunity to cooperatively generate solutions to CR referral and implementation challenges. Referral and engagement barriers included competing treatment priorities, the pandemic, scheduling around participants' school or work, technology access, and inconsistent transportation to in-person sessions. Workforce turnover challenged the consistency of service delivery over time.

**Conclusions:** CR implementation must be flexible to fit within a service model that emphasizes personalization and rapid community engagement. Ongoing work aims to support the process of referral and shared decision making to improve uptake of CR as an evidence-based cognitive health service.

### 36.3 E-COG: An Online Training Platform for Cognitive Remediation Based on the Addie Model

Martin Lepage*[1], Ana Elisa Sousa[2], Caroline Dakoure[2], Christy Au-Yeung[1], Katie Lavigne[1], Delphine Raucher-Chéné[1], Christopher Bowie[3], Steffen Moritz[4], Geneviève Sauvé[5]

[1]*McGill University,* [2]*Douglas Research Centre,* [3]*Queen's University,* [4]*University Medical Center Hamburg-Eppendorf,* [5]*UQAM*

**Background:** Online learning is a convenient and cost-effective solution to deliver training in healthcare. In-person training has long supported mental health practitioners in delivering psychological interventions, however, the increased need of delivering such interventions remotely have brought out the need to offer training that is equally remote, asynchronous and maintain the quality of in- person training. We describe the designing, development, and implementation of E-Cog, an innovative online training platform created to support remote training in two cognitive health interventions in the context of a Canadian multi-site implementation trial to deliver cognitive interventions to individuals diagnosed with psychosis. We designed the E-Cog platform to be engaging, accessible, easy to use and effective in training health care practitioners to deliver such interventions.
**Methods:** The ADDIE educational model, consisting of 5 phases (analysis, design, development, implementation, and evaluation) was followed to develop our training platform and the curriculum of two cognitive health online certifications over two years by a team composed of mental health researchers, a web developer, and content creators/consultants with expertise in science communication and education. The two interventions consisted of Action-Based Cognitive Remediation (ABCR) and Metacognitive Training (MCT). Here, we describe the first four phases of our work and report on feasibility and acceptability of the ADDIE model as perceived by our development team.
**Results:** Five pilot users assessed the platform and certifications pre-release, consensually finding it easy to use, with trustworthy content, and expressing an average 86% likelihood to use it again/recommend it to a friend or colleague. Currently, 11 therapists have completed training using E-Cog. Technical challenges related to content progression were identified and resolved, with ongoing improvements based on user feedback. ADDIE was perceived as feasible and acceptable as a framework for e-learning content, depending on flexibility to adapt its structure to research challenges and constraints.
**Conclusions:** E-Cog has been implemented as a tool to deliver remote training that is engaging, asynchronous, and potentially cost-effective, maintaining the quality of in-person training. Successful uptake of mental health practitioners was observed during the first year of implementation. Next steps involve a qualitative assessment of the platform's usability and its impact on cognitive health intervention delivery.

### 36.4 Examining the Effectiveness of a Provincial Cognitive Remediation Program in British Columbia

Mahesh Menon*[1], Jan van der Tempel[2], Nicole Legg[2], Nicole Gevaux[2], Sarah Liu[2], Teak Daniel[3], Anisha Jethnani[3], Melissa Yeung[3], Corina Campbell[3], Tammy Vanrooy[4], Chris Bowie[4]

[1]*University of British Columbia,* [2]*Fraser Health Authority,* [3]*Vancouver Coastal Health,* [4]*Queen's University,*

**Background:** In 2022, the British Columbia Ministry of Mental Health and Substance Use funded a pilot program to evaluate the effectiveness of cognitive remediation when delivered in routine clinical practice. The funding allowed the health authorities (HA) to hire 2 clinicians per HA, and set up the BC Cognitive Remediation Training Advanced Practice (CRT-AP).
**Methods:** The British Columbia CRT-AP trained clinicians to deliver Action-Based Cognitive Remediation (ABCR) across BC's six geographically distinct health authorities, and provided them with ongoing supervision and support for the delivery of CR. ABCR was offered to individuals living with affective and non-affective psychotic disorders, across a range of settings- including early psychosis (EPI) programs, outpatient mental health teams, and inpatient settings.
**Results:** In the first year of the program (2023), 210 participants (113 male, 64 female, and 2 non-binary/other), aged 16-67 years old took part in the groups. Around 75% of the sample completed the program, with the main causes of dropout being school or work demands (33% of dropouts), or relapse (20% of dropouts). Clients completed the Screening for Cognitive Impairment in Psychiatry (SCIP) as a measure of cognition, as well as measures of subjective cognition, disability, self-reported symptoms and recovery. Clinicians also completed the goal attainment scaling (GAS) questionnaire with participants. We found significant improvements in objective cognition, subjective cognition and self-reported symptoms, as well as significant increases in progress towards recovery (as measured by the QPR) and goal achievement, as well as reduced perceived disability (as measured by the Sheehan Disability scale).
**Conclusions:** The results suggest that CR is not just feasible in routine clinical practice, but associated with high rates of retention and satisfaction, and provides robust improvements across a range of neurocognitive and functional outcomes. Factors that helped with sustaining the implementation initiative included the creation of the CRT-AP to provide ongoing training and support for clinicians, hiring dedicated clinicians to run the groups and support capacity building initiatives, as well as buy-in from management and leadership across the health regions.

## 37. Emerging Advances in Transdiagnostic Phenotyping From Large-Scale Studies of Clinical High Risk for Psychosis

Henry Cowan*, Michigan State University*

**Overall Symposia Abstract:** In recent years, research on clinical high risk (CHR) for psychosis has been transformed by large international consortium studies such as the multiple waves of the North American Prodrome Longitudinal Study (NAPLS) and the Accelerating Medicines Partnership® Schizophrenia (AMP-SCZ). These large-scale projects advance our understanding of psychosis and predict clinical trajectories and outcomes. Importantly, these studies contain a wealth of data on transdiagnostic symptoms and mechanisms that provide novel opportunities to parse heterogeneous clinical presentations in CHR. This symposium will present findings from four diverse projects, each contributing to the advancement of transdiagnostic precision phenotyping in CHR samples. The work highlights how large-scale, multimodal data—ranging from self- and clinician-rated symptoms to neuroimaging to speech data—have transformative potential to improve prediction and intervention in psychosis risk.

The first portion of the symposium will focus on uncovering transdiagnostic symptom structures across diverse, international CHR cohorts. Dr. Williams will present foundational data modeled within the Hierarchical Taxonomy of Psychopathology (HiTOP) framework, offering insights into shared symptom dimensions that cut across traditional diagnostic categories. This transdiagnostic approach allows for a more nuanced understanding of psychosis risk, considering the interplay between various forms of psychopathology (e.g., mood, anxiety, and cognitive symptoms) that co-occur with attenuated psychotic symptoms. Further elaborating on the theme of developmental trajectories, Dr. Cowan will investigate whether premorbid functioning patterns can distinguish between attenuated psychotic symptoms and non-psychotic internalizing symptoms such as anxiety and depression.

The second portion of the symposium will examine important transdiagnostic mechanisms that provide insight into CHR beyond traditional symptom-based classifications. Mx. Aberizk will present work that interrogates relations of perceived and neuroendocrine stress with brain morphometry among youth in the NAPLS cohorts. These samples subsume both healthy comparisons and youth at CHR for psychosis to underscore the transdiagnostic relevance of exposures to stress. Dr. Reinen will present work using large language models (LLMs) to analyze narrative speech data. This work moves beyond quantitative symptom assessments to capture the richness of lived experience. Dr. Reinen will also discuss feedback from CHR participants, emphasizing the importance of incorporating patient perspectives into the development of phenotyping tools.

As discussant, Dr. Bearden's will provide an integrative overview, focusing on the balance between unique and shared mechanisms underlying psychosis risk. She will explore how distinct neural pathways and environmental factors, including social determinants, contribute to different outcomes across individuals. Special attention will be given to the role of developmental timing in the emergence of symptoms and its implications for prognosis, as well as targeted and personalized treatment. Taken together, this symposium will showcase the potential of transdiagnostic phenotyping to revolutionize early identification and treatment of psychosis risk, developing precision mental health tools that are both predictive and personalized.

### 37.1 Transdiagnostic Hierarchical Symptom Models in a Clinical High Risk for Psychosis Sample

Trevor Williams*[1], Vijay Mittal[2], Accelerating Medicines Partnership® Schizophrenia[3]

[1]*Kent State University,* [2]*Northwestern University,* [3]*Global*

**Background:** Individuals at clinical high risk for psychosis experience a range of comorbid diagnoses and symptoms (depression, anxiety, substance use, etc.). Increasingly, evidence suggests that the categorical diagnoses, which define existing diagnostic frameworks, poorly

capture the complex array of symptoms that may characterize psychosis risk. Hierarchical transdiagnostic models of psychopathology (e.g., HiTOP) have emerged as alternatives to existing diagnostic frameworks and aim to reformulate symptoms into narrow dimensions (e.g., anxiety), which can be organized hierarchically into broader psychopathology dimensions (e.g., internalizing). Research applying such frameworks to psychosis risk has shown great promise, but is nonetheless in an early stage.
**Methods:** The present study aimed to advance our understanding of hierarchical transdiagnostic models in individuals at clinical high risk for psychosis, using the Accelerating Medicines Partnership® Schizophrenia-ProNET/Prescient data set (N = 1023). Participants completed symptom interviews covering psychosis, depression, substance use, and other symptoms with trained raters and additionally were rated on social and role functioning. The sample was randomized into exploratory and confirmatory subsets, with exploratory factor analyses in the first subsample used to develop competing, confirmatory models for the second subsample. The best fitting models were further compared in terms of their relations to functional outcomes.
**Results:** Preliminary results using exploratory factor analysis and sequential exploratory factor analysis indicated a viable hierarchical structure. The broadest, most parsimonious level of the factor hierarchy included 3 factors: internalizing, thought disorder, and detachment. In contrast, the most differentiated and interpretable level of the factor structure included nine factors: internalizing, emotional (in)expressivity, motivation and pleasure, general positive symptoms, suspiciousness, grandiosity, disorganization, oddity, and suicidality. Although all levels of the hierarchy were substantially predictive of social functioning at baseline (e.g., single factor model, $\beta$ = -.51, R2 =.31), lower levels provided increasing nuance and predictive power (e.g., 9 factor model for all regression coefficients $p < .05$, R2 = .45).
**Conclusions:** Further analyses will build upon these results to formalize the preliminary factor model using confirmatory factor analysis and broaden prediction results to include changes in social functioning over time. Nonetheless, these preliminary results suggest that hierarchical transdiagnostic models can provide the psychosis risk literature with a flexible and parsimonious approach to understanding comorbidity, with potential benefits for mechanism research and outcome prediction.

### 37.2 Premorbid Adjustment Trajectories as a Developmental Signal to Differentiate Attenuated Negative Symptoms From Depression and Anxiety

Henry Cowan*[1], Vijay Mittal[2], Scott Woods[3], Elaine Walker[4], Jai Shah[5], Luis Alameda[6], AMP SCZ Consortium[7], NAPLS Consortium[8]

[1]*Michigan State University,* [2]*Northwestern University,* [3]*Yale University,* [4]*Emory University,* [5]*McGill University,* [6]*Lausanne University,* [7]*Global,* [8]*North America*

**Background:** People with clinical high risk for psychosis (CHR) commonly report depression (38% with depressive disorders; Solmi et al., 2023), anxiety (34% with anxiety disorders; Solmi et al., 2023), and negative symptoms including deficits in motivation, pleasure, sociability, and emotional expression (54% with moderate or severe negative symptoms over 12-month follow up; Piskulic et al., 2012). Recent factor analyses have found cross-sectional associations between depression/anxiety and negative symptoms in CHR (e.g., depression loading .48 on a negative symptoms factor; Cowan and Mittal, 2021). This suggests that depression/anxiety and negative symptoms may be more clearly differentiated by their developmental course than by their current presentation. This talk examines whether

negative symptoms and depression are associated with distinct trajectories of premorbid functional problems in CHR.
**Methods:** CHR participants in NAPLS-3 (N=496) and the second AMP SCZ release (N=361) completed the premorbid adjustment scale to assess retrospective reports of social and academic functioning from childhood through late adolescence. Negative symptoms (NAPLS: Structured Interview for Psychosis-Risk Syndromes; AMP SCZ: Negative Symptom Inventory—Psychosis Risk), depression (Calgary Depression Scale for Schizophrenia), and anxiety (AMP SCZ only: Overall Anxiety Severity and Impairment Scale) were also assessed. Multilevel growth curve models tested whether overall adjustment problems (main effect) and trajectories of worsening adjustment problems (interaction with time) in the premorbid phase were associated with more severe negative symptoms, depression, or anxiety at baseline (Aim 1). Combined models then tested shared and unique associations between symptoms and premorbid adjustment (Aim 2).
**Results:** Aim 1. Robust associations between premorbid adjustment problems and negative symptoms were observed in NAPLS-3. Negative symptoms were associated with worse overall premorbid adjustment (social $\gamma$ =.37, $p < .001$, academic $\gamma$ =.19, $p < .001$), and trajectories of progressively worsening premorbid adjustment (social $\gamma$ =.18, $p < .001$, academic $\gamma$ =.11, p = .001). When negative symptoms were divided into avolition vs. emotional deficits, social adjustment effects were significant for avolition and emotional deficits, whereas academic adjustment effects were only significant for avolition.

In AMP SCZ, motivation/pleasure-related negative symptoms were associated with worse overall premorbid adjustment (social $\gamma$ =.24, p = .045; academic $\gamma$ =.30, p = .015), but emotional expression-related symptoms were not (social $\gamma$ =-.00, p = .983; academic $\gamma$ =-.08, $p < =.468$). Depression was associated with worse overall social premorbid adjustment in NAPLS-3 ($\gamma$ =.53, $p < = .001$) but not in AMP SCZ ($\gamma$ =.00, p =.973). Anxiety was not associated with premorbid adjustment. No significant interactions with time were observed in AMP SCZ.

Aim 2. In combined models with negative symptoms, depression, and anxiety, all effects for negative symptoms described above remained significant. In addition, unique effects were observed in AMP SCZ for motivation/pleasure-related negative symptoms. When controlling for depression/anxiety, motivation/pleasure symptoms were associated with worse overall premorbid adjustment (social $\gamma$ =.50, $p < .001$, academic $\gamma$ =.58, $p < .001$), and trajectories of progressively worsening premorbid adjustment (social $\gamma$ =.30, p = .011, academic $\gamma$ =.23, p = .044). In combined models, depression had a unique effect only on overall social adjustment problems in NAPLS-3 ($\gamma$ =.53, $p < .001$), and anxiety had no unique effects.

**Conclusions:** The present study found that negative symptoms, but not depression/anxiety, are associated with trajectories of worsening social and academic problems in the premorbid period. While chronic social impairment is consistent with both depression and negative symptoms, a longstanding pattern—since childhood—of progressively deteriorating social and academic functioning is a unique signature of the chronic avolition and motivation/pleasure deficits associated with negative symptoms. This suggests that retrospective developmental reports can be used as a key phenotypic marker not only of overall risk for psychosis (e.g., NAPLS risk calculator), but also of unique aspects of the CHR syndrome that operate independently of depression and anxiety.

## 37.3 Relations of Perceived and Neuroendocrine Stress With Brain Morphometry on the Psychosis Spectrum

Katrina Aberizk*[1], Meghan Collins[2], Benson Ku[3], Elaine Walker[1], NAPLS Consortium[1]

[1]*Emory University,* [2]*Yale University,* [3]*Emory University School of Medicine*

**Background:** Prolonged or repeated exposure to stress is associated with increased risk for a range of psychiatric conditions, including psychotic disorders, and poorer global functioning in healthy people. Many psychiatric conditions display overlapping neuroanatomical phenotypes, including reductions in cortical thickness and hippocampal volume. Findings suggest that these deficits may be attributable to common insults, including exposure to stress. The present research explores the roles of cortical thickness and hippocampal volume in mediating the neurobiological effects of stress in healthy youth and youth at clinical high-risk (CHR) for psychosis in the North American Prodrome Longitudinal Study (NAPLS).
**Methods:** Study 1 (n = 626) explores relations of pre-baseline cumulative life event stress (LES) and CHR status with cortical thickness at baseline in the second NAPLS cohort. A hierarchical linear regression model is used to examine additive effects of the following blocks of variables: 1) age and gender, 2) LES (defined by an aggregate measure of self-reported perceived stress), 3) CHR status, and 4) an interaction of LES and CHR status. A post hoc mediation analysis explores whether cortical thickness in brain regions significantly associated with LES partially mediates the association between LES and clinical outcome. Study 2 (n = 571) employs multigroup structural equation modeling (SEM) in the combined baseline samples of the second and third NAPLS cohorts. Multigroup SEM allows parameters to be freely estimated (with unique coefficients per group) or constrained (as identified by a coefficient shared between groups). Thus, candidate models evaluate how imposed constraints influence model fit. In this study, parameters relevant to age, gender, LES, and basal cortisol were iteratively constrained to predict bilateral hippocampal volume among healthy individuals and people at CHR for psychosis. Specifically, fit statistics for three candidate models were examined: 1) all parameters freely estimated, 2) parameters germane to age and gender constrained to shared coefficients, and 3) parameters germane to LES and cortisol constrained to shared coefficients.
**Results:** Study 1 demonstrates that LES is significantly inversely associated with thickness of bilateral superior and middle temporal cortex as well as additional aspects of temporal, parietal, occipital, and orbital frontal cortex. CHR status is significantly inversely associated with thickness across much of bilateral parietal, temporal, and occipital cortex. Cortical thickness in areas associated with LES partially overlapped with those associated with CHR status and partially mediated the association of LES with clinical outcome. Study 2 demonstrates that the candidate model with best fit constrained the relations of LES and cortisol with hippocampal volume to shared coefficients. Significant inverse relations of basal cortisol with bilateral hippocampal volume are observed.
**Conclusions:** Considered together, findings are consistent with evidence demonstrating that stress is a nonspecific risk factor for aberrant brain morphology in both healthy and clinical samples. Future studies aimed at elucidating the complex interplay between neuromaturation, neuroendocrine changes, and stress sensitivity are warranted. Investigators are advised to include healthy comparisons in their analysis plans, especially when interrogating relations of perceived and neuroendocrine stress with brain morphometry, to arrive at a more mechanistic understanding of the transdiagnostic relevance of exposures to stress.

## 37.4 Using Large Language Models and Lived Experience Patient Narratives to Characterize Linguistic Features of Clinical High Risk

Jenna Reinen*[1], AMP SCZ Consortium[2]

[1]*IBM Research,* [2]*Accelerating Medicines Partnership® in Schizophrenia*

**Background:** Patient narrative provides nuance about the lived experience of at-risk states in a way that is difficult for standard assessments to capture. While it has been known that valuable psychiatric information is captured in these narratives and in language more broadly, it has been historically difficult to quantify. However, artificial intelligence (AI), natural language processing (NLP), and large language models (LLMs) have allowed for better quantification of language, and thus for more precise comparisons between linguistic measurements and clinical symptoms. Here, we combined input from literature reviews, Clinical High Risk (CHR) individuals, and computational experts to identify linguistic themes that characterize the high-risk state, and used this information to measure differences between community controls (CON) and CHR.
**Methods:** To identify key themes and specific examples of lived CHR experience, we performed an extensive literature review and held a two-day meeting with a group of researchers, clinicians, NLP experts, and a representative from the National Alliance on Mental Illness (NAMI) at the Accelerating Medicines Partnership® in Schizophrenia (AMP® SCZ) hackathon. These themes and examples were used in an NLP lexical similarity analysis intended to quantify how similar interview statements were relative to the themes identified in the meeting. After transcribing the open-ended participant interviews (CON and CHR) in the AMP SCZ study, we processed each statement using robust BERT Transformers (RoBERTA) to compute lexical similarity to each theme by tokenizing the content in each sentence using Natural Language Toolkit. Cosine similarity was computed between interview statements and themes. Mean scores across each individual's interview were computed, and group differences were calculated.
**Results:** Data were acquired from baseline interviews (297 CHR individuals, 21.3 +/- 4.2 years, 153F/144M; 60 CON, 21.5 +/- 3.9 years, 36F/24M). Key themes identified in the focused meeting included changes in identity, feelings of isolation, feelings of suspiciousness and changes in salience processing, trauma/stress, fear/anxiety, appreciation for help and connection, cognitive changes, and future thoughts and planning. Lexical similarity results showed that feelings of isolation ($p=0.02$), including reports of engagement with family and friends ($p < 0.01$), suspiciousness ($p < 0.01$), anxiety ($p=0.01$), fear ($p < 0.001$), and cognitive properties, including ability to think ($p < 0.001$), and school performance ($p < 0.01$) differed between CHR and CON groups.
**Conclusions:** We will discuss this approach, which combines patient lived experiences, literature review, and AI technical expertise, and its capacity to create features for use with LLMs to characterize the CHR experience, as well as how it compares to standard assessments in identifying the importance of affective experience in CHR. Limitations, such as longitudinal considerations of these data, will be discussed. Finally, we will contextualize these findings that can lay the groundwork for future CHR-guided, AI-empowered research aimed to characterize the CHR experience.

## 38. Treatment Resistance: Are Patients not Responding to Treatments or are Clinicians not Responding to Guidelines?

Ingrid Melle*, Institute of Clinical Medicine*

**Overall Symposia Abstract:** Schizophrenia is a severe and often chronic illness, and the view of schizophrenia spectrum disorders as poor outcome disorders is prevalent in treatment

services. At the same time, many potent pharmacological and psychosocial interventions are available, and treatment guidelines outline the appropriate application of these interventions. Early intervention services, comprising a more comprehensive range of first-episode schizophrenia spectrum disorders, increasingly focus on the potential for recovery based on prospective studies showing considerable potential for recovery in this group. While short-term studies indicate an improved outcome for patients in EIS services, longer-term studies still show that a significant subgroup experiences chronic symptoms and poor functioning. To what extent do these outcomes primarily reflect "the natural course of the disorder?" and to what extent do they reflect an under-use of available treatments because the clinician believes poor outcomes are unavoidable?

This symposium aims to describe the gap between what is recommended as best practice in treatment guidelines and the treatment received by individuals with schizophrenia spectrum disorders. This gap affects goal-setting and treatment planning, with a subsequent focus mainly on symptom management and harm prevention also in first-episode psychosis (FEP) patients that have a potential for even better outcomes. Here, knowledge from first-episode research in general and long-term prospective FEP cohorts can inform and be integrated with clinical practice, as illustrated by the current symposium. By including prospective long-term data from different treatment systems across three continents, we aim to tease out factors consistent across treatment cultures.

Jose Rubio-Lorente will present data on treatment discontinuation in one large epidemiological FEP cohort from Finland with 18 years of follow-up and on persistent psychosis and patterns of psychopharmacological utilization in another large epidemiological FEP cohort from the US with 25 years of follow-up showing high risks of discontinuation during the first years of treatment. Maximizing treatment continuity during the early phase and thus mitigating residual psychosis could have consequences over their lifetime for individuals with psychosis.

Kristin Wold will present data on the full range of outcomes in a cohort of FEP patients followed over the first ten years of treatment in Norway. She will present data on the variety of antipsychotic treatments received by patients without complete remission and to what extent this complies with current treatment guidelines. She will also present data on how initial diagnoses, gender, and risk of medication side effects are distributed over outcome groups.

Sherry Kit Wa Chan will present data on antipsychotic use before starting clozapine in population-based data and data from a long-term follow-up of FEP in Hong Kong. The data show the variety of prescription patterns and potential lack of adherence to the guidelines. She will also present survey results on adherence to treatment guidelines in the context of patients with treatment resistance in Hong Kong and Singapore.

Katherine Jonas will present data on psychopharmacological and psychosocial treatment in a large, comprehensively followed-up cohort of FEP patients from the US who have been followed up repeatedly for over 25 years. She will focus on how early treatment complies with adequate psychopharmacological treatment as outlined in current guidelines and the extent of access to psychosocial treatments documented in clinical research at four and 25 years of follow-up.

Finally, Oliver Howes will serve as a discussant of the symposium presentations and consider how naturalistic prospective studies may inform the development and implementation of guidelines.

### 38.1 Treatment Continuity and Persistent Psychosis in Early Phase Psychosis: Long-Term Implications

Jose Rubio*[1], Katherine Jonas[2], Heidi Taipale[3], Christoph Correll[4], Antti Tanskanen[5], Daniel Guinart[6], Roman Kotov[2], Jari Tiihonen[5], John Kane[1]

[1]*Northwell Health,* [2]*Stony Brook University,* [3]*Niuvanniemi Hospital, University of Eastern Finland,* [4]*Zucker School of Medicine at Hofstra/Northwell,* [5]*Karolinska Institutet,* [6]*Hospital del Mar Research Institute*

**Background:** Most guidelines recommend setting as treatment target symptom remission, and to continue maintenance treatment for at least 2 years after achieving remission to prevent relapses. Clinicians however are probably familiar with the fact that most patients discontinue treatment sooner than recommended, and that residual psychosis is indeed very prevalent in individuals receiving care for early phase psychosis. The extent to which this occurs in the clinic, the factors that explain this deviation from clinical guidelines under real world conditions, and the long-term implications are explored and discussed in this symposium.
**Methods:** We drew data from 2 large epidemiological cohorts. The first cohort consisted in all individuals in Finland who received their first treatment for psychosis between 2000 and 2014, both included, who were followed up for up to 18 years. For this incident psychosis cohort, we ran a 'within-individual' Stratified Cox proportional hazards regression, in which the outcome was time to treatment discontinuation, defined as a gap in access to antipsychotic drugs for > 30 days. Risk of treatment discontinuation for each individual was compared to that of their first treatment episode. We also compared 'within-individual' risk of discontinuation between drugs and formulations (i.e., LAIs vs their oral counterparts). For the second cohort, we drew data from the Suffolk County Mental Health Project, representing individuals starting their first treatment for psychosis between 1989 and 1995, and who were followed up for up to 25 years. Here we had daily estimates of residual psychosis on a daily basis for the first 4 years of treatment, which we defined as the persistent psychosis group. We ran multivariable regressions testing the association between baseline predictors and persistent psychosis, and between persistent psychosis and 25-year outcomes.
**Results:** For the Finnish first episode treatment cohort, among 3343 participants followed up for a mean of 8 years (SD = 4.93), the median number of continuous treatment episodes was 6 (interquartile range [IQR] = 3–11) with a median duration of 11.4 months (IQR = 5.3–25.6). In the first year after diagnosis, the incidence rate of treatment discontinuation was

30.12 (95% CI = 29.89–30.35) events per 100 participant-years, decreasing to 8.90 (95% CI = 8.75–9.05) in the 10th year. The risk of discontinuation progressively decreased over successive treatment episodes (aHR = 0.30; 95% CI = 0.20–0.46 for episodes after the 15th compared to the first). Individuals were 67% less likely to interrupt treatment with long-acting injectable than oral antipsychotics (aHR = 0.33; 95% CI = 0.27–0.41). For the Suffolk County Cohort, out of 526 individuals with sufficient data, 101 (19.2%) presented with persistent psychosis. Low premorbid IQ (OR=2.08, 95%CI=1.05-4.12), and GAF (OR=0.63, 95%CI=0.47-0.86) before first admission, as well as lower role function (OR=0.67, 95%CI=0.46-0.97) and worse social function (OR=0.66, 95%CI=0.45-0.97) 6 months after initial hospitalization were predictive of persistent psychosis. At 25-year follow-up (n=307, 58.9%), persistent psychosis during the initial 4 years of follow-up was associated with worse avolition, (b=0.25, 95%CI=0.14-0.35), more severe reality distortion (b=0.19, 95%CI=0.07-0.31), disorganization (b=0.21, 95%CI=0.09-0.32), worse social function (b=-0.18, 95%CI=-0.06- -0.30), role function (b=-0.22, 95%CI=-0.09- -0.34), and global function (b=-0.28, 95%CI=-0.17- -0.38), greater odds of being on public assistance (OR=2.13, 95%CI=1.15-3.95), and lower odds of living independently (OR=0.43, 95%CI=0.23-0.80) or being in recovery (OR=0.09, 95%CI=0.02-0.38).
**Conclusions:** The early phase of psychosis treatment is highly consequential for long-term outcomes, as it concentrates the greatest risk of treatment discontinuation, and already presents with persistent psychosis which may evolve into a range of poor long-term outcomes. Maximizing treatment continuity during the early phase and by doing it mitigating residual psychosis could have consequences over their lifetime for individuals with psychosis.

### 38.2 Long-Term Outcomes in First-Episode Psychosis: Examining Partial Recovery and Rethinking Therapeutic Goals

Kristin Wold*[1], Isabel Kreis[1], Gina Åsbø[2], Carmen Simonsen[2], Ingrid Melle[1]

[1]*Institute of Clinical Medicine, University of Oslo,* [2]*University of Oslo*

**Background:** The course and outcome after the first treatment for psychosis show considerable individual variations, and we need tools to help identify patients requiring different treatments. Recently, efforts have been made to establish consensus criteria defining specific outcome categories, including Clinical Recovery (CR) and Treatment Resistance (TR). The definition of TR is dependent on receiving two adequate treatment trials with different antipsychotics. However, some poor-outcome patients have not received two adequate treatments, leading to uncertainty about whether poor outcomes are based on inadequate treatment effects or treatment efforts. This presentation aims to describe the full range of long-term outcomes in a prospective study of first-episode psychosis (FEP), focusing on patients not meeting the criteria for either CR or TR.
**Methods:** A total of 102 participants with FEP DSM-IV Schizophrenia spectrum disorders were recruited within their first year of treatment and followed in a prospective longitudinal study for 10 years. Treatment history was gathered through interviews and medical charts. Side effects were reported using the UKU Side Effect Scale. Treatment resistance (TR) was defined based on the Treatment Response and Resistance in Psychosis Working Group (TRRIP) criteria, and Clinical Recovery (CR) was defined using the Remission in Schizophrenia Working Group (RSWG) criteria for remission with the addition of functional recovery.
**Results:** At ten years, 29 % of the sample met the criteria for CR and 31 % for TR, leaving 40 % of the sample in a heterogenous middle group (MG). The outcomes in the MG ranged

from an unstable recovery group, (18% of the MG) on the one hand, with members experiencing both symptomatic and functional remission at follow-up but with a duration of symptom remission that was too short to meet the criteria for CR, to the poor outcome group (26 % of the MG) with members without symptomatic and functional remission who had not received two adequate treatment trials and thus not meeting criteria for TR. A large proportion of this latter subgroup had been continuously psychotic throughout the 10-year follow-up period. The largest part of the MG (53 %) was the no-functional recovery group with members currently in symptomatic remission but without functional recovery. Finally, one participant met the criteria for functional recovery while still experiencing psychotic symptoms. There was a significant difference in baseline diagnosis ($\chi2=23.32$, p. < 001) and gender ($\chi2=3.77$, p=.04) between the CR, MG, and TR groups, with the TR group consisting of more men and baseline schizophrenia diagnoses than the CR group. There were no such significant differences between MG sub-groups. A total of 77% of the whole sample reported a high side effect burden. There were no differences in side-effect burden between the CR, MG, and TR groups. Within the MG, the no-functional recovery and the poor-outcome-without-sufficient-treatment group reported a higher side effect burden at baseline than the other two groups. There was a significant difference in the duration of untreated psychosis (F=11,78, p=.002) and in the number of medication attempts ($\chi2=12.53$, p. < 001) between MG subgroups, where patients in current symptomatic remission had a shorter DUP and more adequate treatment trials.
**Conclusions:** Our findings remind us that partial recovery is the most common outcome of FEP, which also needs clinical and research attention. This includes the well-known observation that current treatments have better effects on clinical symptoms than function and the need for better intervention for negative- and cognitive symptoms. However, the substantial proportion of patients with poor symptomatic outcomes but with < two adequate treatment trials with different antipsychotics raises questions about whether clinicians treating FEP patients may settle for a partial response too early.

### 38.3 Prescription Pattern of Clozapine in Hong Kong and Preferences of Psychiatrists

Sherry Kit Wa Chan*[1], Huiquan ZHOU[1]

[1]*The University of Hong Kong*

**Background:** Despite clear evidence of the efficacy of clozapine in patients with treatment resistant schizophrenia, there is still significant delay in clozapine prescriptions. It has been suggested that the average delay of clozapine prescription is up to 7 years and delay of clozapine prescription has been suggested to be related to effectiveness of clozapine. Many factors have been suggested as barriers of the clozapine initiation, including concerns of side effects of clozapine and the frequent blood taking requirement. We will be reporting antipsychotic prescription pattern before the initiation of the clozapine in a population-based study in Hong Kong and results of survey of treatment preferences of psychiatrists for patients with treatment resistant schizophrenia.
**Methods:** Patients diagnosed with schizophrenia and were prescribed with clozapine for the first time since illness onset between 1 January 2003 and 31 December 2012 was identified from the electronic health record system of Hospital Authority of Hong Kong which is responsible for all the public psychiatric service provision in Hong Kong. The time of clozapine prescription was considered as the index date. Number of different antipsychotics prescribed to the patients before the index date was calculated. An anonymous online survey of psychiatrists in Hong Kong was conducted between September 2019 and February 2020 to

assess the perception clozapine prescriptions and preferences of treatment for treatment resistant schizophrenia patients.
**Results:** A total of 3152 patients who were prescribed with clozapine for the first time was identified between 2003 to 2012. The median number of different antipsychotics prescribed to the patients were 6 and about 25% of patients had 8 or more antipsychotics before the index date. Details of the pattern of antipsychotics will also be reported. For the survey, 22% of registered psychiatrists (N=105) in Hong Kong responded to the survey. About 54% psychiatrists would consider clozapine initiation after three adequate antipsychotic trials despite 74% of psychiatrist refer to Maudsley guidelines for clozapine initiation. For patients who are treatment resistant schizophrenia not prescribed with clozapine, 71% of psychiatrists opt for antipsychotic polypharmacy, 56% opt for depot antipsychotics and 25% choose ECT.
**Conclusions:** Both the population-based study on the antipsychotic use pattern before clozapine and the opinion from the psychiatrists, there is a clear delay in clozapine prescription for patients with treatment resistant schizophrenia, despite the high degree of familiarity of treatment guidelines. A wide range of treatment options have been considered for those with treatment resistant schizophrenia other than clozapine. Further studies to understand and alleviate the barriers of clozapine initiations as well as development of alternative effective treatment strategies for patients with TRS would be important.

### 38.4 Receipt of Pharmacological and Psychological Treatment in the 25 Years Following First Admission for Psychosis

Katherine Jonas*[1], Wenxuan Lian[1], Roman Kotov[1]

[1]*Stony Brook University*

**Background:** Clinical trials of both pharmacological and psychosocial interventions for psychosis have established both as reliable interventions for this population. Furthermore, treatment guidelines outline best practices for implementation of these interventions. However, it is unclear how many individuals with schizophrenia and other psychotic disorders receive the kind of treatment indicated by these guidelines. This investigation of services received in an epidemiological cohort of first-admission psychosis highlights the typical course of treatment received over the 25 years following first admission.
**Methods:** Data are drawn from the Suffolk County Mental Health Project, a first-admission psychosis cohort with a baseline recruitment period spanning 1989-1995 and subsequently followed for 25 years. Psychiatric medications received were assessed on a daily basis for the first 4 years of the study, and cross-sectionally at subsequent follow-ups. Medications were recorded based on self-report, informant report, medications brought to in-person assessments and medical records. Psychological interventions received were recorded based on self-report, informant report, and medical records. Pharmacological interventions received were compared to the standards for a sufficient course of treatment set out in TRRIP guidelines.
**Results:** In the four years following first admission, 75% of the cohort did not receive a course of pharmacological treatment that met TRRIP guidelines. Of those with a diagnosis with schizophrenia (N=299), this number was 41%. Only 25 individuals out of the schizophrenia subsample received more than 2 trials, the number necessary to establish treatment resistance according to TRRIP guidelines. Over 70% of those with schizophrenia were receiving antipsychotic medication at any given follow-up. Many of these trials, however, were at insufficient dosages. Approximately a third of those with schizophrenia were receiving psychotherapy as of the 4-year follow-up, but this number dropped to < 20% as of the 25-year follow-up.

**Conclusions:** A minority of individual with psychotic disorders receive pharmacological interventions consistent with treatment guidelines. This was most often due to inadequate dosing. While individuals with schizophrenia receive more treatment than those with other psychotic disorders, interventions still fall short of what is recommended. At no point during the 25 years following first admission did more than 30% of the cohort receive psychotherapy. Greater support for implementation and outreach is needed in order to ensure that this population receives the level of support indicated by clinical research.

## 39. From Molecules to Minds: Highlights of Psychosis Research in Asia

Eric YH Chen, *University of Melbourne*

**Overall Symposia Abstract:** Psychosis research largely has assumed a paradigm free from cultural and ethnic contexts, emphasising the universality of the core biological mechanisms. Recent advances have highlighted possible interactions between biological, environmental, and psychosocial factors. This highlights the need to attend to population-specific aspects of pathogenic and therapeutic factors. In Asia, several established teams have been conducting empirical studies on psychosis populations that are exposed to unique cultural, psychosocial and even biological environments. In this symposium, we highlight diverse investigations ranging from molecular studies of immune biomarkers to multi-modal molecular imaging, social cognitive function investigations and psychological interventions. We have chosen investigators in various stages of career development in four different locations. Dr Li (Singapore) will present profiling of psychosis patients based on immunological responses. Dr Suen (Hong Kong) will report on the relationship between dopamine synthesis, glutamate activity and formal thought disorder. Prof Nemoto (Japan) will report on his study of social cognitive impairment in Japanese patients, while Prof Kim (South Korea) will present a study of psychological intervention in psychosis. This symposium offers a unique opportunity to review the latest results on several key aspects of psychosis research and to reflect on the contrast between studies and findings between Asian and Western locations.

### 39.1 Immunophenotyping Schizophrenia Subtypes Stratified by Antipsychotic Response

Yanhui Li*[1], Jocelyn Wen Xin Ong[2], Yuen Mei See[1], Jie Yin Yee[1], Charmaine Tang[1], Shushan Zheng[1], Boon Tat Ng[1], Bernett Teck Kwong Lee[3], Olaf Rotzschke[2], Anand Kumar Andiappan[2], Jimmy Lee[1]

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**Background:** Immune dysfunction has been proposed to play a role in the pathophysiology underlying psychosis. However, current immunophenotyping studies are limited by small sample sizes and number of immune markers investigated. Pharmacological subtypes in schizophrenia based on antipsychotic response have also been proposed, but few studies have examined immunophenotypes in schizophrenia with varying degrees of treatment resistance. In this study, we performed comprehensive immunophenotyping on 196 subjects comprising 147 schizophrenia patients stratified by antipsychotic response (49 antipsychotic-responsive, 70 clozapine-responsive, 28 clozapine-resistant) and 49 healthy controls. We aimed to

identify significant immune cell populations associated with schizophrenia and increasing treatment resistance, as potential modulators of underlying psychosis and treatment response.
**Methods:** Patients with schizophrenia were recruited and assessed on the Clinical Global Impression – Schizophrenia (CGI-SCH). Treatment response was defined as a rating of three (mild severity) or less on the CGI-SCH positive symptom item after at least 8 weeks of adequate antipsychotic or clozapine treatment. Peripheral blood mononuclear cells were collected, and flow cytometry was performed to identify 66 immune cell populations. Differences in cell population proportions were compared between schizophrenia cases and controls, and across all 4 groups, with post-hoc pairwise comparisons.
**Results:** Mucosal-associated invariant T (MAIT) cells, total, exhausted and memory CD8+ T cells, VD1+ ϒδ T cells, plasmablasts, IgG+ B cells and conventional dendritic cells 2 (cDC2) were among the top cell populations downregulated in schizophrenia. We observed increased downregulation with increasing treatment resistance. Conversely, naïve and exhausted CD4+ T cells, CD4/CD8 ratio and CCR5+CCR2+ HLA DR+ Myeloid cells were found to be upregulated in schizophrenia and with increasing treatment resistance.
**Conclusions:** We show significant immunophenotypic differences between schizophrenia cases and healthy controls, and consistent trend differences across varying degrees of antipsychotic resistance. We also examined immune cell populations not previously reported in schizophrenia and highlight the CD4/CD8 ratio as a potential biomarker of antipsychotic resistance in schizophrenia. Future studies may further explore immune markers identified as potential biomarkers of treatment resistance and clarify on the relationship between immunological changes and pharmacological subtypes in schizophrenia.

### 39.2 Relationship Between Striatal Dopamine Synthesis, Anterior Cingulate Glutamine-Glutamate Levels, and Formal Thought Disorder in First-Episode Psychosis

Yi Nam Suen*[1], Sherry Kit Wa Chan[1], Wing Chung Chang[1], Christy Lai Ming Hui[1], Ho Ming Edwin Lee[1], Oliver Howes[2], Eric Yu Hai Chen[1]

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**Background:** Formal thought disorder (FTD) is a core symptom of schizophrenia, often manifesting during the first episode of psychosis (FEP). Although dopaminergic dysregulation, particularly in the striatum, is linked to psychosis, the specific neurochemical underpinnings of FTD remain unclear. Emerging evidence suggests that glutamatergic dysfunction, particularly in the anterior cingulate cortex (ACC), may also contribute to FTD. This study investigates the interaction between striatal dopamine synthesis capacity and ACC glutamate levels and their relationship to FTD severity in individuals with FEP.
**Methods:** We recruited a prospective cohort of 34 first-episode psychosis patients (53% female and mean age 40.9 ± 13.6 years). Positron emission tomography–magnetic resonance imaging was used to measure striatal dopamine synthesis capacity (Kocc(min-1)), while magnetic resonance spectroscopy (MRS) assessed ACC glutamine-glutamate levels. Based on the median cutoff levels of each measure, we categorised participants into four groups: (I) low levels in both measures, (II) low dopamine but high ACC glutamine-glutamate, (III) high dopamine but low ACC glutamine-glutamate, and (IV) high levels in both measures. We then compared FTD-related symptoms, as measured by items in the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), and Clinical Language Disorder Rating Scale (CLANG), using analysis of covariance (ANCOVA). The models were adjusted for duration of untreated psychosis, age, sex, years of education, and medication use at the time of scanning.

**Results:** FEP patients exhibited significantly higher striatal dopamine synthesis capacity and elevated ACC glutamine-glutamate levels compared to controls (both $p = 0.02$). While no overall correlation was observed between dopamine and glutamate levels, a moderate positive correlation emerged in younger-onset patients ($rs = 0.47$, $p = 0.047$). Individually, neither dopamine nor glutamate levels were significantly associated with FTD symptoms. However, when both neurochemical systems were considered together, significant differences in FTD severity were found. Compared to other three groups, patients with low levels of both dopamine and glutamine-glutamate showed the most severe FTD symptoms, including higher SAPS FTD subscale scores, pressure of speech, distractible speech, clanging, and CLANG referential failures and subscale score of items 4 (semantic association deficits) and 5 (referential failures). These patients also displayed increased SAPS incoherence and CLANG subscale scores (items 1 to 6, and 4 to 6), compared to those with low dopamine but high glutamine-glutamate, or high levels of both measures. Furthermore, patients with low levels of both dopamine and glutamine-glutamate exhibited higher levels of tangentiality, compared to patients with high dopamine but low glutamine-glutamate, or high levels of both measures. These patients demonstrated significantly higher CLANG total scores and poverty of speech compared to those with high levels of both measures and high pressure of speech compared to those with low dopamine but elevated glutamine-glutamate levels.
**Conclusions:** The findings indicate that impairments in striatal dopamine synthesis capacity and anterior cingulate glutamate function are linked to more severe formal thought disorder in first-episode psychosis patients. This is particularly noteworthy, as positive symptoms in psychosis are typically associated with elevated striatal dopamine synthesis, which is often accompanied by decreased glutamate neurometabolic levels. Further research with larger sample sizes is needed to confirm these results and elucidate the specific biological mechanisms underlying the relationship between neurotransmitter dysregulation and disorganised cognition in the early stages of psychosis.

### 39.3 Advances in Research on Social Cognition in Patients With Schizophrenia and Other Mental Disorders in Japan

Takahiro Nemoto*[1]

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**Background:** Social cognition mediates the relationship between neurocognition and social functioning and impacts patients' recovery in schizophrenia. However, little is known about how patients themselves perceive social cognition. Meanwhile, patients with major depression also exhibit cognitive impairments, which are often prolonged, but little is known about the role of social cognition in major depression.
**Methods:** We investigated their knowledge of social cognition, clinical experiences related to social cognition, awareness of social cognition's role in one's social life, using an internet survey.
Furthermore, we focused on the clinical subtypes classified by the discrepancies between the subjective difficulties in social cognition and actual cognitive impairment.

We also examined the mediation effects of social cognition on the relationship between neurocognition and social functioning in schizophrenia and depression.

**Results:** Patients with schizophrenia had substantial subjective difficulties in social cognition, which they perceived as being related to social functioning. However, their knowledge of social cognition was limited. And, it was suggested that the assessment and treatment are not widespread in clinical settings in Japan (Uchino, Nemoto et al., 2022).

An analysis yielded three clusters in patients with schizophrenia and awareness about such clinical subtypes of social cognition seems to serve as a guidepost for providing individualized, targeted interventions (Uchino, Nemoto et al., in press).

The role of social cognition in major depression was similar to that in schizophrenia (Uchino, Nemoto et al., 2023).

**Conclusions:** We also examined the relationship between antenatal mental health and social cognition bias among pregnant women (Takubo, Nemoto et al., 2022). Social cognition could be a common endophenotype for various psychiatric disorders.

### 39.4 Effectiveness of Group Metacognitive Training and Cognitive Behavioral Therapy in Patients With Early and Chronic Schizophrenia and its Digital Application

Sung-Wan Kim*[1], Jae-Kyeong Kim[2], Cheol Park[3], Min Jhon[4], Ju-Wan Kim[1], Ju-Yeon Lee[1], Seunghyong Ryu[1], Jae-Min Kim[1], Seung-Hwan Lee[5], Young-Chul Chung[1]

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**Background:** Psychosocial interventions are essential for recovery in patients with schizophrenia, particularly during the early stages, to improve long-term functional outcomes. This study evaluates the effectiveness of group Metacognitive Training and Cognitive Behavioral Therapy (MCT and CBT) in patients with early and chronic schizophrenia. Additionally, a digital platform was developed to deliver MCT and CBT via a smartphone application, expanding access to these therapies.
**Methods:** Psychosocial interventions are essential for recovery in patients with schizophrenia, particularly during the early stages, to improve long-term functional outcomes. This study evaluates the effectiveness of group Metacognitive Training and Cognitive Behavioral Therapy (MCT and CBT) in patients with early and chronic schizophrenia. Additionally, a digital platform was developed to deliver MCT and CBT via a smartphone application, expanding access to these therapies.
**Results:** The MCT and CBT group showed significant improvements in cognitive insight and social functioning, with repeated measures ANOVA indicating significant time × group interactions for BCIS and SOFAS scores. Additionally, paired t-tests revealed reductions in the BDI and negative symptoms of the PANSS within the MCT and CBT group. No significant differences in treatment efficacy were observed between early-stage and chronic patients.
**Conclusions:** Group MCT and CBT led to significant improvements in cognitive insight and social functioning in both early-stage and chronic schizophrenia patients. The initial results from the digital delivery of MCT and CBT through the smartphone application indicate promising engagement and effectiveness.

## 40. Paranoia Across the Psychosis-Spectrum From Complimentary Cognitive Neuroscience Perspectives

Krista Wisner*, Indiana University Bloomington*

**Overall Symposia Abstract:** Paranoia, also called persecutory ideation, is a construct occurring in the general population along a continuum. When extreme, it is considered quintessentially psychotic and frequent in schizophrenia. When mild, it presents as

suspiciousness, which can deteriorate social relationships and impair functioning. This symposium combines exciting research from a diverse set of speakers who employed robust experimental paradigms to investigate neural correlates of paranoia in samples spanning the full continuum. We aim to integrate recent innovations to identify common mechanisms for future study.

First, Lincoln addresses the overlap of paranoia and fear processing, relevant to high rates of co-occurring traumatic experiences. Data from a fear conditioning paradigm was collected during electroencephalography (EEG). Analyses aimed to identify aberrant fear psychophysiology in people in At-Risk Mental States and healthy controls. Participants were split into low or high paranoia groups based on self-report ratings. Results suggest during the fear acquisition phase, the high paranoia group showed more pronounced late positive potentials in the EEG signatures to conditioned stimuli, relative to the low paranoia group, indicating more differential fear conditioning.

Second, Kazinka advances by testing prior beliefs about other people in a first-person social decision-making task. The Minnesota Trust Game was collected during neuroimaging (fMRI), which differentiates suspiciousness-driven mistrust (i.e., sensitivity to others' spitefulness), from rational mistrust (i.e., sensitivity to others' selfishness). Using clinical and non-clinical samples, Kazinka identified brain functioning associated with suspiciousness-driven mistrust that was associated with individual differences in paranoia. In the community participants who were monozygotic twins, discordance analyses highlighted environmental variance had a causal role in findings.

Third, Sheffield probes mechanisms in the context of a manualized clinical trial. A probabilistic reversal learning task was employed during neuroimaging (fMRI) in schizophrenia-spectrum patients randomized to receive either cognitive behavioral therapy for psychosis or a befriending therapy, plus typical care. Task performance, brain functioning, and symptoms were evaluated pre- and post-intervention. Computational models derived metrics of patients' prior expectations about volatility in the environment from task data. Delusional severity (including paranoia), volatility priors, and task-related brain activation all reduced after intervention and were significantly associated.

Fourth, Miyata integrates lines of research focused on hastiness, inaccurate confidence, and inefficient belief-updating for judgements in people who experience delusions (including paranoia) in the psychosis-spectrum using tasks focused on reasoning tendencies. Neuroimaging (fMRI) analyses examining how predispositions in brain states related to such altered reasoning reiterated regions from earlier presentations, highlighting involvement of the striatum, medial prefrontal plus precuneal cortices, and frontoparietal connectivity.

Importantly, neuroimaging analyses across studies emphasized brain regions involved in salience processing and executive control were aberrant in people with high paranoia. EEG results by Lincoln align with this consensus, as the late positive potential reflects sustained attention and controlled elaborations of motivational salience to evaluate stimuli. Together, these presentations provide a compelling argument to focus future paranoia research on the interaction of these two systems.

## 40.1 The Association of Paranoid Ideation With Fear Acquisition and Extinction in a Novel Imagery-Based Fear Conditioning Paradigm Using EEG

Tania Lincoln*[1], Nilay Demirdal[1], Metin Özyagcilar[1], Anja Riesel[1], Tina Lonsdorf[2], Eric Müller[3]

[1]*University of Hamburg, Institute of Psychology,* [2]*University of Bielefeld, Institute of Psychology,* [3]*Philipps University Marburg, Institute of Psychology*

**Background:** Background:
The classic fear conditioning paradigm has provided a powerful model of emotional learning that has helped to optimize exposure treatments for anxiety disorders. Paranoid delusions share several core features with anxiety disorders, such as fear, psychophysiological arousal, and avoidance. Maladaptive fear acquisition and extinction learning might therefore have a prominent role in the formation and maintenance of paranoid delusions. A critical issue here is that, unlike most anxiety disorders, paranoid delusions are not directly linked to real life threat experiences. Although social traumata are a prominent risk factor, they are not direct precipitators of paranoid delusions, and the specific content of delusions tends to be detached from tangible threat experiences. Recent research, however, suggests that de novo fear conditioning can occur even in absence of external aversive stimulation if anxiety provoking mental imagery (US) becomes associated with other stimuli (CS). It is therefore promising to explore whether paranoid ideation is linked to aberrant fear learning from socially relevant aversive mental images.

Using a novel paradigm, this study aims to identify the psychophysiological and neural aberrancies in fear acquisition and extinction associated with paranoid ideation and their predictive value for subsequent symptom development of psychosis.

**Methods:** Participants were trained in imagery to conduct a novel imagery-based differential-conditioning paradigm – including habituation, acquisition, and extinction phases. Neutral faces (CS) were paired with different cues (shapes) in randomized order, followed by an imagined aversive scenario (US) of stepping on a thumbtack, a neutral scenario of stepping on a coin or no cued imagery at 80% contingencies. Neural responses in form of the Late Positive Potential (LPP, as the mean amplitude in the time window from 300 to 1000 ms, averaged across centro-parietal sites) were recorded via a 64-channel EEG. In addition, self-reported fear and US expectancy ratings and skin conductance responses (SCRs) were assessed.
To capture the symptom formation phase while securing heterogeneity in symptom scores, the sample (n=112, anticipated total sample size at the end of data collection in Feb 2025, n = 135) encompasses participants fulfilling criteria for an At Risk Mental Stare, participants with elevated psychosis proneness (score ≥ 2.8 on the positive subscale of the Community Assessment of Psychic Experiences) and mentally healthy participants. Paranoid ideation was measured by the persecutory subscale of the Green Paranoid Thoughts Scale-revised (GPTS-R) and participants were subdivided into low paranoid ideation (n=79, mean age 23,6, 76% female) versus high paranoid ideation (n=33, mean age 26, 78% female) based on the cut-off-criteria for elevated paranoia provided by the authors of the GPTS-R.

**Results:** In the acquisition phase, the high paranoia group showed significantly more pronounced LPP amplitudes to the CS+ vs. CS- than the low paranoia group with no

significant difference in responses to the CS-, which indicates more differential fear conditioning in the high paranoia group. No group differences were evident in the SCR response or fear and expectancy ratings. Contrary to our expectations, there were no significant group differences in extinction learning.
**Conclusions:** The findings tentatively indicate that people holding paranoid beliefs could show a pronounced preparedness to acquire fear to neutral faces. The indication for the further development of exposure-based therapies for paranoid delusions will be discussed.

### 40.2 Left Lateral Orbitofrontal Cortex Shows Potentially Causal Role in Spite Sensitivity

Rebecca Kazinka*[1], Sylia Wilson[2], Angus MacDonald, III[1]

[1]*University of Minnesota,* [2]*University of Minnesota Institute of Child Development,*

**Background:** Persecutory ideation can cause significant distress, yet not all individuals with psychosis have persecutory delusions. Furthermore, individuals without psychosis can experience elevated levels of suspiciousness of others, which may be related to a similar process in psychosis. We examined spite sensitivity, or the fear that others are willing to take a loss to ensure that you will as well, in both people with psychosis (PwP) and a non-clinical sample with elevated persecutory ideation to assess similarities in neural mechanisms of persecutory ideation.
**Methods:** The Minnesota Trust Game (MTG) was designed to measure spite sensitivity in a MR scanner. Individuals decide whether to trust an anonymous partner who can choose to give an equal amount of money between themselves and the player, or either receive more or less money to give the player a varying smaller amount of money. We propose that specific distrust when the partner is incentivized to be trustworthy (suspiciousness condition) represents persecutory ideation and is distinct from distrust when the partner is incentivized to be untrustworthy (rational mistrust condition). We have also established a normative model of spite sensitivity from this task, which separates spite-guilt beliefs about a partner's intentions and risk aversion related to losing money. In two studies, we administered the MTG during fMRI to 1) 49 individuals with early psychosis with a range of persecutory ideation symptoms and 2) a community sample with 46 probands with elevated persecutory ideation and 23 of their monozygotic twins.
**Results:** In Study 1, we found that PwP with greater persecutory ideation were more distrustful during the suspiciousness condition specifically ($\beta = -.56$, $p < .001$). Neural activation during this condition was associated with lateral OFC, dmPFC, and vmPFC. Performance during the suspiciousness condition and persecutory ideation were also associated with dysconnectivity between the left frontoparietal network and the lateral OFC/salience network (task performance: $r = -.25$, $p = .041$; persecutory ideation: $r = -.38$, $p = .007$). In contrast, the rational mistrust condition was associated with bilateral caudate activation; left caudate activation during the rational mistrust condition was negatively correlated with risk aversion ($r = -.49$, $p < .001$). In Study 2, elevated persecutory ideation was associated with distrust during the suspiciousness condition ($\beta = -.56$, $SE = .036$, $p = .007$), and twin discordance in spite-guilt beliefs predicted persecutory ideation, more strongly suggesting an underlying causal relationship ($\beta = -2.18$, $SE = .63$, $p = .002$). Bilateral OFC and dmPFC were also related to task performance in the suspiciousness condition. Furthermore, twin discordance in left lateral OFC activation predicted task performance in the suspiciousness condition, again suggesting a causal relationship ($\beta = -.14$, $SE = .06$, $p = .019$). As seen in Study 1, bilateral caudate was activated during the rational

mistrust condition, and risk aversion was negatively associated with left caudate activation (β = -.007, SE = .003, p = .013).
**Conclusions:** Lateral OFC was associated with spite sensitivity, a proxy for persecutory ideation, in two separate samples, suggesting it may be a valuable target in better understanding paranoia. Components of the default mode network (dmPFC and vmPFC) were also associated with spite sensitivity, and connectivity between the frontoparietal and salience networks demonstrated a relationship with persecutory ideation, suggesting both regional activation and their relationship play important roles in social decision-making.

**40.3 Changes in Neural Substrates of Prior Expectations of Environmental Volatility Following Psychotherapy for Persecutory Delusions: A Randomized Clinical Trial**
Julia Sheffield*[1], Ali Sloan[2], Philip Corlett[3], Aaron Brinen[1], Stephan Heckers[1]

[1]*Vanderbilt University Medical Center,* [2]*Vanderbilt University,* [3]*Yale University*

**Background:** Persecutory delusions are common, distressing, and difficult to treat. Elevated prior expectations about environmental volatility represent a putative cognitive mechanism contributing to persecutory delusion severity. Identifying whether volatility priors, and their neurocomputational substrates, are amendable to change with treatment will facilitate identification of therapeutic targets. The current study used a clinical trial intervention to determine whether change in computationally-derived volatility priors and their neurobiological correlates are observed following the reduction of delusions with psychological treatment, and to examine associations between changes in symptoms, volatility priors, and task-evoked brain activity.
**Methods:** This assessor-blind, randomized clinical trial recruited participants from Vanderbilt University Medical Center (VUMC) and the Nashville area from April 9, 2021 to December 5, 2023. Eligible participants were between 18-65 years old and had a schizophrenia-spectrum or delusional disorder diagnosis, accompanied by an active, persistent ( > = 3 months) persecutory delusion with strong conviction ( > 50%). Fifty-three individuals were randomized 1:1 to a manualized, 8-week cognitive behavioral therapy for psychosis (CBTp) intervention plus usual care (n=28) or Befriending Therapy plus usual care (n=25). All participants completed a 3-option probabilistic reversal learning task (3PRL) and clinical assessments immediately before and after treatment. A subset of those (N=35) completed the 3PRL during collection of functional magnetic resonance imaging (fMRI) data. Performance on the 3PRL task was modeled using a Hierarchical Gaussian Filter (HGF), which estimates prior expectations of volatility. The striatum and prefrontal cortex (PFC) were included as a-priori regions of interest. Associations between changes in volatility priors, symptom severity, and task-evoked activation was examined. The Positive and Negative Syndrome Scale (PANSS) positive symptom subscale was included as a secondary clinical outcome.
**Results:** We observed a significant reduction in volatility priors following treatment ($F(1,100)=8.5$, $p=.004$, Cohen's $d=.58$). This was in the context of a significant reduction in delusion severity ($F(1,100)=50.9$, $p < .001$; Cohen's $d=1.4$) and positive symptom severity ($F(1,101)=9.4$, $p=.003$; Cohen's $d=0.61$) across all participants. Volatility priors were significantly associated with clinical improvement in PANSS positive symptoms ($F(1, 95.3)=13.4$, $p < .001$) but not PSYRATS total ($F(1,93.7)=2.0$, $p=.16$). Activation in the right caudate and left PFC during decision-making significantly reduced following treatment. Reduced activation in the caudate was associated with reduced volatility priors ($F(1,58.3)=16.6$, $p < .001$) and positive symptoms. Positive symptom improvement also

correlated with reduced PFC-activation ($F(1,35)=15.4$, $p < .001$). Results were robust to individual differences in antipsychotic medication.
**Conclusions:** Using a clinical trial, this study reveals that elevated prior expectations of environmental volatility are amenable to change, making them state-markers of delusion severity. Activity in the caudate nucleus is sensitive to change with treatment and relates to changes in volatility priors and positive symptom severity. Over-estimating volatility is therefore a modifiable cognitive mechanism of psychosis that represents a novel treatment target.

### 40.4 Neurocognitive Three Factor Model of Delusion

Jun Miyata*[1]

[1]*Aichi Medical University*

**Background:** Delusions, as defined by Karl Jaspers in 1913, have three key features: 1) a falsely formed belief, 2) held with conviction, and 3) incorrigibility. This definition remains largely unchanged in the DSM-5-TR. These features map onto current neuroscientific concepts: aberrant salience, inaccurate metacognition, and inefficient belief-updating.
Individuals with delusions exhibit a cognitive bias called "jumping to Conclusions:" (JTC), requiring less evidence for decision-making compared to healthy individuals. This is considered a key cognitive mechanism in delusion formation. Dopamine neurons in the midbrain-striatum code stimulus salience, and in psychosis, the hyper-dopaminergic state of the striatum is thought to cause aberrantly heightened salience attribution, leading to delusions and hallucinations (aberrant salience hypothesis: Kapur, 2003). However, the relationship between cognitive (JTC) and neural (midbrain-striatal aberrant salience) mechanisms was unclear.

Metacognition, particularly confidence in one's own beliefs, plays a significant role in delusions. In schizophrenia, patients show "inaccurate metacognition," with stronger confidence in false memories and weaker confidence in true ones compared to healthy individuals (Moritz et al., 2006). The neural correlates of delusional confidence remain unclear.

Schizophrenia patients also show a cognitive bias of inefficient belief updating, called "bias against disconfirmatory evidence (BADE)", linked to the frontoparietal network (FPN) (Lavigne et al., 2020). If FPN is associated with clinical delusion severity is unclear.

In this study, we explored the neural correlates of delusion formation, confidence, and incorrigibility using cognitive tasks and functional magnetic resonance imaging (fMRI).

**Methods:** We used the beads task for JTC, type 2 signal detection theory for confidence in visual discrimination, Peters et al. Delusions Inventory for delusional confidence, and the Positive and Negative Syndrome Scale for delusion/hallucination severity. Independent component analysis (ICA) was applied to resting-state fMRI (rsfMRI). We performed a task fMRI for the visual discrimination task. A Bayesian model was used for beads task data analysis.
**Results:** We found that anticorrelation between the striatum and precuneus was correlated to both JTC and delusion severity (Miyata et al., PCN, 2024). Bayesian analysis revealed that the weighting value for new evidence was correlated with JTC. Task fMRI showed altered confidence patterns and connectivity in visual discrimination in schizophrenia (Koizumi et

al., Neuroimage Clinical, 2020). The medial prefrontal cortex-precuneus connectivity was related to confidence in delusional beliefs. Finally, the rightward asymmetry of FPN connectivity was correlated to delusion and hallucination severity (Son et al., 2017).
**Conclusions:** We propose a neurocognitive three-factor model of delusion: aberrant salience for formation, inaccurate metacognition for conviction, and inefficient belief updating for incorrigibility. This model, grounded in a Bayesian framework, provides a simple yet comprehensive explanation for the diversity of delusions while resonating with G. Box's famous quote: "All models are wrong, but some are useful."

## 41. Glutamate-Based Drugs for the Treatment of Schizophrenia Symptoms: Data From Human and Animal Studies

Inna Gaisler-Salomon, *University of Haifa*

**Overall Symposia Abstract:** This symposium explores cutting-edge research on glutamate-based pharmacological interventions for schizophrenia, presenting findings from both animal models and human studies. The glutamatergic system has emerged as a promising target for addressing the complex symptomatology of schizophrenia, particularly cognitive and negative symptoms that typically emerge prior to the appearance of psychosis and are inadequately treated by currently prescribed antipsychotics. While research on glutamate in schizophrenia initially focused on the NMDA receptor, recent studies highlight the role of other receptor types as well as presynaptic glutamate synthesis and recycling mechanisms. Our panel will discuss various approaches to modulating glutamatergic neurotransmission and their potential therapeutic benefits.

Inna Gaisler-Salomon will present new research on glutaminase inhibition as a novel therapeutic strategy, citing recent data from studies in genetically modified mice and pharmacological models. Jean-Philippe Pin will discuss positive allosteric modulators (PAMs) for glutamate receptors. Patricia Gassó will focus on metabotropic glutamate receptor 2 (mGluR2) as a potential treatment target. Finally, Josh Kantrowitz will present clinical data on D-serine supplementation in schizophrenia patients.

This symposium aims to provide a comprehensive overview of current research on glutamate-based approaches to treating schizophrenia. In particular, we will discuss the need to develop interventions in the early stages of the disease. By bringing together experts working on different aspects of glutamatergic modulation, from preclinical animal studies to human clinical trials, we seek to foster a deeper understanding of the potential and limitations of these novel therapeutic strategies. The symposium will highlight the importance of translational research in developing new treatments for schizophrenia and stimulate discussions on future directions in this field.

### 41.1 Glutaminase Inhibition in an Animal Model of Schizophrenia

Inna Gaisler-Salomon*[1], Avital Zigman[1], Kfir Asraf[1], Konstantin Andrianov[1]

[1]*University of Haifa*

**Background:** Glutamate neurotransmission is disrupted in schizophrenia, particularly in CA1, and human studies show an association between elevated CA1 glutamate and symptom susceptibility. We previously showed that CNS-Glud1-/- mice, homozygous for a deletion of the glutamate catabolizing enzyme Glutamate Dehydrogenase (GDH; Glud1 gene), show enhanced CA1 glutamate and schizophrenia-like behavioral abnormalities, also present in heterozygous CNS-Glud1+/- mice exposed to mild stress. Conversely, mice heterozygous for a constitutive mutation in the Glutaminase 1 (Gls1) gene, which encodes an enzyme that converts glutamine to glutamate in neurons, display reduced CA1 glutamate and resilience to schizophrenia-like abnormalities. We created double-mutant mice heterozygous for both Glud1 and Gls1 mutations in CNS, to investigate if Gls1 deficiency mitigates CNS-Glud1+/- deficits. Furthermore, we tested the ability of a newly developed Gls1 inhibitor (iGLS1x) to reverse schizophrenia-like abnormalities in CNS-Glud1-/- mice and in mice treated with an NMDA receptor blocker. Glutamate levels ex-vivo were measured in all experiments.
**Methods:** In Experiment 1, CNS-Glud1+/-, CNS-Gls1+/-, CNS-Glud1+/-;Gls1+/- (double mutants) and CNS-Cre+ Controls were exposed to mild stress and tested for cognitive abnormalities, the locomotor response to amphetamine (2 mg/kg) and changes in their CA1 metabolomic profile. In Experiment 2, CNS-Glud1-/- and CNS-Cre+ Controls were treated with iGLS1x. In Experiment 3, wild-type mice were treated with MK-801 or vehicle for 2 weeks in adolescence, and iGls1x in adulthood. Cognitive behavior, amphetamine-induced locomotor activity and glutamate levels in CA1 were assessed ex-vivo in adulthood.
**Results:** In Experiment 1, CNS-Glud1-deficient mice displayed locomotor hyperactivity both at baseline and following amphetamine (2mg/kg) administration, as well as increased hippocampal glutamate and glutamine. CNS-Gls1+/- and double-mutant mice showed no increase in activity and control-like glutamate levels. Data emerging from Experiments 2 and 3 indicate that iGls1x may be effective in counteracting some schizophrenia-like behavioral abnormalities induced by either CNS-Glud1 deficiency or chronic NMDA receptor blockade.
**Conclusions:** These preliminary findings in double-mutant and iGls1x-treated mice indicate that GLS1 inhibition may have therapeutic value in counteracting some behavioral and metabolic abnormalities central to schizophrenia psychopathology. This approach may offer a novel therapeutic venue as well as enhanced understanding of the role played by glutamate synthesis and recycling in glutamate-dopamine interactions and cognitive function, both relevant to schizophrenia symptomatology.

## 41.2 Nanobody Immunotherapy Rescues Behavioral Deficits in Schizophrenia Models

Jean-Philippe Pin*[1], Matthieu Osterlaken[2], Angelina Rogliardo[2], Tatiana Lipina[3], Ali Salahpour[3], Amy Ramsey[3], Carine Becamel[2], Julie Kniazeff[2], Philippe Rondard[2]

[1]*University Montpellier - CNRS - Inserm,* [2]*University Montpellier,* [3]*University Toronto*

*Univ* **Background:** Schizophrenia is associated with an increased glutamate synaptic activity, but a decrease in NMDA receptor function. Metabotropic glutamate receptors, by regulating synaptic transmission either at the pre- or post-synaptic level are considered as possible targets for new antipsychotics. Among these mGlu2 receptors received much attention, with some positive results in clinical trials, but without success at phase 3. Lack of success can come from the difficulty in targeting mGlu2 selectively, and to the existence of mGlu2 containing heterodimers. Our aim was to develop mGlu2 homodimer selective nanobodies® with positive allosteric effect, to test this specific target in mouse schizophrenia models
**Methods:** We selected single domain antibodies (VHH or nanobodies®) able to potentiate mGlu2 receptor activity. These were characterized in transfected cells, and optimized for an improved affinity. The optimized nanobody was tested in a developmental (PCP injection at

P7-P11) and a genetic (GRIN KD) mouse model of schizophrenia. Animals were tested in a novel object recognition, Y maze and pre-pulse inhibition tests.
**Results:** We identified a nanobody® with nanomolar affinity able to potentiate the mGlu2 homodimer selectively. We improved its affinity through the fusion with another mGlu2 selective nanobody®. When injected i.p. the nanobody® remains in the blood for < half a day, but is rapidly detected in the brain, and still detectable at high enough concentration for activity 7 days later. In the PCP treated developmental model of schizophrenia, the nanobody® injected i.p. restored the novel object recognition. In the GRIN-KD mice, the nanobody® also restore the alternance in the Y maze, and the pre-pulse inhibition.
**Conclusions:** These data demonstrate that nanobodies® injected peripherally can penetrate the brain, and reach CNS targets. By enhancing specifically mGlu2 homodimers, the nanobody® can restore many of the defects observed in two mouse models of schizophrenia. These data reveal mGlu2 hiomodimers as a possible specific target for schizophrenia, and bring strong evidence for the possibility to use nanobodies® to treat brain diseases.

### 41.3 Effects of the Glutamate Modulator JNJ-46356479 and Clozapine on Cell Culture and a Postnatal Ketamine Mouse Model of Schizophrenia

Patricia Gassó*[1], Albert Martínez-Pinteño[2], David Olivares-Berjaga[3], Natalia Rodríguez[2], Constanza Moren[1], Eduard Parellada[4]

[1]*University of Barcelona-IDIBAPS-CIBERSAM,* [2]*University of Barcelona-IDIBAPS,* [3]*University of Barcelona,* [4]*Hospital Clinic of Barcelona-IDIBAPS-CIBERSAM*

**Background:** Positive allosteric modulators of the metabotropic glutamate receptor 2 (mGluR2), such as JNJ-46356479 (JNJ), inhibit the presynaptic release of glutamate. Dealing with glutamate storm during early stages of schizophrenia (SZ) may be particularly effective to prevent the disease appearance or slow the progression and the clinical deterioration of patients, especially by improving cognitive and negative symptoms. We assessed the neuroprotective and antiapoptotic effects of JNJ and clozapine, as the reference clinical AP with apparent utility in managing negative symptoms, on human neuroblastoma cell culture, as well as their efficacy in reversing behavioral and neuropathological deficits induced in a postnatal ketamine (KET) mouse model of SZ.
**Methods:** On cell culture, we evaluated changes in cell viability, caspase-3 activity, cell death and gene expression produced by JNJ and clozapine alone and in combination with a high dopamine and glutamate concentration, as apoptosis inducers. In the mouse model, C57BL/6J pups were exposed to KET (30mg/kg) on postnatal days (PND) 7, 9, and 11. Then, mice were daily treated subcutaneously with 10mg/kg of JNJ or clozapine during different periods of time: adulthood (PND 80-120), adolescence (PND 35-60) and both (PND 35-120). Changes in behavior, brain protein levels and gene expression in prefrontal cortex (PFC) and hippocampus (HPC) were analyzed.
**Results:** On cell culture, JNJ attenuated apoptosis, particularly by decreasing the caspase 3 activation and increasing and decreasing the number of viable and apoptotic cells, respectively. Its effects seem to be less neurotoxic and more neuroprotective than those observed with clozapine. Moreover, JNJ partially normalized altered expression levels of glycolytic genes, which could act as a protective factor and be related to its putative neuroprotective effect.
Mice exposed to postnatal KET showed a persistence schizophrenic phenotype in adulthood with molecular and behavioral alterations, especially at the level of negative symptoms and cognitive deficits, including deficits in memory, showing less object recognition, and in

spatial working memory, showing less spontaneous alternation in the Y-maze test, and a decrease in motivation and social memory, assessed using the three-chamber and the social interaction task. Moreover, mice showed a reduction in parvalbumin positive (PV+) GABAergic neurons along with alterations in c-Fos expression, an increase in the number of vGLUT vesicles, an increase in nitrosative stress levels, as well as an increase and decrease in brain levels of pro- and anti-apoptotic proteins, respectively.

JNJ treatment improved most of these behavioral and molecular deficits in animals exposed to KET. Particularly, JNJ recovered the spontaneous alternation in the Y-maze, the expected preference for a novel object, the preference for social novelty in the three-chamber and the expected dishabituation in the fifth trial. Moreover, JNJ reduced the nitrosative stress and partially restored the density of PV+ GABAergic neurons, the pattern of c-Fos activity, the levels of vGLUT and Bcl-2, as well as the Bax/Bcl-2 ratio altered by KET. Although, clozapine also showed partial recovery of certain deficits, higher improvement was always observed with the JNJ treatment.

**Conclusions:** Our findings give evidence for the relevance of clinical effectiveness of early treatment with mGluR2 modulators such as JNJ-46356479 as a potential therapeutic approach for mitigating GLU-related alterations involved in the SZ pathophysiology.

### 41.4 Auditory Learning Induced Plasticity as a Pharmacodynamic Target Engagement Biomarker for Glutamatergic Drug Development in Schizophrenia

Joshua Kantrowitz*[1], Dan Iosifescu[2], Pejman Sehatpour[3], Megan Mayer[4], Preetika Govil[4]

[1]*Columbia University,* [2]*NKI/NYU,* [3]*Columbia University and New York State Psychiatric Institute,* [4]*New York State Psychiatric Institute*

**Background:** Part of the failure of glutamatergic approaches is that the specific compounds and dose ranges for recent trials were largely selected without the benefit of target engagement biomarkers. We will present recent work on the development of validated pharmacodynamic "target engagement" biomarkers that permit determination of the degree to which the compounds successfully produce the same neurochemical effects in humans that are observed in rodents.

**Methods:** Recent studies of high dose D-serine utilizing auditory learning induced plasticity—Serial Frequency Discrimination Task (SFDT), mismatch negativity and time-frequency EEG (BetaERD power) as target engagement biomarkers will be described. In the largest, 45 schizophrenia participants participated in a double-blind, parallel-group, randomized, placebo-controlled study of D-serine (80, 100 or 120 mg/kg) or placebo.

**Results:** Across all treatments and visits, there was a statistically significant treatment effect for SFDT improvement (p=0.014), without a significant baseline or order effect. Both 80 and 100 mg/kg individually showed statistically significant, moderate to large effect size within dose SFDT improvement, demonstrating both acute and sustained improvement. By contrast, placebo-treated participants did not show within-group significant improvement after any visit (~5%, n.s.). Consistent with a U-shaped dose curve for NMDAR modulators, the 120 mg/kg dose showed nonsignificant worsening of plasticity. Similar results were seen for target engagement (MMN and BetaERD power), both of which were individually statistically significant for the 100 mg/kg dose, suggesting generalization of effects beyond improvement in strictly auditory measures.

**Conclusions:** Results are supportive of dose-dependent target engagement for both D-serine, de-risking larger, longer studies for clinically relevant outcomes. Implications for related compounds will be discussed.

## Plenary Session VII: Kenyan Leadership in Research on Schizophrenia in Africa - Dr. David Ndetei

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

### 42. Kenyan Leadership in Research on Schizophrenia in Africa

Craig Morgan, *Centre for Society and Mental Health, King's College London*

**Overall Abstract:** -

### 42.1 Kenyan Leadership in Research on Schizophrenia in Africa

David Ndetei, *University of Nairobi/Africa Institute of Mental and Brain Health*

**Individual Abstract:** Globally, approximately 3% of the people have psychosis, such as schizophrenia, schizoaffective disorder, and certain types of bipolar disorder. Kenya stands as the sole African Nation with prior research experience on diagnostic strategies for identifying people who are at clinical high risk (CHR) for psychosis. In our projects on psychosis, we focus collecting multi- modal prognostic or predictive biomarkers including MRI-based imaging, electroencephalogram (EEG), cortisol and genetics.

Our fully equipped biomarkers laboratory is operational and provides a conducive research environment. The laboratory has successfully conducted 145 EEGs scans (and still counting) demonstrating its functional capacity. Additionally, it is equipped with two freezers (-20°C and -80°C) for storage of biological samples such as saliva, blood and plasma (for DNA, RNA and AD biomarkers). To maintain the integrity of samples, the lab relies on the -80°C freezer for long-term storage and a solar-powered inverter system to ensure continuous power supply during outages, a frequent issue in Kenya.

We have also upgraded an existing local MRI scanner, featuring advanced capabilities in diffusion and advanced imaging. So far, a total of 136 MRIs have successful been conducted (and still counting). This strategic upgrade not only empowers us with cutting-edge imaging capabilities but also contributes to the establishment and enrichment of imaging research expertise in Kenya.

Our team has conducted several experiential training programs, offering researchers hands-on experience and creating an environment for collaborative learning. These efforts, alongside focused training sessions, contribute to the dissemination of knowledge and promote a culture of collective growth within the research community.

Our work, particularly the integration of African populations into Clinical High Risk (CHR) studies, signifies a significant stride bridging a significant research gap and elevating our global understanding of psychosis risk dynamics. Our ongoing collaboration with Washington University further enriches our research capacity through knowledge exchange

and collaborative learning. We are committed to advancing mental health research and look forward to future collaborative studies.

**Concurrent Symposia**

**10:30 a.m. - 12:00 p.m.**

**43. The Impact of Social Disconnection, Defeat and Exclusion in Schizophrenia; From Brain Circuits to Epidemiology**

Anne-Kathrin Fett*, City University of London*

**Overall Symposia Abstract:** Social factors play an important role in the etiology and course of schizophrenia and related disorders. Social stressors including social defeat, exclusion, disconnection, or isolation have been linked to heightened psychosis-risk and poorer outcomes. Laboratory-based studies have shown that social exclusion is associated with neurobehavioral correlates of psychosis in animal models. Despite the clear role of social stressors in schizophrenia-spectrum conditions, a lack of consensus on how these concepts are defined, measured, and integrated across disciplines limits progress in developing effective prevention and intervention measures. This translational symposium will draw together evidence from epidemiology, human experiments, and animal models. By synthesizing findings from multiple levels of analyses, it highlights the need for interdisciplinary collaboration and transdiagnostic investigations in studying social stressors and their impact in psychosis.

First, Dr Fett will present a transdiagnostic investigation of the association between two aspects of social disconnection and real-world clinical and functional outcomes in a large sample of 15,512 individuals treated in Dutch mental health services. The findings show that relationship dissatisfaction and loneliness are independently associated with higher symptomatic distress and poorer role functioning, with particularly strong associations in psychosis and bipolar disorder.

Next, Ms. Rbeiz will present an experimental investigation on the acute effects of social defeat on personal space regulation and self-disturbance in people with and without psychosis. Experience of defeat was induced in participants. Following, an interpersonal distance task in immersive virtual reality was conducted. Self-disturbance was assessed with self-report measures and a body mapping task. Her findings show that acute social defeat resulted in altered personal distance and embodiment of emotions.

Third, Dr. Morishita will present a neurodevelopmental model of early social isolation that dysregulates the boundary of self and others to establish adaptive social processing at circuit, and behavioral levels. He will discuss findings from the rodent models and their implications for pathophysiology, prevention, and treatment of psychotic disorders.

Lastly, Dr. Lincoln will present an experimental study on social inclusion and momentary psychotic-like symptoms in a community sample. When recalling memories of past

experiences of inclusion, participants (N = 1,096) reported a significant decrease in negative symptoms, including amotivation and social anhedonia, and a decrease in paranoia, relative to recalling experiences of exclusion or sadness. A replication study (N = 1,272) corroborated a decrease in amotivation and social anhedonia following an inclusion experience.

The discussant Dr Green will provide a synthesis of the four presentations. He will discuss remaining gaps in the literature and point towards future directions.

### 43.1 Loneliness and Social Relationship Dissatisfaction and Their Impact on Clinical and Functional Outcomes in Dutch Mental Health Service Users

Anne-Kathrin Fett*[1], Evelien van der Ploeg[2], Fabiana Engelsbel[2], René Keet[2], Jessica Apeldoorn[2], Rosa van Mourik[2], Maurice Topper[2], Eva Velthorst[2]

[1]*City University of London,* [2]*GGZ Noord - Holland - Noord*

**Background:** The relationship between social disconnection and mental health outcomes is increasingly acknowledged. Yet, relatively little is known about how loneliness and social relationship dissatisfaction (SRD) are related to clinical and functional recovery. In our study, we therefore focussed on the two separate aspects of subjective social disconnectedness and their differential associations with recovery outcomes, including clinical and functional outcomes (i.e, symptomatic distress, suicidal ideation, and role functioning), as well as treatment duration and mortality.
**Methods:** We investigated the associations between loneliness and SRD with various mental health outcomes in 15,512 outpatients of a Dutch mental health service. Demographic information and data on loneliness, SRD, symptomatic distress, suicidal ideation, and role functioning assessed by the Outcome Questionnaire 45, as well as treatment duration, and mortality, were collected. We analyzed the associations between these factors overall and by diagnostic group, gender, and age, using cross-sectional and longitudinal regression, while controlling for relevant covariates.
**Results:** Across different diagnostic groups, loneliness and SRD were independently and significantly associated with symptomatic distress, suicidal thoughts and role functioning cross-sectionally and longitudinally. Particularly strong associations were found in bipolar and psychosis-related disorders. Gender did not significantly influence the strength of associations. Older patients reported lower levels of loneliness and SRD. However, the impact of loneliness and SRD on clinical and functional outcomes was consistent across ages. Higher levels of loneliness and SRD were associated with longer treatment durations, regardless of age, gender or diagnosis.
**Conclusions:** Our study highlights important transdiagnostic associations between two subjective indicators of social disconnectedness, loneliness and SRD, with clinical and role functioning in real world clinical settings. The findings suggest that interventions aimed at reducing loneliness and enhancing social relationship satisfaction could greatly benefit patients' clinical and functional recovery. Currently, there are only few effective interventions available for these issues.

### 43.2 Effects of Induced Social Defeat on Indices of Self-Disturbance in Psychosis-Spectrum Conditions

Katrina Rbeiz*[1], Yunlai Gui[1], Michael Sangimino[1], Isaac Vega[1], Chloe Pryor[1], Teffina Zheng[1], Sohee Park[1]

[1]*Vanderbilt University*

**Background:** Social defeat is associated with increased risk for psychosis, but it has been difficult to obtain empirical evidence in humans to elucidate causal mechanisms. Experimental investigations of direct manipulation of social defeat in humans are scarce due to the lack of methodology. To address this gap, we developed an experimental paradigm to induce social defeat experiences in humans to quantify behavioral consequences that are relevant to psychosis: self-other boundary. Personal space regulation serves a protective function and is necessary for adaptive social interaction, but it is compromised in people with psychosis-spectrum conditions (PSC). We investigated the effects of induced social defeat on psychosis-related behaviors to understand the link between social disconnection and psychosis. We hypothesized that acute social defeat would increase self-disturbance and disrupt personal space.
**Methods:** We recruited PSC and control participants (CO) to undergo social defeat manipulation. Positive and negative symptoms were assessed in the PSC. Prodromal Questionnaire-16 (PQ-16) were given to CO. Three aspects of self-experiences (embodiment, self-boundary, social disconnection) were assessed before and after induced social defeat. We asked participants to recall and write about personal experiences of exclusion and defeat. After manipulation checks, we assessed emotion embodiment with a mapping tool (emBody; Nummenmaa et al., 2014), which generates bodily maps of sensations associated with distinct emotions. To quantify self-boundary, we used a stop-distance task in virtual reality (VR) to estimate the IPD. Social disconnection was measured with the UCLA Loneliness Scale and social defeat with the Brief Core Schema Scales (BCSS). Self-disturbance was assessed with the Body Disturbances Inventory (B-BODI). Brief Trauma Questionnaire (BTQ) and the Revised Green et al., Paranoid Thoughts Scale (RGPTS) were also administered.
**Results:** We were able to induce social defeat via autobiographical recall. Embodiment: PSC showed reduced emotion embodiment compared with CO at baseline. After social defeat manipulation, there was increased embodiment for negative emotions (sadness, depression, loneliness, isolation, exclusion) regardless of diagnosis. Both groups showed reduced embodiment for positive emotions (happiness, love, pride) after social defeat. Self- boundary: At baseline, IPD was larger in PSC than in CO. Social defeat manipulation did not change IPDs for either group. IPD was negatively correlated with social defeat (BCSS) and trauma (BTQ). BCSS was associated with increased trauma (BTQ) but inversely correlated with self-disturbance (B-BODI). Social disconnection: PSC showed increased loneliness, trauma, paranoia, social defeat, and self-disturbance than CO. Loneliness was associated with increased paranoia and psychotic symptoms.
**Conclusions:** To move forward, we need mechanistic understanding of the link between the daily experiences of social defeat and psychosis proneness. Overall, social isolation, trauma, and self-disturbance were increased in the PSC. We also found that acute social defeat impacted emotion embodiment, which is associated with interoception. Whilst IPD (self-boundary) was larger in PSC, acute social defeat did not change it; preferred IPDs may not change rapidly. Instead, accumulation of chronic defeat experiences might be needed. However, rapid changes in bodily sensations associated with emotions after acute social defeat suggest that exposure to social defeat affects interoception, which may contribute to self-disturbances. Further study is needed to extend these findings to explain how chronic social defeat leads to psychosis.

### 43.3 Impact of Social Isolation on Social Dysfunction: Deprivation or Developmental Mismatch?

Hirofumi Morishita*[1]

[1]*Icahn School of Medicine at Mount Sinai*

**Background:** Recent studies across species collectively suggest that social isolation at youth is particularly detrimental to adult social processes. In mice, juvenile social isolation disrupts adult social investigation via altered functioning of the medial prefrontal cortex (mPFC), but isolation during later periods of development does not produce major social deficits, suggesting the existence of a developmental critical period. However, there is a major gap in our understanding of how isolation during our developmental years ultimately leads to long-lasting social behavioral alterations in adulthood. Her we aimed to fill this gap by mechanistic developmental study using mouse models to highlight the possibility that juvenile social isolation can disrupt not only developmental events that are concurrent with adverse experience, but also developmental events that are subsequent to adverse experience.
**Methods:** To investigate the developmental progression of juvenile social isolation-induced social dysfunction in mice, we assessed sociability at multiple timepoints using the three-chamber test and free reciprocal interaction. During the post-isolation developmental period, we conducted tests of affiliative behavior and aggression among cage mates and used patch clamp electrophysiology to examine the excitability of mPFC-thalamic projection neurons.
**Results:** We unexpectedly found that juvenile social isolation-induced sociability deficits in the three-chamber test (where subjects interact with novel mice) and associated dysregulation of mPFC-thalamic projection neurons were not present at the end of isolation. Instead, deficits emerge during the first 2 weeks of the adolescent rehousing period. Detailed examination of the first week after rehousing revealed a dynamic transition of cagemate interaction from aggression immediately following rehousing to social withdrawal within a week. Of note, chronic social isolation without rehousing did not induce sociability deficits, nor mPFC-thalamic projection neuron deficits, suggesting that developmental mismatch during the post-rehousing period plays a key role in driving the dysregulation.
**Conclusions:** These results suggest that juvenile social isolation may disrupt adult social behavior not only by impairing social development during the isolation period, but also by impairing subsequent development during the post-isolation developmental period. We propose that the prevailing "social deprivation model", where adult social deficits are attributed to disruption of developmental processes occurring during the isolation period, should be supplemented by the "developmental mismatch model", where social deficits are attributed to disruption of developmental processes occurring after the isolation period. Our study implicates mPFC-thalamic projection neuron and adolescent period as a promising circuit and a window for preventing post-isolation social deficits relevant to Schizophrenia.

### 43.4 The Effects of Social Inclusion and Exclusion on Momentary Changes of Psychotic-Like Experiences

Sarah Hope Lincoln*[1], Elyssa Barrick[1]

[1]*Case Western Reserve University*

**Background:** Experiences of isolation, rejection, and exclusion have been associated with increased risk for psychosis and severity of psychotic symptoms. To date, most of the experimental work examining the relationship between social exclusion and psychosis lacks a comparison with other conditions evoking negative affect (e.g., sadness) resulting in a lack of

clarity as to whether the effects of social exclusion are unique to separation from a social group or a result of negative affect more broadly. Additionally, while research suggests that positive social experiences like social inclusion have mitigating effects for anxiety and depressive symptoms, little research has examined the effects of inclusion on psychotic-like experiences. The aim of the following studies was to examine the specific effects of social exclusion and inclusion on changes in momentary psychotic-like experiences in a large community sample.
**Methods:** In both Study 1 (N = 1358) and Study 2 (N = 1096) participants were recruited from the online research platform Prolific. To assess changes in psychotic-like experiences, participants completed a novel, 30-item measure of in-the-moment psychotic-like experiences. Participants were randomly assigned to one of four conditions (inclusion, exclusion, sadness, and neutral), and instructed to engage in a 5-minute writing session where they were asked to recall and write, in-detail, about that experience consistent with their condition. For example, for exclusion, participants were asked to recount a time in which they felt excluded or rejected from a social situation. Psychotic-like experiences were assessed immediately prior to and immediately following the manipulation. All responses were reviewed by lab members to assess for data quality and to ensure accuracy of group categorization.
**Results:** Results from Study 1 demonstrate that in both the inclusion and neutral conditions, participants report a reduction in amotivation/anhedonia compared to the exclusion and sadness conditions ($\chi^2$= 18.05, $p < .001$). Additionally, social anhedonia was significantly reduced following the inclusion condition, while it was significantly increased following the exclusion condition ($\chi^2$= 35.45, $p < .001$). Consistent with the manipulation, we see that negative affect is significantly increased in both the sadness and exclusion conditions ($\chi^2$= 113.35, $p < .001$). Finally, we see a slight decrease in paranoia in response to inclusion ($\chi^2$= 3.38, $p < .001$). There were no significant differences in changes of unusual thought content across the four conditions ($\chi^2$= 2.89, $p = .41$). Study 2 replicates findings of amotivation/anhedonia, social anhedonia, and negative affect ($p < .001$), but the findings for paranoia were not replicated ($p = .34$).
**Conclusions:** The findings from this study offer important insights into the relationship between social exclusion and inclusion on changes in psychotic-like experiences. First, this study uses a novel measure to assess moment-to-moment changes in psychotic-like experiences, consistent with the concept that psychotic-like experiences may change in response to fluctuations in emotions, stress, and social experiences among other variables. Second, results suggest that recounting experiences of exclusion may increase specific negative symptoms associated with psychosis, and that social inclusion may reduce specific negative symptoms of psychosis. This work could have a meaningful impact when considering ways to prevent and reduce severity of psychotic symptoms.

### 44. Inflammation and Schizophrenia: Insights From Microglial Activation, Monocyte-Macrophage Dynamics, and Cytokine Modulation

Iris Sommer, *UMC Groningen*

**Overall Symposia Abstract:** The inflammatory hypothesis of schizophrenia has garnered significant attention as a possible explanation for its pathophysiology, with increasing evidence linking immune dysfunction to the disorder's onset and progression. However, questions remain regarding how central inflammation is to the clinical manifestations of schizophrenia. This symposium brings together findings from multiple perspectives,

showcasing data from diverse approaches to explore the role of inflammation in schizophrenia, while considering a range of views on its potential as a therapeutic target. Oliver Howes provides data on microglial activation in first-episode psychosis (FEP) and the effects of natalizumab, an anti-inflammatory monoclonal antibody. Using [18F]DPA-714 PET imaging, Howes reports elevated microglial activation in grey matter, particularly in the temporal lobe, in FEP patients compared to healthy controls. Although natalizumab did not reduce microglial activation, it did lead to a reduction in symptom severity as measured by PANSS, suggesting that clinical improvements may occur independently of microglial modulation.

Robert Yolken explores the role of matrix metalloproteinase-9 (MMP-9) in schizophrenia and bipolar disorder, focusing on its role in inflammation, neural plasticity, and blood-brain barrier integrity. Elevated MMP-9 levels in patients with residual schizophrenia symptoms indicate that this molecular biomarker could serve as a potential target for therapeutic intervention. However, Yolken's approach invites reflection on whether chronic inflammation is a cause or a consequence of underlying pathology, acknowledging that skepticism about the inflammatory hypothesis is warranted.

Mark Weiser contributes a critical viewpoint through his meta-analysis of three RCTs involving monoclonal antibodies targeting IL-1β and IL-6. The antibodies showed non-significant reductions in PANSS scores, with peripheral immune markers altered but no substantial clinical improvements. Weiser's findings reinforce the view that immune modulation alone may not yield significant therapeutic benefits for schizophrenia. He suggests that future studies should focus on patients with elevated inflammatory markers and consider alternative approaches, as the inflammatory hypothesis may not hold for all patients.

Cynthia Shannon Weickert examines the role of monocytes and macrophages in schizophrenia, finding increased monocyte chemoattractant protein (CCL2) levels and greater macrophage density in the brain. Her transcriptomic data, highlighting upregulated monocyte adhesion and diapedesis, suggest neuroinflammation correlates with neuropathology and astrocyte reactivity. Weickert's findings on the effect of canakinumab, which reduced macrophage biomarkers (sCD163), offer support for the potential of targeting macrophage activity, though she acknowledges the need for further validation in clinical settings.

By integrating molecular, clinical, and cellular approaches, this symposium presents a balanced discussion on the role of inflammation in schizophrenia. While some findings suggest potential therapeutic avenues for targeting immune pathways, the symposium also highlights key uncertainties about the extent to which inflammation drives schizophrenia's clinical manifestations. This reflects a broader debate within the field, encouraging further research to clarify whether inflammation is a core driver of the disorder or a secondary consequence, and how therapies can be tailored accordingly.

### 44.1 Natalizumab for Schizophrenia: Effects on Microglial Activation and Symptom Severity

Oliver Howes*[1]

[1]*MRC LMS and KCL*

**Background:** Neuroinflammation, particularly via microglial activation, has been implicated in the pathophysiology of schizophrenia. This study evaluates the effects of natalizumab, an anti-inflammatory monoclonal antibody that targets integrins expressed by microglia, in patients with first-episode psychosis (FEP). It uses the [18F]DPA-714 distribution volume ratio (DVR) as a biomarker of relative levels of a protein expressed by activated microglial in the brain. Natalizumab has been shown to reduce DVR in patients with multiple sclerosis. Positron emission tomography (PET) imaging was employed to assess DVR and examine the impact of natalizumab treatment on brain DVRs and clinical symptoms.
**Methods:** 62 patients with FEP and 41 healthy volunteers underwent baseline PET imaging to measure DVR in grey matter regions, including the total grey matter (GM), temporal lobe GM, and frontal lobe GM. Following baseline assessments, 47 patients completed a 3-month follow-up after receiving natalizumab or placebo. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS), and DVR values were compared across groups and within specific brain regions to evaluate microglial activity.
**Results:** DVR was significantly elevated in FEP patients compared to healthy controls in total GM ($p=0.038$, $\eta^2=0.043$) and temporal lobe GM ($p=0.016$, $\eta^2=0.057$), but not in frontal lobe GM ($p=0.406$). Natalizumab treatment did not significantly reduce DVR in any of the brain regions assessed (all $p > 0.05$). However, patients receiving natalizumab showed a significant reduction in PANSS symptom severity (mean ± SD change: -3.7 ± 9.1, $p=0.017$, Cohen's $d=0.40$), suggesting a potential clinical effect of natalizumab independent of changes in microglial activity.
**Conclusions:** The findings of higher DVR in grey matter regions, including the temporal cortex, in schizophrenia are consistent with higher levels of a protein expressed by activated microglia in these regions. However, natalizumab treatment did not significantly modulate DVR, suggesting that microglial activation may be a persistent feature of schizophrenia that is not reversed by targeting integrins. The reduction in PANSS scores points to a possible symptomatic benefit of natalizumab, but further studies are needed to elucidate the mechanisms underlying this effect and to explore alternative strategies targeting neuroinflammation in schizophrenia. Overall, elevated DVR in schizophrenia, particularly in temporal grey matter regions, appears to be a stable feature of the disorder. While natalizumab did not significantly affect microglial activity, it may offer symptomatic relief, highlighting the need for continued research into therapeutic strategies that more effectively target neuroimmune pathways and their role in schizophrenia pathology.

## 44.2 Matrix Metalloproteinase-9 and Schizophrenia: Inflammatory Mechanisms in Psychiatric Disorders

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

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

**Background:** The role of inflammation in psychiatric disorders, including schizophrenia and bipolar disorder, is becoming increasingly recognized. Matrix metalloproteinases (MMPs), particularly MMP-9, have been linked to neural plasticity, tissue remodeling, and blood-brain barrier alterations—mechanisms implicated in both schizophrenia and bipolar disorder. Elevated levels of MMP-9 have been found in individuals with these conditions, along with associations with infectious agents like Toxoplasma gondii and Cytomegalovirus (CMV). This study examines MMP-9 as a potential biomarker for schizophrenia, providing insights into the inflammatory hypothesis of its pathogenesis.

**Methods:** We analyzed data from individuals with residual schizophrenia symptoms (N=100) enrolled from outpatient programs, alongside patients with bipolar disorder (mania, N=84; depression, N=78) and a control group without psychiatric disorders (N=87). Blood samples were collected at baseline and follow-up. MMP-9 levels were measured using immunoassays, and changes over time were assessed using mixed-effects models, adjusting for age, gender, race, smoking, obesity, and other relevant variables. Principal component analysis (PCA) was employed to group immune markers, including MMP-9, to identify distinct inflammatory pathways associated with schizophrenia.
**Results:** MMP-9 levels were elevated in patients with residual schizophrenia symptoms compared to non-psychiatric controls, and these levels remained elevated over time. In patients with bipolar disorder, MMP-9 levels were significantly higher during acute episodes (mania and depression) but decreased following hospital discharge. Importantly, MMP-9 was associated with immune responses to specific infectious agents, supporting the idea that chronic infections may contribute to persistent inflammation in psychiatric disorders.
**Conclusions:** The findings suggest that MMP-9 may serve as a key biomarker in schizophrenia, reflecting the involvement of inflammatory processes in its pathophysiology. The persistence of elevated MMP-9 levels in schizophrenia, even during periods of clinical stability, indicates a chronic inflammatory state, possibly driven by ongoing infections or immune dysregulation. These results contribute to the growing evidence for the inflammatory hypothesis of schizophrenia and point to potential therapeutic targets aimed at modulating MMP-9 activity. Further research is warranted to explore the efficacy of interventions targeting MMP-9 in reducing symptom severity and preventing disease progression.
Elevated MMP-9 levels in schizophrenia highlight the significance of inflammatory mechanisms in its pathogenesis. MMP-9 may offer a promising target for novel interventions, providing a pathway to mitigate the impact of chronic inflammation on brain functioning in psychiatric disorders.

### 44.3 Mono-Clonal Antibodies for Schizophrenia: Preliminary Results of an Individual Patient Data Meta-Analysis

Mark Weiser*[1], Ragy Girgis[2], Brian Miller[3], Thomas Weickert[4], Jinyoung Park[5], Linda Levi[1], E. Fuller Torrey[6], John Davis[7]

[1]*Sheba Medical Center at Tel Hashomer,* [2]*Columbia University,* [3]*Augusta University,* [4]*State University of New York Upstate Medical University,* [5]*Duke University,* [6]*The Stanley Medical Research Institute,* [7]*University of Illinois at Chicago*

**Background:** One of the hypotheses regarding the etiology of schizophrenia is that inflammatory mechanisms are involved in its pathophysiology. This is supported by studies showing that patients with schizophrenia have increased brain, plasma, and serum levels of Interleukin-6 (IL-6) and Interleukin 1-beta (IL-1β). The Stanley Medical Research Institute funded three RCTs administering monoclonal antibodies for the treatment of schizophrenia: canakinumab, a monoclonal antibody that interferes with the bioactivity of IL-1β; tocilizumab, a monoclonal antibody against the IL-6 receptor; and siltuximab, a monoclonal antibody that binds IL-6. This study presents an individual patient data meta-analysis of these three studies together.
**Methods:** This is a preliminary individual patient data meta-analysis combining the data of three RCTs, including a total of 75 patients, 39 randomized to drug and 36 to placebo. We examine the endpoints of the Positive and Negative Syndrome Scale (PANSS) Total, Positive, Negative, and General symptoms scores by ANCOVA, with baseline score as a

covariant, and monoclonal antibody and study as factors. Patients in the canakinumab trial were stratified based on their inflammatory status, using peripheral inflammation markers to determine treatment groups. Future analyses will include changes in peripheral inflammation markers (e.g., CRP) and will use peripheral inflammation marker levels to predict PANSS scores. We will also evaluate changes at early and mid-time points and explore other variables that might alter psychopathology.
**Results:** The monoclonal antibodies non-significantly decreased PANSS total by -2.5 points (se=1.9, t=-1.3, p=0.19), positive symptoms by -.84 points (se=.90, t=-.94, p=0.35), and negative symptoms by -.42 points (se=.80, t=-.52, p=0.60), and non-significantly increased general symptoms by .42 points (se=1.4, t=.31, p=0.76).
**Conclusions:** The results of this preliminary meta-analysis did not find efficacy of monoclonal antibodies in the treatment of schizophrenia symptoms. Whereas some blood-based immune markers were altered by these monoclonal antibodies, this did not translate to clinical symptom reduction. One potential reason may be that these drugs do not cross the blood-brain barrier, thus affecting peripheral immune markers but not leading to symptom changes. These results should be interpreted with caution, as they are based on a small number of studies with a relatively small number of patients. However, the canakinumab trial, which stratified patients based on inflammatory status, may offer insights for future studies that focus on selecting patients with elevated inflammation markers.

### 44.4 Monocyte-Macrophage Dynamics: Investigating the Inflammatory Landscape in Schizophrenia

Cynthia Weickert*[1], Thomas Weickert[1]

[1]*State University of New York Upstate Medical University*

**Background:** Monocytes, which differentiate into brain macrophages, are emerging as key players in the inflammatory processes of schizophrenia. Altered monocyte profiles, including increased counts and activation states, are seen at various stages of the disorder, with elevated peripheral levels of monocyte-associated cytokines such as IL-1β, IL-6, and TNF-α. This study investigates monocyte-macrophage activity in the brain, focusing on monocyte chemoattractant proteins, macrophage infiltration, and their potential role in schizophrenia's pathophysiology.
**Methods:** Monocyte chemoattractant protein (CCL2) levels were measured in brain tissue, macrophage activation was assessed via CD64 expression, and macrophage density was examined in brain regions of schizophrenia patients compared to controls. RNA sequencing (RNA-seq) analyzed transcripts related to monocyte adhesion and diapedesis, including integrins (ITGA4, ITGA5) and PECAM1. CD163+ macrophages were analyzed in relation to neuropathology and astrocyte reactivity. The effect of canakinumab, an IL-1β-blocking monoclonal antibody, on macrophage diapedesis biomarkers (sCD163) was tested in chronically ill patients.
**Results:** CCL2 levels were significantly elevated in schizophrenia brains ($F=12.9$, $p < 0.00013$), indicating monocyte recruitment to the brain. Macrophage activation (CD64 expression, 160% > controls, $F(1,130) = 14.82$, $p < 0.001$) and increased density (CD163 mRNA, 327% > controls, $p=1.13-103$) were observed across brain regions. RNA-seq showed significant upregulation of agranulocyte adhesion and diapedesis-related transcripts (ITGA4, ITGA5, PECAM1; all p's $\leq 0.0003$). Most CD163+ macrophages were found around blood vessels, with some in the parenchyma, correlating with neuropathology and astrocyte reactivity. Canakinumab reduced macrophage diapedesis biomarkers (sCD163) at 4 weeks post-injection ($p < 0.05$), suggesting modulation of inflammatory processes.

**Conclusions:** These findings underscore the role of monocytes and macrophages in schizophrenia-related neuroinflammation. Elevated monocyte chemoattractant proteins and macrophage infiltration indicate that monocytes contribute to inflammation in the disorder. Macrophage presence around blood vessels and within brain tissue, alongside evidence of blood-brain barrier disruption, supports the hypothesis of increased permeability allowing peripheral immune cells to infiltrate the brain. The reduction in macrophage biomarkers following canakinumab treatment suggests that targeting specific inflammatory pathways could help modulate these processes and alleviate certain schizophrenia symptoms. Conclusion: Monocyte-macrophage activity is a critical component of schizophrenia's inflammatory landscape. The link between macrophage infiltration, neuropathology, and astrocyte reactivity highlights the role of immune system dysregulation in the disorder. Immunomodulatory therapies, like IL-1β inhibitors, may offer new approaches for treating schizophrenia. Ongoing research is essential to further elucidate macrophage involvement and develop more effective interventions.

**45. Cognitive Impairments in Psychosis: Biology and Pharmacology**

Rob McCutcheon*, University of Oxford*

**Overall Symposia Abstract:** Cognitive impairments remain a major challenge in the treatment of schizophrenia, and frequently preclude achievement of long-term functional recovery. This symposium will bring together cutting-edge research on the underpinnings of cognitive impairments in psychosis, with a focus on how these deficits arise, are maintained, and can potentially be treated.

Sherry Chan will present findings from a large case-control study examining the cognitive impairments in treatment-resistant schizophrenia (TRS) and non-TRS patients. Her research highlights the critical role of anticholinergic burden in driving cognitive dysfunctions, particularly in areas such as executive function and attention, and its contribution to the apparent differences in cognitive performance between TRS and non-TRS patients. This work underscores the importance of addressing anticholinergic burden as part of therapeutic strategies to improve cognitive outcomes.

David Lewis will review the neurobiological mechanisms underpinning cognitive control impairments, focusing on gamma band oscillations in the dorsolateral prefrontal cortex (DLPFC). Alterations in circuits involving parvalbumin-containing GABA neurons and pyramidal neurons in schizophrenia lead to disruptions in gamma oscillations, which are crucial for cognitive control. His findings offer a circuit-based framework for understanding how these neuronal disruptions contribute to the cognitive deficits observed in schizophrenia, suggesting novel molecular targets for intervention.

Rob McCutcheon will discuss findings from a large-scale study using a machine learning approach to examine the impact of various factors, such as socioeconomic status, medication use, and childhood adversity, on cognitive functioning in psychosis across diagnostic categories. This demonstrates that transdiagnostic factors, rather than illness status alone,

may account for much of the variance in cognitive impairments in psychotic disorders, suggesting a need for a transdiagnostic approach.

Ingrid Melle will present an overview of work looking both at relationships between the genetics of cognitive function and those of psychosis, and also at longitudinal data from first-episode psychosis patients. She will discuss the extent to which cognitive impairment in psychosis are best understood from a neurodevelopmental perspective, and the impacts of both treatment and illness course

Finally, as discussant Richard Keefe will consider what are the crucial questions to be answered if we are to better understand and treat cognitive impairments in psychotic disorders.

### 45.1 The Development of Cognitive Function in Early Psychosis and its Link to Clinical Psychopathology

Ingrid Melle*[1], Magnus Engen[2], Camilla B. Flaaten[3], Torill Ueland[3]

[1]*Institute of Clinical Medicine,* [2]*Division of Mental Health and Addiction, Nydalen DPS, Oslo University Hospital, Oslo, Norway,* [3]*Oslo University Hospital*

**Background:** Cognitive dysfunctions are central to functional loss in schizophrenia, but their role in the development of psychotic disorders is unclear. The observation of subtle cognitive problems in relatives of patients with schizophrenia and in children who later develop schizophrenia implies a link between cognitive function and the complex genetic and neurodevelopmental background of the disorder. But are cognitive problems risk markers, risk factors, or drivers of psychopathology?
**Methods:** We will draw on results from studies of the genetic background of cognitive dysfunction and the pre-onset development of cognition. We will present results from our recently completed prospective study of first-episode psychosis focusing on the course of cognitive functioning and its relation to clinical psychopathology over the first ten years of the treated disorder.
**Results:** Molecular genetic studies show an overlap between the polygenetic risk for schizophrenia (PRS) and for cognitive function (PRC) but no direct associations between PRS and cognitive function or between PRC and clinical symptoms. Verbal impairments appear stable from early life. Some non-verbal impairments increasingly lag behind the development seen in healthy peers when approaching adulthood, thus creating an impression of increasing dysfunction without representing functional loss. Study participants meeting the criteria for psychosis high show more cognitive problems than healthy control participants, mainly linked to those who transition to psychosis. There are, however, no apparent signs of deteriorating cognitive function from the prodromal period to psychosis onset. Our prospective study found no signs of deterioration in general cognitive functioning through the first ten years of treatment. However, there was a slight improvement from the study baseline at first treatment. First-episode patients with sustained low negative symptoms outperformed patients with persistently high negative symptoms for composite cognitive functioning and global function. While earlier intervention appears to improve negative symptoms, there have

been no findings of a link between the duration of untreated psychosis and cognitive dysfunction. Still, a recent report from the RAISE study indicated that comprehensive early intervention services had beneficial effects on cognition in the youngest patient group.
**Conclusions:** In conclusion, cognitive dysfunction appears as an indicator of underlying neurodevelopmental risks with no signs of "neuroprogression" over the course of the illness. The severity of cognitive dysfunction is primarily linked to the severity of negative symptoms. Since motivation is an essential factor for cognitive efforts, this relationship may play a part in cognitive remediation. The relationship between cognition and positive/psychotic symptoms and their current treatments appears weak, emphasizing the need for treatments more directed explicitly towards negative symptoms and cognitive dysfunction in schizophrenia.

### 45.2 Using Machine Learning to Understand Cognitive Impairments in Psychosis

Robert McCutcheon*[1], Philip McGuire[1], Richard Keefe[2], Andre F. Marquand[3]

[1]*University of Oxford,* [2]*Duke University Medical Center,* [3]*Donders Institute of Brain, Cognition and Behaviour, Radboud University; Radboud University Medical Centre; Institute of Psychiatry, King's College London*

**Background:** Cognitive functioning is linked to various factors such as age, sex, education, and childhood adversity and is impaired in people with psychotic disorders. In addition to the direct effects of the disorder, cognitive impairments may reflect a greater exposure to general risk factors for poor cognition. The use of machine learning methods with large datasets can potentially disentangle these associations.
**Methods:** Clinical data were obtained from the BSNIP-1 and BSNIP-2 studies comprising six sites. 3,370 participants were included. 840 healthy controls, 709 with schizophrenia, 541 with schizoaffective disorder, 457 with bipolar 1 with psychosis, and 823 relatives of patients

We examined the relationship between exposures and cognitive function. Exposures were chosen based on associations with cognition previously identified in the literatures: age, sex, race/ethnicity, childhood adversity, education, parental education, parental socioeconomic status, parental age at birth, substance use, antipsychotic dose, and diagnosis. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia.

Predictive modelling was then performed using Extreme Gradient Boosting Regression to train a composite cognitive score prediction model using nested cross-validation. SHapley Additive exPlanations values were used to examine the relationship between exposures and cognitive function.

**Results:** Data from 3370 participants was analysed (44% male, mean age 37.9 years). The model predicted cognitive scores with high accuracy: out of sample correlation between predicted and observed cognitive composite score was rp=0.72 (SD=0.03). Individuals with schizophrenia(z=-1.4), schizoaffective disorder(z=-1.2), and bipolar 1 with psychosis(z=-0.5) all had significantly worse cognitive composite scores than controls. IFactors other than diagnosis and medication accounted for much of this impairment (schizophrenia z=-0.73, schizoaffective z=-0.64, bipolar 1 with psychosis z=-0.13). Diagnosis accounted for a lesser proportion of this deficit (schizophrenia z=-0.29, schizoaffective z=-0.15, bipolar 1 with

psychosis z=-0.13), and antipsychotic use accounted for a similar deficit across diagnostic groups (schizophrenia z=-0.37, schizoaffective z=-0.33, bipolar 1 with psychosis z=-0.26).
**Conclusions:** Transdiagnostic factors appear to account for a meaningful share of the variance in cognitive functioning in psychosis. A significant proportion of the cognitive impairment in psychosis may therefore reflect factors relevant to cognitive functioning in the general population. When considering interventions, a diagnosis agnostic, symptom targeted approach may therefore be appropriate.

### 45.3 The Role of Anticholinergic Burden on Cognitive Functions in Schizophrenia and Treatment Resistant Schizophrenia

Sherry Kit Wa Chan*[1], Tiffanie Sze Wing Pang[1], Kam Hung Harry Tsui[3], Christy Hui[1], Edwin Lee[1], Wing Chung Chang[1], Eric Chen[1], William Honer[6]

[1]*The University of Hong Kong,* [3]*Li Ka Shing Faculty of Medicine, The University of Hong Kong,* [6]*University of British Columbia*

**Background:** Cognitive dysfunction is a core clinical feature of schizophrenia and closely related with poor functional outcomes with limited effective treatment. About 15-30% of people with schizophrenia developed treatment resistance and are considered as treatment resistant schizophrenia (TRS) (Chan et al., 2021; Howes et al., 2017). Recent meta-analysis of 17 cross-sectional studies suggested TRS patients had more neurocognitive deficits compared with the treatment responsive patients (Millgage et al., 2022). Large sample of schizophrenia study found anticholinergic burden was negatively associated with multiple domains of cognitive function even after adjusting for age and years of education (Joshi et al., 2021). However, the contribution of anticholinergic burden to cognitive functions in patients with treatment resistant schizophrenia (TRS) is uncertain.
**Methods:** This case-control study of patients with TRS and non-TRS aims to comprehensively examine the association between treatment resistance and cognitive functions and the contribution of anticholinergic burden. Anticholinergic burden of was calculated using the Anticholinergic Cognitive Burden scale based on all the medications prescribed to the patients at point of assessment. Exploratory Factor Analysis of 11 cognitive assessments identified four cognitive domains: verbal memory, attention and general cognitive functions, visual memory and processing speed, and executive function. Two structural equation models (SEM) examined the relationship of TRS and these cognitive functions with, and without considering anticholinergic burden. Other important variables included in the model including age, gender, years of education, smoking status, positive and negative psychotic symptoms assessed with SAPS and SANS.
**Results:** A total of 288 participants were included (TRS N=111, non-TRS N=177). Patients with TRS performed poorer than the non-TRS group only in the executive function domain when other important factors are taken into consideration. The mean anticholinergic burden of patients with non-TRS was 4.39 and that for TRS was 5.44. Most of the anticholinergic burden was contributed by antipsychotics and followed by anticholinergic medications. Anticholinergic burden contributed significantly to the attention and general cognitive functions, visual memory and processing speed, and executive function. The impact of TRS on executive function was no longer significant after adding anticholinergic burden to the SEM. Results suggested that anticholinergic burden contributes to a wide range of cognitive function impairments in patients with schizophrenia and is likely to be part of the apparent differences of cognitive function between TRS and non-TRS.
**Conclusions:** This study comprehensively examine the contribution of the anticholinergic burden to the cognitive functions of patients with schizophrenia while comparing patients

with TRS and non-TRS. The results highlight the impact of the anticholinergic burden on a wide range of cognitive functions in patients with schizophrenia and establish the anticholinergic burden as a contributor to the apparent differences in cognitive functions between patients with TRS and non-TRS. As most of the patients with schizophrenia require long-term psychiatric medication use, adjusting medications to lower the anticholinergic burden, when possible, as well as developing new treatment strategies involving muscarinic acetylcholine receptor agonists, could be important steps toward improving cognitive functions and potentially deterring cognitive decline in these patients, particularly those with TRS.

### 45.4 Dissecting the Neural Circuitry Basis for Cognitive Dysfunction in Schizophrenia

David Lewis*[1]

[1]*University of Pittsburgh*

**Background:** Deficits in cognitive control, the ability to adjust thoughts or behaviors to achieve goals, are now considered to be a core feature of schizophrenia and to be the best predictor of long-term functional outcome. Cognitive control depends on coordinated neural activity across multiple brain regions, with the dorsolateral prefrontal cortex (DLPFC) serving a prominent role in top-down regulation of this activity. Subjects with schizophrenia exhibit altered activation of the DLPFC, and reduced power of frontal lobe gamma band (~40 Hz) oscillations, when performing tasks that require cognitive control. Gamma oscillations require robust activity in the reciprocal connections between the parvalbumin-containing basket cell (PVBC) class of cortical GABA neurons and neighboring pyramidal neurons in layer 3. Thus, alterations in either the excitatory or inhibitory synapses in this local circuit could contribute to impaired gamma oscillations and cognition in schizophrenia.
**Methods:** This presentation will review the evidence, with an emphasis on findings from studies of the postmortem human brain, for alterations in components of this circuit in the DLPFC of subjects with schizophrenia.
**Results:** Current findings converge on the idea that structural alterations (e.g., smaller cell bodies, shorter dendrites and fewer dendritic spines) in layer 3 pyramidal neurons are primary pathological disturbances in the illness. These alterations are thought to result in fewer excitatory inputs to, and lower activity of, layer 3 pyramidal neurons as evidenced by downregulation of both activity-dependent transcripts and transcripts involved in mitochondrial energy production in these neurons. Recent analyses of findings from RNAseq studies of subpopulations of DLPFC layer 3 pyramidal neurons based on their axonal projection targets in macaque monkeys and from single nucleus RNAseq studies in monkey and human DLPFC suggest that a specific subtype of layer 3 pyramidal neurons is preferentially vulnerable in schizophrenia. The accompanying alterations (e.g., lower levels of gene products involved in GABA neurotransmission) in a normal complement of PVBCs appear to represent compensatory responses to maintain excitatory-inhibitory balance in DLPFC circuitry. However, computational studies suggest that these “compensations” also contribute to the alterations in gamma oscillations in schizophrenia.
**Conclusions:** In concert, these findings provide a circuity-based explanation for both gamma oscillations impairments and cognitive disturbances in schizophrenia, and they suggest novel targets and strategies for therapeutic interventions.

## 46. Forecasting Course: What Markers of Psychosis Tell us About Illness Trajectories

Katherine Jonas, *Stony Brook University*

**Overall Symposia Abstract:** Psychotic disorders have remarkably varied courses. While some individuals will experience a single psychosis-like experience, or a single episode, others will encounter continual hallucinations and delusions. While predicting course remains challenging, this symposium will highlight recent advances made through the use of large datasets, novel markers, and a focus on critical windows of time in the course of psychosis. There is a need to consider the full course of illness and the full range of markers available to identify generalizable determinants of course. The findings presented here leverage genetic, neural, environmental, behavioral, and clinical markers. These markers are evaluated as predictors of psychosis across the illness course, from the development of psychosis in adolescence to chronic symptoms in late adulthood.

The first speaker, Dr. Karcher (Washington University St. Louis) begins by describing cognitive and neural risk factor trajectories predicting worsening psychosis-like experiences in childhood and adolescence. These findings come from the Adolescent Brain and Cognitive Development study, a longitudinal cohort of over 10,000 children, over 300 of whom report persistent, distressing psychosis-like experiences. Dr. Karcher's line of research has illuminated whether persistent distressing psychosis spectrum experiences can be differentiated from transient experiences early in the course of psychosis spectrum symptoms. Analyses provide evidence that worsening cognition and global structural metrics over childhood and adolescence may represent mechanisms linking genetic and environmental risk to persistent distressing psychosis-like experiences.

Dr. Mittal (Northwestern University) will describe results from a multi-site investigation aiming to determine how a battery of task, chosen because of conceptual and/or empirical evidence suggesting sensitivity to mechanism and/or disease state, can identify those meeting criteria for a clinical high-risk for psychosis (CHR-P) state from clinical controls and be utilized to predict clinical course. Results show promise for a widely-accessible early screening method, as well for precision medicine-based approaches to prediction and staged-intervention.

Dr. Vassos (King's College London) follows with a discussion of how environmental risk factors, like genetic risk factors, tend to have small individual effects on psychosis risk. However, in aggregate, environmental risk scores can be used to stratify populations by risk for psychosis. Genetic risk scores can be combined with environmental risk scores to increase the precision of risk stratification, with applications for both the prediction and explanation of the development of psychosis.

Last, Dr. Jonas (Stony Brook University) discusses how genetic risk manifests over the illness course following first admission. Data are drawn from the Suffolk County Mental Health Project, a longitudinal study of first-admission psychosis in its 35-year follow-up. Genetic risk scores have been shown to be sensitive to diagnosis, but due to the low base-rate of psychosis may be more useful as prognostic markers. Complications arising from both the discovery GWAS and target samples will be discussed.

Dr. Kotov (Stony Brook University) will act as discussant. Dr. Kotov has led numerous longitudinal epidemiological studies with the aim of understanding illness onset and course, with target phenotypes including depression, post-traumatic stress, and psychosis. The discussion will highlight challenges common to all prognostic research, and the inroads that may be provided by new modalities such as artificial intelligence.

### 46.1 Attenuation of Associations Between Environmental and Genetic Risk With Psychosis Spectrum Symptoms Through Longitudinal Cognitive and Neural Metric Trajectories

Nicole Karcher*[1], Fanghong Dong[1], Sarah Paul[2], Emma Johnson[1], Can Misel Kilciksiz[3], Hans Oh[4], Jason Schiffman[5], Arpana Agrawal[1], Ryan Bogdan[2], Joshua Jackson[2], Deanna Barch[2]

[1]*Washington University School of Medicine,* [2]*Washington University in St. Louis,* [3]*NYU Grossman School of Medicine,* [4]*University of Southern California,* [5]*University of California, Irvine,*

**Background:** Adolescent psychotic-like experiences (PLEs) are transdiagnostic clinical phenotypes that may arise from genetic and environmental risk leading to worsening cognitive and neural metrics over time, which in turn lead to worsening PLEs. Persistence and distress are factors that distinguish more clinically significant PLEs. Analyses used three waves of Adolescent Brain Cognitive Development Study data (ages 9-13) to test whether changes in cognition and structural neural metrics attenuate associations between genetic and environmental risk with persistent distressing PLEs.
**Methods:** Multigroup univariate latent growth models examined three waves of cognitive metrics and global structural neural metrics separately for three PLE groups: persistent distressing PLEs (n=356), transient distressing PLEs (n=408), and low-level PLEs (n=7901). Models then examined whether changes in cognitive and structural neural metrics over time indirectly linked associations between genetic liability (i.e., schizophrenia polygenic risk scores) or environmental risk scores (e.g., poverty) and PLE groups.
**Results:** Persistent distressing PLEs showed greater decreases (i.e., more negative slopes) of cognition and cortical thickness over time compared to those in low-level PLE groups (difference between slope estimates≥-0.092). Increasingly worse performance on picture vocabulary (95%CI:0.047,0.107), pattern processing speed (95%CI:0.010,0.048) and reading (95%CI: 0.006,0.054) tests over time attenuated associations between greater environmental risk scores with persistent distressing versus low-level PLEs group membership.
**Conclusions:** Analyses provide novel evidence for extant theories that worsening cognition and global structural metrics may represent plausible mechanisms linking environmental risk to persistent distressing psychosis spectrum symptoms.

### 46.2 Targeting Mechanisms When Identifying and Predicting the Course of Individuals at Clinical High-Risk for Psychosis

Vijay Mittal*[1], Trevor Williams[2], James Gold[3], James Waltz[4], Jason Schiffman[5], Lauren Ellman[6], Gregory Strauss[7], Elaine Walker[8], Scott Woods[9], Al Powers[9], Joshua Kenney[10], Minerva Pappus[10], Philip Corlett[9], Tanya Tran[12], Steven Silverstein[12], Richard Zinbarg[1]

[1]*Northwestern University,* [2]*Kent State University,* [3]*University of Maryland School of Medicine,* [4]*Maryland Psychiatric Research Center,* [5]*University of California, Irvine,* [6]*Temple University,* [7]*University of Georgia,* [8]*Emory University,* [9]*Yale University,* [10]*Yale University School of Medicine, ,* [12]*University of Rochester Medical Center*

**Background:** The clinical high risk for psychosis (CHR-P) population is important for understanding disease progression and treatment; however, standard approaches to identifying CHR-P individuals are expensive, time-consuming, and have limited predictive validity. Novel mechanism-focused behavioral tasks may increase CHR-P screening and identification efficiency and help to improve prediction of clinical course.
**Methods:** A total of 621 participants who met criteria for a psychosis risk syndrome (CHR-P; n=273) were compared to healthy (n=146) as well as clinical control groups (n=202) intending to match what is seen in the clinic (i.e., the later including those with serious mental illnesses as those with psychosis-symptoms that did not meet criteria for CHR-P). Structured clinical interviews and 11 computerized behavioral tasks, selected based on their hypothesized sensitivity to mechanisms underlying positive (e.g., prior influence on perceptual judgements), negative (e.g., hedonic response, motor slowing) and disorganized symptoms (e.g., visual integration), were administered to participants, who were then evaluated 12 and 24 months.
**Results:** Multinomial logistic regression indicated that the task battery differentiated groups ($p < .001$), with strong utility for identifying CHR-P individuals (Sensitivity = .87, PPV = .51, NPV = .77), though with high false positives (Specificity = .33). Tasks also predicted a psychosis risk calculator score (Adjusted R2 = .1207). Notably, the battery also performed well at predicting long-term clinical course, suggesting differential task profiles for enhanced prediction of long-term declines in social function (tied to task underlying the negative symptom domain) as well as role functioning (linked to task spanning each domain).
**Conclusions:** Mechanism-focused behavioral task performance differentiated CHR-P individuals from control groups and were linked to psychosis risk and clinical course. Use of a computerized battery to more efficiently identify CHR-P individuals (e.g., supplementing time-intensive interviewing with trained experts), may lower barriers and identify individuals that would otherwise be missed, and may be an invaluable predictive tool in supporting clinical planning. Adaptive qualities of a computerized battery also support a sorely needed precision medicine based approach in this area.

## 46.3 Combining Genetic With Environmental Risk in Prediction of Illness Course in Psychosis

Evangelos Vassos*[1]

[1]*King's College London*

**Background:** Polygenic scores (PGS) have been examined extensively as potential predictors of outcome, but their power is currently insufficient for clinical utility. The importance of both genetic and environmental factors in disease liability is indicated by an average twin heritability of all psychiatric disorders of about 46%. Genetic factors act together with the environment in disease causation, and models incorporating both could improve risk prediction, which is central to the development and delivery of precision medicine.
In this session, I will present our studies using polygenic scores and environmental risk factors to predict the development of schizophrenia or affective psychosis among individuals

with first episode psychosis (FEP) and I will discuss challenges and areas that need further development in risk prediction.

**Methods:** In two samples of First Episode Psychosis (FEP) patients and controls, the Genetics and Psychosis (GAP) study from South London (445 cases and 265 controls) and the EUGEI study conducted in six European countries and Brazil (573 cases and 1005 controls of European ancestry), we examined the association of polygenic scores with diagnosis (schizophrenia or affective psychosis). In the later, we added environmental risk factors alongside polygenic scores in prediction of affective and non-affective psychosis, and we tested for gene by environment interaction. We also conducted a study using polygenic scores and environmental risk factors to explore differences between clusters of FEP patients based on cognition and premorbid adjustment.
Finally, to explore whether polygenic scores and environmental risk factors can be used as independent predictors, we performed a study in the UK Biobank, testing the association of polygenic scores for eight psychiatric disorders with urbanicity.

**Results:** In the GAP study we observed that polygenic scores for schizophrenia separated FEP patients who developed schizophrenia from those who developed other psychotic disorders (R2=9.2%, p=0.002). This finding was replicated in the EUGEI study, where we found that adding depression polygenic score in the prediction model improved the separation of affective from non-affective psychosis. Furthermore, we found that combining polygenic and poly-environmental risk scores for psychosis further improves the predictive ability of our model, without strong evidence of interaction. When examining different clusters of patients, we found that the cluster characterised by deteriorating premorbid adjustment in the years prior to psychosis onset had relatively lower polygenic score and higher environmental score.
In the UK Biobank study, we found evidence supporting the hypothesis of genetic selection of the environment we live in, which intersects the traditional gene-environment dichotomy.

**Conclusions:** When patients present with first episode psychosis, it is difficult to establish a definite diagnosis and predict the course of illness and optimal treatment. To that effect, prediction models utilising risk factors identified by the recent progress in genetics and epidemiology could have important clinical implications. In our studies we find that polygenic scores have a significant yet small effect in separating schizophrenia from affective psychoses and that adding non-genetic risk factors improves prediction. Polygenic scores and environmental factors are combined additively without evidence of interaction. Finally, gene by environment correlation needs to be considered when adding both genetic and environmental factors in prediction models.

### 46.4 Challenges and Potential for Genetic Prediction in First-Episode Psychosis

Katherine Jonas*[1], Amna Asim[2], Yuan Yang[1], Roman Kotov[1]

[1]*Stony Brook University,* [2]*University of Washington*

**Background:** Polygenic risk scores (PRS) have promise as biomarkers for psychiatric disorders. PRS have proved to be a clinically useful biomarker of inflammatory bowel disease, coronary artery disease, breast cancer, and type II diabetes. With the advancement of new low-cost and time-efficient genotyping techniques, practical barriers to the deployment of PRS are eroding, and there is hope that PRS may eventually improve the prediction diagnosis and treatment of psychiatric illness. However, there are many challenges facing the clinical implementation of PRS. This talk will cover some of the constraints on genetic

prediction of psychosis, and how those constraints are shaping the future of research in this field. The talk begins with a study of how low-base rates and collider bias impact genetic prediction of illness onset and course, respectively. With these constraints in mind, we discuss how phenotype selection in GWAS can improve the power and specificity of genetic prediction.
**Methods:** Data are drawn from multiple cohorts. GWAS are performed in UK Biobank, a large population-based sample of 500,000 adults from the UK, and the Genomic Psychiatry Cohort, a diverse cohort of 30,000 individuals with schizophrenia and bipolar disorders. Validation analyses are performed in the Suffolk County Mental Health Project, a first-admission psychosis cohort of 628 individuals followed for 25-years, and PsyCourse, a case-control cohort of 1,764 individuals with schizophrenia and bipolar disorder followed for 2 years.
**Results:** A comparison of case-only versus case-control analyses demonstrates that selection bias and collider bias impact genetic structure and the specificity of genetic prediction in psychotic disorders. GWAS in UK Biobank and the Genomic Psychiatry Cohort demonstrate how selecting broad phenotypes as GWAS targets increases power for both discovery and prediction, while selecting narrow target phenotypes increases specificity of genetic prediction.
**Conclusions:** The low-based rate of psychosis in the population, paired with selection bias in clinical cohorts, presents challenges for genetic prediction of psychosis. However, both of these problems are remediable through changes in GWAS design. In population-based samples, broad transdiagnostic phenotypes can increase power for genetic discovery relative to diagnostic phenotypes. In case-enriched samples, specific phenotypes that reflect the genetic structure of psychosis can increase the specificity of genetic prediction. Future data collection efforts, especially biobanks and other large-scale genotyping projects, can benefit from both approaches through the careful design of assessment batteries and sample ascertainment.

### 47. Broadening our Understanding of Antipsychotic Discontinuation by Integrating Lived Experience, Quantitative, and Qualitative Research

Helene Speyer*, Mental Health Centre Copenhagen*

**Overall Symposia Abstract:** The issue of antipsychotic maintenance treatment remains a contentious and often heated topic of debate. On the one hand, quantitative studies on relapse prevention consistently report large effect sizes, demonstrating the significant role of antipsychotics in reducing the risk of relapse. On the other hand, despite this evidence, a large proportion of individuals with psychotic disorders make several attempts to discontinue their medication. This frequent occurrence of low adherence has been the focus of numerous research projects over the years, as it highlights a disconnect between clinical recommendations and patient behavior.

To better understand this seemingly paradoxical situation, it is essential to adopt a pluralistic perspective—one that incorporates the complexity of treatment. Antipsychotic discontinuation is often seen as a "wicked problem" due to its complex, multifaceted nature. A wicked problem is characterized by having no clear solution, involving many interconnected factors, and being highly resistant to resolution through conventional methods.

In this symposium, we aim to bridge various perspectives, integrating insights from lived experience, qualitative research, quantitative research, and clinical practice. Our panel of presenters, who themselves bring expertise across at least two of these domains, will engage in what we hope will be a fruitful and groundbreaking discussion. Together, we will explore how these diverse viewpoints can contribute to more person-centered care, enhance adherence, and ultimately reduce the overall impact of psychotic disorders while empowering patients in their treatment choices. This approach can help uncover more nuanced and innovative solutions that not only improve patient care but also respect individual autonomy, epistemic justice and address concerns about the long-term burden of adverse effects associated with antipsychotic use.

### 47.1 Antipsychotic Prescription/Use Patterns and Outcomes in EPINET

Peter Phalen*[1], Sean Driscoll[2]

[1]*University of Maryland,* [2]*University of Maryland School of Medicine*

**Background:** In the past decade, the USA has made substantial investments in Coordinated Specialty Care (CSC) programs that support First Episode Psychosis (FEP) patients through a multidisciplinary combination of psychotherapy, supported employment/education, peer support, and medication management. Over 340 CSC programs have now been established across all 50 states, with 115 of these participating in the NIMH-funded Early Psychosis Intervention Network (EPINET), a learning healthcare system intended to produce continual improvements in patient care.
**Methods:** We analyzed patterns of antipsychotic prescribing and use among 6,563 EPINET patients receiving CSC services for first episode psychosis. We explored how patterns of antipsychotic prescription and use were related to key outcomes including self-rated recovery, self-rated symptom severity, clinician-rated symptom severity, and psychiatric hospitalization.
**Results:** We will present detailed findings from this analysis including graphs of patient trajectories over time. We find that 29% of CSC patients were known to have discontinued antipsychotics while connected with services. Their subsequent trajectories are often complex: of those who subsequently remain off medication for the duration of treatment, many experience an initial increase in symptoms followed by sustained improvements over and above patients with other medication use patterns (even after controlling for baseline ratings).
**Conclusions:** Many patients discontinue antipsychotic medication during treatment. Outcomes for these patients are naturally variable but often very good. While the EPINET dataset is large it has numerous limitations affecting interpretation. It is crucial to develop a better understanding of antipsychotic discontinuation and ways to best support patients who do choose to discontinue antipsychotics.

### 47.2 "Choosing Your Own Path": Patterns of use of Psychiatric Medication Among Individuals With Serious Mental Illness

David Roe*[1], Maia Asher[2], Ilanit Hasson-Ohayon[2]

[1]*University of Haifa, Israel,* [2]*Bar-Ilan University*

**Background:** It is well documented that despite compelling evidence supporting the effectiveness of antipsychotic medication in reducing symptom severity and risk for relapse, most individuals diagnosed with a psychotic disorder do not use antipsychotics as prescribed. The wide range of individual responses to using, reducing, or stopping antipsychotics has challenged the "one-size-fits-all" model for medication use. The current study attempts to map patterns of medication use among people with Serious Mental Illness (SMI), explore and describe the characteristics of each pattern.

**Methods:** Sixteen participants with a diagnosed SMI that used psychiatric medications for at least one year, were interviewed, and data were analyzed using an ideal-type analysis.

**Results:** Analysis revealed four patterns of medication use: 1) adherence with no doubts; 2) adherence following attempts to stop/reduce; 3) flexible use over time; and 4) tapering.

**Conclusions:** The process of recovery often involves changes in patters of medication use which calls for the need to tailor therapeutic interventions to consumers evolving needs, beliefs, and preferences with regard to medication use. The findings will be discussed with an emphasis on clinical and ethical dilemmas and an emphasis on the importance of communication and collaboration between all key stakeholders involved in the recovery process.

### 47.3 Antipsychotic Discontinuation During Early Intervention in Psychosis

Helene Speyer*[1], Anne Emilie Stürup[1], Helene Gjervig Hansen[1], Carsten Hjorthøj[1], Merete Nordentoft[1]

[1]*Mental Health Centre Copenhagen*

**Background:** Although clinical guidelines recommend long-term antipsychotic treatment for individuals with psychosis, many patients experience periods without medication, and some opt for prolonged medication-free intervals and one third may never have another relapse. However, due to long intervals between assessments in published studies and the fluctuating nature of psychotic symptoms, a design with closer follow up is necessary to decide if those found in remission is only between periods.

**Methods:** This observational study focuses on individuals with first-episode psychosis (FEP) undergoing two years of OPUS treatment. We examine patterns of antipsychotic medication use, including reasons for initiation and discontinuation, and explore the relationships between medication discontinuation, hospitalization due to relapse, and the following treatment response, and level of functioning. Additionally, we analyze the subgroup of patients who remain off medication for extended periods, assessing their level of functioning, psychotic symptoms, and hospitalization rates.

**Results:** Of the 525 individuals with FEP, 90% received antipsychotic medication. Contrary to expectations, 70% continued treatment until the end of the service period, while 30% discontinued at least once. Further analyses will explore the course of illness following medication discontinuation and after severe relapses.

**Conclusions:** Due to the observational nature of this study, causal inferences about the effects of relapses or medication discontinuation cannot be made, as these likely reflect the natural progression of the illness. However, our findings may point to how people fare

without medication at a more detailed level than previously published studies, due to close follow up for 2 years.

### 47.4 Navigating Antipsychotic Decisions in First Episode Psychosis From the Perspective of Service Users

Nev Jones*[1], Shannon Pagdon[1], Sara McNemar[1], Christina Babusci[2]

[1]*University of Pittsburgh,* [2]*University of Pittsburgh School of Social Work*

**Background:** While a growing observational and clinical trials literature suggests that a significant proportion of early psychosis intervention (EPI) clients successfully discontinue antipsychotics, very little has been published regarding client's own decision making experiences, including discussions of discontinuation with prescribers, tapering or withdrawal, and associated impacts.
**Methods:** We conducted in-depth semi-structured interviews with 40 early intervention in psychosis (EIP) in the United States, stratified to include individuals who had consistently used antipsychotics, discontinued and then-restarted antipsychotics and successfully discontinued antipsychotic use. The interview protocol queried participants about their experiences of and views of medication, decisions regarding medication use, relationships with providers, and the broader impacts of medication-related decisions and experiences. Data coding was AI-assisted, leveraging OpenAI in addition to experienced human coders to strengthen analyses.
**Results:** The majority of participants described pressure from clinicians to use and remain on antipsychotics, with only a small minority describing active support for discontinuation. Participants across utilization sub-groups described significant challenges navigating decisions about antipsychotics, often including unresolved concerns about long-term side effects and personal ambivalence, while clinicians were frequently described as downplaying or minimizing concerns about medication use. Among those who discontinued successfully versus relapsed, intentional efforts to identify and engage in strategies to self-manage symptoms or engage in other forms of self-care and wellness practice appeared to play an important role.
**Conclusions:** As the field moves to more fully embrace shared decision making and to support antipsychotic discontinuation among those who opt for it, a deeper understanding of service user perspectives and experiences is essential. Participant data reported here suggests that, in spite of an aspirational goal of shared decision making in EIP settings, many service users continue to experience undue pressure, and inadequate support navigating antipsychotic use decisions, and, where discontinuation is desired, preparation and support for non-pharmacological wellness and self-management.

## 48. Computational Approaches to Understanding Language Alterations in Psychosis

Franziska Knolle*, Technical University of Munich*

**Overall Symposia Abstract:** Language abnormalities are core to schizophrenia and predict illness severity and functional outcomes. Still, the underlying causes of this abnormality remain unclear. Do language alterations give insight into latent neurocognitive processes at the core of pathophysiology, or are they merely epiphenomenal (e.g., reflecting educational disparity or more general working memory impairment)? The study of language in psychosis has advanced considerably in recent years. Generally, the progress has taken one of two

directions: (1) theory-driven examinations of latent cognitive processes (e.g., predictive coding and cognitive mapping models), and (2) data-driven machine learning approaches.

The first approach combines experimental paradigms with mathematical modelling to offer mechanistic insights into cognitive processes, connecting language in psychosis to cognitive neuroscience. Predictive coding models show how listeners integrate prior knowledge (semantics) with sensory input (phonetics), updating their internal models when expectations are violated. Predictive coding models may prove critical for elucidating the origin of psychotic symptoms and language dysfunction. Cognitive mapping, in contrast, infers the structure of internal representations (e.g., narrative schemas) from the statistics of language behaviour itself.

Conversely, data-driven approaches have shown that sophisticated natural language processing (NLP) algorithms may detect subtle dysfunctions in language that are predictive of clinical outcomes. Yet these predictive models often lack explainability and generally do not yield mechanistic insight. Importantly, novel work elucidates how NLP additionally allows for well-powered investigations of disease-mechanisms and symptom-specific language deficits.

This symposium will reconcile current research using these different approaches to discuss if and how language alterations may contribute to the development or aggravation of symptoms, and to provide evidence for computational and neurobiological mechanisms underlying the alterations. First, Elisabeth Sterner (LMU Munich), will show how a combination of single-trial EEG data and computational modelling can shed light on the underlying mechanisms of altered prediction error processing during language processing in individuals with psychotic-like experiences. Second, Franziska Knolle (TUM) using a predictive language task, which lends itself to a Bayesian Inference process, will show how the use of prior semantic knowledge and sensory information during predictive language perception changes with disease-stage and links to striatal dopamine and cortical glutamate. Matthew Nour (Oxford University) will present new NLP algorithms that can infer latent cognitive representations from naturalistic language behavior and show language-based phenotypes covary with schizotypy in a general population sample, pointing a way towards a theory-guided behavioral biomarker. Xinyi Liang (King's College London) will present a study using NLP-based markers—semantic coherence, tangentiality, on-topic score, and graph analysis—to differentiate speech alterations between individuals at clinical high risk of psychosis and healthy controls in an online sample. The findings particularly emphasized changes in semantic coherence, tangentiality, and on-topic score.

Combining novel research from two emerging fields, this symposium sheds light on language-based mechanisms underlying psychotic symptoms. It furthermore shows that for a scientific breakthrough it is essential to combine theory- and data-driven approaches. By incorporating theory-driven models, which capture processes underlying the data, data-driven algorithms may outperform approaches that do not consider such generative mechanisms.

**48.1 Altered Prediction Error Signaling During Semantic Language Processing is Linked to Psychotic-Like Experiences: Insights From a Computational Single-Trial Analysis of the N400 Component**

Elisabeth Sterner*[1], Verena Demler[2], Franziska Knolle[2]

[1]*Chair of General and Experimental Psychology, Ludwig Maximilian University of Munich,* [2]*Technical University of Munich*

**Background:** A growing body of evidence across different cognitive domains and sensory modalities suggests that abnormalities in the processing of prediction errors are central to psychotic disorders and contribute to the development of positive symptoms. In semantic language processing, studies using the N400 component – a neurophysiological index of a semantic prediction error – have demonstrated that individuals across the psychosis spectrum exhibit impaired processing of both predictable and unpredictable input, leading to a reduced N400 effect. According to predictive coding accounts of psychosis, this may be caused by an altered weighting of prior beliefs and incoming sensory information. To investigate this hypothesis in the domain of language processing, we designed a language paradigm that manipulated both the strength of individuals' semantic prior beliefs as well as the reliability of the sensory information. Using a Bayesian Belief updating model and EEG, this study aimed to (1) explore the use of semantic prior beliefs relative to sensory information as a trait marker for psychotic-like experiences and (2) examine whether the computational signature of altered prediction errors is manifested in the single-trial N400 amplitudes.
**Methods:** 55 participants assessed for psychotic-like experiences completed a predictive language paradigm while their brain activity was recorded with EEG. In the task, participants listened to sentences of varying predictability (e.g., high predictability: "The ship disappeared into the thick … fog"; low predictability: "The laptop was on top of a … box"). The sentence-final word of each sentence (e.g., "fog" or "box") was degraded in clarity to different degrees, ranging from fully unintelligible to fully intelligible. Participants were asked to report the word they perceived to assess task-based hallucinations. A Bayesian belief updating model was used to estimate the relative weighting of semantic priors versus sensory information. Single-trial prediction error signatures were simulated from this model and used to assess how prediction errors modulate N400 amplitudes across sensor space and time.
**Results:** Computational modeling results demonstrated that as psychotic-like symptoms increased, semantic priors were overweighted relative to sensory information. By integrating trial-level prediction errors from the Bayesian model with single-trial EEG data, we found that the computational signature of prediction errors captured neurophysiological alterations in the N400 component.
**Conclusions:** Our findings are consistent with predictive coding models of psychosis, suggesting that individuals along the psychosis spectrum display an imbalance between the integration of predictions and sensory evidence. This imbalance is reflected in neurophysiological changes during the processing of semantic prediction errors, specifically in the N400 component. Notably, these alterations were evident even in a healthy, subclinical population, suggesting that such changes may occur prior to the clinical onset of psychosis. Taken together, our results point towards altered semantic prediction error processing as a potential neurocomputational mechanism driving psychotic-like experiences and provide initial evidence of its potential in early detection and intervention strategies.

## 48.2 Alteration in Predictive Language Processing in Different Acute Psychosis and Remission, and Their Neurobiological Mechanisms

Franziska Knolle*[1], Elisabeth F. Sterner[1], Christoph Mathys[2]

[1]*Technical University of Munich,* [2]*Interacting Minds Centre, Aarhus University*

**Background:** Schizophrenia is associated with a broad range of language alterations. The predictive coding framework, which has emerged as a leading theory for explaining positive symptoms in schizophrenia, also offers a promising model for understanding language processing. According to this account, positive symptoms like delusions and hallucinations may stem from disruptions in how the brain balances sensory input and prior beliefs. Experimental evidence suggests that, at lower processing levels (e.g., early sensory areas), an over-weighting of sensory signals—potentially driven by heightened dopamine activity—may create aberrant salience, leading to delusions. In contrast, at higher cognitive levels, an over-weighting of prior beliefs, possibly linked to altered glutamatergic receptor signaling, may contribute to hallucinations. Since language processing relies heavily on prediction, it provides an ideal domain to test this interplay between sensory input and prior expectations. This study aims to investigate (1) how the balance between prior knowledge and sensory information in predictive language tasks shifts as patients with schizophrenia transition from acute psychosis to remission, and (2) how these changes relate to striatal dopamine and cingulate glutamate levels.

**Methods:** Using a longitudinal approach, we assessed 25 patients with schizophrenia during two phases: first, in a state of active psychosis, and approximately three months later, in psychotic remission. Control participants were assessed at two similarly spaced time points. All participants completed a predictive language task in which they listened to sentences with varying levels of predictability (e.g., high predictability: "Goethe was a famous German ... poet"; low predictability: "Next to the window was a ... hole"). The final word of each sentence (e.g., "poet" or "hole") was degraded in clarity using a noise vocoding algorithm, with four levels ranging from fully unintelligible to fully intelligible. After hearing the sentence, participants reported the word they perceived, allowing us to assess conditioned hallucinations. We fitted a linear Bayesian regression model to estimate the prior weight, reflecting the relative influence of prior knowledge versus sensory input. Additionally, we measured cortical glutamate levels using MR spectroscopy and striatal dopamine synthesis capacity via F-DOPA PET. A repeated measures model was employed to compare prior weights and conditioned hallucinations across time points and groups, while also exploring associations with cingulate glutamate, striatal dopamine, and symptom severity at both assessments.

**Results:** The modeling results revealed that patients overweighed prior knowledge relative to sensory information compared to controls, particularly during the first time point, when they were in a state of acute psychosis. Overweighting of priors was associated with elevated glutamate levels, while sensory overweighting was linked to increased dopamine capacity. These relationships were consistent across participants and time points.

**Conclusions:** This study demonstrates that prior knowledge was overweighted during a language perception task in schizophrenia patients, particularly during acute psychosis, and to a lesser extent during psychotic remission. Notably, greater prior weighting and more severe psychotic symptoms were associated with increased conditioned hallucinations. Furthermore, the findings provide experimental evidence linking glutamate and dopamine levels to prior weighting, suggesting a neurobiological mechanism underlying the development of hallucinations and delusions.

## 48.3 Decoding Abstract State Sequencing in Natural Language and Implications For Thought Disorder

Matthew Nour*[1], Isaac Fradkin[2], Daniel McNamee[2], Raymond Dolan[3]

[1]*University of Oxford,* [2]*Max Planck UCL Centre for Computational Psychiatry and Ageing Research,* [3]*University College London*

**Background:** The "aberrant cognitive mapping" hypothesis proposes that psychotic symptoms such conceptual disorganisation and delusions stem from abnormalities in how the brain forms and samples structured representations of the world. The computational analysis of natural language constitutes a burgeoning approach to studying such internal representations in a manner that is clinically scalable and valid.

In this presentation I will showcase work that applies novel machine learning and NLP tools to natural language data from 1000 participants completing narrative construction tasks, and illustrate how these tools can inform neurocognitive theories of schizophrenia - including those pertaining to how related concepts are represented and retrieved.

**Methods:** 1000 participants completed a story construction task as part of an online study, in which they needed to tell the story of Cinderella and describe a typical person's daily routine.

We developed and validated a novel computational analytic pipeline for the analysis of natural language, combining multivariable linear regression, sequenceness analysis, and AI large language models (GPT4o-mini, in both embedding and generative modes). Briefly, this pipeline comprises sentence parsing (splitting the sequence of words into utterances, e.g., using BERT LLM to predict probability of period after each token), semantic embedding (embedding each utterance in LLM vector space, e.g., OpenAI 'embeddings' models), latent state decoding (using GPT4o-mini auto-labelling), and sequential semantic trajectory analysis. The result is that we can construe a participant's language data in both tasks not only as a sequence through an abstract "semantic space" (held constant between tasks), but also as a sequential progression through a more abstract "task space" (which varies in a context sensitive manner).

Participants also completed a large number ( > 200) of self-report psychiatric symptom questions, which were subjected to factor analysis to identify latent transdiagnostic symptom dimensions.

**Results:** I will present three key results. The first demonstrates the validity of the NLP pipeline to infer meaningful latent task states from naturalistic language speech. Second, I will show that inter-individual variance in the atypicality and sequencing of decoded task states is conserved across tasks, indicating that it identifies a generalisable facet of an individual's latent cognitive processes, an important facet of construct validity. Finally, demonstrating predictive validity and potential clinical utility, I will show that atypicality in both semantic content and form track self-reported measures of thought disorder.

**Conclusions:** These findings demonstrate the feasibility of indexing the structure of internal conceptual organisation in clinical samples using advanced NLP tools applied to free speech data, in a manner that can inform cognitive mapping hypotheses of symptoms. More broadly, this work contributes new methods that can be applied to the study of speech and cognition in

psychiatric samples, with minimal attentional or task-comprehension requirements for participants. These methods, and associated proof-of-concept findings, lay the foundation for future transdiagnostic studies, with the ultimate aim of developing NLP-based diagnostic and treatment-prediction tools for patients.

### 48.4 Using Natural Language Processing Based Speech Measures to Distinguish People at Clinical High Risk Of Psychosis From Healthy Controls

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**Background:** Formal thought disorder is one of the core symptoms of psychosis manifesting through the form of disorganised speech. Studies employing natural language processing (NLP) speech measures have gained promising results in differentiating patients with psychosis from healthy controls. There is also growing evidence indicating that formal thought disorder may already be evident in individuals at clinical high-risk (CHR) of psychosis, which occurs before clinical-level psychosis. Studying this period is crucial, as early detection and intervention at this time may effectively mitigate the onset of psychosis. However, most research exploring the relationship between speech alterations and psychosis has been constrained by small sample sizes and findings on CHR populations have remained inconsistent. Recent advances in online recruitment and screening facilitates the inclusion and analysis of large-scale samples. The present study aimed to investigate whether four NLP speech measures—semantic coherence, tangentiality, on-topic score and speech graphs can effectively discriminate CHR from health controls in a moderate-to-large online sample.
**Methods:** The present study recruited participants from the general population through an online platform and asked them to complete a self-reported prodromal questionnaire (PQ16), then selectively invited them to in-person clinical assessments—Comprehensive Assessment of At-Risk Mental State (CAARMS). The present study comprises of 4 groups—a) CAARMS+ group (scored above threshold of PQ16 and identified as “at risk” by CAARMS); b) CAARMS- group (scored above threshold of PQ16 and identified as “no risk” by CAARMS; c) Strong Control (SC) group (scored below threshold of PQ16 and identified as “no risk” by CAARMS) and d) Weak Control (WC) group (scored 0 on PQ16 but not invited to interview). This study now included 82 participants in CAARMS+ group, 181 in CAARMS- group, 65 in SC and 101 in WC. All participants were asked to describe eight ambiguous images from the thematic apperception test for one minute each to generate excerpts which were then used to produce 4 NLP speech measures as previously described by work from our lab.
**Results:** The present study employed a novel online sample with a gender distribution of 70% female and 30% male, which differs significantly from previous studies that recruited participants from local early intervention services. Despite significant difference in sample recruitment and composition, our preliminary results still indicated significant group differences in terms of semantic coherence, tangentiality and on-topic score but not for any of the speech graph connectedness measures. After controlling for cognitive functioning using non-parametric analysis of covariance (Quade, 1967), group differences remained significant for semantic coherence, tangentiality and on-topic score. Post-hoc analysis revealed that the most pronounced differences were attributed to the Weak Control group.

**Conclusions:** The present study demonstrates the promise in distinguishing CHR individuals from healthy controls using three NLP speech measures despite this unique sample composition, highlighting the potential usefulness of speech markers in early detection and intervention of psychosis.

## Oral Session: At-Risk Population and Risk Predictions

### 1. Contingency Management Therapy for Stimulant Use Disorder in Psychosis Patients

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**Background:** The rise in stimulant use disorders (SUD) across North America has resulted in increased psychiatric disorder, medical complications, and death among those who use drugs. Due to limited pharmacologic interventions, behavioral approaches remain the primary treatment avenue for patients with a SUD. Contingency Management (CM), thought to work by stimulating reward pathways of the brain, is among the most widely supported behavioral interventions in the SUD literature. CM protocols operate by providing reinforcement (usually cash or small prizes) to patients who are able to provide a negative urine toxicology screen at regular intervals during the treatment period. While this strategy is proven to be effective in reducing stimulant use, its effectiveness in patients with comorbid psychotic illness remains poorly elucidated.

**Methods:** In this observational pilot-study, we developed a 12-week CM protocol, involving probability-based cash reward system for N=14 patients with comorbid SUD and early psychotic illness enrolled in the Prevention and Early Intervention Program for Psychoses (PEPP) at London Health Sciences Centre. No exclusions were made based on severity of SUD, with patients ranging from mild SUD to severe using DSM-5 criteria. Patients were provided with tokens in the event of negative urine screens (using the Rapid Response Diagnostics multi drug 1-step cup), which could be used to draw variable cash prizes ranging from $0.00 to $100.00. To encourage sustained abstinence, additional tokens were provided with every 2 weeks of negative urine toxicology screens.

**Results:** Of the 14 patients, n=7 completed all 12 weeks, with n=5 meeting criteria for early remission (12 consecutive weeks of negative urine screens). Among patients who did not reach early remission, n=5 were unable to provide any negative urine screens, with n=4 individuals reaching sporadic abstinence (ranging from 2-6 weeks).

**Discussion:** As early-career researchers and clinicians, we aim to address a treatment gap in this vulnerable patient population. Outcome measures of interest include increasing the rates of weeks of abstinence from stimulants, which will therefore reduce the mental and physical complications related to stimulant use. Additionally, studying behavioural interventions that can be integrated in contingency management practices that can be included in hospital and community settings for those who use stimulants and have signs and symptoms of psychosis. The high rate of psychosis and mental health impacts with those that use stimulants, treating and studying this patient population with contingency management and expanding on the intervention will help progress the field of schizophrenia treatment and addiction psychiatry. Currently, there are no contingency management programs in London, Ontario, furthermore this has been the first known program that integrates first episode psychosis and psychosis related disorders, especially within a hospital setting.

Our CM project will be vital in the development of new programs and innovation for those suffering with stimulant use disorders and in the field of developing interventions within those suffering from psychosis and schizophrenia. We have been able to integrate CM in already established first-episode psychosis programming and can aim to provide models of care for other clinics and hospital psychosis programs. In addition, there has been a focus on

training residents and medical students in the context of this current study, with collaboration care approach with colleagues within Family Medicine, Addiction Medicine, and community agencies. This engagement will not only launch paths for promising individuals in clinical research but would be the first of its kind in Canada.

The learning objections of this presentation include: a review of contingency management for stimulant use disorder, development and process of contingency management program in an outpatient psychiatric setting, and review of outcomes, clinical pearls and next steps in contingency management programs for those with psychosis.

## 2. Predictive Validity of Psychotic-Like Experiences in Daily Life 8 Years Later: Examining the Moderating Role of Psychosis-Proneness Polygenic Susceptibility

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**Background:** Psychosis is expressed across a broad dynamic continuum of individual differences in personality, symptoms and impairment, that ranges from nonclinical (psychotic-like experiences) to full-blown clinical manifestations (schizophrenia). This continuum has been referred to as schizotypy. Schizotypy offers a useful and unifying construct for understanding mechanisms involved in the transition from predisposition to disorder. This study analyzed the predictive and ecological validity of psychometric schizotypy dimensions and daily-life psychotic-like experiences in a longitudinal study (Barcelona Longitudinal Investigation of Schizotypy; BLISS) spanning a total of 7.8 years. Additionally, we examined whether prospective associations were moderated by individual genetic differences indexed by a Polygenic Risk Score of Psychotic-Like Experiences (PRS-PLE).

**Methods:** At Time 1 (T1) of the BLISS study, 547 college students completed the Wisconsin Schizotypy Scales, from which positive and negative schizotypy factor scores were derived and employed in the present study. A subset of individuals were oversampled for high schizotypy to ensure variability, and were subsequently re-assessed at four time points spanning a total of 7.8 years. This study reports Experience Sampling Methodology (ESM) data from T2 (n=206) and T5 (n=159). Participants were prompted randomly 8 times daily for one week to complete assessments of their current symptoms and experiences. At T2, participants also provided saliva samples and were genotyped to obtain the PRS-PLE based on the relevant Genome-Wide Association Study. This specific PRS was selected given that it was obtained in a GWAS study in the general population.

**Results:** Positive schizotypy at T1 was significantly associated with T5 ESM ratings of paranoia and disorganization and showed a trend association with PLE. No association was found with T5 ESM negative-like symptoms (lack of thoughts or emotions). Negative schizotypy at T1 showed trend-level associations with T5 ESM ratings of paranoia and negative-like symptoms. ESM ratings of paranoia and PLE at T2 over a week predicted T5 momentary paranoia, PLE and disorganization (6.2 years later). Inversely, T2 ESM negative symptoms predicted T5 ESM negative symptoms but not paranoia, PLE or disorganization. The PRS-PLE significantly moderated the prospective association between T2 ESM paranoia and T5 ESM disorganization and showed some moderating effects in the prediction of T5 paranoia and negative symptoms, although these only reached trend-level significance.

**Discussion:** To the best of our knowledge, this is the first prospective study examining the predictive and ecological validity of psychotic-like experiences in daily life and the role of genetic individual differences indexing psychosis-proneness. The pattern of associations aligns with previous research suggesting that schizotypy dimensions are differentially associated to psychotic-like experiences over time, with the positive dimension more closely tied to positive and disorganized experiences whereas the negative dimension distinctively predicted negative features in daily life. Importantly, findings extend previous research by adding ecological validity to the predictive value of schizotypy dimensions and psychotic-like manifestations in daily life through ESM. As expected, individual differences in genetic susceptibility to psychosis-proneness had a moderating role in the prospective associations of daily-life psychotic-like experiences over a span of 7.8 years—yet some of the associations were detected at a trend level.

### 3. Differential Effect of Childhood Trauma Across Countries on The Risk of Psychosis - A Cross-Cultural Study of Clinical High-Risk for Psychosis Subjects From Brazil, China and Turkey

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**Background:** The clinical high-risk for psychosis (CHR) state has been one of the most studied preventive paradigms in psychiatry. However, there are still gaps concerning transcultural studies and data from low- and middle-income countries (LAMIC). Discussion:s around the differences in course and outcome of psychosis according to different countries began as early as in the 70s, with the International Pilot Study of Schizophrenia (IPSS). Thus, it is long known that socio-cultural factors, shaped by geographical and economic factors, have an important impact on psychosis. One of these factors is childhood trauma. Physical neglect, for instance, was found to be higher in LAMIC when compared to high-income countries. Furthermore, it is acknowledged that childhood trauma is a risk factor for psychosis, being also significantly related to CHR. However, studies examining the interplay between childhood trauma and CHR in LAMIC remain scarce. Our study aimed to analyze childhood trauma in CHR from countries in three different continents, Brazil, China, and Turkey.

**Methods:** The Brazilian sample consisted of 85 CHR and 103 control subjects. The Chinese sample consisted of 19 CHR and 61 controls. The Turkish sample consisted of 149 UHR and 117 controls. A total of 253 CHR and 281 control subjects constituted this study's sample. All subjects were assessed with the Childhood Trauma Questionnaire (CTQ), a self-administered inventory composed by 28 items to be answered in a 5-point Likert scale. It addresses five trauma dimensions: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse.

Statistical analyzes first compared each country's CHR subjects concerning their sociodemographics and clinical variables. Second, all three samples were pooled together and analyzed for CHR versus controls differences. Third, to control for CHR samples' disparities, generalized linear models (GLM) were run including childhood trauma dimensions as

dependent variables. Age, gender, marital status, level of education, alcohol use, and country of origin constituted the independent variables.

**Results:** In CHR subjects, significant differences across countries were observed for age, gender, alcohol use, marital status, and level of education. As for childhood trauma, all CTQ dimensions were also significantly different across countries except for sexual abuse. Considering all samples together, CHR showed significantly higher scores compared to controls for physical abuse (7.38 vs. 6.35, $p=0.011$), emotional abuse (10.58 vs. 8.42, $p < 0.001$), emotional neglect (19.08 vs 17.06, $p=0.005$), and sexual abuse (6.46 vs. 5.68, $p < 0.001$). Only physical neglect was higher in controls than in CHR (9.31 vs. 8.08, $p < 0.001$).

In GLMs, being female ($B=0.232$, $p < 0.001$) and unmarried ($B=0.249$, $p=0.011$) were positively related to sexual abuse in CHR. Chinese CHR had a significant association with emotional neglect ($B=0.347$, $p < 0.001$), as well as with physical abuse ($B=0.218$, $p=0.30$). Physical abuse was also correlated with lower levels of education ($p=0.016$-$0.019$). At last, Brazilian ($B=0.909$, $p < 0.001$) and Chinese ($B=0.820$, $p < 0.001$) CHR subjects had a positive association with physical neglect compared to Turkish CHR individuals.

**Discussion:** Results: suggest that while sexual abuse might be an universal risk factor for CHR, physical abuse, emotional and physical neglect might be culture-specific risk factors. Larger intercultural studies are warranted to further investigate the interplay between the several forms of childhood trauma, socio-cultural factors and risk for psychosis.

### 4. Prenatal Maternal Objective Hardship Predicts Thought Disorder in Adolescence, Moderated by Sex and Timing: Project Ice Storm

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**Background:** Retrospective administrative data suggest that prenatal maternal stress, such as exposure to a natural disaster, increases risk for schizophrenia in the offspring. The effects appear to differ according to the sex of the unborn child and the timing in gestation of the stressor. Yet these studies are unable to determine the active ingredient in the stress effect: is it due to maternal distress, or to the objective severity of the mothers' exposure to the event? Our goal was to answer this question by studying the effects of a natural disaster prospectively, by teasing apart effects of maternal objective hardship and subjective distress, and by assessing subtle signs of thought disorder in offspring during adolescence.
**Methods:** In January 1998 the Canadian province of Quebec experienced a severe ice storm that left three million people with power for up to 45 days in the coldest month of the year. In June 1998 we recruited women who had been pregnant during the disaster and assessed their objective hardship (e.g., days without power) and their subjective distress (Post Traumatic Stress Disorder symptoms) due to the storm. When their children were 15 years of age, we recorded their discourse during the UCLA Life Stress Interview. The last 10 minutes of speech was coded for thought disorder using the Communication Disturbances Index (CDI) ($n = 45$). The CDI codes instances of vague or confused references, structural unclarities, wrong word references, missing information, and ambiguous word meanings.
**Results:** Maternal subjective distress was unrelated to youth thought disorder. A significant Objective Hardship by Sex interaction ($R2 = 0.23$, $p = .01$) showed that, for boys only, the more severe the mothers' ice storm hardship during pregnancy the more severe the boys' CDI

score. When Objective Hardship was high, CDI scores were significantly higher for boys than for girls.

Timing moderated effects of Objective Hardship such that the later in pregnancy the ice storm occurred (after the 5th week) the stronger the effect of the hardship: greater hardship, higher CDI scores ($p < 0.001$), with many cases resembling those of youth with first episode psychosis.

**Discussion:** Using a natural experiment approach, in which the severity of the mothers' objective hardship from the ice storm was randomly distributed within the population, allows us to be relatively confident that there is a causal association between this form of prenatal maternal stress and a range of severity of communication disturbance during adolescence. The moderation by gestational timing suggests that brain regions that are in rapid development in late pregnancy may be especially sensitive to this stress and may be implicated in the development of thought disorder. In this same cohort, we have shown that early, rather than late, exposure to the ice storm presented a risk period for the effects of maternal stress for the severity of autistic-like traits in the children. The precise timing of the onset of the ice storm permits the development of hypotheses linking the development of specific brain regions to specific psychopathologies

## 5. Improving Processing Speed in Adolescents at Clinical High Risk for Psychosis With the Specific Cognitive Remediation Plus Surround (Scores) Intervention: Findings From the Target Engagement (R61) Phase

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**Background:** Recent preventative approaches with young people at clinical high risk for psychosis (CHR-P) have focused on the remediation of cognitive deficits that are readily apparent and predictive of future illness. However, the small number of trials using cognitive remediation with CHR-P individuals have reported mixed results. At-risk youth are considered to be at an age of maximal brain plasticity and thus would be expected to profit the most from treatment. Therefore, the current NIMH-funded R61/R33 trial addresses the previous methodological challenges and optimizes CR procedures in order to maximize prevention. In the present study, we report on the preliminary findings from the first phase on the recently concluded R61 phase of the Specific COgnitive REmediation plus Surround (or SCORES) intervention that targets early processing speed deficits in CHR-P adolescents aged 14-20 years old. The primary aim of the R61 phase of the current project was to demonstrate that we could detect and improve the processing speed target.

**Methods:** In the recently completed first phase (R61), a single-arm 2-year proof of concept study, 29 CHR-P individuals (mean age=16.5, SD=2.34) received SCORES for 10 weeks (goal of 4hrs per wk/40 hrs total) to demonstrate target (processing speed) engagement. The first phase of the SCORES intervention (ClinicalTrials.gov Identifier: NCT05131035) was conducted by the RAP program in the Zucker Hillside Hospital in New York, part of the Northwell Health System. The Northwell Health System IRB approved all procedures. CHR-P participants were included based on the presence of one or more moderate-to-severe level (scores of 3–5) attenuated positive symptoms as assessed by the Structured Interview for

Psychosis-risk Syndromes (SIPS). The current trial also only included CHR adolescents aged 14–20 years-old (narrowed from a typical recruitment age range of 12–35 years-old) with baseline processing speed deficits (as determined with a score that is < 0.5 standard deviations (SD) below the mean on any of the three processing speed tests: animal naming, trails A and symbol digit coding. The R61 included targeted CR training, done at home, with processing speed exercises from commercially available online programs. In addition, participants received a series of features to further enhance motivation for completing the CR exercises. These features included: 1). Cognitive Personal Trainers, 2). Parents as Allies, 3). Biweekly tournaments, and 4). a Personalized Training Tracker.
**Results:** Pre-training, the CHR-P group showed large deficits in processing speed at -1.577SDs, relative to normative healthy control performance. After the initiation of SCORES, the CHR-P group demonstrated dramatic improvements in processing speed performance. Relative to the pre-training baseline performance, significant improvements in processing speed were found post-trial (paired t-test, t15=8.3, P < 0.001) at the 10-week assessment. These improvements from baseline to post-training represent an effect size change of d=1.59. Verbal learning performance over the intervention was consistent and no significant differences (all Ps > .05) were found from pre-training to the Post-training (Pre-training mean -.961, SD=; Post-training Mean -1.18, SD=1.445; paired t-test, t15=.737, P=.472 d=0.184) assessment. In addition to finding that SCORES improved processing speed performance, we also found a significant relationship between the total time trained during the first 5-weeks of the intervention and gains in processing speed improvements (r=.48, P < .05). This suggests that a longer time spent training was associated with greater gains in processing speed performance. Overall attendance at the weekly group was excellent at 92.5%. Exit interviews completed at the 10-week assessment suggested that the participants were very positive about the training battery and the study. Across subjects, the conclusion was strongly stated that they were interested in participating for the potential cognitive gains and that subject payments were secondary in importance.
**Discussion:** The SCORES study is a completely virtual intervention that targets a core cognitive mechanism, processing speed, which is a rate-limiting factor to higher order behaviors and clinical outcomes in CHR-P adolescents. Findings from the initial phase, strongly indicate that SCORES successfully and specifically engaged processing speed performance over the course of the 10-week intervention. This indicates that SCORES is a feasible intervention for CHR adolescents and engages the processing speed target, supporting advancement to the R33 Phase. Finally, additional restrictions to the usual CHR criteria were added to reduce the noise often found in standard CHR populations that typically interferes with clear signal detection. These criteria reduced heterogeneity in developmental stage and limited sample selection to CHR individuals with mild cognitive pre-existing deficits. These modifications in CHR criteria were expected to lead a more homogeneous CHR population which will be optimal for the mechanistic pathway that guides the SCORES intervention, and thereby, resulting in greater processing speed improvement and significant clinical benefits.

## 6. Association Between Neurological Soft Signs and Psychotic Experiences is Mediated by Executive Functions in Children and Adolescents

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**Background:** Neurological Soft Signs (NSS) are subtle impairments in motor coordination, sensory integration, and motor sequencing, and have been identified in individuals across all stages of psychotic disorders, from the premorbid period to chronic stages. Moreover, the presence of NSS has been associated with an increased risk of conversion to schizophrenia in children and adolescents at high risk. The cognitive dysmetria paradigm suggests that sensorimotor and cognitive integrative deficits contribute to the emergence of psychotic symptoms, however there is a lack of evidence of these mechanisms in prodromal stages of psychotic disorders. Our study aims to investigate whether the relationship between NSS and Psychotic Experiences (PE) is mediated by executive functions, these being responsible for the organization and prioritization of cognitive processes and widely impacted in schizophrenia.
**Methods:** This is a cross-sectional analysis of Brazilian High Risk Cohort Study for the Development of Childhood Psychiatric Disorders, a school-based community cohort. NSS was assessed by Luria motor tasks, combining the scores on time, accuracy, fluency, precision and symmetry in a single score to model the latent variables using confirmatory factor analysis. Latent variable analysis of Community Assessment of Psychic Experiences was used to assess PE and neuropsychological tests for executive functions
**Results:** 1437 subjects without mental disorders were included in the analysis, with a mean age of 10.18±1.94 years, and 53% male. No significant differences in PE scores between quartiles of motor performances in the sample were found. Multivariate linear regression analysis controlling for confounders revealed that executive function significantly predicted PE (β: -0.10, $p < 0.017$) and NSS (β: -0.24, $p < 0.000$). A subsequent mediation analysis shows a significant indirect effect between NSS and PE mediated by executive function (NSS - executive function β: -0.353, $p < 0.000$; executive function - PE β: -0.09, $p < 0.012$)
**Discussion:** This study provides evidence that executive function plays a mediating role in the relationship between NSS and PE in children and adolescents. The findings support the cognitive dysmetria paradigm, suggesting that difficulties in integrating brain functions may contribute to psychotic experiences. These highlights the importance of early detection and intervention targeting executive function in young individuals with NSS, potentially mitigating the risk of developing psychosis later in life. Hence, there is a need to determine these longitudinal relations and a need to investigate potential interventions that could enhance executive function in this population.

## 7. Testing the Transportability of the Psychosis Metabolic Risk Calculator (Psymetric) in Canada (Quebec): International External Validation Study

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**Background:** Cardiometabolic morbidity largely explains premature mortality in people with psychot-ic disorders and is detectable from psychosis onset. Currently, no accurate cardiometa-bolic risk prediction tool exists for young people with first-episode psychosis (FEP). The Psychosis Metabolic Risk Calculator (PsyMetRiC) aims to bridge this gap, but its accura-cy and potential clinical usefulness in North American populations remain unverified.
**Methods:** The external validity of PsyMetRiC, developed in the UK to predict the risk of incident metabolic syndrome (MetS) up to six years after a FEP, was assessed using the Quebec Psychosis Early Intervention Clinic Database. Patients aged 17-37 years, diagnosed with FEP between 2004 to 2023 without pre-existing MetS, and with > 12 months follow-up were included. Predictive performance of PsyMetRiC was assessed by discrimination (C-statistic), calibration (calibration plots), and clinical usefulness (decision curve analysis). The race and ethnicity predictor was refined to better represent the North American population.
**Results:** Of 559 included patients (22.5% female), 18.2% developed MetS during a mean follow-up of 1.7±1.3 years. Discrimination performance was acceptable, marginally better in the full (C=0.74,95%CI=0.70−0.77) than in the partial model (C=0.70, 95%CI=0.67−0.74). Calibration plots showed minor degrees of miscalibration. After model updating, dis-crimination improved slightly (full-model: C=0.74,95%CI=0.71−0.77; partial-model: C=0.71, 95%CI=0.68−0.74), with calibration and clinical usefulness improving more considerably.
**Discussion:** This study provides the first external validation of PsyMetRiC in a North American sam-ple. Further research is essential before routine clinical implementation, but PsyMetRiC offers promise as a tool for early detection of cardiometabolic risk in early psychosis, guiding personalized treatments to diminish long-term physical health impacts.

## Oral Session: Biomarkers of Psychosis

### 8. T1W/T2W Ratio Imaging of Cortical Layers in Antipsychotic-NAïVE, First-Episode Psychosis Patients

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**Background:** Myelin, while increasing conduction velocity of action potentials in the white matter, has more recently been shown to play an important role in the consolidation of neural networks and regulation of neurobiological processes such as axonal connectivity and cellular metabolism in the cortex. The co-occurrence of peak cortical myelination and the onset of psychosis-spectrum disorders (PSD) points to the role of abnormal myelination in the development of these disorders. Cortical gray matter myelination follows a rostral to the caudal pattern of development, where unimodal sensorimotor cortices develop first, followed by multimodal association areas; this is known as the sensorimotor-association (S-A) axis. In addition, postmortem and in vivo imaging studies have suggested abnormal myelination in different layers of the cortex. In the present study, we aimed to identify patterns of abnormal myelination in the cortex of antipsychotic-naïve, first-episode psychosis patients (FEP). We expected to find regional and laminar myelin abnormalities which could point to developmental processes that lead to the development of PSD.

**Methods:** Using the T1w/T2w ratio method described in the Minimal Preprocessing Pipelines for the Human Connectome Project, we generated three myelin maps corresponding to three cortical layers for 117 FEP and 127 healthy controls. We parcellated individual myelin maps into 148 regions of interest (ROIs) and calculated the global average myelin content for each subject. We then compared the average myelin content for each group using an ANCOVA with age, sex, and socioeconomic status as covariates. Next, we chose a representative sensorimotor region (left and right postcentral gyrus) and association region (left and right transverse frontopolar gyri and sulci) and performed a MANCOVA to assess differences in myelination along the S-A axis.
**Results:** The results of the ANCOVA revealed an increased T1w/T2w ratio in all three cortical layers in FEP compared to controls ($p < 0.001$ in the deep and middle layer, $p = 0.016$ in the superficial layer). When examining the representative regions, the MANCOVA revealed increased myelin content in the sensorimotor and association areas in the deep and middle layers, but increased myelin only in the association regions of the superficial layer.
**Discussion:** Our findings reveal that myelin-related aberrations are present at the onset of PSD, suggesting a period of abnormal development prior to the onset of clinical manifestations of the disease. Myelin has been shown to act as a dendritic growth inhibitor and is present on the axons of both pyramidal cells and GABAergic interneurons, helping to regulate the excitatory-inhibitory balance. Our finding of increased myelin in all cortical layers could point to decreased synaptic transmission, leading to the loss of neurite density seen in PSD. Further, preferentially increased myelin in association areas followed by sensorimotor areas points to a potential time frame (i.e., adolescence), when myelination is more likely to become dysregulated. These findings add to previous literature by confirming the presence of myelin-related abnormalities in first-episode, antipsychotic-naïve psychosis patients. Future studies would benefit from comparing myelin studies to those which examine neurite density to help determine the impact of myelin on dendritic outgrowth and vice versa.

## 9. WITHDRAWNBackground:Methods:Results:Discussion:

## 10. Dopamine and Mood in Psychotic Disorders: An 18F-Dopa Pet Study

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**Background:** There is limited clinical trial or neurobiological evidence guiding treatment of co-morbid affective syndromes and psychosis, particularly psychotic major depression. Given the widespread use of dopamine blocking antipsychotics, further understanding of the dopamine system in psychotic disorders when different mood states are present is therefore warranted.
**Methods:** This cross-sectional positron emission tomography (PET) study took place in first episode services in an inner-city area (London, England). 38 people with psychosis and current co-morbid affective syndromes (major depressive episode (MDE), n=25, mixed/mania, n=13), underwent fluorodihydroxyphenyl-l-alanine ([18F]-DOPA) PET to examine dopamine synthesis capacity.
Outcome measures included the Positive and Negative Syndrome Scale, Hamilton Depression Rating Scale, Montgomery Asperg Depression Rating Scale and Young Mania Rating Scale.

**Results:** Mean (SD) age of participants was 28.3 (11.02); MDE: 30.7 (12.83), mixed/mania: 23.7 (3.12). Kicer in whole striatum (controlling for age and sex) was significantly lower in people with psychosis and MDE, compared to psychosis and mixed/mania (co-efficient=0.014, SE=0.001, p=0.02). This was most pronounced in the limbic functional striatal subdivision (Cohen's d=1.57, $p < 0.001$).) In the whole sample, there was a linear association between positive psychotic symptoms and whole striatal Kicer (co-efficient=0.011, SE=0.001, p=0.03), most pronounced in associative striatum (co-efficient=0.011, SE=0.001, p=0.02), and not seen in limbic striatum, (p=0.19).
**Discussion:** Limbic striatum dopamine synthesis capacity in psychotic disorders is lower in people with psychosis and concomitant MDE than those with mixed/mania states. Trans-diagnostically, severity of positive psychotic symptoms is directly associated with dopamine synthesis capacity in the associative striatum, though no significant association is seen in the limbic, striatum. This has relevance for use of dopamine modulating compounds as therapeutic agents.

## 11. Brain Network Dynamics During Working Memory as a Predictor of Antipsychotic Response in First-Episode Psychosis

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**Background:** Early response to antipsychotic medications is a key predictor of long-term outcomes in psychosis. However, identifying reliable biomarkers to predict individualized response to treatment in the early stages of psychosis remains a challenge in precision psychiatry. This study aimed to investigate whether brain network dynamics during working memory (WM) could be a biomarker of response in first episode psychosis (FEP), given evidence that WM deficits are state-independent, over-expressed in unaffected siblings and co-segrated with psychosis within families.
**Methods:** 75 FEP patients (ICD-10) performed an fMRI 3-Back WM task in a 3T scanner. Response to treatment was defined as a reduction in PANSS (Positive and Negative Syndrome Scale) symptom severity at 12 weeks, according to the Schizophrenia Working Group Criteria. Based on these, 35 patients were classified as Responders (R), and 40 patients were classified as Nonresponders (NR). We estimated within- and between-networks functional connectivity.
**Results:** At baseline, R and NR did not differ in socio-demographic (age, gender, premorbid IQ, education, handedness) and clinical factors (duration of untreated psychosis, PANSS positive at baseline, antipsychotic dose at 12 weeks), except for PANSS Negative (p=0.009) and PANSS Total (p=0.05) scores (NR > R). Imaging findings indicated an altered WM load-dependent functional connectivity between the executive and basal ganglia networks. Specifically, greater load-dependent modulation from the executive network (IC55) to the basal ganglia network (IC30) at baseline was predictive of antipsychotic response (p=0.008 Bonferroni corrected) at 12 weeks. Furthermore, while load dependent inter-network connectivity between the executive and basal ganglia networks was significantly inversely

correlated with reaction times during WM performance (r=-0.36; p=0.03), no correlation was found with PANSS negative score (r=-0.174, p=0.16).
**Discussion:** Our findings suggest that in patients with FEP, the modulation of basal ganglia activity by the executive network in response to increasing WM loads is associated with antipsychotic treatment outcomes. This dynamic functional signature may serve as a potential imaging biomarker for the early prediction of response to antipsychotics.

## 12. Cognitive Functioning in Psychosis: Exploring the Interplay of Perinatal Stress, Prolactin, and Hypothalamic-Pituitary-Adrenal Axis Feedback Sensitivity

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**Background:** Perinatal stress (PS) has been linked to adverse neurodevelopmental outcomes and increased vulnerability to psychiatric disorders, including first-episode psychosis (FEP). Hormonal dysregulations, such as altered cortisol and prolactin (PRL) levels, may further modulate cognitive functioning in individuals with FEP. This study aimed to explore the interplay between PS, hormonal profiles, and cognitive outcomes in patients with FEP compared to healthy controls (HCs).
**Methods:** The sample comprised 101 individuals aged 18–35 years: 51 FEP patients (39.2% women) and 50 HCs (44% women). Perinatal stress—defined by low birth weight, preterm delivery, obstetric complications, and/or fetal distress—was reported by mothers or documented in birth records (HC: 18%; FEP: 31%). Clinical and neuropsychological data included the MATRICS battery, Trail Making Test-B, Stroop test, and Rey Complex Figure Test (RCFT). For FEP patients, symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Hormonal variables included morning prolactin (PRL), cortisol levels (pre- and post-dexamethasone suppression test), and were log-transformed for analyses. The dexamethasone suppression test (DST) involved the administration of a low dose of dexamethasone (0.25 mg) at 23:00 hours, with the DST ratio (DSTR) calculated by dividing cortisol levels at 10:00 hours on day 1 (pre-dexamethasone) and day 2 (post-dexamethasone). Multiple linear regression tested the effects of PS and hormonal variables on cognitive outcomes, adjusting for diagnosis, age, sex, education, and tobacco use. Moderation effects (PS × hormones) were also examined.
**Results:** Significant interactions between PS and hormonal variables emerged as predictors of cognitive performance. For processing speed, the interaction PS × PRL was significant ($\beta = 1.736$, $p = 0.022$), indicating an exacerbated effect of elevated PRL in individuals with PS. In verbal memory (HVLT-R) and visual memory (BVMT-R), PS × PRL interactions ($\beta = -2.175$, $p = 0.007$; $\beta = -2.070$, $p = 0.004$) showed that higher PRL was associated with poorer performance in participants with PS. Similar patterns were observed in social cognition (MSCEIT-ME; $\beta = -2.588$, $p = 0.002$) and delayed recall on the RCFT ($\beta = -1.920$, $p = 0.040$).

Conversely, interactions involving PS × DSTR were significant for Stroop interference ($\beta = 0.581$, $p < 0.001$) and Stroop Words-Colours ($\beta = 0.406$, $p = 0.003$), suggesting that higher DSTR ratios were associated with improved executive function in individuals with PS.

**Discussion:** This study highlights the differential impact of hormonal profiles on cognitive outcomes in the context of perinatal stress and psychosis. Elevated PRL levels appear to exacerbate cognitive deficits in FEP patients with PS, particularly in memory and social cognition, while cortisol regulation (DSTR) may buffer executive dysfunction in this subgroup. These findings underscore the importance of early-life stress and endocrine factors in shaping cognitive trajectories in psychosis, offering potential targets for personalized interventions.

## 13. WITHDRAWNBackground:Methods:Results:Discussion:

## 14. The Inflammatory Pathology in the Olfactory Epithelium of Patients With Schizophrenia and Related Psychotic Disorders: an Impact on the Olfactory-Prefrontal Circuit

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**Background:** Recent studies have demonstrated that olfactory dysfunction is reproducibly observed in patients with schizophrenia (SZ) and related psychotic disorders. The significance of this clinical observation is highlighted by its specificity in its correlation with negative symptoms, but not with positive symptoms, indicating that this dysfunction may reflect a fundamental disease pathophysiology rather than confounding effects such as medications. This is supported by the observation that smell deficits occur in the disease's initial stages. Meanwhile, in studies with animal models, an induction of chronic, local inflammation in the olfactory epithelium (OE: the most peripheral component of the olfactory system) is sufficient to elicit the overall deficits in the olfactory-prefrontal circuits, resulting in deficits in motivation-associated behaviors, which are relevant to negative symptoms. Nevertheless, as far as we are aware, there is no systematic study that aims to address inflammation in the OE of patients with SZ and related psychotic disorders, at histological, molecular, and cellular levels.
**Methods:** We performed immunohistochemistry (IHC) on OE tissues to assess potential signs of inflammation and alterations in neuronal architecture in patients with SZ and related psychotic disorders. Additionally, we conducted bulk RNA sequencing (RNA-seq) analysis on olfactory neuronal cells (ONCs) enriched from biopsied OE tissues to explore correlations between molecular signatures and clinical manifestations. For IHC, 15 patients with SZ and related psychotic disorders and 15 healthy controls (HCs) were examined. For RNA-seq analysis, 44 patients and 59 HCs were included in the study
**Results:** We first observed a significant increase in the infiltration of CD45-positive cells, a marker of inflammation, in the OE of a subset of patients. Additionally, there was a marked reduction in the number of mature neurons in the OE of patients compared to HCs. Consistent with these findings, we noted elevated levels of phosphorylated p65, an inflammation marker, in the ONCs of patients. RNA-seq analysis of ONCs stratified the patient group into two subgroups: the P (inflammation-positive) group, characterized by increased immune/inflammatory molecules and decreased redox signaling molecules, and the N (inflammation-negative) group, characterized by decreased immune/inflammatory molecules

and increased redox signaling molecules. Notably, these molecular changes in ONCs correlated with a reduction in olfactory bulb volume in patients but not in HCs. Furthermore, these molecular alterations were associated with the severity of negative symptoms. **Discussion:** Our findings indicate that patients with SZ and related psychotic disorders, at least a subset, exhibit pronounced inflammation in the OE along with a significant reduction in mature neurons. These pathological changes were confirmed through both IHC and molecular analyses of ONCs. Importantly, multimodal data suggest that OE pathology likely affects the olfactory-prefrontal circuit, contributing to the negative symptoms observed in patients with SZ and related psychotic disorders.

**15. WITHDRAWNBackground:Methods:Results:Discussion:**Results:

**Oral Session: Early Psychosis: Diagnostic, Predictive, and Neural Factors**

## 16. Towards Individualized Risk Prediction of Disengagement From First Episode Psychosis Coordinated Specialty Care

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**Background:** Despite the effectiveness of coordinated specialty care for treating first-episode psychosis, 70-80% of participants do not complete the intended treatment course. Many factors are associated with participant engagement, but the lack of an individualized, empirically developed approach to assess risk of disengagement for individuals has compromised the field’s ability to address this issue. Risk prediction tools can improve accuracy, efficiency, and timeliness of clinical decisions and interventions. Yet, no prior work to our knowledge has applied advanced risk prediction methods to develop and validate a tool to predict CSC disengagement. The objective of this investigation was therefore to develop and validate a risk calculator to predict coordinated specialty care program disengagement among young people experiencing a first episode of psychosis.

**Methods:** This cohort study used core assessment battery data collected at admission from individuals with first episode psychosis enrolled in coordinated specialty care programs between January 1, 2021 and February 24, 2024 to develop personalized risk prediction models of disengagement. Twenty-three coordinated specialty care programs participating in the Connection Learning Healthcare System hub of the Early Psychosis Intervention Network in the United States contributed data. Services include individual therapy, pharmacotherapy, employment and education support, and family support. The participants were individuals (n=750) with recent onset psychosis admitted to hub programs. Thirty-nine participant- and site-level predictors collected at admission were employed, including demographic, treatment history, clinician- and self-reported symptoms and functioning variables. Three primary discharge outcomes were program completion vs. disengagement (binary outcome), number of months in the program (continuous outcome), and completion status (completed, disengaged, or transferred; multinomial outcome).
**Results:** Random forest models were trained and tested using cross-validation to predict the three discharge outcomes. The risk calculator demonstrated acceptable performance in predicting completion vs. disengagement (AUC=0.71), months in program (R-squared=0.21), and completion status (accuracy=25% above chance). Top predictors of program completion included: higher site-based proportion completing the program, older age at first hospitalization, lower total symptom score, and older age at admission.
**Discussion:** We demonstrate the feasibility of identifying individuals at high risk of coordinated specialty care disengagement using only program admission data. Further validation against real-world outcomes in independent data sets paired with user informed development of guidelines for individualized decision-making are essential next steps we are taking to bridge the gap between promising innovation and clinical implementation. The findings contribute to a solid empirical foundation for addressing the pervasive problem of coordinated specialty care disengagement.

## 17. Exploring National Standards in Early Psychosis Intervention in Canada

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**Background:** Early psychosis intervention (EPI) services have been shown to lead to improved outcomes in young people with early phase psychosis in both clinical trials and real-world effectiveness studies. Based on this robust evidence, international practice as well as national standards in several countries (e.g., Australia, United Kingdom) have been developed to guide the delivery of high-quality services. While EPI programs have existed in Canada since the 1990s, no national standards exist and only 4 provinces have published standards. In 2021, the Government of Canada and Standards Council of Canada launched the National Mental Health and Substance Use Health Collaborative, an initiative to inform the development of national standards for mental health and/or substance use services. They identified EPI services for a competitive process to develop a National Workshop Agreement (NWA), a structured project that begins the consensus process generally associated with a National Standard of Canada. As a collaborative team led by early psychosis and health standards experts from across Canada, we aimed to explore the development of Canadian EPI standards.
**Methods:** A team led by the Centre for Addiction and Mental Health and Health Standards Organization established a collaboration with the Canadian Consortium for Early Intervention in Psychosis and Shkaabe Makwa, a centre leading culturally responsive system initiatives

for First Nations, Inuit and Metis communities in Canada. We assembled a Working Group consisting of clinicians, people with lived experience of psychosis and their family members, researchers, and policymakers from across Canada. We started with an environmental scan of existing standards and published materials relevant to the delivery of EPI services with a focus on the Canadian context to summarize best practices and identify potential knowledge gaps, reviewing both peer-reviewed and grey literature. We developed a survey to capture perspectives on what a Canadian standard should address and distributed it electronically through relevant networks, including provincial associations and advocacy groups. We structured a series of in-person and virtual engagements using the 2023 CAN/HSO Mental Health and Addictions Services Standards as a framework to guide small- and large-group discussions.
**Results:** We synthesized results from 97 service or clinical standards, guidelines, peer-reviewed research, and patient-facing materials, highlighting areas of agreement and disagreement. Nearly 300 individuals completed the survey and/or participated in the interactive engagements. In addition to standards organized by the Mental Health and Addictions Services Standards for program delivery, we also made recommendations in the areas of system design and implementation. Overall, the National Workshop Agreement recommended a set of national standards with commensurate funding, implementation support, monitoring and accountability. The final report was published in September 2024 and remains open for public comment.
**Discussion:** An environmental scan and engagements with key representatives support the need for national standards in EPI service delivery in Canada. It is recommended that a future standard addresses the areas highlighted in our report and continues to incorporate best practices in order to ensure that high-quality EPI services are accessible across Canada.

## 18. Preliminary Evaluation of Synaptic Density in Individuals at Clinical High Risk for Psychosis and First Episode Psychosis: A [18f]Synvest-1 Positron Emission Tomography Imaging Study

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**Background:** Psychotic disorders, including schizophrenia, are associated with significant distress, poor functioning and premature mortality. Functional outcomes in psychotic disorders are influenced by duration of untreated psychosis, and interventions delivered at the earliest stages of illness can significantly impact functional trajectories in affected individuals. The concept of the clinical high risk (CHR) for psychosis state was conceived to inform the earliest detection of individuals at higher risk of psychosis and provide indicated interventions and prevent progression to more severe outcomes. Schizophrenia has long been considered a neurodevelopmental disorder resulting from exaggerated synaptic pruning during late adolescence and early adulthood. Compelling evidence for reduced synaptic density in schizophrenia has come from recent in vivo positron emission tomography (PET) imaging studies using tracers targeting synaptic vesicle glycoprotein 2A (SV2A). Reduced SV2A levels (i.e., synaptic density) have been shown in multi-episode schizophrenia, first episode psychosis (FEP) and recently in CHR individuals compared to healthy controls

(HCs). Despite the purportedly central role of synaptic changes early in life and in the disease course of psychosis, few studies have evaluated synaptic density in CHR. A large body of literature shows accelerated gray matter decline in CHR compared to HCs, which may be correlated with synaptic loss, with most consistent reductions in the hippocampus, frontal and cingulate cortex. This study aimed to replicate and extend the recent findings of reduced synaptic density in individuals with CHR and FEP compared to HCs.
**Methods:** Participants with FEP and CHR were recruited from the Early Intervention for Psychosis inpatient and outpatient services at the Center for Addiction and Mental Health, Toronto, Canada. Eligibility: FEP participants had a diagnosis of psychotic spectrum disorder and were within 5 years of initial diagnosis; CHR participants met criteria for a psychosis risk syndrome based on the Structured Interview for Psychosis-Risk Syndromes (SIPS); Both FEP and CHR participants had a total lifetime exposure of antipsychotic medication < 3 months.
**Results:** Participants with FEP (n=10; 6 M/4F; mean age=24.5 years), CHR (n=8; 2M/6F; mean age=21.5 years) and HCs (n=9; 5M/4F; mean age=26.7 years) successfully completed a 120 minute [18F]SynVesT-1 arterial PET (187±10MBq). A T1-weighted MRI image was acquired and used for ROI delineation in PMOD 4.2. Volume of distribution (VT) was estimated using the 1-tissue compartment model with arterial input function in 3 pre-specified ROIs: frontal cortex (FC), anterior cingulate cortex (ACC), and hippocampus. Compared to HCs, [18F]SynVesT-1 binding was lower in FEP (FC: -10.4±1.4%, ACC: -12.9±1.9, hippocampus: -12.4±1.4) and lower in CHR (FC: -8.8±1.2%, ACC: -12.3±1.8, hippocampus: -11.8±1.4). Across ROIs, average [18F]SynVesT-1 binding was 11.9±1.4% lower in FEP (Cohen's d=1.34) and 11.0±1.4% lower in CHR (Cohen's d=1.46) compared to HCs.
**Discussion:** Preliminary data indicate that [18F]SynVesT-1 binding is lower across brain regions in FEP and CHR participants compared to HCs. These findings are consistent with existing literature showing reduced synaptic density in individuals with multi-episode schizophrenia, FEP and CHR. While these preliminary results are limited by the small sample and group differences in age, our ongoing recruitment of a larger sample (recruitment target: FEP, n=30; CHR, n=30; HC, n=30) will provide a more definitive evaluation of synaptic density and associations with clinical and cognitive measures in these populations.

## 19. Leaving the Context Behind: Neurochemical and Network-Level Correlates of Diminished Sensitivity to Linguistic Context in Psychosis

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**Background:** Formal thought disorder (FTD), a core feature of schizophrenia, manifests as disorganized and impoverished speech. These symptoms start in early psychosis and can persist into chronic schizophrenia despite treatment, impairing patients' social functioning. To date, the neural basis of FTD remains poorly understood.
We recently reported that in the speech of patients with psychosis, words are less predictable based on global linguistic context (i.e. words used by patients are not predictable based on the last 50 words they said) (Sharpe et al., 2024). Nevertheless, predictability based on local

context (last 5 words) is not altered. The global vs. local difference can be quantified with a single index reflecting contextual sensitivity, which predicts FTD symptoms. In this study, we examine the neural basis of this differential contextual sensitivity.

Pathophysiological studies highlighted two multilevel processes in persistent symptoms: reduced glutamate (Glu) and glutathione (GSH) in the dorsal anterior cingulate cortex (dACC) (Dempster et al., 2020) and higher variability (instability) in a triple network system (TPN: Supekar et al., 2019). The TPN comprises the salience network (centered on the anterior insula and ACC), which switches between the internally focused default mode network (DMN) and externally driven central executive network (CEN). Here, we related contextual insensitivity to TPN stability and the dACC concentration of GSH and Glu. We expected to see indicators of persistent illness - lower Glu and GSH, higher instability of TPN - in the presence of lower contextual sensitivity.

**Methods:** We included 46 FEP patients with < 2 weeks of antipsychotics exposure and 33 sociodemographically-matched healthy controls (HC) from London, Ontario. All subjects completed transcribed speech tasks, 7T resting fMRI scans, and 7T single-voxel 1H-MRS to measure dACC Glu and GSH concentrations. Using a large language model GPT-3 (openAI), we extracted lexical probabilities (i.e. predictability) based on local linguistic context (1-5 preceding words) and global context (46-50 preceding words) (Sharpe et al., 2024). A difference of global to local predictability was computed to assess sensitivity to global context. To compute dynamic NII, we first identified distinct states of dynamic functional connectivity using k-means clustering. The NII of each brain state was then computed as the difference in correlation between SN and CEN time series and correlation between SN and DMN. After that, the standard deviation (SD) of the NII across all dynamic brain states was computed (Supekar et al., 2018).
**Results:** Contextual sensitivity is lower in FEP than HC ($p = 0.03$, $d = 0.50$) as reported before. The SD of dynamic NII is smaller in FEP ($p = 0.02$, $d = 0.26$) indicating less variability in TPN than expected. Interestingly, FEP patients with lower contextual sensitivity have more unstable TPN, i.e., higher SD of NII ($R = -0.39$, $p = 0.008$), lower dACC GSH ($R = 0.47$, $p = 0.001$), and marginally lower Glu ($R = 0.3$, $p = 0.049$) levels. Multiple linear regression shows that GSH concentration and SD of the NII together explain 31% of adjusted variance of contextual sensitivity in FEP ($p < 0.001$), with Glu making negligible contribution.
**Discussion:** Contextual insensitivity of spoken words is seen in FEP. Network-level (higher TPN instability) and neurochemical (low Glu and GSH) indicators of persistent symptoms vary with the severity of contextual insensitivity. We are limited by TPN dynamics being estimated at rest, without task demands or whilst speaking. Nonetheless, our Results: prompt us to consider whether we can predict the likelihood of illness outcomes using easily obtainable speech measurements in patients experiencing first episodes of psychosis.

## 20. Cognitive Presentation at Psychosis Onset Through Premorbid Deterioration and Exposure to Environmental Risk Factors

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**Background:** Previous studies identified clusters of first-episode psychosis patients (FEP) based on cognition and premorbid adjustment. This study examined a range of socio-environmental risk factors associated with clusters of FEP, aiming a) to compare clusters of FEP and community controls using the Maudsley Environmental Risk Score for psychosis (ERS), a weighted sum of the following risks: paternal age, childhood adversities, cannabis use, and ethnic minority membership; b) to explore the putative differences in specific environmental risk factors in distinguishing within patient clusters and from controls.
**Methods:** A univariable general linear model (GLS) compared the ERS between 1,263 community controls and clusters derived from 802 FEP, namely low (n=223) and high-cognitive-functioning (n=205), intermediate (n=224), and deteriorating (n=150), from the EU-GEI study. A multivariable GLS compared clusters and controls by different exposures included in the ERS.
**Results:** The ERS was higher in all clusters compared to controls, mainly in the deteriorating (=2.8, 95% CI 2.3 3.4, 2=0.049) and the low-cognitive-functioning cluster (=2.4, 95% CI 1.9 2.8, 2=0.049) and distinguished them from the cluster with high-cognitive-functioning. The deteriorating cluster had higher cannabis exposure (mean difference=0.48, 95% CI 0.49 0.91) than the intermediate having identical IQ, and more people from an ethnic minority (meandifference= 0.77, 95% CI 0.24 1.29) compared to the high-cognitive-functioning cluster.
**Discussion:** High exposure to environmental risk factors might result in cognitive impairment and lower-than-expected functioning in individuals at the onset of psychosis. Some patients' trajectories involved risk factors that tailored interventions could modify.

## 21. Large-Scale Structural Brain Networks in First-Episode Psychosis

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**Background:** Anomalies in structural brain networks (connectomes) have been implicated in the pathophysiology of psychotic disorders. This study investigates changes in structural brain networks in youth experiencing first-episode psychosis.
**Methods:** This study included 32 individuals with first-episode psychosis and 26 healthy controls. Diffusion-weighted magnetic resonance imaging was employed, and whole-brain streamline counts were generated using MRtrix3. Following preprocessing, structural connectivity networks were constructed using the Schaefer parcellation with 400 non-overlapping cortical regions. Network analysis was conducted in MATLAB using the REST toolbox. Statistical analysis was performed with the Network-Based Statistics toolbox, employing permutation testing with family-wise error correction.
**Results:** Significant differences in structural connectivity were found between the first-episode psychosis group and healthy controls. The most prominent findings in the psychosis group, compared to controls, included reduced connectivity ($p < 0.05$) in the following regions: (I) within visual networks, (II) between visual and default mode networks, (III) between dorsal attention and somatomotor networks.
**Discussion:** While the visual network is not traditionally viewed as a primary contributor to psychosis pathophysiology, emerging evidence highlights abnormalities in the visual system in psychotic disorders. This growing body of evidence underscores the need for further research to elucidate the specific contributions of visual system dysfunction to the development of psychotic disorders.

## 22. Predicting 5-Year Risk of Self-Harm in Patients With First-Diagnosed Schizophrenia-Spectrum Disorders: A Risk Prediction Model Development and Internal-External Cross-Validation Study

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**Background:** Schizophrenia-spectrum disorders (SSD) is associated with increased self-harm risk, particularly in early stage of the disorder. Notably, prior data focused on self-harm risk evaluation and identification of risk factors in SSD, with limited investigation on development of risk predictions tools that quantified individualized self-harm risk to facilitate personalized medicine for early detection and intervention of high-risk individuals. This study aimed to develop and validate a risk prediction model for self-harm in 5 years after first-diagnosed SSD.
**Methods:** This population-based cohort study comprised 81101 individuals who received their first-ever diagnosis of SSD for public psychiatric inpatient admission or outpatient care and aged ≥12 years at diagnosis within 1-January-2001 and 31-December-2021, using a territory-wide medical-record database of pubic healthcare services in Hong Kong (HK). Literature-informed prediction selection was performed, including socio-demographics, physical and psychiatric comorbidity, history of self-harm, psychiatric service utilization and psychotropic medication use at SSD diagnosis. Multivariable Cox proportional-hazard regression with backward selection was performed for 5-year risk model development.

Internal-external cross-validation was conducted partitioning dataset by seven clusters of healthcare service receipt in HK, with six catchment areas as development cohort and internal validation, and the seventh catchment area as held-out dataset for external validation. Standard model fit (area-under-the-curve [AUC], brier score), calibration (calibration slope, observed/predicted [O/E] risk ratio) and discrimination (Harrell's C, D statistics) metrices were adopted to evaluate prediction performances.
**Results:** Incidence rate of self-harm was 0.7 per 1,000 person-years (95% CI: 0.6–0.7), over the median follow-up of 4.4 years. In the development cohort of 67780 patients, younger age at SSD diagnosis (HR=0.43 [0.39–0.47]), male sex (1.22 [1.17–1.26]), alcohol/substance use disorders (2.00 [1.87–2.13]), history of self-harm (6.58 [6.26–6.92]), greater age-adjusted Charlson-Comorbidity index (CCI) score (1.11 [1.09–1.13]), and use of first-generation antipsychotics (1.15 [1.11–1.20]), antidepressants (1.20 [1.15–1.25]) and benzodiazepines/Z-drugs (1.43 [1.37–1.49]), reduced use of lithium (0.65 [0.56–0.76]) and attendance in clinical psychology service (1.44 [1.26–1.65]) within 1-year prior to SSD diagnosis were risk factors retained in the final model, with an event-per-variable ratio of 234. In held-out data from Kowloon-Central catchment area [n=13321], the model showed a similarly consistent performance in overall model fit (AUC: 0.68 [0.65–0.71]; Brier score: 0.03 [0.03–0.04]), calibration (calibration slope: 1.05 [0.97–1.14]; O/E risk ratio: 1.06 [0.97–1.16]) and discrimination (C-statistic: 0.69 [0.66–0.71]; D statistic: 1.25 [1.10–1.40]).
**Discussion:** This is the first prediction model internally-externally validated for self-harm risk in people with first-episode SSD, with satisfactory calibration and discrimination performances. External-validation studies in other populations are needed before implementation studies test impact of this tool on clinical decision-making and patient outcomes.

## 23. Early Identification of Organic Psychosis: Development and Validation of a Diagnostic Classification Model

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**Background:** A subset of patients presenting with psychosis have an underlying medical ("organic") cause. Early identification of these patients is essential to ensure they receive optimal care, often involving targeted treatment of the underlying condition. Identifying patients at increased risk of an underlying medical cause during the initial clinical assessment could allow prioritization for further investigation. Using a large, representative retrospective sample of patients presenting with psychosis, we aimed to develop a diagnostic classification model to identify cases of psychosis secondary to an underlying medical condition based on clinical assessment data.
**Methods:** We analyzed mental health records from the largest mental health provider in the UK, utilizing a case-control cohort of patients diagnosed with psychosis secondary to an underlying medical ("organic") cause (ICD-10: F06.0, F06.2, F06.1, F06.8) and those with primary ("non-organic") psychotic disorders (ICD-10: F20-F29, F31.5, F32.3, F33) between 2007 and 2022. Underlying aetiologies for secondary psychosis cases were manually validated from individual patient records.

Validated natural language processing (NLP) tools extracted 61 psychopathological symptoms from clinical notes recorded during the month preceding diagnosis, alongside demographic variables (age, gender, ethnicity, and socioeconomic status). A weighted regularized logistic regression model was trained to predict whether patients received a diagnosis of "organic" psychosis. Model performance was evaluated using 10-fold cross-validation with 5 repeats, with balanced accuracy (BA) and area under the receiver operating characteristic curve (AUC) as the primary metrics.

**Results:** A total of 21,092 patients (mean age: 41 years; 45% female) were included in the analysis. Of these, 573 (3%) were diagnosed with "organic" psychosis, with the most common underlying causes being epilepsy (n=79), Parkinsonian disorders (n=60), and stroke (n=39).
The binary classification model achieved a balanced accuracy of 73% and an AUC of 81% (95% CI: 78–84%). Feature importance analysis identified age, visual hallucinations, and agitation as the most predictive features for "organic" psychosis, while negative symptoms, thought withdrawal, and amotivation were most predictive of "non-organic" psychosis. Predictive performance decreased when psychopathological features were excluded (BA=70%; AUC=75%, 95% CI=73–79%).

**Discussion:** In this large, representative sample of patients presenting with psychosis, our findings suggest that bedside clinical information collected during the initial assessment can help estimate the likelihood of an underlying medical disorder prior to formal diagnostic investigation. Specific psychopathological features were identified that differentiate "organic" psychosis from primary psychotic disorders. By incorporating psychopathological and demographic data, this prediction model demonstrates potential utility in helping to prioritize patients for further investigation to exclude underlying medical causes of psychosis.

## Oral Session: Neuroimaging, Electrophysiology and Psychophysiology

### 24. Down to the Nitty-Gritty of "Cognitive Dysmetria": Mapping Cerebellar Connectivity to Cognition in Psychosis

Hengyi Cao*[1], Miklos Argyelan[1], Joanna Yan[1], Halil Aziz Velioglu[1], Franky Fang[1], Andrea Joanlanne[1], Simran Kang[1], Lara Prizgint[1], Jenna Schugart[1], Kadeem Brown[1], John Cholewa[1], Philip Watson[1], Sunny Tang[1], Ricardo Carrion[1], Jose Rubio[1], Moein Foroughi[2], Todd Lencz[1], Anil Malhotra[1]

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**Background:** Cerebellar dysfunction has been strongly implicated in both cognition and psychosis, and the "cognitive dysmetria" hypothesis posits that cognition is the intermediary in the pathway from cerebellar dysfunction to psychopathology. However, the nuanced pattern linking cerebellum-behavior relationships in patients remains unclear. Establishing such link is important to understand cerebellar mechanisms and to identify neural targets for treatment of cognitive deficits in psychosis.
**Methods:** In the first study, we investigated a total of 100 patients with early-stage psychosis from the Human Connectome Project Early Psychosis (HCP-EP) study (mean age 22.8 years,

64 males). The entire cerebellum was parcellated into 125 fine-grained functional parcels, and the cerebellar functional connectome measuring connectivity between each cerebellar parcel and the whole brain was computed from the resting-state data. Cognitive functions were assessed using the NIH toolbox including six distinct domains (working memory, episodic memory, attention, executive function, verbal processing, and processing speed). We used connectome-based predictive modeling to probe cognitive functions most predicted by cerebellar connectivity. Mediation analysis was subsequently conducted linking cerebellar connectivity to PANSS symptoms, with cognitive scores as mediator.
In the second study, 12 patients with a schizophrenia spectrum disorder were recruited for a randomized, sham-controlled cerebellar TMS treatment trial (6 active TMS, 6 sham). Each patient was treated for two weeks with an iTBS protocol, targeting the posterior-most part of the cerebellum left to the midline under neuronavigation (corresponding to the left crus 1 and 2 area). Cognitive evaluations were performed using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline and end of the 2nd week.

**Results:** In the HCP-EP sample, the cerebellar connectome significantly predicted three cognitive functions in patients, namely, verbal ability (r [predicted vs observed] = 0.47, $p < 0.001$), working memory (r [predicted vs observed] = 0.42, $p = 0.002$), and cognitive flexibility (r [predicted vs observed] = 0.33, $p = 0.01$). While each cognitive domain was predicted by a distinct cerebellar connectivity pattern, the left crus 1 and 2 area turned out to be a common region whose connectivity consistently predicted all three functions. The mediation analysis further unveiled that verbal ability score was a significant mediator that fully mediated the relationship between cerebellar connectivity and negative symptoms ($p < 0.001$).

In the TMS sample, stimulation of the left crus 1 and 2 area showed a significant group by time interaction effect on overall cognitive composite score ($p = 0.02$, Cohen's $d = 1.52$), with score improvement in the active TMS group ($p = 0.04$) but not sham group. Domain-specific analysis revealed large interaction effect on working memory (Cohen's $d = 1.51$) and medium-to-large interaction effects on verbal memory (Cohen's $d = 0.76$) and executive function (Cohen's $d = 0.73$), remarkably consistent with the domains identified in the HCP-EP sample.

**Discussion:** These findings suggest a potential causal pathway from cerebellar connectivity to domain-specific cognitive deficits and psychopathology in schizophrenia. Moreover, they also point to the cerebellum as a potential neural target for treatment of cognitive dysfunction in patients with psychotic disorders.

### 25. In Vivo Evidence Serotonin Release is Higher in Schizophrenia and Associated With Greater Negative Symptom Severity: A [11c]Cimbi-36 Pet Study With a D-Amphetamine Challenge

Martin Osugo*[1], Thomas Whitehurst[2], David Erritzoe[3], Richard Carr[4], Abhishekh Ashok[5], Ellis Chika Onwordi[6], Grazia Rutigliano[4], Nikola Rahaman[7], Antonio de Marvao[3], Gaia Rizzo[8], Roger Gunn[9], Eugenii Rabiner[10], Tiago Reis Marques[1], Mattia Veronese[11], Oliver Howes[12]

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**Background:** The involvement of the serotonin 5-HT2a system in the pathophysiology of schizophrenia (SZ) has been proposed for over 60 years, but there has been no prior study to test if there is altered serotonin release in vivo in people with schizophrenia. We used the 5-HT2a receptor agonist radioligand, [11C]Cimbi-36, which is sensitive to increases in extracellular serotonin induced by an acute d-amphetamine challenge to conduct the first investigation of serotonin release in schizophrenia.
The frontal cortex was the primary region of interest based on its key role in schizophrenia pathophysiology, including meta-analyses of postmortem studies which show abnormalities in the 5-HT2a system in this region in schizophrenia. We hypothesised a priori that frontal cortex serotonin release capacity would be correlated with baseline negative symptoms.

**Methods:** 54 subjects [26 with DSM-V SZ, 28 healthy controls (HC)] completed clinical assessments and neuroimaging. Schizophrenia subjects (mean age 33 ± SD 9, 62% male/38% female, PANSS 55 ± 14) were clinically stable and well matched to the healthy controls (age 32 ± 10, 68% male/32% female). 81% with schizophrenia were antipsychotic free, whilst 19% were medicated with haloperidol or amisulpride, which do not bind to 5-HT2a receptors. No subjects had used antidepressants/other serotonergic medications in the past month. In subjects with schizophrenia, validated scales (PANSS, BNSS) were used to assess clinical symptoms at baseline and following d-amphetamine (DEX) administration.
All subjects had T1-weighted MRI scans, and dynamic 90 minute [11C]Cimbi-36 PET scans at baseline and 3 hours after a 0.5mg/kg dose of oral d-amphetamine. Regional volume of distribution (VT) was quantified using 2TCM modelling, with metabolite corrected arterial plasma input function. The primary index of serotonin release capacity was delta VT: [(VT DEX - VT baseline)/VT baseline], expressed as a percentage. We also conducted sensitivity analysis using delta binding potential (BPND), calculated with the cerebellum as a reference region.

VT was compared between the baseline and DEX scans for each group using 2-tailed paired t-tests. Delta VT was compared between the schizophrenia and control groups using 2-tailed ANCOVA, to adjust for group differences in injected mass. Baseline clinical symptoms were compared to symptoms following d-amphetamine using 2-tailed paired t-tests.

**Results:** d-amphetamine led to robust reductions in frontal cortex VT in both groups [HC: baseline mean 29.2 ml/cm3 ± SD 6.2 vs DEX 26.1 ml/cm3 ± 5.1, p=8x10-4]; [SZ: baseline 29.4 ml/cm3 ± 6.7 vs DEX 24.5 ml/cm3 ± 5.6, p=6x10-5]. Frontal cortex delta VT was significantly greater in schizophrenia than controls [HC: mean 7.6% ± SE 2.8 vs SZ: 16.8% ± 2.9, p=0.034]. Results were similar with delta BPND as the outcome measure (p=0.040).

Administration of d-amphetamine significantly reduced negative symptoms in schizophrenia [BNSS: mean difference -4.6, $p < 0.001$], and did not change positive symptoms ($p=0.14$). Greater frontal cortex serotonin release was correlated with higher baseline negative symptom severity in schizophrenia [BNSS: $r=0.42$, $p=0.032$], but serotonin release was not associated with symptom changes following d-amphetamine, or with the baseline severity of positive symptoms or total symptoms.

A subgroup analysis of 21 antipsychotic free schizophrenia subjects similarly found greater delta VT compared to controls (mean difference=10.5%, $p=0.014$), and a positive correlation between increased serotonin release and greater baseline negative symptoms (BNSS: $r=0.47$, $p=0.032$).

**Discussion:** This is the first direct assessment of serotonin release in people with schizophrenia. We show that there is significantly greater frontal cortical serotonin release in people with schizophrenia relative to matched controls, and that this is directly associated with higher baseline negative symptom severity, but not the effect of amphetamine on negative symptoms. These findings indicate serotonergic dysfunction in the pathophysiology of schizophrenia linked to negative symptoms and identify the regulation of serotonin release and 5-HT2a receptors as potential targets to treat negative symptoms.

## 26. Associations Between Glutamate and Cerebral Blood Flow in Treatment Resistant Schizophrenia During Clozapine Treatment

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**Background:** Nearly a third of all patients with schizophrenia may be considered as having treatment-resistant schizophrenia (TRS)1, for which clozapine is the gold-standard treatment2. Alterations in both brain glutamate (Glu)3,4 and perfusion (Cerebral Blood Flow, CBF)5 may be more apparent in TRS. These alterations may be directly related, as increased glutamatergic neuronal activity will result in local increases in CBF6. In this study we examined the relationship between regional Glu and CBF in TRS before and after 12 weeks of clozapine treatment.

**Methods:** Pulsed continuous arterial spin labelling acquired whole brain CBF maps and proton magnetic resonance spectroscopy acquired glutamate and glutamate plus glutamine (Glx) in the anterior cingulate cortex (ACC) and striatum in participants with TRS before ('baseline', N=30) and after 12 weeks of clozapine ('week 12', N=20). CBF analyses were conducted using a region of interest (ROI) based approach (ACC and striatum). Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS). Within-region relationships between CBF and Glu or Glx levels at baseline or their change over 12 weeks of clozapine treatment were estimated using correlations with/without controlling for global CBF in SPSS. Exploratory analyses using hierarchical regression examined the relationships between regional CBF, Glu and Glx and change in symptom severity. The threshold for statistical significance was $p < 0.05$, 2-tailed.

**Results:** In participants with TRS prior to starting clozapine (baseline), no significant relationships were observed between CBF and Glu or Glx within the same region (ACC or striatum). During 12 weeks of clozapine treatment, decreases in striatal CBF were positively

associated with decreases in striatal Glu ($r = 0.56$, $p < 0.01$) whereas in the ACC no relationship between CBF and Glu or Glx was detected. In the ACC, baseline CBF and Glx were positively associated with subsequent total symptom improvement (controlling for global CBF: overall model: $R^2 = 0.411$, $F(3,16) = 3.723$, $p = 0.033$) which was mainly driven by ACC Glx ($\beta = 0.45$, $p < 0.05$), ACC CBF ($\beta = 0.97$, $p > 0.05$). Change in CBF and glutamate or Glx were not associated significantly with symptom improvement during clozapine treatment in either the ACC or striatum.
**Discussion:** During clozapine treatment, parallel decreases in striatal glutamate and CBF, suggesting that reductions in neurochemical activity may be accompanied by local decreases in blood flow. While activity within the striatum is implicated in the positive symptoms of schizophrenia, we did not detect an association between these changes and symptom improvement, although this may be due to sample size limitations. In the ACC, higher Glx and CBF prior to starting clozapine may facilitate subsequent symptomatic response.

## 27. Multi-Scale Analysis of Cerebral Blood Flow and Gabaergic Network Alterations in Psychosis Spectrum

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**Background:** Brain activity relies on the complex integration of varied neurochemical signalling, synchronised in networks and across multiple spatio-temporal scales, to produce behaviour. Many of these processes are disrupted in psychosis. Recent advances in neuroimaging analyses have highlighted multi-scale relationships in psychosis. For instance, cortical thickness abnormalities in schizophrenia have been linked spatially linked to the distribution of specific cellular and neurotransmitter systems. Recently, we have shown that brain-wide patterns of regional cerebral blood flow (rCBF) alterations in individuals with schizophrenia and at clinical high-risk for psychosis (CHR) covary with distinct neurochemical and cellular systems. These approaches rely on correlating case-control neuroimaging phenotypes to external gene expression and neurotransmitter datasets, warranting follow-up with multi-modal data acquired from the same individuals. Here, we used a novel individualised network covariance perturbation approach to examine rCBF network connectivity in CHR individuals and people experiencing their first episode of psychosis (FEP), relative to a normative model of healthy rCBF covariance. Furthermore, we investigated the relationship between rCBF network deviations in CHR and FEP and GABAergic metabolic network covariance at the individual level.
**Methods:** This multimodal PET/MR cross-sectional study involved 24 CHR individuals, 23 healthy controls, and 10 FEP participants. We measured rCBF with arterial spin labelling and quantified the volume of distribution of [11C]Ro15-4513, a radiotracer highly selective for α5-GABAA receptors subunits. Normative models of rCBF and α5-GABAA network covariance were constructed from healthy controls, including key brain regions in a psychosis-relevant circuit: the hippocampus, striatum, midbrain, anterior cingulate, orbitofrontal cortex, and amygdala. Next, clinical group participants were individually introduced to measure subject-specific network perturbations, calculated as the deviations from the healthy reference connectome. These perturbation z-scores represent subject-specific positive and negative deviations from the normative model. Permutation tests were used to compare perturbations across the rCBF and α5-GABAA networks across groups. Finally, Pearson's correlation assessed the correspondence between rCBF and α5-GABAA

covariance perturbations within groups, with group differences compared using permutation tests.
**Results:** Both rCBF and α5-GABAA networks showed significantly lower in covariance in CHR-P and FEP groups compared to healthy controls (F=4.0058, p=0.0244; F=6.2647, p=0.0027, respectively). Lower covariance was also significantly different in clinical groups for hippocampal ROIs (F=4.0058, p=0.0244; F=3.1359, p=0.0453, respectively). In the CHR group, higher covariance in rCBF relative to healthy controls was associated with lower positive symptoms (r=-0.5157, p=0.0099). In FEP, higher α5-GABAAR covariance relative to healthy controls was associated with higher general symptoms (r=.72, p=0.0183), However, no significant correlations between rCBF and α5-GABAA network perturbations were found.
**Discussion:** Our findings provide evidence for altered functional and metabolic hippocampal circuit organisation in CHR and early psychosis. These alterations include lower covariance between rCBF and α5-GABAAR availability between regions in this circuit relative to a normative group. This highlights the the hippocampus as hub of dysfunction in psychosis and suggests its potential as a biomarker for psychosis risk, as well as a target for novel therapeutic interventions. This study underscores the value of an individualised covariance perturbation approach for examining rCBF and PET functional networks and their subtle alterations in psychosis spectrum disorders.

## 28. Double-Dante-Press: Development and Validation of a Single-Shot Multi-Metabolite-Selective 1H-Mrs Sequence for in Vivo Human Brain Measurements of Glutamate and Glutathione at 7T

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**Background:** The question of how to measure schizophrenia-related brain metabolites in a precise manner is an important but unanswered problem. Single-voxel proton-magnetic-resonance-spectroscopy (1H-MRS) is a non-invasive in vivo imaging technique used to quantify the concentration of human brain metabolites. To achieve metabolite-selectivity, MRS techniques often use spectral editing sequences. However, spectral editing techniques increase scan time, more sensitive to motion artifacts, and provides lower signal-to-noise ratios (SNR) efficiency. Furthermore, non-metabolite-selective techniques are optimized for one metabolite but reduce precision of other metabolites1. Finally, non-metabolite selective sequences produce complex spectra increasing algorithmic variability when performing spectral modelling. Therefore, we will be introducing an advanced single-shot multi-metabolite-selective sequence known as double-Delays-Alternating-Nutation-Tailored-Excitation Point-RESolved-Spectroscopy (double-DANTE-PRESS)2,3. This sequence will only preserve the signal of two metabolites of interest while suppressing unwanted signals through a narrow-band frequency-selective refocusing pulse. Unlike spectral editing where metabolite-selectivity is achieved through the difference or sum of edit ON and OFF spectra, double-DANTE-PRESS achieves selectivity via multiple narrow-band refocusing pulse centered on the peaks or multiplets of interest. The double-DANTE pulse uses interleaved constant phase and linearly increasing phase terms of its component hard pulses. The objective is to develop, test and validate double-DANTE-PRESS at 7 Tesla to target glutamate at 2.35ppm (4C multiplet) and glutathione at 3.77ppm (singlet) in phantoms and in vivo.

**Methods:** Double-DANTE-PRESS with custom fine adjustment calibration loops was programmed within Siemen's IDEA VE12U F50 version. All scans were performed on a 7T MR scanner (Siemens MAGNETOM 7T Plus, Erlangen, Germany) with an 8 transmit channel head-only radiofrequency coil and 32 channel receive coil at the Centre for Functional and Metabolic Mapping (CFMM) at Robarts Research Institute in London, Ontario4.
For T1-weighted anatomical images, the vendor-provided MP2RAGE sequence (works-in-progress package 925B) was used, featuring Compressed Sensing (CS) acceleration [1] and dynamic parallel-transmission (pTx) RF pulses [2] (FOV: 246x246x168 mm, sagittal orientation, 0.70 mm iso-volume voxels, CS acceleration: 4, flip-angle: 4/5 degrees, TI: 860/2700 ms, TR: 6000 ms)5,6. The MRS voxel (2.0x2.0x2.0cm3) was positioned at isocenter in phantom and at the dorsal anterior cingulate cortex in vivo. In vivo voxel placement was based on positioning the posterior face immediately against the precentral gyrus and the caudal face directly on the line separating the anterior cingulate and tangential to the corpus callosum.

A water unsuppressed spectrum was acquired as a reference for absolute quantification and a water-suppressed spectra was acquired to identify large singlets as in vivo chemical-shift references. A water-selective DANTE pulse was used to quantify any signal loss due to the DANTE pulse ON condition. The double-DANTE-PRESS pulse was centered on glutamate's 2.35ppm multiplet and glutathione's 3.77ppm singlet and generated online by the pulse sequence. Metabolite positions were determined relative to N-acetylaspartate (NAA) singlets observed in our water-suppressed PRESS sequence and used for fine power and chemical shift adjustment loops of the DANTE pulse.

A spherical multi-metabolite phantom (diameter=7.5cm) containing a water solution of glutamate [12mM], glutathione [4mM], NAA [20mM], Cr, gamma-amino butyric acid [4mM], TSP, 0.025% sodium azide and PBS buffer were used to build prior knowledge basis set (basis set contains glutamate at 2.35ppm, 3.74ppm and glutathione at 3.77ppm), protocols, and perform test-retest reproducibility before performing in vivo proof of concept. We acquired 10 acquisition to assess within session variability and repeated a week apart.

Spectra visualization and metabolite fitting was done using an in-house post-processing software known as FitMangui7. FitMangui is a time-domain fitting algorithm that uses a non-linear, iterative Levenberg-Marquardt minimizing technique to estimate metabolite chemical shift, concentration, linewidth and phase (0th and 1st order).

**Results:** Qualitatively, double-DANTE-PRESS was able to isolate the glutamate multiplet at 2.35ppm and the glutathione singlet at 3.77ppm along with the glutamate multiplet at 3.74ppm in vivo. The mean inter-individual (n=5) % Coefficient-of-Variation (CV) were 6.67% and 5.46% for glutathione and glutamate respectively in vivo.
**Discussion:** Double-DANTE-PRESS could be an alternative to spectral editing to achieve metabolite-selectivity with high SNR efficiency, reduced scan times, and provide measurements of high precision (%CVs < 7%) of glutamate and glutathione. Future work involves including double-DANTE-PRESS in cross-sectional study of comparing between patients living with schizophrenia and healthy controls.

## 29. Inflammation Trajectories in Youth and Their Association With Brain Structure

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**Background:** Early exposure to inflammation is a key risk factor for psychosis, however, the underlying mechanisms remain unclear. Early life infections may alter normal neurodevelopment to predispose individuals to develop schizophrenia. This study examines inflammatory trajectories of C-reactive protein (CRP) in children and adolescents and its later impact on brain grey matter volume.
**Methods:** C-reactive protein (CRP) was measured in ALSPAC participants at age 9 and 17. MRI scans of 20-year-olds with psychotic experiences (PEs) and controls without PEs from the Avon Longitudinal Study of Parents and Children (ALSPAC) were analysed. The association between CRP at age 9 and grey matter volume was assessed, testing for an interaction with PE group (PE n=70, controls n=174). Sensitivity analyses compared grey matter volume between controls with persistently low CRP (n=324) and two groups with raised CRP: (i) an early peak group with elevated CRP at age 9 (n=14), and (ii) a late peak group with elevated CRP at age 17 (n=16).
**Results:** There was a significant interaction between PE group and CRP level at age 9, whereby higher CRP was associated with larger superior frontal gyrus volume in those with PEs (pFWE=0.003, Z=4.24). The early peak CRP group showed larger volumes in superior frontal (pFDR=0.05, Z=4.06), occipital (pFDR=0.004, Z=3.72, pFDR=0.05, Z=3.74), and temporal gyri (pFDR=0.02, Z=4.68) compared to controls with persistently low CRP. There were no significant differences in grey matter volume between the late peak CRP group and controls.
**Discussion:** Elevated CRP levels at age 9 were associated with later increases in grey matter volume in those who go on to develop psychotic experiences. Early peaks in CRP level during childhood were associated with increased grey matter volume across the cortex in adulthood, whilst a late peak in CRP was not associated with brain alterations. This research indicates that childhood represents a sensitive period whereby inflammation impacts brain development. This is consistent with research showing that early, but not late, inflammation is linked to psychosis risk.

## 30. Shared and Distinct Signatures of Childhood Trauma, Personality and Depressivity in Adolescents and Young Adults: A Transdiagnostic Machine Learning Study

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**Background:** Adolescence and young adulthood are critical periods of vulnerability to mental disorders, including depression and psychosis. These conditions are influenced by key determinants of vulnerability and resilience, such as childhood trauma and personality traits, alongside overlapping symptomatic dimensions, including depressivity. While each of these factors has been independently linked to neurobiological changes, an integrated understanding of their interplay at both clinical and neurobiological levels across diagnostic boundaries remains limited. Advancing such insights could enhance early intervention and improve clinical outcomes.

**Methods:** We applied the multivariate Sparse Partial Least Squares algorithm to identify and validate associations between voxel-wise whole-brain grey matter volume (GMV) and measures of depressivity, personality, and childhood trauma (i.e., BDI-II, NEO-FFI, CTQ, SPI) as well as age and sex. Data were drawn from the multi-centric prospective PRONIA study, including a discovery sample (n = 633) of young, minimally medicated individuals (52.9% female, mean (SD) age = 25.41 (5.98) years) with recent-onset depression (n = 127) or psychosis (n = 124), clinical high-risk states for psychosis (n = 122), and healthy control individuals (n = 260), as well as a replication sample (n = 343) for model validation. We used these signatures to predict 9-month functional outcomes via support-vector-machine classification within a nested cross-validation framework.

**Results:** Sparse Partial Least Squares analysis identified six significant latent variables: two linked to age (Rho = 0.56) and sex (Rho = 0.23), three demonstrating distinct signatures for depressivity (Rho = 0.22), personality (Rho = 0.33), and childhood trauma (Rho = 0.40), and one revealing a shared signature of depressivity, personality and childhood trauma (Rho = 0.24). The depressivity signature was associated with GMV in basal ganglia, thalamic regions, hippocampi and amygdalae, while the childhood trauma signature was characterized by associations with GMV in thalamic, frontal and temporal regions, and the personality signature, predominantly reflecting agreeableness and conscientiousness, showed associations with GMV in thalamic and posterior temporal regions. The shared signature of childhood trauma, personality and depressivity encompassed GMV in the thalami, basal ganglia, amygdalae, hippocampi and occipital cortex. Using these latent variables as predictors, support vector machine models predicted 9-month functional outcomes with a balanced accuracy of 75.8% (AUC = 0.82) in the discovery sample and 83.2% (AUC = 0.91) in the replication sample.

**Discussion:** Our findings reveal both distinct and shared neurobiological signatures of childhood trauma, personality and depressivity, reflected in GMV patterns spanning several key brain networks. While childhood trauma, personality and depressivity exhibited sparse, distinct signatures, they culminated in a dense shared signature integrating all three. Notably, these signatures are observable even at such an early stage in young adults and adolescents, highlighting their relevance for understanding the neurodevelopmental underpinnings of early-stage mental disorders. The robust predictive accuracy of functional outcomes underscores the potential of multivariate approaches in informing personalized intervention strategies for early-stage mental disorders.

**Oral Session: Cognition, Emotion, and Motivation**

## 31. Modeling the Relationship of Matrix Reasoning With the Dual Mechanisms of Cognitive Control Involved in Early Psychosis

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**Background:** Neuropsychological and behavioral studies have shown that people with early psychosis (EP) experience cognitive impairments that predate symptom onset. In particular, they demonstrate deficits in cognitive control, which are also associated with the unexpressed predisposition to psychosis (Snitz, et al., 2006). Cognitive control impairments may prove an explanatory component of the broader cognitive difficulties observed in EP.
**Methods:** 164 participants (EP=93, Healthy Controls=71) completed the Translational Orientation Pattern eXpectancy (TOPX) task, a novel variant of the expectancy AX task which estimates cognitive control. Participants also completed the Matrix Reasoning subtest from the Test My Brain battery, which estimates fluid intelligence and visual reasoning. We conducted Pearson correlation tests and Welch Two Sample T-tests to explore the relationship between these tasks.
**Results:** Preliminary results show small group differences in matrix reasoning, with controls performing better than EP patients ($t(146.07) = 2.39$, $p = .02$, $d = .36$). Moderate group differences were observed in BX accuracy, a measure of proactive control ($t(145.2) = 3.35$, $p = .001$, $d = .52$); people with EP showed proactive deficits relative to controls. There were no significant group differences in AY accuracy, a measure of reactive control ($t(150.94) = 1.58$, $p = .12$). Across all participants, there was a moderately strong positive correlation between matrix reasoning scores and proactive cognitive control ($r = .54$, $p < .001$) as well as a small positive correlation between matrix reasoning and reactive control ($r = .37$, $p < .001$).
**Discussion:** People with EP had greater difficulties meeting task demands for general fluid intelligence, as well as proactive cognitive control. General fluid intelligence was more strongly associated with proactive control compared to reactive control; however, this should be interpreted with caution as significant relationships were present for both cognitive control types. These results suggest that cognitive control, and especially proactive control, could be associated with general cognitive difficulties. Future directions in this project include expanding these analyses to a factor analysis to further explore the connections and differences between these cognitive constructs and their associations with various clinical symptoms of psychosis. More fully understanding the cognitive deficits in psychosis may help guide the development of targeted treatment strategies for psychosis patients early in their course of illness.

## 32. The Role of Disorganized Symptoms in Mediating the Relationship Between Emotion Management and Functioning in Veterans With Psychotic-Spectrum Disorders

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**Background:** Impaired functioning is a pervasive and disabling feature of psychotic-spectrum disorders (PSD). Both disorganized and negative symptoms are related to dysfunction. These symptom domains have also been linked to social cognitive deficits,

including deficits in understanding and managing emotions. Given these links, some have theorized that symptomatology may be a mechanism through which cognition affects functioning. Indeed, there is preliminary evidence that negative symptoms may be one symptom dimension through which social cognition, including emotion management (i.e., the ability to be open to feelings, and to modulate them in oneself and others), affects functioning. However, no studies to date have tested the unique role of disorganized symptoms or disorganized speech, a core feature of PSDs.
**Methods:** Veterans with PSD (n=103) completed measures of emotion management (MSCEIT-ME), functioning (QLS; Heinrichs' Quality of Life Scale), and symptoms (PANSS; Positive and Negative Syndrome Scale). The present study aimed to examine: 1) which symptom domains (i.e., PANSS positive, negative, cognitive/disorganized) mediate the relationship between emotion management and functioning, and 2) the mediating contribution of conceptual disorganization (i.e., disorganized speech) specifically as a more concrete treatment target. We employed parallel mediation models, first examining QLS total score as an outcome. If there was significant mediation, we performed post hoc analyses with individual QLS subscales (Intrapsychic Foundations and Interpersonal Relations) to better understand aspects of functioning most closely related to symptoms. Models for Aim 1 included the PANSS positive, negative, and disorganized symptom factors as mediators; for Aim 2, the model was the same but used the conceptual disorganization item in place of the disorganized factor.
**Results:** Disorganized symptoms, but not positive or negative symptoms, mediated the relationship between emotion management and overall functioning, which was driven by the Intrapsychic Foundations subscale (i.e., foundational psychological elements needed for interpersonal connection). Disorganized speech as a specific symptom also significantly mediated these relationships, though the effects were smaller than for disorganized symptoms measured broadly. No symptom domains mediated the relationship between emotion management and the Interpersonal Relations subscale.
**Discussion:** Results provide preliminary evidence that disorganized symptoms mediate the relationship between the ability to manage emotions and functioning in Veterans with PSD. Specifically, these symptoms appear to disrupt the link between the ability to modulate emotions and foundational elements needed for interpersonal connection (e.g., empathy, curiosity). Findings also suggest that these effects are partially driven by disorganized speech, which is in line with previous work showing that disorganization's close link with functional outcomes in PSD may be due to communication difficulties. In contrast with previous findings, we did not find that negative symptoms mediated this relationship. With replication, our results suggest that disorganized symptoms may be an intervention target for improving dysfunction.

### 33. Comparative Analysis of Social Cognitive and Neurocognitive Performance Across Autism and Schizophrenia Spectrum Disorders

Ayesha Rashidi*[1], Lindsay Oliver[1], Iska Moxon-Emre[2], Colin Hawco[1], Erin W. Dickie[1], Ruyi Pan[1], Maria T. Secara[1], Ju-Chi Yu[2], Peter Szatmari[3], Pushpal Desarkar[1], George Foussias[1], Robert W. Buchanan[4], Anil K. Malhotra[5], Meng-Chuan Lai[6], Aristotle Voineskos[1], Stephanie H. Ameis[3]

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**Background:** Social cognitive and neurocognitive performance is impacted in Autism and Schizophrenia Spectrum Disorders (SSDs). Here, we compared social cognitive and neurocognitive performance across a large transdiagnostic sample of participants with autism, SSDs, and typically developing controls (TDCs).
**Methods:** Participants (total N=585; autism N=100, SSDs N=275, TDCs N=209; aged 16-55 years; 61% male assigned at birth) completed lower-level (e.g., emotion processing) and higher-level (e.g., theory of mind) social cognitive tasks, the MATRICS Consensus Cognitive Battery, and a measure of social functioning. Non-parametric group-wise comparisons were undertaken, adjusting for age and sex, and within-group correlations were used to examine associations between social cognition, neurocognition, and social functioning.
**Results:** Autistic and SSDs groups performed worse than TDCs on lower- and higher-level social cognitive tasks, with few autism-SSDs differences found. Autism and SSDs had lower neurocognitive scores than TDCs; SSDs demonstrated lower processing speed, working memory, verbal learning, and visual learning versus autism. Positive associations between social cognitive tasks and neurocognition were found across groups, and self-reported measures of empathy were consistently correlated with social functioning.
**Discussion:** This study represents the largest transdiagnostic comparison of both social cognition and neurocognition in an autism/SSDs sample reported to date. Autistic participants and those with SSDs showed similar performance on lower- and higher-level social cognitive tasks relative to controls, while neurocognition was less impacted in autism versus SSDs. These findings underscore the importance of transdiagnostic research into the mechanisms underlying social cognitive deficits and highlight the potential for developing transdiagnostic interventions.

## 34. Increased Social Withdrawal in Schizophrenia Following Social Exclusion

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**Background:** People with schizophrenia are at heightened risk of social exclusion, which contributes to more severe and enduring psychological and emotional impact. The social defeat model of negative symptoms suggests that social exclusion and social withdrawal may create a self-perpetuating cycle in this population, contributing to the maintenance of negative symptoms. However, behavioral responses have yet to be studied in schizophrenia. We hypothesized: 1) people with schizophrenia would be more likely to withdraw following social exclusion compared to controls; 2) withdrawal intentions would be greater following exclusion compared to disappointment; 3) withdrawal behavior would be predicted by rejection sensitivity, alternative sources of acceptance, chronicity of exclusion, and perceived fairness; and 4) withdrawal following exclusion would be associated with more negative symptoms and poorer functioning.
**Methods:** People with (n = 43) and without (n = 43) schizophrenia or schizoaffective disorder played Cyberball – Behavioral Response, a novel version of the exclusion task. Participants responded to social exclusion with affiliative, retaliatory, and withdrawal behaviors within a 2 (Group: Schizophrenia vs. Control) X3 (Game Type: Exclusion vs.

Disappointment vs. Inclusion) mixed design. Participants reported their social experiences, affective and psychological responses following exclusion, negative symptoms, and functioning.
**Results:** People with schizophrenia demonstrated greater in-game withdrawal responses (mean difference [MD] = 0.66, $p < .001$) and intentions (MD = 2.00, $p < .001$) compared to controls. Withdrawal was more pronounced following exclusion versus disappointment (MD = 1.77, $p < .001$). Withdrawal responses were associated with chronicity of exclusion ($\beta = .34$, $p = .024$), and withdrawal and exclusion in daily life were linked to functional outcomes. Despite similar affective responses, people with schizophrenia attributed exclusion more to personal factors ($p = .018$) and reported less desire for future interaction ($p = .002$).
**Discussion:** People with schizophrenia experience frequent social exclusion in daily life, and this predicts withdrawal responses to social exclusion. Findings provide initial evidence of vulnerability to a cycle of exclusion and withdrawal. Interventions to help people with schizophrenia address self-blame tendencies and develop skills for relational repair may mitigate these effects.

## 35. Social Motivation Deficits and Negative Symptoms in Treatment-Resistant Schizophrenia Patients

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**Background:** The traditional criteria defined treatment-resistant schizophrenia (TRS) based on persistent positive symptoms and functional deterioration, but subsequent criteria accepted negative symptoms as a defining feature. Prior empirical findings suggested that negative symptoms influenced TRS patients' functional outcome, and cognitive deficits in TRS patients were > that in non-TRS patients. However, relatively few studies had focused on reward learning impairments in TRS patients. Motivational deficits are core features of negative symptoms. In particular, social motivation deficits related closely to negative symptoms, but its nature and impact on TRS patients remained unclear. This study attempted to compare social motivation in TRS patients, remitted schizophrenia patients and healthy people, using an computerized Social Incentive Delay (SID) task. We also aimed to explore the relationship between social motivation and negative symptoms in TRS patients and remitted schizophrenia patients.
**Methods:** Participants were 60 TRS patients, 60 remitted schizophrenia patients and 60 controls. In the SID task, participants first viewed cues indicating the potential social outcome (reward, neutral or punishment). After a short delay, a target appeared on the screen, and participants had to press the button as soon as possible to "hit the target". Immediate feedback regarding "hit" or "miss" was then given, followed by presentation of the social outcome. During anticipation and receipt of social outcome, participants self-rated anticipatory and consummatory pleasure. To measure negative symptoms, we administered the second-generation negative symptom scales, i.e., the CAINS and the BNSS. We conducted Group (between-group variables: TRS, remitted schizophrenia, controls) x Cue condition (within-group variables: positive, neutral, negative) mixed ANOVA models to compare the SID performances (number of hit, reaction time, anticipatory pleasure and consummatory pleasure ratings) between the three groups. To examine the association

between SID performance and negative symptoms, we conducted Spearman's correlational analyses in TRS patients and remitted schizophrenia separately.
**Results:** The mixed ANOVA model results showed that TRS patients had lower accuracy ("hit rate") in SID than the two other groups, indicating social motivation deficits. Moreover, TRS patients self-reported a "less discriminative" pattern of consummatory pleasure as the social reward valences varied, relative to the other two groups. The correlational analysis results with FDR adjustments showed that the connection between social motivation deficits and negative symptoms was weaker in remitted schizophrenia patients, but stronger in TRS patients.
**Discussion:** TRS patients exhibited reduced efforts to purse social reward or avoid social punishment. In the development of TRS, the connection between social motivation deficits and negative symptoms appeared to be tightened. Early intervention on social motivation deficits in TRS patients may reduce the risk of further development of negative symptom.

## 36. Motor Development Impacts Trajectories of Psychotic-Like Experiences Throughout Adolescence

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**Background:** Gross motor function expands rapidly between ages 0-2, where infants obtain knowledge of the world in part through motoric actions (e.g., rolling, walking, talking), laying the foundation for later behavioral and cognitive development. Evidence implicates delayed motor development in the etiology subclinical psychotic-like experiences (PLEs; e.g., mild delusional thoughts, perceptual abnormalities). However, research is limited by methodological and conceptual challenges (small, older-aged, high-risk samples; cross-sectional analyses). It remains unclear whether accelerations or delays in motor milestone development are related to trajectories of PLEs in a population-based, non-clinical sample of youth.
**Methods:** The current analysis leverages longitudinal data from 11,846 youth ages 9-15 enrolled in the Adolescent Brain Cognitive Development (ABCD) study. Objective motor development was assessed via the age (in months) the child first rolled over, sat upright, walked, and said their first word. Subjective motor development was assayed via caregiver's perception of the child's motor and speech development relative to other children. PLEs were assessed with the Prodromal Questionnaire-Brief Child version, a validated self-report measure that assays 21 unique positive PLEs. Latent growth models tested the effects of each motor milestone on intercepts (baseline) and slopes (rate of change) of trajectories for both the total number of, as well as the subjective distress associated with, PLEs. All models controlled for biological sex, race/ethnicity, and general psychopathology.
**Results:** Conditional latent growth models fit the data well (total: CFI=0.97, TLI=0.96; distress: CFI=0.96, TLI=0.94). On average, total and distressing PLEs decreased 0.47 and 1.1 units per year, respectively with elevated intercepts being associated with greater rates of decline (r total=-0.70, r distress=-0.75). Delays in rolling over and subjective perception of speech development were associated with elevated intercepts for both total and distressing PLE trajectories (Bs=0.08-0.49), whereas delays in subjective perception of motor development were associated with lower intercepts for total and distressing PLEs (Bs=-0.16--0.48). For both PLE trajectories, delays in rolling over and caregiver perception of speech development were associated with a steeper decline in trajectory slopes (Bs=-0.02- -0.14).

**Discussion:** Consistent with previous research, youth delayed in early motoric action (rolling over) and perceived to be delayed in speech development reported elevated PLEs at age 9-10. Inconsistent with previous research, delays in motor and speech development were associated with a steeper decrease in PLEs across ages 9-15. While this may be a function of relatively low PLE endorsement across time in this non-clinical population-based sample, it is also possible that delayed motor development in isolation does not confer risk for elevated PLEs across time. Future research will test whether motor development interacts with perinatal risk (e.g., toxin and/or substance exposure) and neurodevelopment (e.g., cerebellum) to amplify the effect of motor development on PLEs.

## 37. Disentangling Volatility and Noise in Psychosis: A Gamified Approach

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**Background:** Learning depends on determining whether new observations are meaningful, relying on beliefs about two interconnected sources of uncertainty: volatility (change) and noise (stochasticity). Although psychosis has been linked to altered volatility processing, prior studies have insufficiently addressed the interdependent relationship between volatility and noise. To disentangle deficits in these types of uncertainty, we developed a novel learning task that required participants to give explicit trial-by-trial estimates of both volatility and noise. The task was designed in an online, gamified format to boost engagement and allow participation from large, diverse samples.
**Methods:** We conducted two online experiments and one on-campus experiment with participants from the general population. Additionally, we collected data from individuals at clinical high risk of psychosis (34 at clinical high risk, 64 controls so far). Online participants completed the task at home on their own devices, while on-campus participants used a laptop in a quiet room. In the general population samples, we capitalized on the presence of psychotic-like experiences and psychosis susceptibility, while the clinical high-risk study involved screening using the prodromal questionnaire, with confirmation of at-risk status through clinical assessments.

The task was set within a narrative where participants, stranded on a planet, had to catch falling space junk to build a rocket and escape. The junk fell from a hidden spacecraft, and participants had to infer its location (mean) and width (standard deviation) to make accurate predictions. They controlled a rover on the x-axis and an adjustable beam on the y-axis, aiming to catch the junk with the smallest beam possible to conserve fuel and maximize their score. Beam width adjustments reflected their estimation of noise, with smaller beams earning more points. The game featured multiple levels with increasing stakes, evolving visuals, and a rocket being built in the Background:, which participants could launch to escape the planet upon completion.

Linear mixed-effects models were used to assess metrics directly derived from the task, including score, beam width (standard deviation estimate), performance error (mean estimate), and learning rates (prediction error/position change). A computational modeling

approach (HGF:JGET) was applied to data from experiments 1 and 2 to examine how individuals update beliefs about both volatility and noise.

**Results:** Completion rates and debriefing indicated the task was feasible and enjoyable, with most participants preferring it over traditional computerized tasks. Across samples, participants followed a normative learning pattern, suggesting they understood the task. However, psychosis susceptibility and increased delusional ideation were linked to non-normative learning, while elevated paranoia was associated with impaired performance, driven by consistent misestimation of both the mean and width of space junk distributions. Computational modeling suggested these impairments stem from difficulties in accurately inferring environmental noise, leading to misinterpretation of noisy inputs as meaningful changes.
Individuals at clinical high risk of psychosis used higher learning rates, with an interaction between uncertainty and group: controls performed better in noise and combined conditions, while at-risk individuals performed better in the volatility condition. Though more data is needed, overestimating volatility might have helped in volatile conditions but harmed performance in noisy environments.

**Discussion:** Our gamified task produced reliable outputs across four experiments, including general population participants and individuals at clinical high risk of psychosis. This study shows that capturing the multivariate nature of uncertainty can reveal subtle mechanisms in how individuals with psychosis susceptibility, psychotic-like experiences, and those at clinical high risk process information. These insights may improve understanding of symptom formation and persistence and aid the development of clinically meaningful phenotypes.

## 38. Cognitive Impairment in Early Onset Psychosis Probands and Their Siblings: The Influence of Age and Sex

Josephine Mollon*[1], Nuria Lanzagorta[2], Samuel Mathias[1], Amanda Rodrigue[1], Emma Knowles[1], Emma Deaso[1], Jimena Unzueta Saavedra[1], Laura Cadavid[1], Catherine Brownstein[1], Eugene D'Angelo[1], Joseph Gonzalez-Heydrich[1], Emmanuel Sarmiento[3], Christopher Walsh[1], Laura Almasy[4], Humberto Nicolini[5], David Glahn[1]

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**Background:** Most research on cognitive impairment in early onset psychosis (EOP) has focused on childhood onset schizophrenia (COS), but EOP patients present with a variety with nonaffective and affective psychotic disorders. Moreover, the influence of age and sex on this impairment remains unclear.
**Methods:** EOP probands (N=708), their siblings (N=144), and non-psychotic controls (N=735) were recruited into the Early Psychosis Investigation in Mexico City (EPIMex) study. EOP probands were divided into affective (N=458) (schizoaffective, psychotic depression, psychotic bipolar), and nonaffective (N=250) (schizophrenia, schizophreniform, other psychoses). Cognitive tests measured verbal memory, face memory, processing speed, complex reasoning, working memory, executive function, and verbal fluency. General cognitive ability (g) was the first component of principal component analyses (PCA) of these 7 measures.

**Results:** Nonaffective EOP probands showed impairments on all cognitive measures (d=0.27-0.50; p < .001), affective EOP probands on 7 of 8 measures (d=0.16-0.24, p < .03), and their siblings on 2 measures (d=0.18-0.20, p < .02). Group-by-sex interactions (p < .03) for nonaffective probands showed that impairments on g, verbal memory, executive function, complex reasoning, and working memory were larger in males than females. Group-by-age interactions for nonaffective probands (p < .008) showed that impairments on g, verbal memory, and working memory increased between childhood (age 10) and adulthood (age 21). Group-by-age interactions for affective probands (p < .02) showed that impairments on g, processing speed, working memory, and verbal fluency emerged gradually between childhood and adulthood. Group-by-age interactions for siblings (p < .02) showed that impairments on g, face memory, and processing speed also emerged throughout this developmental period. In nonaffective probands, a small (d=0.2) g impairment in childhood increased to large (d=0.8) by adulthood. Conversely, affective probands and siblings did not show a g impairment in childhood, but a medium impairment emerged by adulthood (d=0.5).
**Discussion:** Early onset psychosis (EOP) is associated with substantial and widespread cognitive impairment. This impairment is larger in males with nonaffective psychoses and increases with age. Siblings of EOP probands show more specific impairments that emerge throughout the developmental period between childhood and adulthood.

## Oral Session: Clinical Trials of Treatments for Positive and Negative Symptoms

### 39. Hepatic Safety of Xanomeline and Trospium Chloride: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled Emergent Trials

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**Background:** Xanomeline and trospium chloride was recently approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults and comprises the dual M1/M4 preferring muscarinic receptor agonist xanomeline and peripherally restricted muscarinic receptor antagonist trospium chloride. The efficacy and safety of xanomeline/trospium in people with schizophrenia experiencing acute psychosis were demonstrated in the three 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. Long-term safety and tolerability of xanomeline/trospium in adults living with schizophrenia were assessed in two 52-week, outpatient, open-label trials: EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309).
**Methods:** Data from the completed acute EMERGENT trials and interim data from the long-term EMERGENT-4 and EMERGENT-5 trials as of April 17, 2023, were pooled separately to characterize the hepatic safety of xanomeline/trospium. The acute EMERGENT trials enrolled people with a recent worsening of psychosis warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score 80-120, and Clinical Global Impression–Severity (CGI-S) score ≥4. EMERGENT-4 enrolled participants who completed EMERGENT-2 or EMERGENT-3. EMERGENT-5 enrolled adults with schizophrenia with no prior exposure to xanomeline/trospium, a PANSS total score ≤80, and a CGI-S score ≤4. Oral xanomeline/trospium was dosed twice daily at xanomeline 50 mg/trospium 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for either 5 weeks (acute trials) or 52 weeks (long-term trials). Any liver transaminase elevations ≥3× upper limit of

normal (ULN) for alanine transaminase (ALT) or aspartate transaminase (AST) were monitored as AEs of special interest (AESIs). All safety analyses were conducted in the safety population, defined as all participants who received ≥1 dose of trial drug.
**Results:** A total of 683 participants (xanomeline/trospium, n=340; placebo, n=343) in the acute EMERGENT trials and 674 participants in the long-term EMERGENT trials were included in the safety analyses.
In the acute trials, 1.8% (n=6) in the xanomeline/trospium group experienced liver transaminase elevations meeting criteria for an AESI. All but 1 participant receiving xanomeline/trospium (5 of 6) had transaminase elevations resolve with continued treatment; 1 participant had transaminase normalize shortly after treatment discontinuation.

In the long-term trials, 1.9% of participants (n=13) experienced liver transaminase elevations meeting criteria for an AESI. Seven of 13 continued xanomeline/trospium treatment, and their transaminase levels normalized. Three participants had transaminase levels return to normal after brief treatment interruptions, two had transaminase levels normalize following discontinuation of xanomeline/trospium, and 1 participant was lost to follow-up.

The majority of liver transaminase elevations occurred within the first month of treatment and resolved rapidly with continued xanomeline/trospium treatment, consistent with hepatic adaptation to xanomeline.

**Discussion:** In the EMERGENT trials, treatment with xanomeline/trospium up to 52 weeks was generally well tolerated in people with schizophrenia. The incidence of liver transaminase elevation meeting AESI criteria was low and the pattern was similar in both acute and long-term trials. Transaminase elevations occurred early during the course of xanomeline/trospium treatment, with evidence of hepatic adaptation as events resolved over time, resulting in few discontinuations or interruptions in treatment.

## 40. Evenamide as Add on Treatment is Associated With Significant Benefits: Positive Results From a Phase 3 International, Randomized, Double Blind, Placebo Controlled Trial in Patients With Schizophrenia Inadequately Responding to SGA

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**Background:** The development of novel therapeutic agents in schizophrenia with different mechanisms of action (MoA) not involving the modulation of the dopaminergic system has greatly expanded in the latest years (Citrome et al., 2023). This need emerged from the unsatisfactory treatment provided by the currently available antipsychotics (APs), which failed to provide additional benefit even when they were used as combination therapy (Galling et al., 2017). In fact, although second-generation antipsychotics (SGAs) certainly reduce psychotic symptoms improving the patients' functioning and quality of life, they do not ameliorate negative symptoms and cognitive deficits; in addition, a substantial proportion of patients is either resistant to treatment or does not benefit adequately. Among the newly explored MoAs, the modulation of the glutamatergic system has emerged as a promising target, especially in patients who are treatment-resistant. In fact, evidence has pointed out that patients with limited/no response to APs exhibit increased glutamate levels, rather than an increased dopamine synthesis capacity, compared to those who respond to dopaminergic APs (Mouchlianitis et al., 2023).

Evenamide, a voltage-gated sodium channels blocker, is a new chemical entity that normalizes excessive glutamate release without affecting its basal levels, and it does not interact with > 150 CNS targets. It has been shown to be effective in animal models of psychosis both when used as monotherapy and as add-on to APs, and previous clinical trials have indicated that add-on treatment with evenamide is associated with long-term clinically important benefits in patients with treatment-resistant schizophrenia (Anand et al, 2023).

**Methods:** Study 008A is a phase 2/3, 4-week, international, randomized, double-blind, placebo-controlled trial that determined the efficacy and safety of evenamide 30 mg bid as add-on in patients poorly responding to an SGA. Outpatients with a diagnosis of schizophrenia, still symptomatic (PANSS 70-85; PANSS positive > 20; CGI-S 4-6) despite treatment with an atypical AP at a therapeutic dose (compliance confirmed through plasma levels before randomization) for an adequate period, were enrolled. Efficacy was assessed on the PANSS, CGI-S/C, Strauss-Carpenter LOF, and MSQ through the comparison of changes from baseline to Day 29 between evenamide and placebo groups. Safety measures comprised: TEAEs, vital signs, lab exams, ECG, seizure checklist, EEG, physical/neurological/eye examinations, C-SSRS, ESRS-A, CDSS.
**Results:** A total of 291 patients were randomized across 11 countries (Europe, Asia and LATAM), with 280 completers at Day 29. The low attrition rate ( < 4%), small proportion of patients with TEAEs (~25% in both groups), and absence of patterns of clinically significant abnormalities on any of the safety measures (e.g. EEG, seizure checklists, ECG, lab, etc.) indicate that evenamide was well tolerated. Add-on treatment with evenamide was associated with a statistically significant greater improvement at the endpoint (Day 29) on the PANSS total, PANSS positive subscale, PANSS negative subscale, and CGI-S, and a statistically significant lower score on the CGI-C compared to placebo. In addition, all the sensitivity analyses performed confirmed the same pattern of improvement.
**Discussion:** This is the first international, randomized, double-blind, placebo-controlled trial that demonstrated statistically significant and clinically important benefits of adding a glutamate modulator in patients with chronic schizophrenia not adequately responding to SGAs. Based on these results, a phase 3 trial will be initiated to determine the benefits of glutamate modulation in patients with treatment-resistant schizophrenia.

## 41. Impact of Paliperidone Palmitate 1-Month and 3-Month Long-Acting Injectable Antipsychotics on Clinical and Psychosocial Outcomes in Rwandan Patients With Schizophrenia: Results From the Caspar Study

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Inc, New Brunswick, New Jersey, USA, [9]Janssen Scientific Affairs LLC, Titusville, New Jersey, USA, [10]Cytel, Cambridge, Massachusetts, [11]Johnson and Johnson Middle East, FZ LLC, Kenya, [12]Janssen Research and Development, LLC, Titusville, NJ, USA, [13]Johnson and Johnson Middle East, FZ LLC, Ghana, [14]N/A

**Background:** Schizophrenia presents a substantial unmet medical need in Rwanda, underscoring the need to prioritize mental health initiatives and strengthen health systems to improve patient outcomes. In resource-limited settings, adoption of long-acting injectable (LAIs) antipsychotics offers a valuable alternative to daily oral medication, potentially improving treatment adherence and outcomes for patients. The CASPAR study (NCT04940039) aimed to evaluate the effectiveness of paliperidone palmitate (PP) 1-month (PP1M) and 3-month (PP3M) LAIs on clinical outcomes and psychosocial functioning in patients with schizophrenia in the real-world Rwandan healthcare setting. Caregiver burden, patient and clinician satisfaction were also assessed.

**Methods:** Adults (18-35 years) with schizophrenia, basis MINI-Screen/ MINI (Module K), requiring either initiation of treatment or change in existing treatment were included in an open-label, multicenter, interventional study. Outcomes were evaluated during 2 phases: observation phase (OR) with standard of care oral antipsychotics (OA; 0-24 weeks [W]) and lead-in/maintenance (LM; W25 to end-of-study [EOS; W66]) phase with PP1M/PP3M. Primary endpoint: change in Clinical Global Impressions-Severity Scale for Schizophrenia (CGI-SS) from baseline (FU) to EOS. Secondary endpoints: change in Personal and Social Performance (PSP) scale total score, Schizophrenia Quality of Life Scale (SQLS), patient and clinician satisfaction scores, caregiver experience and burden. Mean changes from corresponding phase baselines were evaluated using a paired t-test. Safety was evaluated as treatment-emergent adverse events (TEAEs).

**Results:** Of 100 patients screened, 93 were enrolled and received OA in OR phase. Of 93 patients, 92 switched to PP1M lead-in treatment for ≥17 weeks then maintenance with PP3M for 24 weeks (men: 76 [81.7%]), median age: 29 years). A statistically significant and clinically meaningful change in overall CGI-SS score from FU (OR+LM) to EOS was observed (mean [SD] −1.4 (0.69); 95% CI: −1.50; −1.22, $p < 0.001$). In OR phase, no clinically meaningful changes in mean (SD) CGI-SS (-0.1 [0.47] p=0.049), PSP total scores (0.2 [5.82] p=0.736) and SQLS scores (0.8 [11.00 p=0.467) were observed. In LM phase, statistically significant and clinically meaningful changes (from LM baseline to endpoint LM) in mean (SD) CGI-SS score (−1.2 [0.67]; 95% CI: −1.38, −1.10; $p < 0.001$), PSP total scores (17.1 [13.62]; 95% CI: 14.29, 19.93; $p < 0.001$) and SQLS scores (−17.7 [16.61]; 95% CI: −21.15, −14.23 $p < 0.001$) were observed. Patient satisfaction improved from 98.9% at Week 25 to 100% at Week 66, with parallel increase in satisfaction with medications (80.5% to 94.5%). Clinician satisfaction with overall treatment increased from 85.9% at W25 to 97.8% at W66. Median number of times caregivers felt patients sought more help and when caregivers felt lack of personal time, both reduced from 6 at W25 to 2, by W66. Median (range) work hours caregivers lost decreased from 10 h (0-25) at W25 to 1 h (0-36) at W66. In OR phase, 32 (34.4%) patients experienced ≥1 TEAE and 8 (8.6%) had ≥1serious TEAE; in LM phase,62 (67.4%) patients had ≥ 1 TEAE and 4 (4.3%) patients had ≥1serious TEAE. No deaths in OR phase and 2 deaths (assessed by investigator as not related to study treatment) were reported in LM phase. Nasopharyngitis, asthenia, urinary tract infection, tremor, and fatigue were most frequently ( > 5%) reported TEAEs.

**Discussion:** The CASPAR study findings showed that switching from OAs to PP LAI led to statistically significant and clinically meaningful improvements in long-term symptomatic response, psychosocial functioning, patient and clinician satisfaction, and reduction in caregiver burden, in Rwandan patients with schizophrenia.

## 42. Long-Term Safety and Tolerability of Xanomeline and Trospium Chloride: Pooled Results From the 52-Week, Open-Label Emergent-4 and Emergent-5 Trials

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**Background:** Xanomeline/trospium combines the dual M1/M4 muscarinic agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride. The combination was recently approved for the treatment of adults with schizophrenia by the U.S. Food and Drug Administration. Xanomeline/trospium was well tolerated and associated with significant improvement in symptoms of psychosis in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials of adults with schizophrenia. Here we report a pooled analysis of long-term safety from the 52-week EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials.

**Methods:** The acute EMERGENT trials enrolled participants with a confirmed diagnosis of schizophrenia, worsening psychosis symptoms requiring hospitalization, Positive and Negative Syndrome Scale (PANSS) score of 80-120, and Clinical Global Impression–Severity (CGI-S) score ≥4. EMERGENT-4 was an open-label extension trial of participants who completed the treatment period in EMERGENT-2 or EMERGENT-3. EMERGENT-5 employed a similar trial design but enrolled de novo participants with stable schizophrenia symptoms, no prior exposure to xanomeline/trospium, a PANSS score of ≤80, and a CGI-S score ≤4. All participants initiated twice-daily oral doses of xanomeline 50 mg/trospium 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for 52 weeks. Incidences of spontaneous adverse events were monitored from the time of first trial medication dose during the open-label treatment period until the end of treatment at week 52. Safety analyses were performed in the pooled EMERGENT-4/EMERGENT-5 safety population, defined as all participants who received ≥1 dose of trial medication.

**Results:** The pooled population included a total of 718 participants treated with xanomeline/trospium. Xanomeline/trospium was generally well tolerated, with no new safety issues compared with the acute trials. Across long-term trials, 549 (76.5%) of people reported ≥1 adverse event (AE). Treatment-emergent AEs (TEAEs) reported by ≥5% of people were nausea (20.2%), vomiting (17.8%), constipation (15.2%), hypertension (9.3%), dry mouth (8.5%), diarrhea (8.4%), dizziness (7.8%), dyspepsia (7.5%), headache (7.2%), and somnolence (5.4%). Treatment-related TEAEs reported by ≥5% of people were nausea (18.8%), vomiting (15.7%), constipation (13.9%), dry mouth (8.2%), dizziness (6.7%), dyspepsia (6.4%), hypertension (6.3%), diarrhea (5.8%), and somnolence (5.0%). Incidences of treatment-related weight decreases (2.5%), weight increases (2.1%), and increases in blood prolactin (0.6%) were low. Further analyses of these investigations are underway and will be presented at the meeting.

**Discussion:** Pooled analysis of these long-term, open-label trials found that xanomeline/trospium was generally well tolerated in individuals with schizophrenia in an outpatient setting across 52 weeks. In combination with positive efficacy data from the acute and long-term EMERGENT trials, the present results provide additional support for xanomeline/trospium as a new therapeutic option for people living with schizophrenia

## 43. Engagement, Efficacy, and Patient Experience of an Investigational Digital Therapeutic for Experiential Negative Symptoms Of Schizophrenia: An Exploratory Study

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**Background:** There are currently no FDA-approved pharmacotherapies for treating experiential negative symptoms (ENS) of schizophrenia, with negative symptoms themselves often a barrier to receiving necessary care. CT-155/BI 3972080, an investigational digital therapeutic for the treatment of ENS of schizophrenia, has been granted breakthrough device designation by the FDA. This study assessed engagement, potential efficacy, and user experience of an abbreviated version of CT-155/BI 3972080 (CT-155 beta) in adults living with ENS of schizophrenia.

**Methods:** This was a multicenter, 7-week, single-arm, exploratory study (NCT05486312). Participants ≥18 years with a clinically confirmed diagnosis of schizophrenia for ≥1 year, moderate-to-severe ENS (score of ≤30 on the Motivation and Pleasure-Self Report) and receiving a stable dose (≥12 weeks) of ≤2 different antipsychotic medications were included. Engagement with CT-155 beta was measured passively throughout the study by the app. ENS severity was assessed using the clinically administered Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP). User experience and acceptability were assessed using a non-validated customized feedback survey and the validated Mobile App Rating Scale (MARS). In the survey, participants were asked at Weeks 3, 5, and 7 how often they used CT-155 beta and whether they would recommend CT-155 beta to a friend. Three free-response questions covering benefits of, frustrations with, and suggested improvement to CT-155 beta were also asked. At the end of the study (Week 7), participants rated the quality of CT-155 beta through MARS and shared their expectation of therapeutic benefit of CT-155 beta via a brief 3-question survey.

**Results:** 43 of 50 (86%) enrolled patients completed the study; most were male (80%) and non-white (70%); mean (standard deviation; SD) age was 48.1 (12.4) years. Study app engagement during the last week of the study was 82% until Day 47 (62% on last day of 7-week treatment period). Participants' ENS severity assessed by mean (SD) CAINS-MAP total score decreased from 20.2 (8.6) at baseline to 16.8 (7.8) at Week 7 ($t[42]=2.2$, $p=0.004$). User experience survey showed most participants (Week 3: 91% [41/45], Week 5: 91% [41/45]; Week 7: 84% [37/44]) reported using CT-155 beta either once or multiple times a day. Most participants reported that they would recommend CT-155 beta to a friend at Weeks 3 (93%), 5 (89%), and 7 (95%). For the free-response questions, participants reported how CT-155 beta helped to stabilize their mood and improve their confidence and helped them to change their perspective. Twenty-nine participants provided suggestions for improving CT-155 beta such as "shorter videos" and increasing interactivity to "have the app speak to you, more verbalized". Participants (n=43) rated the quality of CT-155 beta as either acceptable or good after 7 weeks of using CT-155 beta across the engagement (mean [SD] MARS scores: 3.8 [0.8]), functionality (4.2 [0.8]), esthetics (3.9 [0.8]), and information quality (4.0 [0.9]) domains. Finally, 89% (39/44) of participants either agreed or strongly agreed that CT-155 beta was an effective treatment for their experience of negative symptoms.

**Discussion:** Participants engaged with CT-155 beta, indicated that it positively impacted their approach to life, and that they would recommend it to a friend. Furthermore, participants highlighted their satisfaction with the functionality and information contained in CT-155 beta. These valuable insights into participants' experiences with CT-155 beta will guide the continued development of CT-155/BI 3972080.

Funding: Boehringer Ingelheim.

**44. WITHDRAWN Background:Methods:Results:Discussion:**Results:

## Oral Session: Social, Cognitive, and Public Health Influences on Illness Course

### 45. Socioeconomic Trajectories Throughout Childhood and Risk of Psychotic Disorders During Adolescence and Early Adulthood: A Birth-Cohort Study Using Population Based Health Administrative Data

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**Background:** Childhood is known to be a key exposure period for the later development of mental disorders, including psychotic disorder. Although socioeconomic deprivation is a known risk factor for psychotic disorders, less is known about the impact of longitudinal trajectories of socioeconomic status throughout childhood. We sought to examine the association between neighbourhood-level income trajectories during childhood and the subsequent risk of psychotic disorder during adolescence and early adulthood.
**Methods:** We constructed a population-based retrospective birth cohort using data from the Ontario health care system. This birth cohort includes 602,945 children born in Ontario between 1992 and 1996, linked to maternal health records, and followed to age 25-30 years within the databases to identify incident cases of non-affective psychotic disorder. We used longitudinal latent class modelling to identify neighbourhood-level income trajectories from birth to age 12. We used modified Poisson regression models to estimate the incidence rate ratios (IRR) and 95% confidence intervals (CI) for the association between childhood income trajectories and the incidence of psychotic disorder during adolescence and early adulthood. Estimates were adjusted for sex, birth year, rurality, neighbourhood ethnic diversity, maternal migrant status, maternal mental and substance use disorders, chronic physical conditions, and the presence of developmental disability.
**Results:** The longitudinal latent class models identified four distinct trajectories of neighbourhood-level income throughout childhood: (i) Stable Moderate/High Income (39.1% of sample), (ii) Upwardly Mobile (19.4% of sample), (iii) Downwardly Mobile (18.6% of sample), and (iv) Stable Low Income (22.9% of sample). The incidence rate ranged from 54.7 per 100,000 person-years in the stable moderate/high income group, to 93.2 per 100,000 person-years in the stable low-income group. The risk of psychotic disorder was elevated among all people who were exposed to low neighbourhood-level income during childhood and was highest among people who had stable low income throughout childhood (IRR =

1.59, 95%CI = 1.51-1.67), relative to those who had stable moderate/high income. Risk was also elevated in the other two income trajectories, with evidence of a decreasing trend across groups (Downwardly Mobile: IRR = 1.43, 95%CI = 1.36-1.50; Upwardly Mobile: IRR = 1.32, 95%CI = 1.25-1.39).
**Discussion:** Our findings suggest that exposure to any degree of low neighbourhood-level income during childhood is associated with an increased risk of psychotic disorder, with a larger magnitude of effect with increased persistence of exposure. Further research on factors that mitigate the adverse effects of socioeconomic deprivation on psychosis risk could help to identify targets for primary prevention.

## 46. Inequities in Mortality Following Covid-19 Infection for People With Severe Mental Illness: A Nationwide Data Linkage Study From England

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**Background:** People with schizophrenia and bipolar disorders ("severe mental illness", SMI) experienced a higher risk of death following COVID-19 infection compared to people without SMI. It is less clear whether this risk reduced in later stages of the pandemic. We analyzed national electronic health record data from England to assess this for the first time. Our primary research question was: to what extent did all-cause mortality following a COVID-19 infection vary across different stages of the pandemic among SMI compared to non-SMI populations?

**Methods:** We accessed data in NHS England's Secure Data Environment, via the British Heart Foundation (BHF) CVD-COVID-UK/COVID-IMPACT Consortium, which contains de-identified linked records for over 58 million people across England who were registered in primary care practices as of November 2019. This innovative population level linkage includes national primary care records, hospital records, COVID-19 Testing and Vaccination records, and mortality records. This work was supported by the BHF Data Science Centre (BHF grant no. SP/19/3/34678), awarded to Health Data Research UK.
The study population included people with a COVID-19 infection recorded during the study period (30th January 2020-30th June 2023). SMI was defined by the presence of at least one diagnostic record in primary care or hospital records for schizophrenia, schizoaffective disorder, bipolar disorder or other non-organic psychosis prior to the pandemic. The non-SMI population were the comparator group.

People were followed up from the time of COVID-19 infection to the date of death or the end of the study period. Cox regression was used to estimate differences in all-cause mortality adjusting for age and sex. We stratified analyses by the pandemic stages: 30th Jan 2020-30th Sep 2020 (first stage); 1st Oct 2020-18th July 2021 (second stage); 19th July 2021-30th June 2023 (third stage – post vaccination roll-out and easing of restrictions).

**Results:** Our total sample consisted of 13,463,950 people who had COVID-19, out of whom 160,190 (1.19%) had SMI. A higher proportion of people with SMI had not received a complete course of COVID-19 vaccination by the end of the study period (20.6% compared to 12.8%). People with SMI had a higher risk of death compared to people without SMI

(HR=2.05, 95% CI 2.02-2.08). When stratified by stages of the pandemic, we observed a decline in survival probabilities, which was steeper among the SMI population during the first wave. The inequality in all-cause mortality experienced by the SMI population was greatest in the third stage, after the vaccination roll-out (first stage: HR=1.53, 95% CI 1.48-1.57; second stage: HR 1.91, 95% CI 1.86-1.95; third stage: HR=2.11, 95% CI=2.06-2.17).
**Discussion:** From this whole-country analyses of linked data from England, we found a two-fold increased risk of all-cause mortality following a COVID-19 infection among people with SMI throughout the pandemic. We observed that inequalities in mortality between people with SMI and the general population were most pronounced after the vaccination roll-out. Despite people with SMI being prioritized for vaccination, there was evidence of under-vaccination in this group, which may explain the growing gap in survival in the latter stage of the pandemic. A key strength of our study is that we used a national linked dataset including all registered patients in primary care during the pandemic, which enhances the generalizability of the findings. We had an extended follow-up period which enabled us to better understand longer-term trends. A limitation is that our study didn't measure covid-related mortality. The reasons for the variability in all-cause mortality trends across the pandemic waves requires further investigation.

## 47. The Effect of Cannabis Withdrawal on Psychosis Relapse and Admission to Psychiatric Intensive Care

Edward Chesney*[1], Dominic Oliver[2], Edoardo Spinazzola[1], Aliyah Malik[1], Hitesh Shetty[3], Thomas Reilly[2], Samuel Atkinson[3], Yasamine Farahani-Englefield[3], Fraser Scott[3], Amelia Jewell[1], Diego Quattrone[1], Robin Murray[1], Marta Di Forti[1], Philip McGuire[2]

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**Background:** Cannabis use is common in people with psychosis and is associated with poor outcomes. Cessation of heavy use can lead to the development of cannabis withdrawal syndrome (CWS), which includes symptoms such as irritability, aggression, agitation, and insomnia. It typically peaks after 3-5 days and can be more severe in women.
The objective of Study 1 is to compare patients with first-episode psychosis (FEP) whose onset of acute illness was attributed to CWS with two control groups: i) FEP heavy cannabis users without a history of CWS, and ii) FEP non-cannabis users.

The objective of Study 2 is to assess whether cannabis use prior to psychiatric hospital admission increases the risk of transfer to psychiatric intensive care (PICU) during the peak of CWS (days 3-5). This hypothesis was pre-registered.

**Methods:** Study 1: We used a large database of psychiatric healthcare records from South London, UK, for a nested case-control study. CWS-associated FEP cases were identified following the methods used in Chesney et al. (BJPsych 2025). Controls were matched on age, gender, and ethnicity. All data were extracted from case notes by psychiatrists. The effect of cannabis use during recovery on the risk of relapse was assessed using Cox proportional hazard models.
Study 2: The same database was used to identify inpatient admissions between January 2008 and December 2023. Cannabis use status was determined via Natural Language Processing and case notes review. Multivariable logistic regression models, adjusting for age, gender, ethnicity, diagnosis, tobacco use, stimulant use, and co-morbid alcohol or substance use

disorder, were used to investigate the effect of cannabis use prior to admission on two outcomes: i) risk of admission to PICU at any timepoint; and ii) the risk of transfer to PICU on days 3-5 after admission.

**Results:** Study 1: Sixty CWS-associated FEP cases were matched with 60 heavy cannabis users and 60 non-users. No differences were found in demographics, clinical characteristics, or psychosis symptoms at illness onset. There were no differences in the frequency or amount of cannabis use across the two cannabis user groups. The CWS group reported significantly more cannabis withdrawal symptoms ($p < 0.001$) and severe sleep impairment ($p < 0.001$) than the other groups.
Over three years, relapse risk was similar across the three groups (p=0.48). However, cannabis use during recovery increased the risk of relapse in the CWS group (HR=19.4 [95% CI: 2.6–144.1], p=0.004) but not in the heavy cannabis user group (HR=2.3 [95% CI: 0.8–6.6], p=0.13).

Study 2: Out of 52,088 admissions, 4,691 (9.0%) involved PICU. Cannabis use increased the risk of PICU admission at any timepoint (adjusted odds ratio [aOR]=1.4 [95% CI: 1.3–1.6], $p < 0.0001$).

Among the 1,325 patients who were transferred to PICU after initial admission to a general ward, more cannabis users (31.0%) than non-users (24.0%) were transferred on days 3-5 (aOR=1.4 [95% CI: 1.1–1.8], p=0.008). Risk was elevated in women (aOR=2.0 [95% CI: 1.2–3.4], p=0.007) but not men (aOR=1.1 [95% CI: 0.8–1.6], p=0.60) and in those older than 35 years (aOR=2.5 [95% CI: 1.5–4.2], p=0.0004) but not those younger than 35 years (aOR=1.0 [95% CI: 0.7–1.4], p=0.91).

**Discussion:** FEP patients with a history of CWS may be particularly vulnerable to the effects of ongoing cannabis use during recovery. CWS may also affect inpatients, as the risk of PICU transfer is heightened during days 3-5, coinciding with the peak of CWS severity. Interventions for cannabis use in people with FEP may be more effective if they target those with a history of CWS. Clinicians should recognize CWS in both outpatient and inpatient settings and offer interventions to alleviate withdrawal symptoms. Future studies should prospectively assess the prevalence of CWS in FEP and examine sex- and age-specific effects.

## 48. The Effects of Immigration Policies on Psychosis Outcomes in Minoritized Racial Groups in the UK

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**Background:** In 2014, the UK Government introduced a series of immigration policy changes collectively known as the hostile environment policy, which ultimately led to the Windrush scandal whereby people who migrated to the UK after the Second World War in return for Citizenship were illegally targeted for deportation. We investigated the impact of

this policy on psychosis outcomes in minoritized ethnic groups. We hypothesised that following the Immigration Act 2014 and the media coverage of the Windrush Scandal in 2017, psychosis outcomes would be poorer for individuals from Black Caribbean Background:s, who were disproportionately targeted by these policies, compared with those from White ethnic Background:s.
**Methods:** We used electronic health record data from an inner-London inpatient and community mental health service (Camden and Islington NHS Foundation Trust) to assess rates of treated first episode psychosis, psychosis inpatient admissions, accident and emergency referrals to psychosis services and involuntary detentions for people with psychosis between 2011-March 2020. We performed a Bayesian interrupted time series, accounting for fixed effects of confounders (age, sex, deprivation) and random effects for residual spatial and temporal variation. We compared rate ratios (RR) and 95% credible intervals (CrI) by minoritized ethnic group (Black African, Black Caribbean, Black Other, Asian Other, South Asian, Other, White Other) relative to people of White British ethnicity during three time periods: before the Immigration Act 2014, after the Act, and after the start of the Windrush scandal media coverage in 2017.
**Results:** We included 6102 participants treated for psychosis, with a median age of 41.5 years (IQR 31.6-50.6), including 2533 (41.5%) female participants. Sixty-eight percent of the cohort were from a minoritized ethnic group, including 502 (8.2%) Black Caribbean participants. People from Black Caribbean backgrounds had higher rates of A and E referrals to psychosis services after the 2017 media coverage (RR 3.36 [CrI 1.24 to 9.11]). We did not observe effects for other outcomes, minoritized ethnic groups or with implementation of the Immigration Act 2014.
**Discussion:** Our finding that media coverage of the Windrush Scandal increased rates of emergency department contacts for people with psychosis from Black Caribbean backgrounds suggests that acute exposure to political violence can exacerbate mental health crises which bypasses standard care pathways resulting in emergency service presentation. This has implications for both policy and media guidelines in minimising avoidable harms for people from minoritized ethnic backgrounds.

## 49. Comparison of Psychosis and Healthy Groups on Retrospective Bullying Reports

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**Background:** Individuals with psychotic disorders likely vary in their disease etiologies in terms of mixes of genetic and environmental factors. The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study identified three Biotypes among people with psychotic disorders (PWP) based on neurobiological measures. Briefly, Biotypes 1 and 2 show cognitive impairment and altered intrinsic neural activity, while Biotype 3 is largely similar to healthy individuals (HI). Whether these groups are defined by common etiological factors remains to be established. A prior analysis suggested Biotype 3 was uniquely associated with exposures to environmental risk factors for psychopathology including childhood abuse and neglect, early substance use, and their relation to symptoms. Being bullied in childhood has been identified as a psychosis risk factor, but remains to be

examined among the B-SNIP Biotypes. We predicted worse bullying experiences would be associated with Biotype 3.

**Methods:** Data was collected from subjects at the University of Chicago site of the B-SNIP2 study, which included individuals diagnosed with schizophrenia, schizoaffective, and bipolar disorder with psychotic features, as well as healthy individuals. Participants were administered a battery of neurocognitive tests used to calculate Biotype. They also completed the self-report Retrospective Bullying Questionnaire (RBQ) which asked about three types of bullying (physical, verbal, or indirect), its severity and frequency, and assessed these elements separately for primary and secondary school. They also completed the Childhood Trauma Questionnaire (CTQ) to assess abuse and neglect and were administered the Positive and Negative Syndrome Scales (PANSS) for current symptom severity. The plan of analysis was to assess correlations between the RBQ measures and the CTQ to characterize their relationship. Next, we planned to compare the whole PWP group to the HI group on the RBQ measures, and then to compare the psychosis Biotypes to one another, using ANOVAs and follow-up pairwise comparisons. Finally, we compared strength of correlation of RBQ with 1) age of symptom onset, and 2) PANSS scores between the Biotype groups.

**Results:** Data was available from 227 PWP (Biotypes 1, 2, 3 n's = 73, 50, 104, respectively) and 57 HI. Groups were matched on sex and age. For PWP and HI combined, CTQ total score correlated rho = 0.343 with bullying frequency ($p < .001$) and rho = 0.374 for bullying severity ($p < .001$). The total PWP group endorsed more bullying than HI on all measures (bullying types experienced, severity, frequency for both primary and secondary school; p's < 0.001). Biotype 2 endorsed higher severity of bullying compared to Biotype 3 ($p = 0.041$) and compared to Biotype 1 at a trend level ($p = 0.097$). There were no significant differences between Biotypes for number of bullying types experienced or bullying frequency. Across PWP, there was a negative correlation between age of symptom onset and bullying frequency (rho = -0.174, $p = .009$), bullying severity (rho = -0.149, $p = .027$), and, at a trend level, number of bullying types experienced (rho = -0.140, $p = .065$). While Biotype 2 reported a significantly later age of symptom onset (mean age 19.6) than Biotype 1 (age 16.5, $p = .02$) and Biotype 3 (age 16.1, $p = .006$), Biotypes did not differ on correlations between symptom onset and any bullying measure. Similarly, there were no significant differences between Biotypes for their correlations of the bullying measures to PANSS scores, which were generally low and non-significant.

**Discussion:** The psychosis sample as a whole reported worse experiences with bullying in each approach to measuring it compared to healthy individuals, as expected. Hence, our study is consistent with the hypothesis of experiences of being bullying in childhood as a possible contributing factor leading to psychosis. The whole psychosis sample also showed an association between earlier symptom onset with more/worse bullying experiences. This raises questions about possible interaction of being bullied and prodromal signs of illness or early symptoms. The moderate correlation of RBQ measures with the CTQ total score suggests the RBQ captured at least some unique information about adverse childhood experiences but also confirms some expected overlap. Even so, contrary to expectation, Biotype 2 rather than Biotype 3 was the only Biotype group distinguished by more severe bullying experiences. Further investigation is needed to determine whether the Biotype 2 finding can be replicated and whether it has any implication for understanding the illness. Future work will include further assessment of the association of bullying to additional environmental risk factors for psychosis to continue to gain insight into their contribution to illness etiology as well as any potential unique contribution to particular psychosis subgroups.

## 50. Associations of Cognitive Impairment With Increased Mortality in People With Schizophrenia: A Linked Insurance Claims and Electronic Health Record Study

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**Background:** People with schizophrenia have reduced life expectancy versus the general population, which may be partly due to higher rates of cardiovascular (CV) disease. Cognitive impairment associated with schizophrenia (CIAS) contributes to a substantial impairment in functioning. However, little is known regarding the degree to which CIAS may be associated with mortality in people with schizophrenia, with previous studies being conducted in relatively small populations. The lack of a standardized diagnostic code for CIAS makes identifying CIAS in insurance claims datasets difficult. Combining claims data with data from electronic health records (EHRs) may enable better ascertainment of CIAS. Here, we identified the presence of CIAS in a linked claims and EHR dataset and its relationship with all-cause mortality (ACM) and CV-related mortality (CVM).
**Methods:** This non-interventional retrospective cohort study used de-identified real-world data from US-based linked administrative claims and EHRs in the Optum Market Clarity database. Adult patients were included if they had ≥2 schizophrenia diagnosis claims during the study period (Oct 1, 2016 to Mar 31, 2022) and ≥1 year of continuous enrollment during the baseline period (12 months prior to index date [first schizophrenia diagnosis]). CIAS was defined using structured codes recorded in claims and natural language processing-derived clinical features from EHRs recorded within 90 days of the index date. ACM data were ascertained from the claims-linked social security master file or the discharge status of inpatients' EHR. CVM was defined as having a CV diagnosis code within 14 days of the date of death. Associations of CIAS with ACM or CVM were assessed using a Cox proportional hazard model adjusted for relevant baseline demographics and clinical characteristics.
**Results:** In total, 98,081 patients were included, of whom 10,237 (10.4%) had CIAS. Most patients were male (CIAS: 61.7%; non-CIAS: 63.3%) and mean (SD) age was similar (CIAS: 51.3 [15.8] years; non-CIAS: 50.4 [14.8] years). Mean (SD) duration of follow-up among patients with and without CIAS was 4.11 (1.54) and 4.12 (1.46) person years, respectively. Overall, 9505 patients died during the study (CIAS: 1356 [13.2%]; non-CIAS: 8149 [9.3%]). The number of patients with CVM was 586 (5.7%) in the CIAS group and 3129 (3.6%) in the non-CIAS group. Among patients with CIAS, ACM rate per 100 people years was 3.23 (95% confidence interval [CI]: 3.06, 3.40) versus 2.25 (2.21, 2.30) in the non-CIAS group. Among patients with CIAS, CVM rate per 100 people years was 1.39 (1.29, 1.51) versus 0.87 (0.84, 0.9) in the non-CIAS group. Cox regression analysis showed that CIAS was associated with significantly greater ACM risk (crude hazard ratio [cHR; 95% CI]: 1.43 [1.35, 1.51]; adjusted HR [aHR]: 1.13 [1.06, 1.20]), and greater CVM (cHR: 1.61 [1.47, 1.76]; aHR: 1.20 [1.10, 1.32]) versus patients in the non-CIAS group.

Baseline demographics and comorbidities associated with increased risk of ACM or CVM included Caucasian or Black race, age, male sex, being uninsured (ACM only), and having comorbid metastatic cancer or congestive heart failure.

**Discussion:** Using linked claims and EHR data enabled ascertainment of CIAS and associations with mortality in a larger sample size than previous studies. A substantial

number of patients with schizophrenia had CIAS recorded; nevertheless, CIAS is likely to have been underreported. CIAS was associated with greater ACM and CVM rates independent of other known risk factors. This study highlights the importance of CIAS and the need to develop and deliver effective treatments to improve clinical outcomes of people with schizophrenia.

Funding: Boehringer Ingelheim

## 51. Development and Evaluation of a Cognitive Battery for People With Schizophrenia in Ethiopia

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**Background:** Cognitive difficulties significantly burdened people with schizophrenia (PWS). However, cognitive assessment is often unavailable in low- and middle-income counties (LAMICs) due to a lack of validated and culturally adapted cognitive assessment tools.
**Methods:** This study was conducted in three phases. First, we selected appropriate tests through a four-step instrument selection procedure and created a new battery. Then, we rigorously adapted the tests using culturally competent procedures, including cognitive interviewing among 15 purposively selected PWS followed by expert meetings. Finally, we tested the new battery in 208 PWS and 208 controls. We evaluated its psychometric properties using advanced statistical techniques, including Item Response Theory (IRT).
**Results:** The Ethiopian Cognitive Assessment battery for Schizophrenia (ECAS) was developed from three different batteries. The ECAS includes seven tests to address six cognitive domains. The ECAS took an average of 35 minutes for administration. Participants reported that the tests were easy to complete, and the raters found them easy to administer. All tests had good inter-rater reliability, and the composite score had very high test-retest reliability (ICC = 0.91). One-factor structure better represented the data with excellent internal consistency ($\alpha = 0.81$). ECAS significantly differentiated PWS from controls with 77% sensitivity and 62% specificity at a Z-score $\leq 0.12$ cut-off value. Item Response Theory (IRT) analysis suggested that the battery functions best among moderately impaired participants (difficulty between -0.06 and 0.66).
**Discussion:** ECAS is a practical, tolerable, reliable, and valid assessment of cognition. ECAS can supplement current assessment tools in LAMICs for PWS and can be used to measure cognitive intervention outcomes.

## 52. Childhood Emotional and Physical Bullying in Psychotic Disorders

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**Background:** Childhood trauma is a well-established risk factor for psychosis. However, peer bullying, whether emotional or physical, has received relatively less attention than childhood trauma perpetrated by caregivers and other adults. While nearly 30% of all children report a lifetime experience of bullying, the rates of bullying victimization are substantially higher among individuals with psychosis. Identification of developmental periods most sensitive to the effects of bullying is critical to understanding the effects of

bullying on psychosis risk. However, few studies have evaluated the ages of exposure to bullying victimization among people with psychotic disorders, and none have examined how the timing of exposure to peer bullying compares in affective and non-affective psychosis patients.

**Methods:** In this survey study, 46 participants with schizophrenia (SZ), 53 participants with bipolar disorder with psychotic features (BD), and 51 healthy control participants (HC) completed the Maltreatment and Abuse Chronology of Exposures (MACE) questionnaire, developed by Teicher and Parigger (2015). The MACE is a 52-item self-report questionnaire that assesses exposure (yes/no) to ten different categories of adverse childhood events and additionally asks participants to specify the ages (1-18 years) at which they were exposed to those events. For this study, we focused on the two MACE categories which focus on childhood bullying: "peer emotional abuse" (items 26-30) and "peer physical abuse" (items 31-35). First, using chi-squared tests, we tested the null hypothesis of no difference in the proportion of individuals reporting each form of bullying across the three diagnostic groups. We categorized participants as having been bullied if they met the clinically significant thresholds (Teicher and Parriger, 2015) of reporting 4 or more items for peer emotional abuse and 2 or more items for peer physical abuse. Next, we summed the number of endorsed bullying items to compute a childhood bullying severity score (range 0-5 for each category) and tested the effects of bullying timing and diagnosis on emotional and physical bullying severity. For these analyses involving participants' chronology of bullying exposure, we used multilevel mixed-effects models with a 3-knot cubic spline function, adjusted for age, sex, and education level. We excluded data from ages 1-3 years due to the higher likelihood of reporting bias for events in the earliest years of life.

**Results:** We found significant between-group differences in the proportion of individuals who reported clinically significant emotional bullying ($X2=10.943$, $p=.004$) and clinically significant physical bullying ($X2=14.404$, $p=0.001$). Post-hoc analyses showed that a significantly higher proportion of both SZ (34.8%) and BD (28.3%) patients, compared to HC (7.8%), reported clinically significant childhood emotional bullying (X2 SZvsHC=10.720, $p=0.001$; X2 BDvsHC=7.286, $p=0.007$); SZ and BD did not differ (X2 SZvsBD=0.481, $p=0.488$). Similarly, a significantly higher proportion of both SZ (30.4%) and BD (18.9%) patients reported clinically significant childhood physical bullying compared to those in the HC group (2.0%) (X2 SZvsHC=15.000, $p=0.0001$; X2 BDvsHC=7.855, $p=0.005$); again, SZ and BD did not differ in their reports of exposure to physical bullying in childhood (X2 SZvsBD=1.794, $p=0.180$).

In the mixed effects model for childhood emotional bullying, there was a main effect of bullying timing ($\beta$ ages 6-11=0.064, $p < 0.0001$, $\beta$ ages 12-17=-0.080, $p < 0.0001$) as well as timing x diagnosis interactions for both SZ ($\beta$ ages 6-11=0.096, $p < 0.0001$, $\beta$ ages 12-17=-0.079, $p < 0.009$) and BD ($\beta$ ages 6-11=0.096, $p < 0.0001$; $\beta$ ages 12-17=-0.074, $p < 0.012$) on the emotional bullying severity score. In the mixed effects model for childhood physical bullying, there was a main effect of bullying timing ($\beta$ ages 6-11=0.020, $p < 0.032$, $\beta$ ages 12-17=-0.037, $p < 0.002$) on the physical bullying severity score, and a timing x diagnosis interaction only for SZ ($\beta$ ages 6-11=0.046, $p < 0.019$). Graphic visualization shows both childhood emotional and physical bullying severity peaking near ages 11-12 years.

**Discussion:** Both SZ and BD patients reported clinically significant childhood emotional and physical bullying at higher rates than healthy control participants. Both SZ and BD participants, relative to healthy control participants, reported greater severity of childhood emotional bullying throughout childhood, and especially around ages 11-12. For childhood physical bullying, only SZ participants (but not BD participants) reported significantly higher

severity of childhood physical bullying in early childhood. While the Results: from this survey study are limited in their ability to infer causality, they suggest the need for carefully timed interventions to minimize exposure to bullying in the early teenage years as an approach to reducing risk for psychosis.

**Oral Session: Neural and Molecular Mechanisms**

### 53. Associations Between Self-Reported Cannabis Use and Brain Glutamate in Young Patients With Psychosis: A 7t MRI Study

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**Background:** Accumulating evidence supports an association between cannabis use and psychosis. Notably, frequent cannabis use during adolescence is associated with subclinical positive and negative symptoms and predicts the onset of psychotic disorders in adulthood. Similarly, longitudinal studies report an increased likelihood for developing schizophrenia and other non-affective psychoses after cannabis use. Despite these findings, the mechanisms underlying the relationship between cannabis use and psychosis remain incompletely understood. Hypofunction in glutamate transmission has been hypothesized as a primary contributor to dopamine abnormalities in schizophrenia, and recent work suggests alterations in glutamatergic metabolites across various brain regions in individuals with schizophrenia. Similarly, sustained cannabis use has been shown to reduce glutamate signaling in both pre-clinical models and studies in humans through its action on cannabinoid receptors. Here we measure the relationship between self-reported cannabis use and glutamate levels in young psychosis (PSY) patients using 7T proton magnetic resonance spectroscopy (1HMRS).
**Methods:** Participants included 31 Typically Developing (TD; mean age =23) and 21 patients with DSM diagnosis of a psychotic disorder (mean age = 25). Cannabis use was measured using the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory. 1HMRS data was acquired using a 7T Siemens Terra scanner. Data was acquired in an ROI covering the anterior cingulate (FOV: 10x5x5mm).
**Results:** More PSY individuals reported use of cannabis (71%) as compared to TD (46%). Age of first use was marginally younger in PSY (16.2 +/- 3.2 years) individuals ($p=0.09$) than TD (18.0 +/- 2.3). Anterior cingulate glutamate (Glu; $p < 0.005$) levels were lower in PSY cannabis users (13.2 +/- 1.8) as compared to TD cannabis users (15.5 +/- 2.0). Glutamine levels were also lower in PSY cannabis users ($p=0.05$) when compared to TD cannabis users. PSY non-users had marginally higher Glu levels (15.1 =/- 1.3) as compared to PSY cannabis users ($p=0.09$).
**Discussion:** We report that psychosis patients are more likely to use cannabis and that brain glutamate levels are lower in psychosis patients that use cannabis when compared to patients who do not use cannabis and typically developing individuals. Future longitudinal studies that monitor cannabis usage and glutamatergic levels are needed to better elucidate this relationship.

### 54. Differentiating Schizophrenia's Negative Symptoms From Comorbid Depression Through Acoustic Analysis

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**Background:** Accurately differentiating negative symptoms like blunted affect in schizophrenia from comorbid depressive symptoms is vital for precise prognostic assessment of suicidal risk and tailoring treatment, including the selection of antidepressants or antipsychotics. Traditional diagnostic Methods: often rely on subjective clinical judgment, highlighting the need for more objective approaches. This study explores the potential of acoustic speech analysis as a tool to distinguish between blunted affect and depression. We introduce novel deep learning techniques that visualize speech as spectrograms, preserving acoustic and temporal features, and utilize convolutional neural networks for classification. This method is applied to detect blunted affect in schizophrenia-spectrum disorders (SSD) and distinguish these from depressive symptoms.
**Methods:** Speech samples from the DISCOURSE protocol were collected from 319 participants, including 227 individuals with SSD (ranging from medication-naive to over 10 years post-diagnosis) and 92 matched healthy controls. Speech from structured interviews was segmented into 10-second intervals and converted into log-mel spectrograms, resulting in a dataset of 110,246 spectrograms—59,562 for the within-SSD model. SSD participants were categorized by blunted affect severity (N1 symptom) using PANSS scores of ≤3 or ≥4. Data were divided into training (70%), validation (15%), and testing (15%) sets, training the ResNet-18 convolutional neural network to classify SSD, HC, and blunted affect presence. Only testing set performance is reported.
**Results:** The diagnostic model achieved 87.83% accuracy and an AUC of 0.8651 in distinguishing SSD from healthy controls using log-mel spectrograms. For blunted affect, the classifier achieved 87.84% accuracy and an AUC of 0.7856. Notably, the diagnostic classifier failed to identify the severity of blunted affect (AUC = 0.4954), while the blunted affect model failed to identify the severity of depression (AUC = 0.5144), indicating both the sensitivity and the specificity of voice markers in identifying the negative syndrome.
**Discussion:** These findings demonstrate that convolutional neural networks using acoustic spectrograms can effectively classify SSD from HC and assess symptom severity, offering a promising method for distinguishing negative symptoms from comorbid depression. The model's specificity suggests distinct acoustic features in blunted affect. This approach could enhance the objectivity of clinical assessments. Future research should focus on identifying key acoustic features, refining models for depressive symptoms, and extending this method to other psychiatric conditions.

## 55. Effects of Trauma History on Mood and Motivation in Schizophrenia: Possible Neural and Behavioral Mechanisms

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**Background:** Adverse childhood events (ACEs) have been linked to both increased risk of being diagnosed with a mood or psychotic disorder and increased severity of psychopathology related to mood and psychotic disorders. Importantly, the effects of acute stressors on psychopathology are compounded by the experience of ACEs. We hypothesized that ACEs impact mood and motivation in people diagnosed with schizophrenia or

schizoaffective disorder (PSZ) by altering mechanisms of learning in neural circuits for stress reactivity, reward processing, and salience signaling.
**Methods:** Fifty-eight PSZ (mean age = 39.3) and 37 healthy volunteers (HV; mean age = 42.2) performed a 3-choice probabilistic reversal learning (PRL) task, in conjunction with fMRI scanning, once after being administered an acute stressor (the Socially-evaluated Cold Pressor Task/SECPT), and once after not being stressed. Behavioral choice data were aggregated resulting in the following variables of interest: (1) correct responses indicating choosing the currently best option, (2) achieved reversal stages, (3) lose-shift behavior indicating switching cards following a loss, and (4) win-stay behavior indicating repeating the same choice following a reward. For computational analyses of trial-by-trial choice data, we: 1) compared three learning models with different formulations of learning rates, to determine which explained the data best, and 2) concatenated trials for both task sessions, on a subject-wise basis, and tested whether learning and/or choice parameters from the best-fitting model differed between conditions. Participants also completed measures of general psychopathology, including positive symptoms (Brief Psychiatric Rating Scale/BPRS), negative symptoms (Clinical Assessment Interview for Negative Symptoms/CAINS), depression (Calgary Depression Rating Scale/CDS and Beck Depression Inventory/BDI), and ACEs (28-item Childhood Trauma Questionnaire/CTQ).
**Results:** Comparing model families revealed that the Hierarchical Gaussian Filter model family explained the data best [XP(HGF)=0.74]. A MANOVA revealed main effects of group on two free parameters: 1) the step-size update parameter omega-2 [$F(1,75)=4.6$, $p=0.035$] and 2) beta-loss [$F(1,75)=5.7$, $p=0.019$], with patients showing higher parameter values, relative to HV, in both cases. Model-free analyses revealed a main effect of Group on win-stay behavior [$F(1,75)=7.3$, $p=0.008$], as well as a Group x Condition interaction ($F=6.6$, $p=0.012$), such that PSZ showed reduced overall win-stay behavior, relative to HV, and reduced win-stay behavior in the stress condition, relative to the control condition [$t(47)=2.7$, $p=0.011$]. While there were no significant main effects of Group or Condition on percent correct responses or achieved stages, nor a Group or Condition interaction (all p's $> 0.11$), PRL performance scores in PSZ associated with both CTQ Physical Abuse scores ($r= 0.334$) and Total BDI scores ($r=-0.341$), suggesting a potential mediating role for reinforcement learning. Furthermore, analyses fMRI data revealed that BOLD responses within the salience network (medial prefrontal cortex, striatum, and insula) tracked the magnitudes of precision-weighted prediction errors (PEs) across conditions and subjects, at p(FWE for the whole brain) $< 0.05$. We observed only weak main effects of the acute stressor on the precision-weighted PE signal across all subjects (left posterior cingulate cortex: $F=15.6$, $p < 0.001$ uncorrected; right putamen: $F=12.5$, $p < 0.001$). In volumes-of-interest, however, we observed a between-group difference (HV > PSZ) in responses to PEs in right [$F=12.48$, $p=0.015$] and left [$F=5.53$, $p=0.02$] ventral striatal (VS; small volume corrected). Furthermore, responses to PEs in the VS associated with both CTQ Neglect scores ($r=-0.444$) and CAINS Motivation and Pleasure scores ($r=-0.343$), suggesting a potential mediating role for PE signaling in relating childhood neglect to schizophrenia negative symptoms.
**Discussion:** This study provides evidence that effects of trauma on brain circuits for reward processing and salience signaling impact learning and clinical symptoms in PSZ. Further research is required to elucidate the mechanisms by which trauma-induced alterations of specific neural circuits bring about depressive and negative symptoms in schizophrenia.

## 56. The Retina Across the Psychiatric Spectrum: A Systematic Review and Meta-Analysis

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**Background:** The identification of structural retinal layer differences between patients diagnosed with certain psychiatric disorders and healthy controls has provided a potentially promising route to the identification of biomarkers for these disorders. Optical coherence tomography has been used to study whether retinal structural differences exist in schizophrenia spectrum disorders (SSD), bipolar disorder (BPD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and alcohol and opiate use disorders. However, there is considerable variation in the amount of available evidence relating to each disorder and heterogeneity in the results obtained.
**Methods:** We conducted the first systematic review and meta-analysis of evidence across all psychiatric disorders for which data was available. The quality of the evidence was graded, and key confounding variables were accounted for. Of 381 screened articles, 87 were included.
**Results:** Meta-analyses revealed that compared to healthy controls, the peripapillary retinal nerve fiber layer (pRNFL) was significantly thinner in SSD (SMD = -0.32; $p < 0.001$), BPD (SMD = -0.4; $p < 0.001$), OCD (SMD = -0.26; $p=0.041$), and ADHD (SMD = -0.48; $p=0.033$). Macular thickness was only significantly less in SSD (SMD = -0.59; $p < 0.001$). pRNFL quadrant analyses revealed that reduced pRNFL thickness in SSD and BPD was most prominent in the superior and inferior quadrants. Macular subfield analyses indicated that BPD may have region-specific effects on retinal thickness.
**Discussion:** In conclusion, these findings suggest substantial retinal differences in SSD and BPD, reinforcing their potential as biomarkers in clinical settings.

## 57. Differential Network Patterns Underlie Heterogeneity in Negative Symptoms Treatment Response: Evidence From the Roluperidone Phase 3 Trial

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**Background:** Negative symptoms contribute to significant psychosocial impairment in people with schizophrenia and the development of treatment approaches remains a critical need. A network perspective suggests interactive causal effects among negative symptoms and indicators of disability and the changing or manipulation of networks in successful treatment. Roluperidone is a novel cyclic amide derivative with primary antagonistic properties for 5-hydroxytryptamine 2A (5-HT2A) and sigma-2 receptors and added affinity for α1A-adrenergic receptors. Two major clinical trials support the efficacy of Roluperidone at improving negative symptoms and social functioning. However, there is also evidence of remarkable heterogeneity in treatment response. The current study attempts to elucidate the heterogeneity of response to roluperidone by using 1) latent variable mixture modeling to identify trajectories of treatment response over the 12-week trials; and 2) network analysis to describe the network properties in patient groups that differ in their treatment response.
**Methods:** In the 2 RCTs, participants with predominantly negative symptoms were randomized to receive in 1:1:1 ratio either roluperidone 32 mg/day, roluperidone 64 mg/day, or placebo for 12 weeks. In Phase 2b (N=244), participants were recruited from 36 sites and 6

European countries. The Phase 3 trial (N=513) recruited from 60 sites and 8 countries including the United States. Both trials assessed negative symptoms using the Positive and Negative Syndrome Scale (PANSS) and social functioning with the Personal and Social Performance (PSP) scale. Assessments were completed at baseline, Week 2, Week 4, Week 8, and Week 12 (endpoint). Growth Mixture Models were fitted to the data sequentially beginning by identifying the model of change (intercept only, linear, quadratic) that best fit the data. Next, the number of non-arbitrary subgroups that differed in their change trajectory over the 12-week trial was determined by fitting two to four latent classes to the data. Third, a series of network comparison tests at each study visit in roluperidone versus placebo samples.
**Results:** Growth mixture modeling favored a two-class quadratic growth model with class varying intercepts and slopes for both negative symptoms and functioning. This suggests two trajectories of clinical response in the clinical trial. For negative symptoms, the first trajectory of fast responders (class 1 = 23.8%) was characterized by rapid and steep response to treatment that threshold at around week 8. The second trajectory (class 2=76.2%) comprised slow responders who showed steady reduction in negative symptoms through week 12. The roluperidone 64 mg (37%) and 32 mg (24%) groups had greater odds off belonging to Class 1 than the placebo group (10.8%) [$\chi 2$ (2, 496) = 31.28, $\varphi$=0.251, $p < 0.0001$]. Pairwise comparison between each roluperidone group and the placebo group was significant [MIN-101 32mg vs. Placebo Odds Ratio (OR) = 2.61 (95% CI: 1.42-4.77), $p < 0.002$] and [MIN-101 64mg vs. Placebo OR = 4.87 (95% CI: 2.72-8.73), $p < 0.0001$)]. The social functioning data similarly identified a small subgroup of fast responders (class 1=8.69%) and gradual responders (91.31%). The roluperidone 64 mg group had the greatest odds of belonging in Class 1 (14.81%) followed by the 32mg group (6.63%) both > the placebo group (4.79%) [$\chi 2$ (2, 495)=11.75, Phi=0.151, $p < 0.01$)]. Pairwise comparison between each roluperidone group and the placebo group was significant [(MIN-101 32mg vs. Placebo Odds Ratio (OR) = 1.41 (95% CI: 0.55-3.60), p =0.047 and MIN-101 64mg vs. Placebo OR = 3.46 (95% CI: 1.50-7.94), $p < 0.001$)]. At baseline, PANSS items N2, G16, and N3 were the most strongly associated with social functioning, with N2 and G16 indicators of avolition factor of the PANSS. Changes in items N2 and N4 of the avolition factor and N3 were most associated with change in social function.
Out Strength indicates which symptoms exert the most influence on other symptoms. Hypothetically, this is the most viable treatment target because it is likely to have downstream effects on other symptoms if intervened upon. In this trial, Passive social withdrawal had the strongest outstrength in the gradual responders (Class 2). Poor rapport had the strongest outstrength in the fast responders (Class 1). Overall, in the 64mg networks, Class 1 had greater strength centrality values for N2 emotional withdrawal.

**Discussion:** Treatment response has traditionally been depicted using a priori cutoffs such as percentage change, but this method ignores inter-individual heterogeneity in response. Roluperidone is associated with reductions in negative symptoms and improvements in social functioning. There are however distinct trajectories of change in roluperidone response when negative symptoms and social function are examined over the course of this Phase 3 clinical trial that reflect the impact of the compound and underlying inter-individual variability. Latent variable models are adaptable to studying repeated measures data when collected longitudinally at fixed time points.

## 58. Disorganized Inhibitory Dynamics in Hippocampal Area CA1 of 22q11.2 Deletion Mutant Mice

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**Background:** Individuals with the 22q11.2 deletion syndrome (22q11.2DS), one of the largest known genetic risk factors for schizophrenia, demonstrate cognitive impairments, including episodic memory (EM) dysfunction. Our group previously showed that EM and place cell stability in the hippocampus is impaired in a mouse model for the 22q11.2DS (Df(16)A+/-). Place cells are under strong inhibitory control by heterogeneous subtypes of GABAergic interneurons, several of which are implicated in the pathophysiology of schizophrenia. In this study, we examined the unique contributions of hippocampal interneuron subtypes to local microcircuit dysfunction in CA1.
**Methods:** Wild-type and Df(16)A+/- mice performed a spatial navigation task on a cued belt while undergoing large-scale, unbiased 3D GCaMP-Ca2+ imaging of in vivo CA1 interneuron dynamics. Molecular identification of interneuron subtypes was performed post-hoc with immunohistochemistry. Interneuron subtype-specific activity was assessed through Pearson cross-correlations with velocity, peristimulus time histograms around behavioral indicators, spatial bin occupancy, and a linear classifier support vector machine to decode position.
**Results:** We found that multiple interneuron types exhibit aberrant responses to rewarded locations and delayed reward enrichment extinction. Df(16)A+/- inhibitory interneurons also carry markedly reduced spatial information in a subtype-dependent manner. We observed task-dependent changes in the correlation structure and coactivity among multiple GABAergic subtypes, suggesting a broadly disorganized microcircuit functionality in mutant mice.
**Discussion:** Overall, we identify widespread and heterogeneous subtype-specific alterations in interneuron dynamics during spatial reward learning, reflecting impaired flexibility and organization in CA1 inhibitory microcircuits. Our study provides critical insights into how schizophrenia-risk mutations affect local-circuit interactions among diverse cell types in the mouse hippocampus during learning and spatial navigation.

## 59. The Genetic Architecture of Human Cortical Networks is Aligned With Dual Origins, Coupled With Brain Function and Associated With Risk of Schizophrenia and Other Neuropsychiatric Disorders

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**Background:** The genetic architecture of human brain networks is central to understanding cortical organization, the causal relationships between brain structure and function, and the pathogenesis of neuropsychiatric disorders such as schizophrenia. However, our current understanding of genetic influences on brain network organization, and the implications for psychotic disorders, remains fragmented.
**Methods:** Here, we investigated common genetic effects on Morphometric INverse Divergence (MIND), a novel, biologically-validated tool to compute structural similarity between cortical areas based on the divergence between distributions of multiple MRI features. We estimated subject-specific MIND networks for N > 30,000 adults from the UK-

Biobank dataset and tested for genetic effects independently at each of 276 inter-areal edges. On this basis, we then addressed three linked questions concerning the genetic architecture of human cortical networks: 1) Are genetic effects on structural similarity networks systematically coordinated along gradients associated with the theoretically predicted origins of cortical evolution? 2) Is there correlative and causal genetic overlap between structural similarity and functional connectivity? And 3) how are the genetics of structural similarity networks related to the genetics of disorders such as schizophrenia, which putatively lie downstream of both structural similarity and functional connectivity phenotypes?
**Results:** We found that 54 independent genomic loci were significantly associated with at least one of the 276 MIND edges (at an experiment-wide threshold of $P < 1.8x10^{-10}$). Strong genetic correlations between multiple edges were largely reducible to two gradients of genetically-determined cortical similarity, each of which was aligned with geodesic distance from one of the two phylogenetically primitive areas (paleocortex and archicortex) predicted by the dual origin theory of cortical evolution. Genetic MIND gradients were more heritable than comparable gradients derived from functional MRI connectivity networks; and the paleocortical trend was genetically correlated with, and causally predictive of, functional connectivity.
Finally, we identified multiple global and local genetic correlations between both MIND gradients and 9 clinical diagnoses or biomedical traits, including schizophrenia and bipolar disorder, indicating that the normative genetic architecture of human brain networks is pleiotropically associated with risk of neuropsychiatric disorders. Follow-up Mendelian Randomization analysis provided some evidence for a causal effect of the paleocortical trend on schizophrenia (MR-APSS $\beta=0.037$, $P = 0.04$ uncorrected); with no evidence for a causal effect in the reverse direction or for the archicortical trend in either direction.

**Discussion:** Overall, we found strong evidence that the paleocortical and archicortical trends predicted by dual origin theory conform to the first two principal axes of genetically coordinated variation in the human cortical architectome. These two gradients of cortical similarity were distinctly related to the genetic architecture of brain functional networks and pleiotropically associated with neuropsychiatric disorders, including schizophrenia and bipolar disorder. Our results provide fresh insight into the dual origins of the human cortex and the implications for brain function and neuropsychiatric disorders.

## Oral Session: Neuroimaging and Neurophysiology

### 60. The Neurophysiological Basis of Violent Behaviour in Patients With Schizophrenia

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**Background:** Patients with schizophrenia are often more vulnerable to aggressive or violent behaviour induced by the adverse impact of their psychiatric symptoms, which may constitute a public health concern and stigmatization of patients. The specific brain functional and structural changes may be the most important physiological feature for the high incidence of violent behaviour in patients with schizophrenia compared with normal people. Comprehensively investigating brain features of violence in schizophrenia could help us understand its specific pathogenesis and find effective biomarkers. However, previous

findings are controversial. Our study aimed at identifying reliable brain changes associated with violence in patients with schizophrenia by conducting a meta-analysis and meta-regression of magnetic resonance imaging studies.
**Methods:** This study searched for studies on brain functional and structural changes in patients with both schizophrenia and a history of violence (VSCZ) on Web of Science, Medline and PubMed. The literature search for this study was conducted in accordance with the PRISMA guidelines. The search time was from the establishment of the database to July 1, 2024. After two researchers independently screened the literature, Seed-based d mapping (SDM, version 6.2.1, https://www.sdmproject.com) was used to perform meta-analysis, meta-regression and risk assessment of bias. A p-value threshold of $< 0.005$ with a cluster extent of 20 voxels was used.
**Results:** Brain functional and structural imaging meta-analysis finally included twenty and eight studies, respectively. The former results showed that compared with non-violence patients with schizophrenia, patients with VSCZ had increased regional homogeneity values in the right inferior frontal gyrus and the right superior temporal gyrus, and decreased regional homogeneity values in the right inferior occipital gyrus at resting-state, and had increased activation at the middle occipital gyrus and rectus when performing tasks. Subgroup analysis in five studies performing emotional tasks revealed that patients with VSCZ showed increased activation at the middle occipital gyrus compared with non-violent patients with schizophrenia. The latter results showed there was no significant difference of gray matter volume between patients with VSCZ and non-violence patients. Compared with controls, patients with VSCZ exhibited decreased gray matter volume in the insula, the superior temporal gyrus, the left inferior frontal gyrus, the left parahippocampus, and the right putamen. Compared with individuals with a history of violence only, patients with VSCZ exhibited decreased volume in the right insula and the right superior temporal gyrus. Meta-regression analysis revealed a negative correlation between the duration of schizophrenia and the volume of the right insula in patients with VSCZ.
**Discussion:** These findings indicated that changed brain regional synchrony of the frontal, temporal, and occipital gyri, as well as a hyper-activated middle occipital gyrus associated with abnormal emotion perception and regulation could be key neurophysiological correlates associated with increased risk of violence in patients with schizophrenia. Our findings could facilitate the comprehension of neuropathological mechanism underlying the interaction between schizophrenia symptoms and violence based on existing findings. Furthermore, they provide potential avenues for identifying effective neural markers to assess and predict violent behaviour and to develop targeted intervention.

## 61. Meg in Psychosis: Individual Differences in Neuronal Oscillations Underlying Language Disorganization and Impoverishment

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**Background:** Language disorganization and impoverishment are hallmark symptoms of schizophrenia, manifested as incoherent speech and reduced linguistic output. Schizophrenia is characterized by dysconnectivity in spatial and temporal neural dimensions, with aberrant oscillatory activity and connectivity in large-scale networks. However, the relationship between these neuronal alterations and communication deficits remains unclear. This project explores the hypothesis that neuronal dysfunction underlies language disorganization and

impoverishment by investigating associations between neuronal oscillations and language features derived via automated processing pipelines in individuals with and without psychosis.
**Methods:** This case-control study includes 25 patients with schizophrenia and 25 matched healthy controls. Participants completed 60 minutes of symptom and speech assessment, 60 minutes of Magnetoencephalography (MEG), and 60 minutes of Magnetic Resonance Imaging (MRI). MEG recordings were obtained during an audiovisual simultaneity judgment task and open-eye resting. MEG data were source-localized to each participant's normalized structural MRI, preprocessed, and epoched to motor responses and sensory stimuli to assess event-related power modulations. Speech data collected during interviews were analyzed for acoustic/linguistic features (e.g., prosody, tones, pauses, fluency) using Python.
**Results:** Preliminary analyses of 16 controls (Age M=31.81, SD=9.59) and 13 schizophrenia (SZ) patients (Age M=34.46, SD=9.38) revealed attenuated post-movement beta rebound (PMBR) in patients, bilaterally in frontal regions. Reduced PMBR likely suggests diminished interhemispheric beta-mediated functional inhibition. Notably, weaker PMBR correlated with hallucinatory behavior ($r(27)=-.38$, $p=0.04$) and blunted affect ($r(27)=-.38$, $p=0.04$) on the PANSS. Speech analysis showed that apathetic social withdrawal was linked to fewer syllables ($r(27)=-.41$, $p=0.03$) and unnatural mannerisms and postures on PANSS related with reduced syllables ($r(27)=-.51$, $p < 0.01$), phonation time ($r(27)=-.48$, $p < 0.01$), and pauses ($r(27)=-.38$, $p=0.04$). Stronger PMBR in the frontal region correlated with greater syllable production ($r(27)=.37$, $p < 0.05$).
**Discussion:** These findings indicate that clinical ratings correlate with speech performance and beta-band oscillatory power. SZ participants have lower PMBR compared to controls, and PMBR is associated with clinical symptoms and speech measures. Additionally, stronger beta oscillations in the frontal network are linked to higher language production, suggesting a relationship between beta activity and speech. PMBR is the strongest in HC, followed by more verbal SZ than in less verbal SZ patients. Future analyses will include personalized spectral power characteristics, bilateral frontotemporal oscillatory connectivity, and speech coherence and content richness feature extraction. With an expanded sample and more comprehensive analysis, this project aims to elucidate individual differences linking neuronal oscillations to language symptoms in psychosis.

## 62. A Combined TSPO Positron Emission Tomography and Free-Water Imaging Study in First-Episode Psychosis

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**Background:** Neuroinflammation is implicated in schizophrenia pathophysiology, with microglial activation and inflammation contributing to synaptic dysfunction. Understanding

these mechanisms could enable novel immune-targeted therapies. Free-water (FW) imaging is a diffusion Magnetic Resonance Imaging technique which allows the quantification of extracellular water content. It has been suggested to be a possible correlate marker of neuroinflammation. We tested whether FW in white matter is elevated in early-stage schizophrenia compared to healthy controls and explored its associations with clinical variables. Additionally, we examined whether white matter FW correlates with translocator protein (TSPO) PET binding, a marker of inflammatory cell density, in schizophrenia and controls.

**Methods:** 48 first-episode psychosis (FEP) patients (age 27.9±8.0 years mean±SD, 18F, < 5y of illness duration) and 24 matched healthy controls (age 26.8±7.3 mean±SD, 10F) underwent diffusion-weighted MRI to calculate white matter FW, fractional anisotropy (FA), and tissue-specific FA (FAt), as well as PET imaging with the TSPO tracer [$^{18}$F]DPA-714. Group-level analyses employed Tract-Based Spatial Statistics (TBSS) with voxel-wise analyses using FSL's Randomise, controlling for age, sex, and motion. White matter TSPO binding was quantified as non-displaceable binding potential (BPND) using a supervised clustering algorithm to define reference regions without invasive arterial sampling. Associations between [$^{18}$F]DPA-714 BPND and FW were tested using a general linear model, with TSPO genotype (rs6971) included as a covariate to account for binding affinity differences.

**Results:** Patients exhibited significantly higher FW compared to controls ($p < 0.05$, TFCE-corrected) across extensive white matter regions, including the corpus callosum, corticospinal tract, superior and inferior longitudinal fasciculi, anterior thalamic radiations, forceps major and minor, and uncinate fasciculus. No significant differences were observed in FA ($p=0.717$) or FAt ($p=0.353$) between groups. In schizophrenia patients, FW was negatively correlated with age ($t= -3.4$, $p=0.004$), driven by younger patients. Although no significant difference in white matter [$^{18}$F]DPA-714 BPND was observed between groups ($t(62) = -0.90$, $p = 0.369$), a positive correlation between total white matter FW and white matter [$^{18}$F]DPA-714 BPND was found only in the schizophrenia group ($F = 5.16$, $p = 0.002$) but not in controls ($F = 3.96$, $p = 0.062$). FW correlated positively with the Global Assessment of Functioning (GAF) score ($r=0.36$, $p=0.011$) but not with the Positive and Negative Syndrome Scale (PANSS) score ($r= -0.17$, $p=0.238$).

**Discussion:** This is the first study to combine TSPO-PET with FW imaging in schizophrenia. In this study, we found elevated white matter FW in FEP without changes in FA or FAt, suggesting increased extracellular free water without compromised tissue microstructure. The increase in FW in schizophrenia was associated with TSPO binding. However, there was no difference in white matter TSPO binding between healthy controls and FEP groups. These findings suggest that FW might be affected to some degree by increased inflammatory cell density, although evidentially there are additional aspects that differ in FEP and affect FW but not TSPO. This raises the question of whether FW imaging may be more sensitive to neuroinflammatory changes undetectable by TSPO imaging. The link between increased white matter FW and better global functioning suggests that higher FW might be associated with improved overall functioning in FEP patients. Given the lack of association with symptom severity, this could indicate that FW increases represent adaptive or compensatory mechanisms rather than pathological processes directly contributing to psychosis symptoms.

**Conclusions** This study found higher levels of FW in the white matter of schizophrenia subjects in their early stages of illness, which was associated with TSPO levels. It highlights FW imaging as a potential non-invasive marker of neuroinflammation in schizophrenia.

## 63. Slowed Alpha Oscillations in Relation to Visual Perceptual Disturbances in Schizophrenia

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**Background:** Investigations point to neural oscillations embodied in the cyclic patterns of the electroencephalogram (EEG) as reflecting the waxing and waning of excitability in neuronal populations that compose brain circuits. Although there is clear evidence that schizophrenia is associated with atypical neural oscillations, the ultimate significance of the abnormalities is unclear. Recent studies highlight the role of the dominant resting state oscillation - the alpha rhythm - in visual percept formation. Despite schizophrenia being associated with both slowed alpha oscillations and aberrant percept formation it is unknown whether slow alpha accounts for visual perceptual disturbances in the disorder. To examine the relationship of slowed alpha oscillations to visual perceptual anomalies that in part define schizophrenia, we carried out a magento-encephalography (MEG) study to characterize the speed of resting state alpha in relation to visual percept formation as measured with a binocular rivalry task.

**Methods:** We gathered eyes-closed resting-state MEG from people with schizophrenia (PSZ) or bipolar disorder (PBD) with psychosis, their first-degree biological siblings, and healthy controls. Groups in addition to PSZ allowed us to examine the diagnostic specificity of alpha abnormalities and relevance to genetic liability for psychotic psychopathology. Follow-up MEG sessions were performed after several months for PSZ and PBD. We appraised visual perceptual function, absent the confound of cognitive ability and effort, through the use of a passive visual binocular rivalry task that was also presented during MEG collection. Although the visual stimulus remained constant during the task, what was seen by participants alternated between two percepts which were reported via button presses. Because the two percepts were frequency tagged through different rates of luminance flicker we were able to compute steady-state visual evoked potentials (SSVEPs) that reflected neural activity specifically associated with each percept. SSVEPs time courses were used to characterize the enhancement and suppression of neural signals during the alternation of the two percepts.

**Results:** We found that slowed pace of alpha oscillations in psychotic psychopathology was associated with longer percept durations during binocular rivalry (eyes closed: $t(56.7) = 2.62$, $p = 0.006$, Cohen's $d = 0.68$; eyes open: $t(50.82) = 1.98$, $p = 0.026$, Cohen's $d = 0.53$), consistent with the assertion that occipital alpha oscillations govern the rate of accumulation of neural information related to percept formation. Alpha speed varied widely across individuals with psychotic psychopathology and was highly stable across several months (eyes closed: ICC = 0.84, eyes open ICC = 0.9) indicating that it is likely a trait characteristic of neural function that is relevant to visual perception. Lower speed of alpha oscillation was associated with a lower IQ (eyes closed: $r = 0.43$, $p < 0.001$; eyes open: $r = 0.29$, $p = 0.017$) and greater disorder symptomatology (eyes closed: $r = -0.29$, $p = 0.016$; eyes open: $r = -0.33$, $p = 0.006$) implying that the effects of the endogenous neural oscillation on visual perception may have wider consequences for everyday functioning. The strength of SSVEPs oscillated with percepts and depended on whether the percept was reported as dominant or suppressed, consistent with SSVEPs reflecting the accumulation of neural information supporting percept formation.

**Discussion:** This investigation revealed evidence that slowing of the alpha rhythm in psychotic psychopathology is predictive of visual perceptual processes. The association between the speed of alpha oscillations and the duration of percepts during binocular rivalry

was across individuals with schizophrenia or bipolar disorder, their siblings, and healthy controls suggesting that the effect of slowed alpha on visual perception may extend beyond a diagnosis of schizophrenia. A lower IAPF was additionally related to worse cognitive functioning and greater symptomatology consistent with a decreased pace of alpha oscillations as contributing to signs of more generalized brain pathology. The stability of IAPF across several months in people with psychotic psychopathology bodes well for the measure to function as a predictor of visual perceptual difficulties and perhaps as an indicator of brain abnormalities tied to the development of psychotic psychopathology. Finally, SSVEPs revealed neural functions associated with the waxing and waning of percept formation during binocular rivalry.

## 64. Neural Evidence of Distinct Atypical Plasticity in Sensory Updating in Non-Affective and Affective Psychosis

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**Background:** Predictive coding is a theoretical framework that suggests our brain constantly attempts to predict sensory inputs based on past experiences to guide our learning and behavior. Prediction error (PE), the discrepancy between our predicted and actual sensory input, allows the brain to update these sensory predictions for the future. Patients with psychosis (PwP) have difficulty tracking reward expectations, resulting in stochastic choice behavior. However, it is unknown whether choice behavior is influenced in a similar manner by affective and non-affective psychosis. Furthermore, PwP have known visual processing deficits. Using a three armed-bandit task with EEG, our goal was to directly test for links between neural PEs (reward positivity [RewP], P300) and subsequent sensory updating (P1, N1) in PwP. We also sought to understand differences between the impact of neural PEs on subsequent sensory updating in non-affective versus affective psychosis.
**Methods:** We collected simultaneous EEG/fMRI from n=34 healthy controls (HC), n=14 non affective PwP, and n=20 affective PwP, employing a 3-armed bandit task that resulted in an outcome of +1 or +0 points. Trial-by-trial PEs were generated to investigate the relationship of a neural manifestation of PEs on subsequent sensory processing. Feedback-locked Reward Positivity (RewP) served as an neural index of PEs, and P1 and N1 evoked potentials served as indices of subsequent visual processing of the stimuli. The Brief Psychiatric Rating Scale (BPRS) was used to assess positive and negative symptoms of psychosis. A mixed-effects model was employed to examine the impact of the RewP on N1 and P1 responses in subsequent trials through a single-trial analysis.
**Results:** Results revealed that psychosis patients exhibited a significantly smaller slope in the RewP when encoding PE in rewarded trials ($p < .001$) and had significantly smaller N1 across PEs than HCs ($p=0.003$). In addition, the RewP predicted higher switch rates in psychosis patients than HCs in rewarded trials (when PE is not coded as expected) (ps=0.03, 0.006). Furthermore, greater RewPs predicted greater N1s to visual stimuli on the following trial more strongly in non affective PwP than HC ($p=0.0044$). Additional analyses focusing on the non-affective PwP revealed that this RewP-N1 relationship was more pronounced in patients with higher levels of positive symptoms ($p=0.02$). Furthermore, in non affective PwP, greater RewPs also predicted smaller P1 responses to stimuli of the next trial ($p < 0.001$). However, in the affective psychosis group, greater RewPs predicted greater N1s only in the low salience PE condition ($p=0.005$). In affective PwP, greater RewPs also only

predicted larger P1 responses to stimuli in the following trial in the high salience PE condition (p=0.03). HCs did not show a RewP-P1 relationship.
**Discussion:** Our results provide novel evidence of sensory updating via prediction errors and reveal that non-affective PwP have difficulty tracking PEs but demonstrate robust sensory updating when the RewP is present. Variable RewP responses in non-affective psychosis may reflect a heightened reliance on immediate trial feedback, resulting in stochastic trial-by-trial sensory updating. Furthermore, greater positive symptoms in non affective PwP appear to impair the ability to maintain a stable reward representation. Findings also highlight distinctions between non-affective and affective psychosis in prediction error-based updating, with affective psychosis showing a PE-dependent sensory updating. These distinctions suggest that affective PwP prioritize feedback atypically, depending on the salience of the prediction error.

## 65. The Relationship Between Environmental Risk, the Brain and Psychosis Proneness: A Causal Discovery Analysis in Adolescents and Young Adults

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**Background:** Experiencing mild symptoms of psychosis, like delusions and hallucinations, occurs sometimes in general, nonclinical populations, often termed psychosis proneness (PP), potentially part of the psychosis continuum. Understanding the neural and environmental factors contributing to PP in young individuals during critical developmental periods remains unclear. We aimed to explore these directional relationships using causal discovery analysis (CDA).
**Methods:** Participants were 194 healthy adolescent and young adult twin and sibling pairs aged between 14-24 years. They completed comprehensive assessments evaluating sociodemographic status, environmental risk, general intelligence, self-schema, psychosis proneness score (PPS), and working memory performance during fMRI consisting of 37 variables. We applied CDA, a novel machine learning algorithm that infers causal relationships from data, to understand the causal relationships of PPS.
**Results:** Our analysis identified negative self-schema as having the largest causal effect among our assessments in PPS [Effect size (ES)= 0.55]. Secondly, experiencing low levels of social cohesion and trust (SC and T) had a causal effect on PPS [ES= -0.18]. Although our analysis could not exclude the possibility that other unmeasured factors may confound these relationships, the effect sizes (ES) were substantial. PPS, on the other hand, was identified as a direct cause of greater activation in DLPFC (BA9a-BA46v) during manipulation in the working memory (ES= 0.14). CDA provided simultaneous directionality for 37 variables collected on the same individuals.
**Discussion:** The findings highlight the significance of negative self-schema and social cohesion and trust in the general population with psychosis proneness, emphasizing the

potential for preventive interventions targeting these factors. These findings also suggest a role for DLPFC as a potential target in this regard. This study represents the first data-driven analysis to model causal mechanisms in psychosis proneness in the general population.

## 66. Transdiagnostic Profiles of Bold Signal Variability in Autism and Schizophrenia Spectrum Disorders: Associations With Cognitive Functioning and Neurobiology

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**Background:** Autism spectrum disorder (autism) and schizophrenia spectrum disorder (SSD) exhibit neurobiological heterogeneity, impacted social and non-social cognition, and demonstrate impaired functioning. Emerging evidence suggests that intra-regional blood-oxygen-level dependent (BOLD) signal variability may provide insights into the flexibility and integration of neural networks, reflecting the brain's capacity to adapt to varying cognitive demands. This study aimed to examine BOLD signal variability across a sample of participants diagnosed with autism, SSD, and typically developing controls (TDC). We hypothesized that lower BOLD signal variability (previously linked to older age and increased symptom severity) would be present in SSD and autism and would correspond with poorer cognitive performance.
**Methods:** Intra-regional BOLD variability, measured by mean squared successive difference, was obtained at rest and during the Empathic Accuracy task in 176 SSD, 89 autism, and 149 TDC participants. Group comparisons were conducted using ANCOVAs, controlling for age, sex, and motion, to evaluate associations between network-level BOLD signal variability with social functioning, symptom severity, and social cognitive and neurocognitive performance.
**Results:** SSD participants exhibited the lowest network-based BOLD signal variability, followed by intermediate levels in autism participants, with TDC participants showing the highest variability across both rest and task in the somatomotor and auditory networks (all $p < 0.001$). Lower variability was related to significantly poorer social functioning and decreased social cognitive and neurocognitive performance across groups.
**Discussion:** Decreased BOLD signal variability aligned with decreased social cognitive and neurocognitive performance, reinforcing the potential for variability-focused biomarkers to advance individualized, transdiagnostic treatment approaches targeting cognitive impairments across clinical populations.

## 67. Thalamo-Cortical Contributions to Altered Corollary Discharge Signaling in Schizophrenia

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**Background:** Disturbances in a sense of self, and specifically in agency, have long been considered at the root of many symptoms of schizophrenia. Corollary discharge (CD) signals – copies of motor signals sent to sensory areas in the brain – permit predictions about the sensory consequences of action; thus, CD provides important sensorimotor information that supports a sense of agency (i.e., "I am in control of my actions."). Studying CD related to saccades has unique advantages over other sensorimotor systems. First, well-established and rigorous psychophysics paradigms can measure the influence of CD on visual perception and eye movements. Second, neurophysiology studies in non-human primates have used eye movement tasks to articulate a oculomotor network that transmits CD signals from the thalamus to the frontal eye fields (FEF) and the intra parietal sulcus (IPS), and also from the FEF to IPS. Sequential saccade planning requires CD signals that provide information about the planned landing location of an eye movement. In prior work we have used the double-step task, which measures sequential saccade planning, to identify performance deficits in people with psychosis that are consistent with altered CD, providing a potential mechanism to explain passivity and anomalous self-experiences, broadly. In the current study, used dynamic causal modeling (DCM) on functional MRI (fMRI) data acquired while participants performed the double-step task. DCM has the unique advantage of gaining mechanistic understanding of the dynamic causal influences that multiple brain regions have on each other during specific tasks. Here, we aimed to understand whether and, if so, how key pathways that transmit oculomotor CD signals are altered in schizophrenia.
**Methods:** Functional MRI data was collected during double-step task performance in 30 individuals with schizophrenia and 29 demographically-matched healthy controls. We modelled fMRI data using DCM to examine patient-control differences in effective connectivity evoked by a task condition that required CD signaling, using both a parametric empirical Bayes analysis and family model comparison. The interrogated network was formed from a combination of a) functionally identified FEF and IPS regions that robustly responded on double-step trials and b) anatomically identified thalamic regions involved in CD transmission. We also examined the relationship between clinical symptoms and effective connectivity parameters associated with task modulation of network pathways.
**Results:** Network connectivity indeed modulated by the double-step task, which involves CD transmission. More importantly, results of the parametric empirical Bayes analysis revealed reduced effective connectivity from thalamus to IPS in SZ during trials that required CD, which was further correlated with passivity symptom severity. Findings from the family model comparison analysis corroborated findings from the parametric empirical Bayes analysis, supporting this thalamo-cortical dysconnection in SZ: while the winning model for controls included double-step modulation of pathways from thalamus to both IPS and FEF, the winning model for people with schizophrenia only included the thalamus to FEF pathway.
**Discussion:** These data corroborate findings from non-human primate and human lesion studies, and we found that a pathway from thalamus to frontal and parietal eye movement regions is indeed modulated by the task condition that requires CD signaling for accurate performance (double-step saccades). Our results contribute to this basic science literature by providing new insights into thalamo-parietal involvement in CD signaling. Importantly, we observed reduced effective connectivity in the pathway from thalamus to an oculomotor region in the parietal, but not frontal, cortex in people with schizophrenia. Because CD signals are considered a basic sensorimotor mechanism of agency, our results suggest that altered functioning in specific thalamo-cortical pathways may contribute to complex self-related symptoms of schizophrenia.

**Oral Session: Factors in Recovery and Long-Term Outcome**

## 68. Sex-Specific Factors Associated With Clinically Relevant Weight Loss in Psychotic Disorders

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**Background:** Weight gain and obesity present a substantial problem for people with a psychotic disorder, with three quarters being overweight or obese. Notably, those starting antipsychotics experience clinically relevant weight gain (≥7%) in the first 6 to 12 months of treatment, and this weight gain does not appear to plateau. The high prevalence of risk factors including sedentary behaviour, poor diet and use of antipsychotic medication all contribute to the increased risk of weight gain. The amount of weight gained during antipsychotic treatment may also be influenced by sex. Crucially, a 5-10% reduction in weight has a positive impact on risk factors for cardiovascular disease, the leading cause of death in people with a psychotic disorder. While weight gain associated with antipsychotic use has been well documented, it is less clear whether weight gained can be reversed, what factors are associated with achieving weight loss, and whether there are sex differences. This study aimed to investigate clinically relevant weight loss (CRWL), defined as a 7% or greater loss in baseline body weight, and its associated factors, separately by sex.
**Methods:** The Survey of High Impact Psychosis Wave 2 was a 3-5-year follow-up of a nationally representative sample of people with a psychotic disorder. In this naturalistic longitudinal study, the weight of 372 people (231 men and 141 women) was examined at baseline and at follow-up. We compared those who had lost ≥7% of their baseline weight with those who had not, separately for each sex. Bivariate logistic regression analyses were used to calculate unadjusted odds ratios of CRWL for a comprehensive range of clinical and lifestyle factors. At baseline, these included: age, weight, marital status, and socio-economic disadvantage. At follow-up, we examined: physical activity, food security, attempts to lose weight, quality of sleep, past year GP contacts and current smoking status; we also looked at patterns of use of antipsychotics, antidepressants or mood stabilisers associated with higher weight gain and medication associated with weight loss. In addition, we assessed changes over time in cannabis use, depressive symptoms, and loneliness. Stepwise backwards elimination with exclusion probability $p > 0.15$ and inclusion probability $p < 0.1$ was used to determine minimal sets of multivariable predictors. Variables with p value of $< 0.05$ in minimal multivariable models were considered statistically significant.
**Results:** A total of 20.2% of participants had CRWL (20.3% of men and 19.9% of women), with 8.6% having a reduction of between 11% and 20% of their baseline weight, and 3.8% losing more than 20%. For men, factors found in unadjusted analyses to be associated with CRWL were older age, greater baseline weight, socio-economic disadvantage, attempts to lose weight, being food secure, greater amounts of physical activity, stopping cannabis use, stopping using all antipsychotic medication and using only first-generation antipsychotics compared to using antipsychotics with a high weight-gain profile. After stepwise backwards regression, older age (OR 1.04, 95% CI=1.01-1.08), greater baseline weight (OR 1.03, 95% CI=1.02-1.05) and stopping antipsychotics (OR 12.59 95% CI=2.30-68.95) compared to using antipsychotics with high-risk of weight gain showed increased odds of CRWL. Few significant differences were seen between women with and without CRWL. In the final model, three factors remained: baseline weight, number of GP visits and quality of sleep.

Only sleeping without difficulty was significantly associated with increased odds of CRWL (OR 2.50, 95% CI=1.02-6.13, p=0.04).
**Discussion:** Ongoing weight gain should not be considered inevitable for people living with a psychotic disorder. Our findings showed that achieving clinically relevant weight loss is possible, with one in five participants losing 7% or more of their baseline body weight. Importantly, we also found that factors associated with CRWL differed for men and women. Given the challenges of reversing weight gain, implementing pharmacological and non-pharmacological strategies tailored to men and women early in the course of their illness may prevent or minimise weight gain.

## 69. Development and Validation of the Mental Health Personal Recovery Scale (MHPRS) for a Low-Income, African Country Context

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**Background:** The concept of personal recovery is rooted in value systems that are embedded within cultures; for example, about what brings meaning in life and the nature of identity. It is not, therefore, surprising that there have been critiques regarding the applicability of personal recovery concepts in non-western cultures
**Methods:** The study comprises the development and validation of the psychometric properties of a mental health personal recovery scale (MHPRS). The study had six phases:1) reviewing existing measures; 2) secondary analysis of qualitative data exploring the concept of recovery in Ethiopia (n=25 interviews); 3) conducting expert meetings (n=3) and 4) cognitive interviewing for semantic and content validity (n=20); 5) pilot study for item reduction and exploratory factor analysis of dimensional structure (n=213); and 6) assessment of construct (confirmatory factor analysis) and convergent validity (n=401) in an independent sample, and test-retest reliability in a sub-sample (n=48). Convergent validity was assessed against symptom severity (Brief Psychiatric Rating Scale; BPRS-E) and disability (World Health Organization Disability Assessment Scale 2.0; WHODAS 2.0.).
**Results:** Existing measures did not align with valued aspects of the recovery journey in Ethiopia, which gave less emphasis to self-actualisation and greater priority to social recovery. We piloted a combination of 45 items extracted from existing tools and 20 new items. The tool was unidimensional and had excellent psychometric properties. Expert review led to item reduction, resulting in a 20-item scale. The validation study findings showed that the new scale, the MHPRS, is unidimensional with acceptable goodness of fit indices and good test-retest reliability. MHPRS was significantly correlated with symptom severity and functioning. The final version of MHPRS takes an average of ten minutes to complete.
**Discussion:** Based on a rigorous process, MHPRS was found to be a valid and reliable measure of mental health personal recovery in Ethiopia. The measure could be used in clinical settings or research studies to foreground the perspectives of people with lived experience of mental health conditions on their recovery journey. The MHPRS has potential applicability to other non-Western settings.

## 70. Impact of Childhood Trauma on Long-Term Outcomes in First-Episode Psychosis: A Four-Year Follow-Up Study

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**Background:** Childhood trauma, including various forms of abuse and neglect, is associated with an increased risk of psychotic disorders as well as greater severity and earlier onset of psychotic symptoms. However, longitudinal research on the impact of childhood trauma remains limited, and many prior studies fail to capture its complexity. This study applied cluster analysis to identify distinct trauma profiles and examine their association with longitudinal clinical outcomes in individuals with first-episode psychosis.
**Methods:** Data were analyzed from a longitudinal cohort of 293 individuals with first-episode psychosis assessed at baseline, 3 months, 6 months, and annually for four years. Childhood trauma types—including various forms of abuse and neglect—were clustered into distinct profiles. Linear mixed-effects models were used to compare these profiles in terms of longitudinal clinical trajectories, controlling for age and sex.
**Results:** Three trauma profiles were identified: low/no trauma (n=92), emotional trauma (n=140), and multiple trauma (n=61). At baseline, no significant differences were observed in age, socioeconomic status, antipsychotic medication use, or age at psychosis onset across the groups. However, participants in the multiple trauma cluster demonstrated lower premorbid functioning, longer durations of untreated psychosis, and less social support compared to the other groups. Over the 48-month follow-up, participants in the multiple trauma cluster exhibited significantly more severe psychotic symptoms ($\beta$=6.68, $p < 0.001$), lower global functioning ($\beta$=-9.58, $p < 0.001$), and poorer quality of life ($\beta$=-5.01, p=0.009) compared to the low trauma cluster. Additionally, those in the multiple trauma cluster showed lower global functioning ($\beta$=-4.24, p=0.04) compared to the emotional trauma cluster, although differences in psychotic symptoms and quality of life were not significant. The emotional trauma cluster also displayed worse outcomes, with more severe psychotic symptoms ($\beta$=4.10, $p < 0.001$), lower global functioning ($\beta$=-4.80, p=0.001), and lower quality of life ($\beta$=-2.04, p=0.19) compared to the low trauma cluster. Across all participants, psychotic symptoms significantly decreased ($\beta$=-0.31, p=0.003), while global functioning ($\beta$=0.60, $p < 0.001$) and quality of life ($\beta$=0.97, $p < 0.001$) significantly improved over the 48-month follow-up. No significant interaction was found between trauma profiles and clinical trajectories over time.
**Discussion:** Childhood trauma, encompassing various forms of abuse and neglect, is associated with differences in clinical and functional outcomes in individuals with first-episode psychosis. Future research is needed to further explore the relationship between childhood trauma and the clinical profiles of patients during remission following their first psychotic episode.

## 71. Low Risk of Breakthrough Symptoms on Antipsychotic Medication When Remitted Patients With Schizophrenia are Treated With Long-Acting Injectable Medications

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**Background:** The risk that psychotic symptoms will return is known to be very high if individuals with schizophrenia discontinue maintenance antipsychotic treatment. However, the risk of breakthrough psychotic symptoms is less clear when patients receive maintenance

antipsychotic treatment. Recurrences may occur despite maintenance treatment for a number of reasons including poor treatment response, suboptimal maintenance dose, and incomplete adherence. This study was initiated to estimate the risk of breakthrough psychotic symptoms when these considerations are minimized by limiting our study to individuals with schizophrenia who: 1) have experienced a remission of psychotic symptoms with antipsychotic treatment, 2) are receiving maintenance treatment with a second-generation long-acting antipsychotic medication (LAI), and 3) have established adherence.
**Methods:** All participants were recruited from the outpatient services of the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Individuals 18 years of age and older who met DSM-5 criteria for schizophrenia were invited to participate if they met the following inclusion criteria: 1) receiving treatment with long-acting paliperidone, risperidone, or aripiprazole, 2) on a stable dose for at least three months, and 2) a history of improvement as defined by a rating of mild or lower on the Clinical Global Impression Schizophrenia (CGI-SCH) – Severity Scale for Positive Symptoms , and 4) demonstrated adherence to LAI treatment defined as not having received any injections more than 7 days past the due date for the past three months. Participants were excluded if, in the previous three months, they had: 1) been treated with oral antipsychotic medication, 2) had a psychiatric hospitalization, or 3) met criteria for a current major depressive or manic episode. After undergoing a screening visit, participants were assessed at the time of their next LAI injection, and then at 12 weeks, 24 weeks, 36 weeks and 48 weeks using the Clinical Global Impression Schizophrenia (CGI-SCH) and the 24-item Brief Psychiatric Rating Scale (BPRS). Breakthrough psychotic symptoms were defined as a rating of "Much Worse" or "Very Much Worse" on the CGI-SCH–Improvement Scale for Positive Symptoms. Psychiatric hospitalizations and emergency room visits were documented at each visit. Medication side effects and measures of functioning including the Personal and Social Performance Scale (PSP) were assessed at baseline, 24 weeks and 48 weeks. Trough antipsychotic levels were assessed at baseline, 24 weeks and 48 weeks.
**Results:** To date, 42 participants (14F, 28M) have completed a baseline assessment including 23 receiving paliperidone (Invega Sustenna or Invega Trinza), 2 receiving risperidone (Risperdal Consta) and 17 receiving aripiprazole (Abilify Maintena). Mean age of the sample is 38.2 years (s.d. = 12.3). Race/ethnicity was reported by 31% as White, 33% as Black, 36% as Other. At the baseline visit, mean BPRS was 30.3 (s.d.= 5.2) and mean PSP was 68.7 (s.d.= 16.5). Follow-up assessments have been completed for 33 participants at 12 weeks, 26 at 24 weeks, 20 at 36 weeks, and 18 at 48 weeks. To date, one participant has had a psychotic recurrence.
**Discussion:** In this study, we have been assessing the 1-year risk of breakthrough psychotic symptoms in individuals with DSM-5 schizophrenia who have experienced a remission of psychotic symptoms and have been adherent with treatment with a long-acting injectable formulation of a second-generation antipsychotic medication. Our preliminary results suggest that the risk of breakthrough symptoms is low. Additional data will be presented on antipsychotic plasma levels and medication side effects.

### 72. Both Sides, Now: Clinical Impacts of Physical Multimorbidity Experienced by People Living With Schizophrenia

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**Background:** Experiencing an additional chronic condition, either physical or psychiatric, unfortunately remains the rule rather than exception for people living with schizophrenia. Multimorbidity, the simultaneous presence of two or more chronic conditions, is an emerging framework useful for framing the complex burden of multiple chronic diseases experienced by people living with schizophrenia. Whilst there is existing evidence that co-occurring physical and psychiatric illness exacerbates a variety of pertinent clinical health outcomes, such as increased risk of rehospitalisation, longer admissions, and mortality, this has not been extensively studied with multimorbidity-based frameworks that account for varying types and combinations of chronic physical and psychiatric disease for people already living with schizophrenia.

**Methods:** This submission plans to present a series of analyses conducted from an Australian hospital dataset that captured 3421 individuals with schizophrenia and other severe mental illnesses that had inpatient psychiatric admissions across a ten-year period (2010-2020). Through multivariable logistic regression models and Cox proportional hazard models, we estimated how different models of physical multimorbidity impacted different pertinent clinical outcomes. Given multimorbidity is an emerging term with varying definitions and frameworks, we developed different multimorbidity models of increasing complexity to measure how cumulative exposure to additional chronic illnesses impacted people with schizophrenia in these hazard analyses. Specifically, we examined physical multimorbidity as a binary exposure variable (i.e., as either present or absent, denoted as 'multimorbidity status') as well as a dynamic quantitative variable (i.e., incorporating the number of conditions accumulated over time, denoted as 'cumulative multimorbidity total'). We examined pertinent clinical outcomes available from the dataset, such as risk of mortality, increased length of stay, and adverse discharge disposition. Through multivariable modelling, we also adjusted for the impact of other available variables as possible confounders, such as age, sex, country of birth, smoking status, and socioeconomic status.
Local ethics approval was attained in order for the researchers to analyse the relevant de-identified administrative health data extracted for this study.

**Results:** This dataset featured over three thousand individuals with a history of schizophrenia and other severe mental illnesses who had at least one admission to a psychiatric inpatient hospital unit in Brisbane, Australia between 2010 and 2020. This cohort had a mean age on initial admission of 38.3±12.2 years; 41% and 59% were female and male respectively; and approximately one third of the cohort had been born overseas.
Regarding health service impact, cumulative multimorbidity total was found to be associated with longer admissions (≥14 days duration, odds ratio [OR]: 1.20, 95%CI: 1.14, 1.26, $p < 0.001$) and adverse discharge dispositions (OR: 1.14, 95%CI: 1.04, 1.24, $p = 0.0027$); these figures were adjusted as per the above demographic variables. Statistical significance was preserved when these same outcomes were tested using a binary variable for multimorbidity status, however the estimates produced had larger effect sizes but less precise confidence intervals. Using multimorbidity status, the odds ratio of a longer admission was 1.72 (95%CI: 1.44, 2.04, $p < 0.001$) and for adverse discharge dispositions was 1.77 (95%CI: 1.27, 2.45, $p = 0.0006$).

Multimorbidity exposure, as measured through the above cumulative multimorbidity total, was a statistically significant predictor of mortality ($p < 0.001$), with an adjusted hazard ratio of 1.27 (95%CI: 1.15, 1.40), which was adjusted for age, sex, obesity, smoking status, country of birth, socioeconomic disadvantage, and childhood adversity. This finding indicated that each additional physical illness conveyed an increased 27% risk of mortality.

When instead treated as a binary variable (i.e., multimorbidity status), the estimated adjusted hazard ratio was 2.13 (95%CI: 1.36, 3.36, p = 0.0011).

**Discussion:** These presented analyses highlight the pertinent risk that physical multimorbidity plays for both short-term outcomes, such as prolonged psychiatric admission, as well as long-term health outcomes such as mortality, for people living with schizophrenia. Whilst these results were from a relatively small clinical population, they signal the need for more holistic models of care that account for both the physical and mental health of people living with schizophrenia. Whilst the more traditional but binary construct of comorbidity is useful for examining specific conditions (e.g., type 2 diabetes mellitus) that co-occur in people with schizophrenia, this study is part of an emerging body of research that signals the relevance of multimorbidity in accounting for the different combinations of chronic physical illnesses experienced by people with schizophrenia.

## 73. Social Determinants of Health Among Patients With Experiential Negative Symptoms Living With Schizophrenia: Medical Expenditure Panel Survey

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**Background:** Schizophrenia, a chronic mental health disorder, manifests through positive, cognitive, and negative symptoms (NS). NS disrupt normal emotions and behavior, and experiential NS include avolition (lack of motivation), asociality (decreased social interactions), and anhedonia (diminished ability to feel pleasure), impacting quality of life and functioning. Social determinants of health (SDOH) are non-medical factors influencing health outcomes, such as economic stability, education, and community context. The SDOH of patients with schizophrenia, especially those with experiential NS, remains unclear. This study assessed the association between SDOH and experiential NS among patients with schizophrenia.

**Methods:** This study utilized 1997-2021 data from the Medical Expenditure Panel Survey. Avolition and anhedonia were determined based on having little interest or pleasure doing things for the past two weeks, while asociality was based on a question asking about being limited in social, recreational, or family activities due to mental or physical health problem. When an individual reported either avolition and anhedonia or asociality, it was categorized as having experiential NS. The outcomes included prevalence, demographics, and SDOH, including education, employment status, annual income, insurance coverage, and food stamp use. Descriptive and comparative analyses stratified by experiential NS were conducted using $\chi 2$ test and t-test and were weighted to produce national estimates, with income adjusted to 2024 US dollars.

**Results:** Altogether, 1,804 individuals had schizophrenia, representing a weighted population of 616,530. Among these, 71.3% was reported having experiential NS. The mean age was 47.5 years with 53.2% of those being male. The racial distribution was predominantly White (68.0%), followed by Black (23.6%), with other races being < 6%. Sex, race, and ethnicity, separately evaluated, were similar between the groups. Those with experiential NS were 1.4 times more likely to have no completed degrees of education (20.1% vs. 14.1%) compared to

those without. Those with experiential NS were 2.6 times less likely to be fully employed than those without experiential NS (9.5% vs. 24.6%). This translated to $6,760 less income for individuals with experiential NS versus those without experiential NS ($16,208 vs. $22,968). Patients with experiential NS were 1.3 times more likely to have Medicaid (65.1% vs. 51.3%) versus those without experiential NS. Private insurance was 1.9 times less common among those with experiential NS (17.1% vs. 33.2%). Among those with experiential NS, food stamp use was 1.3 times higher versus those without (39.4% vs. 29.3%). All p-values were < .0001.
**Discussion:** This study highlights significant disparities in SDOH among individuals with schizophrenia experiencing experiential NS. These individuals are more likely to have lower educational attainment, higher unemployment rates, and lower incomes. They are also more reliant on Medicaid and food stamps, indicating greater economic burden. These adverse SDOH can lead to worse health outcomes due to increased financial stress. This study is limited by self-reported data with potential recall bias. The identification of experiential NS is based on self-reports and proxy questions, which may result in less accurate identification and under-estimated of individuals with experiential NS. Additionally, the MEPS data do not cover institutionalized populations, potentially underestimating the burden of the disease. Addressing these SDOH disparities is crucial to improving health outcomes for this population, emphasizing the need for targeted interventions for experiential NS.

## 74. Baseline Cognitive Function as a Prognostic Marker for the Long-Term Course of Positive Psychotic Symptoms: A 10-Year Follow-Up Study in First-Episode Psychosis

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**Background:** Impaired cognitive functioning is considered a core symptom of schizophrenia spectrum disorders. The prognostic potential of cognitive function for long-term psychosis outcomes has only recently emerged as a focus of research, with findings indicating an association between baseline cognitive dysfunction and treatment resistance. However, as measures of treatment resistance often comprise symptoms and functioning across multiple domains, it remains unknown to what extent the observed associations are specific to the (un)responsiveness of positive symptoms to antipsychotic medication. This makes it difficult to uncover mechanistic underpinnings. In a first-episode psychosis sample (FEP) followed up after 10 years, we therefore tested whether baseline cognitive performance could specifically predict adverse positive symptom outcomes, possibly reflective of treatment resistance.
**Methods:** This study included 121 individuals with FEP from the Norwegian Thematically Organized Psychosis (TOP) project, recruited during their first treatment and followed up after 10 years. At baseline, five cognitive domains were assessed: verbal learning and memory, attention and working memory, processing speed, verbal fluency, and cognitive control. At follow-up, the course of positive psychotic symptoms was captured using two different methods, to test for replicability across different course definers: A) “episodes” = the recurrence of psychotic episodes during the entire follow-up period measured as time spent in active psychosis, B) “positive symptom severity” = positive symptom scores at baseline and follow-up, using a five-factor solution for the Positive and Negative Syndrome Scale (PANSS). Logistic regression analyses were employed to predict extreme groups of both course definers in two separate models: persistent psychosis (active psychosis > 70% of

the follow-up period) vs. remitting psychosis (active psychosis < 20%) in the episodes model, and adverse (any positive item score > =4 at follow-up) vs. favorable symptom course (mild/no positive symptoms) in the symptom severity model. Baseline cognitive domain scores were the main predictor of interest, corrected for baseline characteristic (age, gender, negative symptoms) in adjusted models.
**Results:** Preliminary findings are presented.
With episodes as the course definer, 30.6% of participants were categorized as having persistent psychosis (43% remitting psychosis), and using symptom severity, 33.1% showed an adverse symptom course (62.8% favorable).

Verbal learning and memory scores were a significant predictor in both the episodes and the symptom severity model, with better performance associated with lower risk of persistent psychosis (OR= 0.39, CI [0.20,0.72], p = .004; adjusted: OR = 0.49, CI [0.24,0.95], p = .042) or adverse symptom course (OR = 0.45, CI [0.26,0.73], p = .002; adjusted: OR = 0.48, CI [0.27,0.81], p = .007). Similar results were observed for cognitive control, where higher scores indicate poorer performance, though effects were no longer significant after controlling for covariates (persistent psychosis risk: OR = 1.71, CI [1.08,2.84], p = .027; adjusted: OR = 1.45, CI [0.88,2.50], p = .158; OR = 1.66, CI [1.09,2.61], p = .021; adjusted: OR = 1.52, CI [0.98,2.42], p = .065).

**Discussion:** These findings highlight baseline verbal learning and memory performance as a promising and independent prognostic marker of the long-term course of positive psychotic symptoms, suggesting shared underlying neurodevelopmental vulnerabilities. In contrast, associations with cognitive control seem less specific, and are likely driven by overlap with negative symptom severity.

## 75. Transforming Access to Care for Serious Mental Disorders in Slums (The Transform Project)

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**Background:** The TRANSFORM project aims to improve access to mental health services for people with serious mental disorders (SMDs) residing in slums in Bangladesh and Nigeria. These communities experience high rates of SMDs, and limited access to mental health services. Help is commonly sought from faith-based and traditional healers (TFHs), but individuals with SMDs require medical treatment, support, and follow-up. The mental health treatment gap (the difference between the number of people who need care and those who receive it) is reported at 80% in Nigeria and 92% in Bangladesh.
The World Health Organisation's Mental Health Gap Action Programme (mhGAP) aims to reduce the treatment gap by training non-specialists to screen for SMDs and refer where needed. However, local contextualisation is required.

We have co-developed, with TFHs, an intervention to support TFHs screen, detect, and refer people with SMDs to mental health services. Establishing such collaborations is not without its challenges, including long-held beliefs about mental health and illness and the power differentials between TFHs and biomedical practitioners. Our bottom-up approach, where

intervention and training are co-developed with TFHs, addresses these challenges and promotes participatory inclusiveness.

**Methods:** We systematically captured information about the number of patients seeking medical care pre intervention. Here, we present initial findings of our ongoing intervention (from 03/2024 - 03/2025), as we measure changes in the number of people from the slum sites with SMDs seeking medical care through TFH referrals and following these patients up over time to test clinical changes.
We outline findings from our interim analyses and will present our full intervention outcomes if accepted for SIRS 2025.

Quantitative data includes sociodemographic characteristics, duration of untreated psychosis (DUP; the time between onset of psychotic symptoms and start of adequate treatment), service satisfaction, medication adherence, and functioning and symptom outcomes, which are analysed using descriptive and inferential statistics.

**Results:** There has been an increase in people with SMDs from the slum seeking medical care post intervention (+16%, N = 26,291).
Participants from Bangladesh (Mage = 36.51±12.91) and Nigeria (Mage = 32.78±12.47) showed improvements in functioning and psychiatric status over time, with a peak at 5 months in Bangladesh, and 4 months in Nigeria. The median DUP was similar in both countries (Bangladesh: 84.29 weeks; Nigeria: 91.93) with no correlation to function or symptom severity.

There was high satisfaction for biomedical services at both sites, with increasing satisfaction after 4 months of medical treatment in Nigeria.

**Discussion:** Our recruitment of 26,291 patients across both countries provides a unique platform to test the effectiveness of our intervention.
Our interim analysis of the TRANSFORM intervention demonstrates promising improvements in service satisfaction, functioning and symptoms among individuals with SMDs in the targeted urban slums, indicating that the intervention may be effectively addressing barriers to mental health service access.

By the time of the SIRS 2025 conference, we anticipate completing the intervention and conducting a comprehensive final analysis to evaluate its overall effectiveness. This future analysis will provide an in-depth assessment of the TRANSFORM project's impact on mental health service access and outcomes in urban slum settings. We will further test and present findings on how patient satisfaction plays role in improving treatment adherence amongst slum residents, and test if the intervention's benefits are broadly applicable across demographic characteristics.

## Oral Session: Pharmacological and Non-Pharmacological Interventions

### 76. **Effects of 40 Hz tACS Stimulation on Cognition and Symptoms in Patients With Schizophrenia**

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**Background:** Transcranial alternating current stimulation is a technique of brain stimulation to modify neural activity and plasticity by entraining more specifically defined cortical oscillation frequencies. Recent reviews of tACS effects in schizophrenia suggest that tACS stimulation may affect symptoms and cognition in schizophrenia, mostly from open label trials and case reports, but there have been very few randomized controlled trials, especially with tACS targeting γ band oscillations. There is considerable evidence or disturbances in gamma cortical oscillations in schizophrenia; there are also deficits in the modulation of γ oscillations during working memory tasks in schizophrenics, and lack of an increase in γ oscillations strength with working memory load similar to that seen in healthy controls.
**Methods:** The current study was a randomized double-blind trial of 10 sessions of active vs. sham tACS 40 HZ gamma band stimulation in 50 patients with schizophrenia evaluating effects changes in cognition and symptoms conducted in Shanghai China. The primary outcome measure was change in the overall composite score on the MATRICS battery. Secondary outcomes were additional cognitive measures. on the MATRICS battery and other neuropsychological tests, and symptoms as measured on the PANSS scale. tACS stimulation was performed using a star-stim stimulator. Placement of stimuli electrodes was: a) active electrode over the left DLPFC (F3), and b) reference electrode over the right parietal region (P2). Comparison to baseline values were done with evaluations 1-2 days after completion of 10 tACS sessions and 2 and 4 weeks later. The main analysis was a mixed model analysis of difference scores from baseline using SAS mixed procedure with three time points (immediately after 10 TACS sessions, 2 weeks later, and 4 weeks later, and also on-line during stimulation session 1) with baseline scores as covariate. Additional analysis used actual scores at the four time points in a mixed model without baseline covariate. Side effects were evaluated with a modification of a scale developed by Bruononi and associates. Blinding was assessed by questionnaires of subjects and guesses whether they received active or sham stimulation.
**Results:** The analyses showed no statistically significant ($P < .05$) effects on improvement in any of the cognitive measures or PANSS rated positive or negative symptoms. There was a trend ($P < .06$) for the MATRICS Domain of verbal learning to show greater improvement compared to sham within 1-2 days after the 10 tACS sessions. tACS was well tolerated and side effects were minimal. Results of guess questionnaire showed effective blinding of subjects.
**Discussion:** The results of this RCT do not support the efficacy of 40 Hz γ tACS stimulation to improve cognition or symptoms in patients with chronic schizophrenia. Three RCTs using alpha or theta band tACS stimulation and other reports of theta band stimulation have shown some more positive effects in patients with schizophrenia and should be investigated further to define the optimal stimulation parameters for tACS trials in patients with schizophrenia.

## 77. Targeting Microglial Activation in Schizophrenia: A Longitudinal [18f] DPA-714 Pet Imaging Study Investigating the Effects of 3-Month Treatment With Natalizumab

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**Background:** It is hypothesized that activation of microglial cells in the brain play a key role in the pathophysiology of schizophrenia. Aiming to pharmacologically reduce microglial activation, we investigated the effects of 3-month treatment with the monoclonal antibody natalizumab on [18F]DPA-714 distribution volume ratio (DVR) and symptom measures in patients with first-episode psychosis (FEP). Natalizumab antagonizes the cell adhesion molecule α4β1-integrin, which prevents migration of peripheral immune cells across the blood-brain barrier. We selected natalizumab due to its known effects in suppressing activation of microglia in neuroinflammatory disorders. We hypothesized that FEP patients receiving natalizumab would show a decrease in [18F]DPA-714 DVR at follow-up, and this change would correlate with symptom improvement.

**Methods:** The study consisted of a baseline case-control comparison of patients with FEP and healthy volunteers, and a nested longitudinal study where the patient group was assessed following 3-month treatment with natalizumab 300mg or placebo. All patients were symptomatic despite receiving stable doses of antipsychotic treatment. Participants with the low affinity binder TSPO genotype were excluded upon screening. Baseline and follow-up brain imaging was carried out using [18F]DPA-714, a positron emission tomography (PET) radiotracer for the mitochondrial 18-kDa translocator protein (TSPO), which is upregulated in activated microglia. Total gray matter (GM), frontal lobe GM, and temporal lobe GM were defined as a priori regions of interest (ROI). We used DVR as our outcome measure to quantify TSPO binding in these ROIs, while using a supervised clustering approach to define a pseudo-reference region. For the baseline case-control comparison, we used ANCOVA to test the effects of group on DVR, with age and TSPO genotype included as covariates. Paired t-tests were used to analyze changes in DVR and symptom measures between baseline and follow-up. Repeated-measures ANOVA was used to test if effects of natalizumab on symptom measures were significantly different from placebo. Spearman's correlation was used to examine correlations. All analyses were conducted using a two-tailed significance level, with p-values $< 0.05$ considered statistically significant.

**Results:** Participants with FEP (n=62) and healthy volunteers (n=41) received baseline PET imaging. Demographics including age, sex, ethnicity, body mass index, TSPO genotype, and injected dose of [18F]DPA-714 were similar between groups (all $p > 0.05$). The patient group had a median duration of illness of 22 months, and a median PANSS total score of 55 in the context of ongoing antipsychotic treatment (median chlorpromazine equivalent dose 287mg/day). Of the 62 patients completing baseline, a total of 47 patients completed follow-up imaging after receiving natalizumab (n=31) or placebo (n=16). At baseline, DVR was significantly higher in patients relative to controls in the total GM ($\eta2=0.043$, $p=0.038$) and temporal lobe GM ($\eta2=0.057$, $p=0.016$), but not in the frontal lobe GM ($\eta2=0.007$, $p=0.406$). There was no significant change in DVR in the total GM (mean ± SD change: +0.001 ± 0.018, $p=0.825$), temporal lobe GM (+0.002 ± 0.017, $p=0.497$), or frontal lobe GM (+0.001 ± 0.024, $p=0.851$) in patients treated with natalizumab. PANSS total scores significantly improved at follow-up in patients who received natalizumab (mean ± SD change: -3.7 ± 9.1, Cohen's $d=0.40$, $p=0.017$). However, the magnitude of improvement in PANSS total scores were similar between the natalizumab and placebo groups, with the model indicating a significant effect of time ($F=14.41$, $p < 0.001$), but not a time*group interaction ($F=0.09$, $p=0.768$). There was no significant correlation between percent change in PANSS total

scores and change in DVR from baseline to follow-up in the total GM, temporal lobe GM, or frontal lobe GM (all $p > 0.05$).
**Discussion:** To our knowledge, this is the largest PET TSPO study to date in FEP, and the first study to test the effects of natalizumab in patients with schizophrenia. Our findings indicate higher TSPO levels in the temporal and total GM in patients with FEP compared to healthy controls, with a small to medium effect size ($\eta 2=0.043 – 0.057$). Contrary to our expectation, natalizumab treatment did not normalize this signal or improve symptom measures relative to placebo, indicating this is unlikely to be an efficacious therapeutic approach for schizophrenia.

## 78. Development of Global Consensus Guidelines for Clozapine Adverse Drug Reaction Monitoring Through Delphi Methodology

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**Background:** Clozapine is the most effective treatment for individuals with treatment-resistant schizophrenia but is associated with serious adverse drug reactions (ADRs), including severe neutropenia. While recent evidence suggests that absolute neutrophil count (ANC) monitoring may not be necessary after the first two years of treatment, continuous monitoring is still mandated in many regions. Additionally, there is a lack of clear guidance on the monitoring of more life-threatening ADRs, such as severe constipation, which poses significant risks to patient health.
**Methods:** To address these issues, a Delphi methodology is being utilized to achieve a global consensus on updated guidelines for ANC and ADR monitoring in patients on long-term clozapine therapy. This Delphi process includes the input of international experts through structured surveys, with the goal of refining monitoring protocols. The focus is on patients who have surpassed the initial phase of clozapine therapy, where current evidence suggests that continued ANC monitoring may be unnecessary.
**Results:** The Delphi survey will provide expert-driven recommendations aimed at modernizing clozapine safety protocols. A global treatment algorithm and a treatment checklist will be developed. The survey results will form the basis of new guidelines that reflect a global consensus on balancing safety and efficacy in clozapine therapy while addressing the need for practical and targeted monitoring strategies.
**Discussion:** The guidelines produced through this Delphi survey will provide clinicians worldwide with updated, evidence-based recommendations for clozapine monitoring. The goal is to use these guidelines to help shift mandated monitoring approaches in jurisdictions globally. By streamlining and focusing on the most critical safety concerns, these guidelines aim to enhance patient outcomes while reducing unnecessary and burdensome monitoring.

## 79. Augmented Reality in Mental Health Training: A Simulation of Schizophrenia Phenomena for Health Students

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**Background:** The stigma of schizophrenia, in addition to being present among mental health professionals (for a review see Valery and Prouteau, 2020), is already present among students (Caïada et al., 2024). There are a whole host of technological interventions to train professionals or students: they have shown contradictory results, particularly in terms of impact on stigma (for a review see Rodriguez-Rivas et al., 2022; Tay et al., 2023). Some have actually proven counterproductive, increasing the desire of subjects for social distance from those with schizophrenia (Brown, 2020; Morgan et al., 2018; Rodriguez-Rivas et al., 2022; Silva et al., 2017). Rodriguez-Rivas et al. (2022) argue that these negative outcomes may be explained by the focus of the interventions on symptoms rather than the recovery process, which may increase stereotypes and prejudice. Moreover, it has been suggested that they should be used with caution and ideally in combination with educational or contact interventions (Ando et al., 2011). A recent study (Tison et al., submitted) shows that students are interested in an augmented reality (AR) simulation of schizophrenia in the context of everyday life and in small groups, which may be compatible with certain recommendations in the literature, particularly on the notion of personal recovery and contact. According to students' recommendations and the literature, we aim at developing an AR intervention for i) training mental health students and ii) reducing stigma among this audience. However, we first conducted a viability and reliability study of the AR intervention.

**Methods:** A study of the viability of the simulation was carried out in the form of two pre-tests. One is currently underway. Mental health professionals, including peer-workers, and psychology students (for now N=37), working alone or in pairs, tested the different parts of the simulation before answering a questionnaire. The questionnaire consisted of several sections: 'Participant information', 'Immersion of the tool in AR', 'Satisfaction and experience of the simulation', 'Feasibility', 'Usefulness', 'Accessibility', 'Other / Comments'. Thematic and descriptive analyses were then carried out.

**Results:** For the moment, the first pretest (initial descriptive analyses of the pre-test) suggest that the simulation enhances the participants' understanding of the symptoms of schizophrenia. The participants also judged that the simulation could be useful for improving student training in schizophrenia, reducing stereotypical beliefs and discriminatory behavior and improving support for people with schizophrenia. The initial thematic analyses show that the participants recognised most of the symptoms presented and that they were able to make personal references to their feelings. Final results of the second pretest and the subsequent study will be presented at the conference. The communication will contain images and concrete examples of the content of the simulation.

**Discussion:** We built an AR prototype to simulate the symptoms of schizophrenia. The AR prototype was built not only on the basis of the scientific literature, i.e. what works best to educate and destigmatize, but also on the basis of the actual needs of the students who will be involved in this training. We are currently conducting a series of pre-tests to assess the viability and reliability of this simulation. So far, participants report a better understanding of

the symptoms of schizophrenia and highlight the pedagogical potential of this tool. Future research will focus on testing the simulation in terms of training and destigmatizing efficacy.

## 80. Emergency Department Visits Involving Hallucinogen Use and Risk of Schizophrenia Spectrum Disorder

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**Background:** Importance: Interest in and use of hallucinogens has been increasing rapidly. While a frequently raised concern is that hallucinogens may be associated with an increased risk of psychosis, there are limited data on this association.
Objectives: To examine whether individuals with an emergency department (ED) visit involving hallucinogen use have an increased risk of developing a schizophrenia spectrum disorder (SSD).

**Methods:** Design, Settings, and Participants: This population-based, retrospective cohort study (January 2008 to December 2021) included all individuals aged 14 to 65 years in Ontario, Canada, with no history of psychosis (SSD or substance induced). Data were analyzed from May to August 2024.
Exposure: An incident ED visit involving hallucinogen use.

Main Outcomes and Measures: Diagnosis of SSD using a medical record–validated algorithm. Associations between ED visits involving hallucinogens and SSD were estimated using cause-specific adjusted hazard models. Individuals with an incident ED visit involving hallucinogens were compared with members of the general population (primary analysis) or individuals with ED visits involving alcohol or cannabis (secondary analysis).

**Results:** The study included 9 244 292 individuals (mean [SD] age, 40.4 [14.7] years; 50.2% female) without a history of psychosis, with a median follow-up of 5.1 years (IQR, 2.3-8.6 years); 5217 (0.1%) had an incident ED visit involving hallucinogen use. Annual rates of incident ED visits involving hallucinogens were stable between 2008 and 2012 and then increased by 86.4% between 2013 and 2021 (3.4 vs 6.4 per 100 000 individuals). Individuals with ED visits involving hallucinogens had a greater risk of being diagnosed with an SSD within 3 years compared with the general population (age- and sex-adjusted hazard ratio [HR], 21.32 [95% CI, 18.58-24.47]; absolute proportion with SSD at 3 years, 208 of 5217 with hallucinogen use [3.99%] vs 13 639 of 9 239 075 in the general population [0.15%]). After adjustment for comorbid substance use and mental health conditions, individuals with hallucinogen ED visits had a greater risk of SSD compared with the general population (HR, 3.53; 95% CI, 3.05-4.09). Emergency department visits involving hallucinogens were associated with an increased risk of SSD within 3 years compared with ED visits involving alcohol (HR, 4.66; 95% CI, 3.82-5.68) and cannabis (HR, 1.47; 95% CI, 1.21-1.80) in the fully adjusted model.
**Discussion:** In this cohort study, individuals with an ED visit involving hallucinogen use had a greater risk of developing an SSD compared with both the general population and with individuals with ED visits for other types of substances. These findings have important

clinical and policy implications given the increasing use of hallucinogens and associated ED visits.

## 81. The Star (Study of Trauma and Recovery) Trial: Effects of an Integrated Trauma-Focused Cognitive Behaviour Therapy for Psychosis on People With Post-Traumatic Stress Disorder and Psychosis

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**Background:** People with psychosis have high rates of trauma exposure and post-traumatic stress-disorder (PTSD), which is associated with worse clinical outcomes. Pilot studies have provided preliminary evidence that trauma-focused psychological therapies can be safe and effective in this population. This trial, the largest to date, evaluated the clinical effectiveness of an integrated, Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp) on post-traumatic stress symptoms in people with psychosis. Secondary aims were to determine the therapy impact on a range of clinical and functional outcomes.

**Methods:** Design, setting and participants: We carried out a rater-blind, parallel arm, pragmatic Randomised Controlled Trial comparing therapy + usual care to usual care only. Adults with comorbid PTSD and F20-F29 schizophrenia-spectrum disorders and the presence of at least one current distressing psychosis symptom were randomized between October 2020-March 2023 from five UK sites. Participants were followed up at 4 (mid-therapy) and 9 months (end of therapy; primary end point) post-randomization.

Interventions: Therapy lasted 9 months and consisted of individual weekly sessions with a clinical psychologist. It was guided by a flexible, manualized protocol integrating trauma-focused CBT and CBT for psychosis. It consisted of four phases: assessment, psychoeducation and goal-setting; formulation; model-based interventions, including trauma memory reprocessing strategies; consolidation and staying well.

Main outcomes and measures: The primary outcome was PTSD symptom severity (Clinician-Administered PTSD Scale for DSM-5; CAPS-5). Secondary outcomes included percentage with loss of PTSD diagnosis (including dissociative sub-type and complex PTSD) and clinically significant change; psychosis symptoms; emotional well-being; substance use; suicidal ideation; psychological recovery; social functioning.

**Results:** Sample characteristics: 305 people were randomized. 170 were women (55.7%) and 223 were White (73.1%), with a mean age of 38.9. Length of psychosis illness was 16.4 years, the majority were on antipsychotic medication (83.6%) and had further concurrent diagnoses (72.8%) in addition to PTSD. 79% met criteria for complex PTSD on the International Trauma Questionnaire, 81% met criteria for severe depression and 80% for severe anxiety on the Depression, Anxiety and Stress Scales, with 81.6% reporting suicidal ideation. 82% presented with delusions and 90.2% with at least one type of hallucination

(80% voices and 82% other modalities hallucinations). All participants reported repeated and multiple traumas, with most across both childhood and adulthood (86%); interpersonal traumas were ubiquitous (99%), with sexual abuse being the most common index event (47%).
CONSORT and therapy adherence: 265 participants attended follow-up assessments at either 4- or 9-months post randomization (86.9%). Primary outcome data were available for 241 participants at 9 months (79.0%). Out of 154 participants randomized to therapy, 144 completed therapy (93.5%), and 117 (81.3%) of therapy completers received 'trauma-focused' interventions such as trauma memory reprocessing. None of the 152 Serious Adverse Events reported across 96 participants were unexpected and related to trial.

Outcomes: Outcome results are embargoed and will be revealed on the day of presentation.

**Discussion:** If successful, TF-CBTp has the potential to provide significant benefit through reductions in distressing PTSD and psychosis symptoms alongside emotional difficulties, and to address clinician concerns about iatrogenic harm when delivering trauma-focused therapy in this population.

## 82. Changes in Immunoglobulin Levels During the First Six Months of Clozapine Treatment in Schizophrenia

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**Background:** Clozapine is the only approved pharmacotherapy indicated for treatment-resistant schizophrenia but is generally underutilised in clinical practice. One reason for limited use is risk of adverse effects. Several adverse effects involve the immune system, such as severe neutropenia and eosinophilia (1), increased risk of pneumonia (2) and COVID-19. (3) It has been suggested that immune modulation may play a role in the efficacy of clozapine (4) as well as in its adverse effects.
Immunoglobulins (Igs) play a key role in the immune system, and they are measured in clinical settings to provide information on immune functioning. Initial cross-sectional analyses shave found higher rates of clozapine prescription among patients with IgG deficiency (5) and an increased risk of IgM deficiency in patients prescribed clozapine compared to those prescribed non-clozapine antipsychotics. As reduced immunoglobulin levels may increase risk of pneumonia and other adverse effects, this association could have important implications for the monitoring of immunoglobulin deficiency during clozapine treatment. However, prospective studies are required to establish temporal relationships between clozapine treatment and changes in immunoglobulin levels.

We tested the hypothesis that reductions in immunoglobulin levels occur over the first 6 months following initiation of clozapine treatment. Relationships between immunoglobulin levels and symptom severity over the course of clozapine treatment were also explored.

**Methods:** This prospective observational study measured immunoglobulin (Ig) levels (A, M and G) in 56 patients with treatment-resistant schizophrenia at 6-, 12- and 24-weeks following initiation with clozapine. Clinical symptoms were also measured at 12weeks using the positive and negative syndrome scale (PANSS). The main analysis used linear mixed models with maximum likelihood estimation to examine the effect of clozapine treatment on immunoglobulin levels over time. Three separate models were applied, with level of IgA, IgG or IgM as the primary outcomes of interest. A fourth model included the level of total Ig (A+G+M) as a secondary outcome of interest. In each model, time was modelled as a fixed effect and treated as a categorical variable (baseline, week 12, and week 24). Models were adjusted for baseline smoking status and exposure to non-clozapine antipsychotic treatment. An exploratory analysis used correlation analyses to investigate whether changes in Ig were associated with percentage change in PANSS total scores after 12 weeks of clozapine treatment. The 12-week time period was chosen as it has been associated with clozapine response in approximately 50% of patients.
**Results:** IgA, IgG and IgM all decreased during clozapine treatment. For IgA and IgG the reduction was significant at 24 weeks (IgA: $\beta = -32.66$, 95% CI = -62.38, -2.93, $p = 0.03$; IgG: $\beta = -63.96$, 95% CI = -118, -9.31, $p = 0.02$). For IgM the reduction was significant at 12 and 24weeks (12 weeks: $\beta = -23.48$, 95% CI = -39.56, -7.42, $p = 0.004$; 24 weeks: $\beta = -33.12$, 95% CI = -50.30, -15.94, $p = < 0.001$). There were no significant differences in baseline IgA, M or G levels between participants who dropped out of the study compared to those who continued. Reduced IgA and IgG levels were significantly correlated with greater reductions in PANSS total score ($n = 32$, IgA $r = 0.59$, $p = 0.005$; IgG $r = 0.48$, $p = 0.03$). The relationship between change in IgM and percentage change in PANSS total score was not significant ($n = 32$, $r = 0.12$, $p = 0.61$). There was no significant relationship between clozapine dose or plasma level with PANSS total scores at 12 weeks.
**Discussion:** In the first longitudinal study of immunoglobulin levels over the first six months of clozapine treatment, all three classes of circulating immunoglobulin reduced during treatment, and this was correlated with treatment response, taken together, these data suggest that immune mechanisms contribute to both desirable and undesirable effects of clozapine.

## 83. Effect of Antipsychotics on Brain Insulin Action in Relation to Glucose Metabolism in Healthy Volunteers: A Pilot Study

Emily Smith*[1], Laurie Hamel[2], Nicolette Stogios[1], Brenda Hughes[3], Marcos Sanches[4], Gary Remington[1], Aristotle Voineskos[1], Ariel Graff-Guerrero[1], Sri Mahavir Agarwal[5], Satya Dash[6], Margaret Hahn[5]

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**Background:** Antipsychotics (APs) are currently the cornerstone of treatment for schizophrenia spectrum disorders. However, despite their efficacy, their use is associated with serious metabolic side effects, including dysglycemia. Previous work from our group has demonstrated that these effects can occur independent of weight gain and in the absence of illness-related risk. Moreover, studies in rodents suggest that this process may in part be mediated by brain insulin; however, this has yet to be explicitly tested in humans. Therefore,

the primary objective of the current proof-of-concept study is to examine whether APs can impact brain insulin action in healthy humans.
**Methods:** We conducted a single-blind, randomized, placebo-controlled crossover trial to test if an acute dose (10 mg) of the AP olanzapine can directly inhibit the brain's response to insulin in healthy, non-obese, AP-naïve participants. Our primary dependent variable was endogenous glucose production (EGP), which we measured using a basal pancreatic euglycemic clamp. Brain insulin receptors were stimulated using 40 IU insulin lispro administered via a metered nasal spray. Each participant completed three different conditions in a randomized order: placebo/placebo, intranasal insulin/placebo, intranasal insulin/olanzapine.
**Results:** In total, 29 participants signed the consent form and 27 participated in a screening visit. At the time of submission, six participants (5 males, 1 female) have completed the full study. To avoid potential batch effects, stored samples will be analyzed together once data collection is complete to identify levels of EGP (our primary outcome) and other metabolic parameters. Therefore, preliminary findings regarding changes in blood glucose levels during the clamp for the current completers are presented below. Compared to the control condition (placebo/placebo), intranasal insulin significantly decreased glucose levels during the last 180 minutes of the clamp (i.e., t=180 to 360 min; difference: -0.039 mmol/L, 95% CI: -0.072, -0.006; adjusted p-value = 0.014) whereas coadministration of olanzapine prevented this effect (difference: -0.007 mmol/L, 95% CI: -0.040, 0.026; adjusted p-value = 0.872). Accordingly, glucose levels were higher in the intranasal insulin/olanzapine condition compared to intranasal insulin/placebo, although this did not meet the threshold for statistical significance (difference: 0.032 mmol/L, 95% CI: -0.001, 0.065; adjusted p-value = 0.055). We also found preliminary evidence for a potential sex effect, with males showing higher glucose levels than females throughout the clamp procedure; however, the small sample size precludes firm conclusions from being made.
**Discussion:** Although blood glucose levels during the pancreatic clamp do not necessarily track with changes in EGP, they can still provide important and relevant insight into how APs interact with brain insulin. Considering this, our preliminary analysis suggests that the metabolic effects of olanzapine (and possibly other APs) may be related to inhibition of brain insulin action. We anticipate that analysis of EGP (our primary outcome) will provide further support for this interpretation. If this is what we find, it could have major implications for the development of early treatments that can help prevent or reverse the negative side effects of APs with the aim of improving patient outcomes and overall quality of life.

## Oral Session: Early Psychosis - Treatment, Recovery, and Relapse

### 84. Effect of Genetic Risk for Schizophrenia on Multi-Organ Structure and Function: A UK Biobank Observational Study

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**Background:** Schizophrenia is hypothesized to be a multi-system disorder, with alterations extending beyond the brain to involve immune, cardiometabolic, and endocrine systems. While previous work has demonstrated an association between schizophrenia polygenic risk and cardiac structure and function, the broader impact of genetic risk for schizophrenia on

other organs remains unexplored. This study investigates the relationship between schizophrenia genetic risk and the structure and function of multiple organs and body composition.
**Methods:** We investigated the causal relationship between schizophrenia and organ structure and function (as assessed using magnetic resonance imaging) using Mendelian randomization in GWAS summary statistic data and individual level data in the UK Biobank (UKBB). The following organs were examined: heart, lung, liver, kidney, spleen, pancreas, and body fat. We performed several sensitivity analyses in the 2-sample MR to assess pleiotropy and potential statistical bias and were able to stratify our analyses in the UKBB to consider sex specific analyses.
**Results:** Magnetic resonance imaging data were available for up to 38,933 UKBB participants. Consistent with previous publications, we observed negative associations between genetic risk scores for schizophrenia (SCZ-GRS) and left and right ventricular end-diastolic and end-systolic volumes. We also observed a positive relationship between SCZ-GRS and right ventricular ejection fraction, lung volume, and liver iron content. Remaining analyses are ongoing and will be presented at the Conference.
**Discussion:** High genetic risk scores for schizophrenia are associated with decreased cardiac volumes, increased right sided ejection fractions, increased lung volumes, and increased liver iron content. This supports the hypothesis that psychotic disorders are associated with multi-organ involvement. Further work is required to determine the clinical significance of these associations, and whether these findings are specific to schizophrenia or are also seen in other psychiatric conditions.

## 85. Brain Cell-Type Shifts in Schizophrenia Interrogated Using Methylomics and Genetics

Chloe Yap*[1], Daniel Vo[2], Matthew Heffel[3], Arjun Bhattacharya[4], Cindy Wen[5], Yuanhao Yang[6], Kathryn Kemper[7], Jian Zeng[7], Zhili Zheng[8], Zhihong Zhu[9], Eilis Hannon[10], Dorothea Seiler Vellame[10], Alice Franklin[10], Christa Caggiano[11], Brie Wamsley[5], Daniel Geschwind[12], Noah Zaitlen[13], Alexander Gusev[14], Bogdan Pasaniuc[3], Jonathan Mill[10], Chongyuan Luo[3], Michael Gandal[2]

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**Background:** Our understanding of the molecular and cellular basis of schizophrenia and other neuropsychiatric disorders remains poorly understood. In fact, we still lack consensus on even foundational questions: whether quantitative shifts in cell types – the functional unit

of life – contribute to schizophrenia. This is a surprisingly hard challenge to solve, as methods that individually count cell-types are not scalable and prone to technical bias. As an alternative, there exist mathematical algorithms that take as input genomic data (e.g., DNA methylation) generated from heterogeneous tissue sample and – using a "reference" specifying the genomic signature of each cell-type – infers proportions of cell-types in the tissue sample. This allows quantification of brain cell-types in disease at scale.
**Methods:** Leveraging advances in human brain single-cell DNA methylation technology, we generated molecular "signatures" for 7 brain cell-types: excitatory neurons, inhibitory neurons, astrocytes, endothelial cells, microglia, oligodendrocytes, and oligodendrocyte precursor cells. We also collated DNA methylation profiles of post-mortem prefrontal cortex tissue from 1270 donors, including from individuals diagnosed with schizophrenia, Alzheimer's disease, and autism. We then input both datasets into a deconvolution algorithm, to estimate for each prefrontal cortex sample the relative proportions of each of the 7 cell-types. Next, we used matched individual-level genetic data to generate "polygenic scores", representing that individual's (common) genetic loading for each of schizophrenia, Alzheimer's disease and autism. Because genetics are immutable from birth, they assist with causal interpretations of statistical associations. That is, an association between a polygenic score for a trait and a cell-type indicates that the genetic aetiology for that trait relates to a change in that cell-type; that is, a causal contribution.
**Results:** We observe and replicate changes in cell-type proportions for schizophrenia (decreased oligodendrocytes) and compare to Alzheimer's disease (endothelial cell loss), and autism (increased microglia). We also find age- and sex-related changes. With respect to potential causality, there were no associations between genetic loading for schizophrenia and oligodendrocyte proportion. This may indicate that oligodendrocyte loss is a consequence of schizophrenia (rather than directly sharing genetic aetiology); alternatively, it may imply that the analysis lacks statistical power to identify a significant difference. However, there was a statistically significant relationship between genetic loading for schizophrenia and reduced astrocytes. In comparison, we found multiple layers of evidence (including based on polygenic scores) indicating that endothelial cell loss causally contributes to Alzheimer's disease.
**Discussion:** We implicate specific cell-type shifts in the pathophysiology of schizophrenia and other neuropsychiatric disorders. The association between schizophrenia and oligodendrocyte loss is likely robust, as our DNA-methylation based results complement results from smaller-scale histological, neuroimaging and transcriptomic studies. While oligodendrocytes may not lie on the causal pathway to schizophrenia, their loss may represent a secondary or compensatory process and therefore warrants further study for association with other outcomes associated with schizophrenia diagnosis.

## 86. Developing and Validating a Primary Care Psychosis Risk Prediction Model (P Risk) Using Electronic Health Records

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**Background:** In the UK, family doctors are an important part of the care pathway for psychotic disorders because most patients are referred to specialist mental health services via primary care. Family doctors find detecting the early signs of psychosis difficult because they are often non-specific and may lead to other, less serious, mental health problems. Family

doctors also lack the opportunity to build diagnostic skills in this area because individually they do not see many patients with early signs of psychosis and lack of care continuity is a further problem. We hypothesised that a data driven approach to detecting early signs might solve this problem.

**Methods:** In a prospective prediction study we used statistical regression prediction methods to develop and internally validated a psychosis risk prediction algorithm, called P Risk, using a linked routine primary and secondary care health records dataset of 300,000 patients, to predict psychosis risk up to 6 years in advance. Study predictors were 13 nonpsychotic mental health problems and medications and age, gender, ethnicity and social deprivation. The outcome was time to an ICD10 psychosis diagnosis and accuracy was calculated using Harrell's C and sensitivity, specificity and likelihood ratios.

We then further externally validated P Risk in a completely separate linked routine dataset of 1.6 million patient records. The same predictors and accuracy measures were used as for the P Risk development study. Results were compared between the two studies.

**Results:** In the development study there were 830 diagnoses of psychosis. Mean age was 45.3 years and 43.5% were male. Median follow-up was 6.5 years (IQR 5.6, 7.8). Overall 8-year incidence of psychosis was 45.8 (95% CI 42.8, 49.0)/100,000 person years at risk. A risk prediction model including age, sex, ethnicity, social deprivation, consultations for suicidal behaviour, depression/anxiety and substance abuse, a history of consultations for suicidal behaviour, smoking history and substance abuse and prescribed medications for depression/anxiety/PTSD/OCD and total number of consultations resulted in good discrimination (Harrell's C=0.774 after internal validation). Identifying patients with predicted risk exceeding 1% over 6 years had sensitivity of 71% and specificity of 84%. In the external validation study psychosis risk increased with values of the P Risk prognostic index. Incidence was highest in younger age groups and mainly higher in males. Harrell's C was 0.79 (95% CI 0.78, 0.79). A risk threshold of 1% gave sensitivity of 65.9% and specificity of 86.6%.

**Discussion:** The accuracy results of the development and external validation studies were similar. P Risk is automatable, low cost and provides an accurate individualised prediction of future risk. It is designed to be a Clinical Decision Support Tool, to help family doctors decide who to refer for a psychosis assessment in secondary care. Since conducting the development and external validation studies we have completed a feasibility and acceptability study with promising results. We are about to start recruiting family doctor practices for an implementation study which consists of a live run of P Risk on 14 family doctor computers for 6 months in two area of the UK (Bristol and London). Further testing is required but P Risk has the potential to be used in primary care to detect future risk of psychosis.

### 87. Migrant Differences in Antipsychotic Treatments in First Episode Psychosis: A Swedish Population-Based Cohort Study

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**Background:** Ethnic and migrant inequalities in psychosis incidence, recovery and treatment have been widely observed in the UK, USA and Netherlands. We sought to examine differences in antipsychotic (AP) treatments by migrant status and region of origin in the 12-months after Non-affective First Episode Psychosis (FEP) diagnosis in Sweden.
**Methods:** We conducted a population-based cohort study of individuals aged 16-65 at non-affective FEP diagnosis using the Swedish National Patient Register. Binary measures (Yes/No) for the receipt of: any AP, First-Generation AP (FGA), Clozapine, Long-Acting Injectable (LAI) AP, and AP Polypharmacy were investigated by migrant status and region of origin for migrants and children of migrants (COM). We ran multivariable logistic regression models adjusted for clinical, demographic and socioeconomic factors, including area-level contextual factors prior to the year of diagnosis (or the closest recorded year).
**Results:** Of 32,282 individuals with FEP, 14,482 (44.9%) were of migrant Background:s. In adjusted models, we found migrant groups were less likely to have received all outcomes, and COM groups were more likely to have received FGA (OR=1.14, 95%CI: 1.01-1.27) and LAI (OR=1.34, 95%CI: 1.14-1.56) than Swedish-born non-migrant groups. Effects were observed in migrants and COM migrants from regions such as Eastern Europe, Middle East and North Africa and Sub-Saharan Africa.
**Discussion:** We identified robust differences in the receipt of AP treatments between some migrant and non-migrant groups not attributable to clinical, sociodemographic, or contextual factors. Further research is needed to understand and address these inequalities.

## 88. Prediction of Early Functional Recovery and Symptom Remission After a First Episode of Schizophrenia

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**Background:** After a first episode of psychosis (FEP) and initial treatment, positive symptom improvement is frequently relatively robust. However, recovery outcomes, e.g., social functioning, role functioning, quality of life in early and established psychosis samples can be highly variable. Recent meta-analyses have reported recovery rates ranging from 21% to 57%, depending on how recovery was defined (Huxley et al 2022; Hansen et al 2023). Identifying potentially modifiable contributors to functional recovery could have critical clinical implications.
**Methods:** Participants were 81 young people with early phase schizophrenia (onset < 2 years before study entry) enrolled in the UCLA Aftercare Program. A 12-month Coordinated Specialty Care intervention included medication management, case management, psychoeducation, group therapy, and cognitive remediation. Premorbid adjustment and cognition were assessed with the Cannon-Spoor Premorbid Adjustment Scale and MATRICS Consensus Cognitive Battery (MCCB), respectively, at baseline. Recovery was assessed longitudinally using the Social and Role subscales of the Global Functioning Scale (GFS) by trained raters using a cut-off of > or equal to 7 that was empirically derived using comparisons with controls. Negative symptoms were assessed with the SANS (Expressive and Experiential) and positive symptoms with the SAPS (Delusions / Hallucinations and Disorganization). Ratings of objective Quality of Life (QOL) were made with the Heinrichs Scale. GFS, SANS, and SAPS assessments were conducted at baseline and then every three months for one year. Negative symptom remission was defined as < or equal to 2 on the

SANS; and Positive symptom remission was defined as < or equal to 2 on the SAPS (Andreasen et al 2005). For participants with at least 6 months of data, we used the Last Observation Carried Forward to month 12 in this analysis.
**Results:** At the 12-month point, social recovery was achieved by 54% of participants and role recovery by 46% of participants. Positive symptom remission was achieved by 72% of participants. Symptom remission for expressive negative symptoms was achieved by 69% of participants and by 58% for experiential negative symptoms. Good QOL at 12 months was achieved by only 24% of participants. Only 18% of our sample achieved a good outcome in all domains combined. Using logistic regression analysis, we found that higher social recovery was predicted by higher premorbid social adjustment (p=.001) and by a higher overall cognitive composite score (p=.039). Better role recovery was predicted by a higher premorbid education level (p=.016) but was not related to the cognitive composite score (p = .339).
**Discussion:** Through this longitudinal analysis we identified treatment targets and clinically meaningful changes in response to treatment interventions. Our participants responded robustly to coordinated care in that 72% achieved positive symptom remission, which is consistent with previous reports. The similarity of expressive negative symptom remission (69%) compared to positive symptom remission (72%) suggests that certain negative symptoms can respond to comprehensive treatment in early course schizophrenia participants. We provide confirmation that high levels of premorbid functioning and baseline level of cognitive performance can predict subsequent social and role functioning even 12 months after study entry. Positive symptom recovery exceeded rates of early social and role functioning and improvements in quality of life. These findings support the view that positive outcomes can be obtained after a first episode of schizophrenia in a coordinated specialty care program and confirm that good work/school functioning and quality of life are among the most difficult outcomes to achieve.

## 89. Prescription of Clozapine in Patients With Recent-Onset Psychosis in the Connection Learning Healthcare System EPINET Hub

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**Background:** Clozapine is the most effective treatment for treatment-resistant schizophrenia, but is highly underutilized. Little is known about clozapine use in the early stages of psychosis. This study aims to determine the characteristics of individuals who were prescribed clozapine in one of the 23 CSC clinics in Maryland and Pennsylvania that together form the Connection Learning Healthcare System (CLHS), one of eight hubs in the NIMH-funded Early Psychosis Intervention Network (EPINET).
**Methods:** The CLHS, along with its predecessor, the Pennsylvania First-Episode Program Evaluation initiative (HeadsUp), enrolled 1445 patients with onset of psychosis within 1-2 years of enrollment. Patients were administered surveys collecting clinical data, supplemented by demographic information and clinician assessments, including clinical symptom and function rating scales and medication information, at enrollment and every 6

months thereafter. A cohort of 1183 patients with complete medication data was used to explore differences among four patient groups: 1) clozapine prescribed before or at the time of admission, 2) clozapine anytime started after admission, 3) other antipsychotics, but never clozapine, prescribed before, at, or after admission, and 4) never prescribed antipsychotics.
**Results:** 32 (2.7%) patients were taking clozapine before or at the time of admission, 48 patients (4.1%) started clozapine after clinic enrollment, 1075 (90.9%) were prescribed other antipsychotics but not clozapine either at admission or during clinic enrollment, and 28 (2.4%) never received antipsychotics. The groups did not vary by age, education, Hispanic ethnicity, insurance status, age when first antipsychotic was taken, or gender. White patients were more likely to receive clozapine than Black patients (4.7% vs. 1.3%, p=0.002), with the greatest disparity seen among those privately insured. Patients taking clozapine at admission were 3x more likely to have a diagnosis of schizophrenia than patients taking another antipsychotic (40.6% vs 13.7%, p = 0.00002). Patients with higher negative and positive symptom scores and lower role and social functioning at admission, and those with more antipsychotic trials during admission, were more likely to receive clozapine after admission compared to patients receiving other antipsychotics. Among the 18 clinics enrolling at least 20 patients, clozapine prescription after enrollment ranged from 0% to 21.7% (mean= 4.9%, median = 3.4%, p = 0.0005). Patients prescribed clozapine during admission remained enrolled in CHLS longer than patients on other antipsychotics or patients not receiving antipsychotics (28.0, 20.9, and 17.5 months, respectively, $p < .05$).
**Discussion:** A minority of patients (6.8%) enrolled in CLHS received clozapine initiated before or during admission. This is a somewhat higher rate than typically reported rates of clozapine use in patients with long-standing schizophrenia, despite the young age of the study cohort, perhaps reflecting the relatively high level of engagement of CLHS patients. However, racial disparities in clozapine prescription and marked differences in clozapine prescription by clinic suggest important targets for improving the provision of clozapine treatment to individuals with treatment-resistant early-onset psychosis.

## 90. A Physical Exercise Program Significantly Boosts the Impact of Cognitive Training on Attention Deficits After a First Episode of Schizophrenia

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**Background:** Systematic cognitive training and physical exercise interventions have been shown to improve the severe cognitive deficits of individuals with schizophrenia to a moderate degree. Our initial smaller study suggested that adding a physical exercise program to cognitive training has promise for enhancing the impact on cognition by improving learning capacity. Focusing on the period after a first psychotic episode may maximize these intervention effects.
**Methods:** In a randomized controlled trial, we provided computerized cognitive training using web-based neurocognitive and social cognitive programs from Posit Science, 4 hours/week for 6 months for all participants, monitoring by cognitive coaches. Half of the 100 recent-onset schizophrenia participants were randomized to a physical exercise program and half to a didactic healthy living group with comparable intervention contact. Group physical exercise sessions were led by a certified fitness trainer, typically with 4-6 participants, for two 45-min sessions/week. Participants were also assigned two 30-min sessions/week of individual exercise homework. The group exercise sessions included

combined moderate-intensity aerobic conditioning (1-min intervals) and moderate-to-high-intensity strength and calisthenic conditioning (1-min intervals). The MATRICS Consensus Cognitive Battery was administered at baseline and at 3 and 6 months. The amount of exercise was measured with the International Physical Activity Questionnaire and by tallying the number of exercise sessions completed.
**Results:** Repeated measures ANOVA with 87 participants with complete data demonstrated that Attention/Vigilance was enhanced to a significantly greater extent by the combination of cognitive training and physical exercise than by cognitive training and the healthy living group (T score gain of 4.6 vs. 0.0 over 6 months, $F = 4.54$, $p = 0.012$). This differential cognitive improvement was not apparent across all cognitive domains, for which both groups showed notable improvement ($F = 26.64$, $p < .001$). The amount of improvement in Attention/Vigilance by 3 months was significantly associated with the number of exercise sessions attended ($p = .02$) and the intensity of exercise ($p = .02$) during that period. The gain in Attention/Vigilance by 6 months was significantly predicted by the total metabolic energy expended during exercise (METs) during the first 3 months ($p = .04$) and the proportion of group exercise sessions attended ($p = .01$) over 6 months.
**Discussion:** Adding a combined aerobic and strengthening exercise program to cognitive training clearly enhances the impact on the core deficit in focused, sustained attention that is present after a first episode of schizophrenia. The gains in focused, sustained attention over 3 and 6 months are significantly related to the amount and intensity of exercise, consistent with the view that the physical exercise is driving the attentional improvements beyond the effect of cognitive training. Considered with the findings of our initial study, these new results encourage adoption of this treatment combination for improving cognitive deficits in the early course of schizophrenia.

## 91. Impact Of Relapse: A Multi-Modal Investigation of Neuroimaging, Molecular, and Cellular Alterations in Psychotic Disorders

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**Background:** Psychotic disorders, such as schizophrenia, present substantial challenges in clinical management, with relapse being a critical factor shaping both clinical and psychosocial outcomes. Combating relapse is a key goal in the treatment of psychotic disorders. While most research on relapse emphasizes identifying risk factors for prevention, meta-analyses have consistently highlighted medication non-adherence, substance use, and stress as common triggers. These factors are often tied to individual traits, lifestyle, and environmental influences, making them difficult to manage. In contrast, neuroimaging studies have shown that despite the diversity of relapse triggers, post-relapse brain changes exhibit common patterns. A deeper understanding of biological consequences of relapse may lead to effective therapeutic strategies to mitigate post-relapse changes and minimize the associated poor disease trajectory. Therefore, this study aims to investigate post-relapse changes using neuroimaging, molecular, and cellular data.
**Methods:** The Johns Hopkins Schizophrenia Center has established a longitudinal cohort of patients with early-stage psychosis (onset within two years at the initial study enrollment), along with matched healthy controls, and we are actively recruiting new subjects to expand this cohort. We have collected multimodal data, including clinical assessments, structural and functional brain imaging, and magnetic resonance spectroscopy (MRS), from the same individuals. A key asset of this cohort is the collection of olfactory neuronal cells (ONCs)

through non-invasive nasal biopsy, providing repeated access to homogeneous neuronal cells that can capture state changes from living subjects. By integrating these datasets, we compared patients who experienced relapses between disease onset and data collection (relapse group) with those who did not (no-relapse group).
**Results:** Patients in the relapse group showed significantly greater deviations from healthy controls compared to the no-relapse group. Resting-state functional MRI (rs-fMRI) revealed widespread hyperconnectivity in the relapse group. 7-Tesla MRS found significant decreases in N-acetylaspartate (NAA) in the thalamus and anterior cingulate cortex among relapsed patients. RNA sequencing (RNA-Seq) of ONCs identified a significant increase in the expression of synaptotagmin-7 (SYT7), which correlated with both pathological rs-fMRI connectivity and NAA levels. Further pathway analysis of RNA-Seq data pinpointed significant alterations in calcium signaling post-relapse. Measurement of ATP-induced calcium dynamics in ONCs revealed that cells from the relapse group exhibited faster and stronger calcium mobilization in response to the stimulation, compared to the no-relapse group. Moreover, calcium peak amplitude correlated with SYT7 mRNA and protein levels, and SYT7 knockdown diminished the augmented calcium dynamics observed in the relapse group.
**Discussion:** Our findings reveal significant post-relapse alterations, with SYT7 emerging as a key hub mediating relapse-associated changes. Ongoing clinical data analyses, cellular biology experiments, and mouse model studies aim to further elucidate the mechanisms underlying these post-relapse changes.

**Lunch and Poster Session I**

## S1. Associations Between Experiences of Discrimination and Symptom Severity Among Individuals Presenting to Coordinated Specialty Care Clinics in Washington State

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**Background:** Prior research has highlighted disparities in mental health disorders associated with social factors, as well as a potential link between personal experiences of discrimination and the severity of mental health symptoms. However, the specific role of discrimination in shaping the severity of psychosis, anxiety, and depression symptoms, particularly at intake to specialized care, remains understudied. The goal of this study was to explore how lifetime and daily experiences of discrimination influence the severity of self-reported symptoms of psychosis, anxiety, and depression among individuals seeking treatment at coordinated specialty care programs.

**Methods:** Participants (N=208) enrolled in New Journeys, a network of coordinated specialty care programs in Washington State, completed standardized measures at intake to assess symptoms of psychosis (Community Assessment of Psychic Experiences -CAPE-P15), depression (Patient Health Questionnaire -PHQ-9), and symptoms of anxiety (Generalized Anxiety Disorder GAD-7). Participants also completed the Experiences of Discrimination questionnaire which captures experiences of lifetime and daily discrimination.
Generalized linear mixed models (GLMMs) were used to examine the effects of gender (male, non-male), sexual orientation (LGBTQ+, heterosexual), ethnoracial group (non-Hispanic White, Hispanic, Black/African American, Asian, American Indian/Alaska Native, Multiracial), lifetime discrimination, and daily discrimination on the severity of self-reported symptoms of psychosis, depression, and anxiety.

discrimination on severity of self-reported symptoms.

**Results:** There were no significant differences in reported lifetime or daily discrimination across any ethnoracial group when compared to non-Hispanic White individuals. However, daily discrimination was significantly associated with increased symptoms of anxiety ($\beta$ = 0.32, CI: 0.27–0.36, $p \leq 0.001$), depression ($\beta$ = 0.40, CI: 0.35–0.45, $p \leq 0.001$), and psychosis ($\beta$ = 0.04, CI: 0.03–0.04, $p \leq 0.001$), after controlling for all other variables. In contrast, lifetime discrimination was associated with significantly lower symptoms of psychosis ($\beta$ = -0.03, CI: -0.03 to -0.04, $p \leq 0.001$).
Regarding sexual orientation, individuals identifying as LGBTQ+ reported significantly fewer symptoms of anxiety ($\beta$ = -2.35, CI: -3.43 to -1.26, $p \leq 0.001$) and psychosis ($\beta$ = -0.01, CI: -0.02 to -0.01, $p \leq 0.001$). For gender, individuals who identified as non-male reported significantly greater symptoms of anxiety ($\beta$ = 2.69, CI: 1.80–3.57, $p \leq 0.001$), depression ($\beta$ = 1.70, CI: 0.59–2.80, p = 0.003), and psychosis ($\beta$ = 0.11, CI: 0.11–0.11, $p \leq 0.001$), compared to males.

There were also significant ethnoracial differences in the severity of self-reported symptoms when compared to non-Hispanic White individuals. Specifically, Black/African American individuals reported significantly higher levels of anxiety ($\beta$ = 5.70, CI: 3.57–7.84, $p \leq 0.001$) and depression ($\beta$ = 3.52, CI: 1.18–5.87, p = 0.003). In contrast, Asian individuals reported

significantly fewer symptoms of anxiety (β = -2.09, CI: -3.65 to -0.54, p = 0.009), and American Indian/Alaska Native individuals reported significantly fewer symptoms of depression (β = -3.58, CI: -6.43 to -0.73, p = 0.014). Hispanic individuals reported significantly fewer symptoms of psychosis (β = -0.09, CI: -0.11 to -0.08, p ≤ 0.001), while Multiracial individuals reported significantly greater symptoms of psychosis (β = 0.07, CI: 0.05–0.09, p ≤ 0.001).

**Discussion:** These findings suggest a significant relationship between discrimination and clinical symptoms at intake for individuals with first-episode psychosis (FEP). The results also highlight ethnoracial differences in the severity of anxiety, depression, and psychosis, with certain groups, such as Black/African American and Multiracial individuals, reporting more severe symptoms. These results underscore the importance of investigating how discriminatory experiences intersect with ethnoracial identity to influence mental health outcomes. Further research is needed to explore these differences in greater depth and assess the long-term impact of discrimination on mental health trajectories.

## S2. Environmental Risk Score as a Predictor for 25-Year Symptom and Functional Trajectories in First Episode Psychosis

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**Background:** The lifetime prevalence of psychotic disorders is approximately 3% of the population. Psychotic disorders have profound personal and social impact and contribute substantially to worldwide psychiatric morbidity and mortality. Environmental exposures, including urbanicity, paternal age, obstetric complications, minority status, cannabis use, and childhood adversity predict schizophrenia. It is unknown, however, whether after psychosis onset environmental risk continues to predict illness course. In this study, we test whether the cumulative burden of environmental risk impacts symptoms and functional trajectories over the 25 years following first admission for psychosis.

**Methods:** Data are drawn from the Suffolk County Mental Health Project, a first admission psychosis cohort. Participants were recruited from all 12 inpatient psychiatric units in Suffolk County, New York (response rate 72%). Environmental risk was quantified using the Maudsley Environmental Risk Score (ERS). The ERS is calculated as the level of exposure to each risk factor, weighted by the strength of the meta-analytic odds ratio linking the risk factor and schizophrenia. Environmental factors included in Maudsley ERS are: urbanicity, paternal age, ethnic minority, cannabis use, childhood adversity, and obstetric complications. Of the 628 individuals in the full cohort, 570 had data on at least 3 of 6 environmental risk factors. Individuals with environmental risk data tended to be younger than those without, but did not differ in terms of other demographic or clinical factors. Symptoms were assessed using the Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms. Cognition was assessed based on premorbid intellectual and academic test data, and post-admission using a comprehensive neuropsychological battery translated to the IQ metric. Functioning was assessed in the premorbid phase using the Premorbid Adjustment Scale translated to the GAF metric, and after illness onset using the Global Assessment of Functioning. Multilevel models were used to estimate symptom, cognitive, and functional trajectories, with ERS added as a predictor of both random intercepts and slopes.

**Results:** We have replicated prior findings showing elevated ERS in schizophrenia. Subsequent trajectory analyses are underway. Based on the established link between environmental risk and neurodevelopment, and the close link between cognitive and functional trajectories, we hypothesize that higher ERS scores will predict more severe downward cognitive and functional trajectories. ERS being consistently inversely associated with GAF scores across the follow-up period ("r" range from -0.10 to -0.19 across the 2-, 4-, 10-, and 20-year follow-ups), and at the 20-year follow-up, ERS was positively correlated with the severity of reality distortion (r=0.14) and avolition (r=0.11).
**Discussion:** If the proposed analyses support the above hypotheses, this would suggest the potential of ERS, in combination with genetic risk, to be incorporated into clinical prediction models. The aim of such models would be to identify at first admission those individuals at risk for a more severe course of illness, who might benefit most from long-term, comprehensive care.

## S3. Ideal and Actual Affect Discrepancies in Clinical High Risk for Psychosis: Implications for Negative Symptoms Across the Schizophrenia-Spectrum

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[1]University of Georgia

**Background:** Negative symptoms are frequently observed across all phases of psychotic disorders and predictive of a number of poor outcomes (e.g., lower quality of life, reduced rates of recovery, probability of illness onset). Unfortunately, pharmacological treatments have not led to clinically significant improvements and the identification of novel mechanisms that can serve as treatment targets remains an urgent need in the field. Recent evidence indicates that discrepancies between ideal and actual affect may be a novel psychological process underlying negative symptoms in adults with schizophrenia. The current study examined whether these same psychological processes are associated with greater negative symptom severity in youth at clinical high-risk for psychosis (CHR) (i.e., those meeting criteria for a prodromal syndrome).
**Methods:** Participants included 27 CHR individuals and 24 healthy controls (CN) who completed the Affect Valuation Index (AVI) and measures of CHR symptom severity. To determine the presence of group differences, Group (CHR, CN) X Arousal Level (High, Medium, Low) mixed-models ANOVAs were calculated for positive and negative conditions of ideal affect, actual affect, and ideal-actual affect difference scores. Spearman correlations were calculated to evaluate associations between symptom severity and the key AVI scores.
**Results:** Results indicated that CHR individuals displayed greater negative affect discrepancy scores than CN, suggesting that they strongly desire to feel less negative in the future than they actually do. Furthermore, CHR reported greater negative actual affect than CN; however, they did not differ in ideal negative affect scores. Groups did not differ in positive affect discrepancy scores, actual positive affect scores, or ideal positive affect scores. Higher negative symptoms were associated with greater positive affect discrepancy scores, lower ideal and actual positive affect, and higher actual negative affect.
**Discussion:** CHR participants demonstrated some similarities to individuals with schizophrenia examined in past studies, as indicated by high discrepancies between ideal versus actual negative affect. However, the pattern of discrepancies was not observed for ideal versus actual positive affect, which was more intact in CHR. Additionally, ideal affect, actual affect, and discrepancies between the two conditions were associated with negative symptoms in CHR, suggesting that these affective processes may be novel transphasic

psychological mechanisms of negative symptoms. To improve anhedonia, avolition, and asociality, it may be important to alter appraisals of ideal positive and negative affect to motivate individuals to engage in goal-directed, recreational, and social activities.

## S4. Ethnoracial Differences in Measurement Based Care in Coordinated Specialty Care Programs

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**Background:** Measurement based care, which is the use of systematic data collection in the treatment process to inform treatment plans and monitor outcomes when implemented correctly has been associated with improved treatment outcomes for mental health. The measurement based care framework consists of four phases: deliver the measure to the client, the practitioner reviewing the measure prior to or during the session with the client, the service user and the practitioner reviewing the measure together during the session, and the service user and practitioner collaborating to adjust the treatment goals and plans as informed by the measure and the discussion. Yet, fidelity to measurement based care is often not attained, particularly in community behavioral health settings, such as many coordinated specialty care (CSC) programs for the treatment of first episode psychosis. Often fidelity fails phase one of the framework. This study sought to better understand the delivery of measures to clients in a CSC network and whether there were measurement delivery differences in the race or ethnicity clients. We then reviewed whether there were ethnoracial differences in the clients actually completing the measures. These measures consisted of the Patient Health Questionnaire – 9 (PHQ-9) measuring symptoms of depression, the Generalized Anxiety Disorder – 7 Item (GAD-7), and a measure of substance use.
**Methods:** 270 individuals were included in the sample of which 40% identified as White, 4% as American Indian Alaska Native, 6% as Asian or Pacific Islander, 9% as Black or African American, 22% as Hispanic, and 17% as Multiracial or Other. A generalized linear mixed model was used for the analysis with non-Hispanic White individuals as the comparison group. The data was collected exclusively from a coordinated specialty care program in the Pacific Northwest. All measures are expected to be delivered monthly to the individuals for the duration of their services.
**Results:** On average 59% of the expected PHQ-9s were delivered, 59% of the GAD-7s, and 66% of the substance use measure. There were significant differences between the ethnoracial differences in the delivery of measures for the PHQ-9, the GAD-7, and the substance use measure compared to non-Hispanic White individuals. The practitioners for the American Indian Alaska Native individuals delivered the PHQ-9 significantly less ($\beta$=-.151, CI: -0.252 - -0.050, p =.001). The GAD-7 was delivered significantly more ($\beta$=0.01, CI: .009 - .012, p $\leq$.001) to Asian and Pacific Islander clients. Black and African American clients were delivered the PHQ-9 significantly less ($\beta$=-.061, CI: -0.114 - -0.008, p =.025). Hispanic individuals were delivered the PHQ-9 significantly less ($\beta$=-.007, CI: -0.012 - -0.002, p =.008), the GAD-7 significantly less ($\beta$=-.007, CI: -0.009 - -0.005, p $\leq$.001), and the substance use measure significantly more ($\beta$=0.47, CI: .025 - .068, p $\leq$.001). Finally, practitioners delivered significantly less PHQ-9 ($\beta$=-.061, CI: -0.067 - -0.056, p $\leq$.001), and GAD-7 ($\beta$=-.059, CI: -0.067 - -0.050, p $\leq$.001) to multiracial and individuals of other races. Upon the delivery of measures there were significant differences in the measures being completed for Black and African American individuals who completed significantly less

PHQ-9 (β=-.038, CI: -0.041 - -0.035, p ≤.001) and substance use measures (β=-.070, CI: -0.071 - -0.069, p ≤.001). There were no other ethnoracial differences.
**Discussion:** The expectations that health care providers are using measures to inform care and treatment are increasing in the U.S. Yet, the consistency of measures being delivered, particularly in community behavioral health programs, is low. Alongside that, providers are delivering measures at a significantly different rate to ethnoracial groups. This would indicate that there needs to be increased training not only in how to deliver measures consistently within CSC programs, but also that increased work needs to be conducted to better understand why measures are being offered less to ethnoracial minorities. Furthermore, additional work should be conducted to better understand why Black and African American individuals who are offered measures to complete are completing significantly less of them. This could indicate a problem with the cultural alignment with the measures themselves, a lack of rapport or trust with providers etc. that should be addressed to improve the quality of care individuals are offered.

## S5. Association of Multidimensional Schizotypy With Cognitive-Behavioral Disorganization in Daily Life: An Experience Sampling Methodology Study

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**Background:** Schizotypy is a multidimensional construct that is composed of positive, negative, and disorganized dimensions. Historically, disorganized schizotypy, which involves disruptions in thoughts, speech, behavior, and affect, has been relatively understudied and less clearly operationalized than the other dimensions. The present study employed experience sampling methodology to examine the associations of positive, negative, and disorganized schizotypy, as measured by the Multidimensional Schizotypy Scale, with daily-life experiences.
**Methods:** A total of 601 young adults were prompted eight times daily for one week to complete ESM questionnaires that assessed affect, social functioning, schizotypic experiences, situation appraisals, and substance use in daily life, with an emphasis on disorganized schizotypic experiences and communication disruptions.
**Results:** As hypothesized, disorganized schizotypy was associated with momentary disorganization, negative affect, and stress over-and-above positive and negative schizotypy. Negative schizotypy was associated with diminished positive affect, poor social functioning, and diminished emotional clarity. Positive schizotypy was associated with momentary reports of strange or unusual thoughts, racing thoughts, and emotions and thoughts feeling out of control. All three schizotypy dimensions uniquely predicted communication difficulties. Cross-level interactions indicated disorganized schizotypy, but not positive or negative schizotypy, predicted stronger associations of simultaneous reports of doing something that requires focus and attention with negative affect and difficulty completing the current task.
**Discussion:** Overall, the present study expands our understanding of disorganized schizotypy's expression in daily life and builds upon previous findings by demonstrating the unique associations of positive, negative, and disorganized schizotypy with daily-life experiences.

## S6. The Barcelona Longitudinal Investigation of Schizotypy Study 1: Multidimensional Schizotypy Predicts Psychopathology Dimensions and Functioning 8 Years Later

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**Background:** Schizotypy is conceptualized as the phenotypic expression of the developmental vulnerability for schizophrenia that is expressed across a dynamic continuum of personality traits and symptoms ranging from subclinical impairment to full-blown schizophrenia.Although the psychometric high-risk method based on schizotypy has proven to be a highly cost-effective strategy for unravelling etiological factors for schizophrenia-spectrum disorders, there is a paucity of longitudinal studies with nonclinical populations. This study analyzed the predictive validity of positive and negative schizotypy in a longitudinal project (Barcelona Longitudinal Investigation of Schizotypy; BLISS) spanning a total of 7.8 years.
**Methods:** At Time 1 (T1), 547 college students completed the Wisconsin Schizotypy Scales. We re-assessed subsamples (oversampled for high schizotypy to ensure variability) at four re-assessments. This study reports psychopathology, psychological and functional outcomes assessed with self-report and interview (CAARMS, Negative Symptom Manual, SCID-II Cluster A) measures at T4 (n = 89; 4.4 years after T1) and self-report measures at T5 (n = 169; 7.8 years after T1). T1 positive and negative schizotypy were entered simultaneously as predictors in linear regression models.
**Results:** Positive schizotypy predicted positive symptoms at T4, whereas negative schizotypy uniquely predicted interview-rated negative symptoms and schizoid personality traits (even when controlling for mood and avoidant personality), and impaired social and global functioning. Both dimensions predicted suspiciousness, and schizotypal and paranoid personality traits, as well as low self-esteem and depression. Similarly, both dimensions predicted suspiciousness, depression and poor social support at T5, whereas only positive schizotypy predicted low self-esteem, anxiety and perceived stress.
**Discussion:** Both schizotypy dimensions consistently showed a meaningful pattern of hypothesized differential and overlapping predictions, which supports their validity as distinct dimensions and their predictive validity in nonclinical samples. The study of schizotypy clarifies our understanding of continuities and discontinuities between subclinical and clinical expressions of schizotypy (i.e., schizophrenia-spectrum disorders), which should improve our knowledge of the heterogeneity in terms of developmental pathways towards both nonclinical and clinical outcomes, helping to identify compensating or protective factors and thus informing early preventative strategies.

## S7. Childhood Trauma and Hippocampal Function: Unraveling Mechanisms Underlying Reward Processing Deficits and Anhedonia

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**Background:** Childhood trauma has been linked to negative symptoms, such as anhedonia. Increasing evidence suggests hippocampal alterations may also play a role in the development of anhedonia, due to its involvement in reward-related cognitive processes, such as reinforcement learning, and connections with reward circuitry. The hippocampus is highly sensitive to the detrimental effects of stress, though the role of childhood trauma in the

relationship between hippocampal function and anhedonia remains unclear. The current study utilizes both resting-state and task-based measures of hippocampal function to examine potential mechanisms underlying the development of anhedonia.
**Methods:** As part of a multi-site study geared toward developing a psychosis-risk screening questionnaire, a subset of participants (n=92) completed a series of self-report questionnaires and fMRI scans. The scanning session included resting-state fMRI and a target-detection task involving novel and familiar stimuli. Resting state functional connectivity (rsFC) was calculated between the hippocampus and other mesolimbic ROIs (VTA, nucleus accumbens). A Q-learning algorithm was applied to the fMRI task to calculate novelty-specific hippocampal prediction error (PE) signal. Hierarchical linear regressions examined the effects of hippocampal rsFC and hippocampal PE signal on anhedonia, assessed with the Temporal Experience of Pleasure Scale, as well as the moderating role of childhood trauma.
**Results:** Childhood trauma interacted with both hippocampal connectivity and function to predict anticipatory, but not consummatory, anhedonia. Specifically, decreased hippocampal-nucleaus accumbens connectivity was associated with increased anhedonia for individuals with higher (+1SD) levels of childhood trauma ($\beta$= 16.84, SE= 6.62, t = 2.54, p = .01 ). Similarly, reduced hippocampal PE-signaling was associated with increased anhedonia, but only for individuals with higher levels of childhood trauma ($\beta$= 11.66, SE = 5.34, t = 2.19, p = .03).
**Discussion:** Results provide novel evidence that early life adversity interacts with hippocampal function to influence specific reward processing difficulties. Findings suggest that hippocampal alterations, specifically those following childhood trauma, may have detrimental effects on cognitive processes underlying motivation and reward, potentially contributing to the development of anhedonia, an important symptom common to psychosis and other disorders.

## S8. Disparities in Psychotic Experiences Among Irish Adolescents: A Focus on Travellers and Marginalised Groups

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**Background:** Irish Travellers, recognized in 2017 as an indigenous ethnic minority in Ireland, experience systemic discrimination, severe health disparities, and suicide rates estimated to be six to seven times higher than the general population. Despite these alarming statistics, little research exists examining the mental health of Traveller adolescents. This study addresses this gap with a focus on psychotic experiences (PEs) (known to be elevated in marginalised groups), the occurrence of adverse life events inclusive of discrimination, suicidality, and protective factors, while considering support structures.
**Methods:** Cross-sectional data were drawn from the 2023 Planet Youth survey, administered to adolescents in Cavan, Monaghan, and North Dublin schools. Participants were assessed for risk of PEs using the 7-item Adolescent Psychotic Symptom Screener (APSS) and mental health challenges using the Strengths and Difficulties Questionnaire (SDQ). The multiple logistic regression analysis focused on the combined effects of ethnic background and mental health challenges, adversity, suicidality and associated help seeking behaviour, and reported experiences of sexual harassment. Protective factors including feelings of safety in the neighbourhood and experiences of adult support at schools on PEs were also examined.

**Results:** Adolescents who reported feeling “almost always” safe in their neighbourhood had a 22% lower odds of being at risk of PEs (OR = 0.78, 95% CI [0.68, 0.90], p = 0.001) compared to those who did not report this level of safety.
Adolescents who received adult support at school, such as noticing struggles and offering help, had a 17% reduction in the odds of risk of PEs (OR = 0.83, 95% CI [0.71, 0.98], p = 0.023) compared to those who felt that such help was not available.

Significantly high differences were observed in the interaction between high SDQ scores (representing mental health challenges) and PE risk between ethnic groups, with comparisons made against the baseline group of Irish adolescents with SDQ scores below 16.

Young Irish Travellers with SDQ above 16 showed fourfold increased odds of risk PEs compared to the baseline (OR = 4.00, 95% CI [1.61, 9.93], p = 0.003). Other Irish Adolescents with SDQ above 16 had approximately twice the odds of PE risk compared to the baseline (OR = 2.01, 95% CI [1.53, 2.65], p < 0.001). Similarly, non-Irish adolescents with SDQ above 16, exhibited 2.35 times higher odds compared to the baseline (OR = 2.35, 95% CI [1.75, 3.17], p < 0.001).

LGBTQIA adolescents had significantly higher odds of reporting risk of PEs compared to heterosexual peers (baseline group) (OR = 1.85, 95% CI [1.45, 2.35], p < 0.001).

Students who experienced instances of sexual harassment had significant occurrence-based-increase of odds of PE risk compared to those who did not report harassment. Adolescents who experienced an event once had a threefold increase in PE risk (OR = 3.01, 95% CI [2.27, 3.98], p < 0.001). Those who reported being subjected to sexual harassment twice or more had the odds increased fivefold (OR = 5.03, 95% CI [3.30, 7.67], p < 0.001).

Among adolescents whose friends had attempted suicide, those who spoke about their own suicidal thoughts had reduced odds of PEs compared to those who did not (OR = 1.31, 95% CI [1.01, 1.71], p = 0.039). Students whose friend attempted suicide and preferred to not speak about their own suicidal thoughts showed no significant difference compared to the baseline group (OR = 1.03, 95% CI [0.76, 1.39], p = 0.865).

**Discussion:** This study provides a comprehensive analysis of PE risk among adolescent Irish students, including Irish Travellers, revealing significant disparities in mental health outcomes. The findings highlight the role of adverse life events inclusive of systemic discrimination and mental health challenges in increasing the risk of PEs, particularly among Traveller youth, even when accounting for protective factors such as adult support and neighbourhood safety.
Protective factors, including neighbourhood safety and school-based adult support were associated with reduced odds of PEs, emphasizing the importance of fostering safe and supportive environments for adolescents. However, significant associations between PEs, sexual harassment, and exposure to suicidality underscore the urgent need for early prevention strategies and accessible mental health resources.

While these findings are significant, the study's cross-sectional design and reliance on self-reported data limit causal inferences. Future longitudinal research should explore the temporal dynamics of these risk factors and extend the analysis to other regions and populations disproportionately affected by mental health challenges. These findings offer actionable insights for developing culturally sensitive interventions and targeted support

systems to mitigate risk and promote mental well-being in high-risk, marginalised adolescent groups.

## S9. Entry to Clinical Research: Ethnoracial Disparities in Youth at Clinical High Risk for Psychosis

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**Background:** Racial/ethnic minorities (REM) make up about 40% of the population across the United States of America (USA). Yet, the NIMH's 2023 Inclusion Statistics Report found that < 20% of mental health research participants identified as REM. This lack of representation in clinical research presents significant drawbacks, including deficits in external validity, an inability to assess effectiveness and safety in minoritized populations, and skewed results due to homogenous samples. It has been well-established that a shorter duration of untreated psychosis (DUP) in those with a psychotic spectrum disorder is associated with better symptom and functional outcomes, yet little work has explored the impact of the duration of untreated prodromal symptoms (DUPS) in youth at clinical high risk for psychosis (CHR-P). Given the REM disparities observed in clinical research participation and the importance of early intervention for psychotic symptoms, this study aims to explore factors associated with time to entry into clinical research in youth at CHR-P.
**Methods:** Data of USA participants (n= 421) from the Accelerating Medicines Partnership Schizophrenia (AMP-SCZ) will be utilized in this analysis. Participants are on average 21.5 +/- 4.2 years of age, 58.3% female sex assigned at birth. Participants identified as Asian (15.9%), Black (14.7%), White (53%), multiracial (12.1%), and other (4.3%). We will first investigate differences between time of CHRp symptom onset and entry to clinical research (i.e., ProNET study) between REM and non-Hispanic white (NHW) youth. Next, we will examine potential moderators of the relationship between race/ethnicity and time to clinical research entry. Demographic data used as covariates in analyses will include age, gender identity, sex assigned at birth, and self-reported race/ethnicity. Time to research entry will be measured as days between onset of psychosis symptoms meeting CHR-P criteria and date of consent (entry) to AMP-SCZ study. Moderators include socioeconomic status (SES) measured using the Hollingshead Index, neighborhood safety, and perceived discrimination as measured on the perceived discrimination scale.
**Results:** Data Analysis
Differences between REM and NHW youth in time to research entry will be assessed with a t-test. Point-Biserial correlations will be conducted to explore differences between racial/ethnic identity (REM vs NHW) and time to research entry. Multiple regression analyses with interactions will be conducted to assess effects of race/ethnicity on time to research entry. SES, race/ethnicity, neighborhood safety, and perceived discrimination will be examined as potential moderators.

**Discussion:** The study findings will elucidate how race/ethnicity and social factors account for differences in participation in clinical research among particularly vulnerable CHR-P youth across the USA and may help inform strategies and intervention points to increase access to clinical research.

## S10. Impact of Bullying on Salience and Sensorimotor Network: A Co-Twin Control Design

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**Background:** Adverse life events experienced in early childhood and adulthood are associated with changes in brain connectivity patterns and with the development of psychosis. Previous studies demonstrate that victims of these adverse life events, such as bullying and trauma, show heightened connectivity in the Salience Network (SN) and Sensorimotor Network (SMN). In this study, we investigated the impact of bullying on SN and SMN by minimizing the familial confounding effects using a co-twin control design in monozygotic (MZ) bullying-discordant twin pairs. Additionally, we utilized traditional methods, such as linear mixed models with random effects that account for family relatedness.

**Methods:** Sixty-eight pairs of MZ twins aged between 14 and 23 were recruited for this study. Based on their exposure to bullying, the twins were divided into three groups: 1) the bullying discordant group (n=33 pairs), where one twin has a history of bullying and the other does not; 2) the bullying concordant group (n=12 pairs), in which both twins have a history of bullying; and 3) the control group (n=23 pairs), where neither twin has a history of bullying. We calculated resting-state functional connectivity values for individuals in the salience and sensorimotor networks. First, we examined whether bullying status predicts connectivity values across the entire sample and if it contributes to alterations in brain networks. Linear mixed models and paired t-tests were used to explore the relationship between connectivity values and bullying status and connectivity differences between the bullied twins and their non-bullied co-twins.

**Results:** The linear mixed models suggested that bullying status significantly predicted connectivity between anterior cingulate cortex (ACC) and superior sensorimotor cortex ($b = 0.11$, p-adj = 0.027), right anterior insula (AI), right lateral sensorimotor cortex ($b = 0.15$, p-adj < 0.001), right supramarginal gyrus (SMG) and right lateral sensorimotor cortex ($b = 0.09$, p-adj = 0.01). Crucially, we found that bullied twins have higher connectivity compared to their non-bullied co-twins between i) ACC and superior sensorimotor cortex ii) right AI and superior sensorimotor cortex iii) right SMG and right lateral sensorimotor cortex ($p < 0.05$).

**Discussion:** Our findings, derived from both traditional linear mixed models and the co-twin design, suggest that the increased connectivity between the SN and SMN can be attributed to hypervigilance induced by bullying, which is a known risk factor for psychosis. Overall, these results indicate that adverse life events, such as bullying, may serve as a causal factor leading to altered brain connectivity patterns that resemble those observed in individuals with psychosis

## S11. Clinical-High-Risk for Mixed Psychosis: Early Phase of Schizoaffective Disorder?

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**Background:** Clinical-High-Risk for psychosis (CHR-P) is an important concept in identifying the potential prodromal phase of psychotic disorder. CHR-P is associated with significant functional impairment and cognitive deficits. Recently, a smaller number of studies investigated clinical-high-risk for bipolar disorder (CHR-BD). However, unlike chronic stages, the early phase of schizoaffective disorders has not been the focus of available studies. In this study, we aimed the characteristics of investigate at-risk subjects who meet the criteria of both CHR-P and CHR-BD (CHR-Mixed Psychoses (CHR-MP)) compared to at-risk subjects meeting only one of these high-risk states.
**Methods:** This study included 89 youth with CHR-P, 65 with CHR-BD and 36 CHR-MP. Structured clinical interviews for at risk for psychosis and bipolar disorder, the Personal and Social Performance Scale and a comprehensive battery including processing speed, verbal memory, visual memory, working memory, executive functions, attention and social cognition were administered to all participants.
**Results:** There were significant differences for clinical, social functioning, neurocognition and social cognition between groups. CHR-MP had more negative symptoms, social functional and neurocognitive impairment compared to CHR-BD. Neurocognitive differences were particularly significant for verbal memory ($p < 0.001$) and processing speed ($p < 0.001$). In general, the cognitive profile of CHR-MP was intermediate between CHR-BD and CHR-P. At follow-up, UHR-MP was associated with conversion to both first-episode psychosis (FEP) and first-episode bipolar disorder (FEBD). In contrast, CHR-BD and CHR-P groups did only convert to expected diagnoses (CHR-BD to FEBD and CHR-P to FEP).
**Discussion:** The clinical, functional and cognitive profile of CHR-MP lies between CHR-P and CHR-BD. CHR-MP might be the early stage of schizoaffective disorder and related mixed psychotic-affective presentations. Follow-up studies are needed to establish long-term prognosis of cases CHR-MP.

## S12. Pro-Inflammatory Markers in Individuals at Psychosis Risk After 12 Weeks of Aerobic Exercise

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**Background:** Evidence suggests that the immune system plays a role in psychosis etiology. Pro-inflammatory markers interleukin (IL)-6, IL-8, tumor necrosis factor (TNF), and C-reactive protein (CRP) have been found to be relevant for symptom presentation and functional outcomes in individuals with psychosis. Limited evidence suggests inflammation is altered in individuals at clinical high-risk for psychosis (CHR-P). Aerobic exercise has been shown to have anti-inflammatory effects. In general population, long-term aerobic exercising may have an impact in pro-inflammatory markers, particularly on tumor necrosis factor (TNF) and interleukin (IL-6) Studies in schizophrenia demonstrated that exercise is associated with alterations in inflammatory markers. However, these associations have not been examined prior to illness onset. The aim of this study is to identify potential benefits of aerobic exercise for reducing inflammation in individuals at CHR-P.

**Methods:** The study included 50 participants (33 CHR-P, 17 healthy controls (HCs)). All participants completed baseline procedures including measures of symptoms, functioning, health, fitness, and a blood draw. A subsample of CHR-P participants was enrolled in an aerobic exercise and repeated all procedures at 3-month follow-up (post-exercise). Exercise protocol was a double-blind, randomized, controlled trial. CHR-P participants were randomized into exercise (N=12) and waitlist-control (N=7) groups. The exercise group completed 12 weeks of supervised aerobic high intensity interval training. Baseline group (CHR-p vs HC) differences in composite inflammation score (CIS) were established using analysis of covariance (ANCOVA). The effect of exercise condition on IL-6 and TNFA (exercise vs waitlist-control) was examined using retreated measures ANCOVAs. The relationship between positive symptoms and pro-inflammatory markers pre and post exercise was examined with Pearson correlations. All analyses controlled for age, sex, and body mass index.
**Results:** First, CHR-p individuals presented with elevated composite inflammation scores compared to healthy controls ($F(4, 50)=7.94$, $p=.009$, $\eta^2(partial)=.14$). Next, repeated measures ANCOVA revealed a significant effect of exercise intervention on TNF ($F(2, 15)=8.05$, $p=.012$, $\eta^2(partial)=.35$) such that individuals who were exercising experienced a significant decline in TNF levels post-exercise compared to the group that did not exercise. In contrast, the there was no significant effect of time by exercise condition interaction on IL-6 levels ($F(2, 15)=.08$, $p=.78$, $\eta^2(partial)=.005$). However, the there was no significant effect of time by exercise condition interaction on IL-6 levels ($F(2, 15)=.08$, $p=.78$, $\eta^2(partial)=.005$). Lastly, Positive symptoms and pro-inflammatory markers (CIS, TNFA, and IL-6) were negatively associated only at the follow-up visit (all $r > .8$).
**Discussion:** Findings from this study are poised to provide insights into the role of exercise in altering pro-inflammatory markers in individuals at CHR-P. This project provides novel insights into the role of exercise in reducing levels of pro-inflammatory markers (specifically TFN) in CHR-p. The results suggest that high intensity aerobic exercise may be a viable intervention targeting elevated inflammation and thereby improving outcomes.

## S13. The Initial Feasibility, Acceptability, and Usability of Workchat: A Virtual Workday Among Adults With Schizophrenia-Spectrum Disorders

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**BACKGROUND:** Sustaining employment remains a challenge for many people living with schizophrenia-spectrum disorders (SSD). Interventions to improve social skills in the workplace may lead to better employment outcomes, including sustained workforce participation and greater economic security. The aim of this study was to evaluate the feasibility, acceptability, and usability of WorkChat, a virtual workplace social skills training intervention delivered to individuals with SSD.
**METHODS:** Adults with psychosis-spectrum disorders who were engaged in Individual Placement and Support employment services participated in a single group feasibility study. Between pre- and post-test visits, participants engaged with the WorkChat virtual workday simulator, which includes learning core social skills for the workplace, practicing conversations with customers, co-workers, and supervisors, and integrating newly developed

skills into a ‘virtual workday’ experience. The simulations provided real-time and scaffolded feedback via a virtual job coach. Feasibility was measured via enrollment of study participants and their completion of study measures and intervention visits. Acceptability and usability were measured via standardized surveys completed by individuals with SSD. **RESULTS:** Twenty three participants consented and 20 were confirmed as eligible; three screen failures were for age, diagnosis, and a below 4th grade reading level. On average participants were 34 years old (SD=11.4) and 17 participants completed high school or above. Ten reported their gender identity as cisgender male, while 7 were cis women, 1 was a trans man, and 2 did not wish to report. Participants described their racial identity as White (n=8), Black/African American (n=4), more than one race (n=7), and American Indian/Alaska Native (n=1). Seven participants reported Hispanic ethnicity. Fifteen participants were unemployed at study entry.

All 20 participants completed pre-test and 12 completed post-test assessments to date. Notably, 18 participants completed all 7 core skills sessions (one is in process and one completed 2 out of 7 skills). On average, participants completed 6.75 practice conversations on easy, 6.05 conversations on medium, and spent 74.95 minutes completing the practice conversations. During the virtual workday, participants on average completed 4.35 conversations with a customer, 1.95 conversations with a coworker, and 3.15 conversations with a supervisor. Over the course of the study two participants withdrew (transferred out of the program, scheduling conflicts with work). Barriers to completing all WorkChat sessions included inadequate technology (e.g., lack of personal device or reliable internet connection) and other logistical concerns (e.g., difficulty consistently scheduling; attending sessions due to limited transportation). Participant ratings of WorkChat acceptability and usability were consistently positive: on a 1-5 scale, the 5-item acceptability mean was 20.5 (SD=3.4, range=15-25), and the 6-item usability mean was 24.2 (SD=5.3, range=16-30).

**DISCUSSION:** Enrollment and retention in this pilot study were adequate, though participants took longer than expected to work through the training sessions. Condensing the training into fewer sessions may be needed; ensuring access to technology and engaging in more intensive assistance/outreach to facilitate participation will also be needed to promote use in this population. With these modifications, WorkChat appears to be a promising intervention to improve social skills and confidence in the workplace, and ultimately may translate to longer job tenure among people with SSD.

## S14. Clinical and Functional Characteristics of Individuals at Clinical High-Risk for Psychosis (CHR) at 5–20-Year Follow-Up: Insights Into The Interactions and Impact Of Cannabis use and Early Life Adversity on Lifetime Outcomes

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**Background:** Significant attention has been placed on investigating risk factors for short-term (2-year) outcomes of those at clinical high-risk for psychosis (CHR). Little is known however how known baseline risk factors interact to influence outcomes past this initial illness phase. The aim of this project is to investigate interactions between epigenetic factors present at identification such as cannabis use and early life adversity among individuals who were identified as CHR 5-20 years prior, and how these factors influence long-term outcomes.
**Methods:** A large sample (N=455) of CHR participants were reevaluated at 5-20 year long-term follow up (LTF). Current clinical status (CCS), functioning, and current/lifetime histories of adverse events and cannabis use were ascertained.
**Results:** Individuals with a history of childhood trauma (CT) had a lower age of onset of cannabis use ($p=.03$) and a higher lifetime use pattern ($p=.01$) than those without CT. Higher cannabis use frequency at LTF was associated with higher reported undesirable life events ($p < .001$). Individuals who were still symptomatic at LTF had significantly higher total lifetime cannabis use and use frequency than those who were in symptom remission ($p < .05$). Individuals who were in remission at LTF reported significantly lower levels of undesirable life events compared to those with active symptoms ($p < .05$). Higher undesirable life events ($p < .05$) and CT ($p=.02$) were associated with lower functioning at LTF.
**Discussion:** The LTF of CHR participants will provide a wealth of information about later clinical status and functional outcomes, enabling robust prediction analyses using baseline clinical information.

## S15. Longitudinal Association Between Psychotic-Like Experiences and Suicidal Behaviors

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**Background:** Suicide is one of the leading causes of death for young adults in China and a global public health issue. college-enrolled students in China are at markedly high risk for suicide. Psychotic-like experiences (PLEs) refer to experiences similar to positive symptoms of psychosis including attenuated hallucinations, delusions, and disorganized thoughts and behaviors, but which do not cause clinically significant distress, disability or loss of functioning. Existing evidence revealed that PLEs in early life are predictive of a series of subsequent mental health problems.

Despite emerging studies on the relationship between PLEs and suicide, most findings come from cross-sectional data, limiting the causal reference. PLEs fluctuate over time, making cross-sectional estimates of PLEs insufficient to reflect clinically relevant PLEs. However, no studies have specifically worked to explore the associations between trajectory of PLEs and suicide. Additionally, most existing research focused on suicidal ideation or intention, but lacking the data of suicidal behavior such as suicide plan and attempt, which are associated with higher risk and lethality. Many studies did not control psychological factors such as depression and anxiety. Furthermore, longitudinal evidence from China and other low-and-middle-income countries remains rare. Thus, it's necessary to understand the PLEs trajectory

and evaluate the trajectory as a risk factor for future suicidal behaviors using prospective longitudinal data.

**Methods:** We conducted a prospective cohort study among college students in Guangzhou, China from 2021 to 2023. Socio-demographic information was collected at baseline, and PLEs, depressive and anxiety symptoms were assessed in all three waves. Suicidal ideation, plan, and suicide attempt were measured in the third wave. The Chinese version of Community Assessment of Psychic Experiences—Positive scale (CAPE-P) was used to evaluate the PLEs. Latent Class Growth Analysis (LCGA) was used to identify PLEs trajectories, and then mixed logistic regression models were employed to investigate the associations between PLEs trajectories and suicidal outcomes. Models were adjusted for socio-demographics, baseline mental disorders, family history of mental disorders, depression, and anxiety.
The study has been approved by The Ethics Committees of the Affiliated Brain Hospital of Guangzhou Medical University. All participants signed the informed consent before each wave of survey as well as at the beginning of interviews.

**Results:** A total of 2 230 college students with complete PLEs data at three waves were included into the analysis. The mean age was 22.0 (SD: 1.2) years old, and 1386 (62.2%) were female. LCGA analysis identified three PLEs trajectories:
(a) Non-PLEs (82.6%): students that never experienced PLEs in three waves.

(b) Remitted PLEs (9.5%): students who experienced PLEs at baseline and showed gradual remission.

(c) Persistent or worsening PLEs (7.9%): students who experienced PLE in three waves or those who develop and persist PLEs after baseline.

The baseline average CAPE-P score was 1.2(SD:0.1), 1.8(SD:0.2), and 1.4(SD:0.3) for students with non-PLEs, remitted PLEs, and persistent or worsening PLEs, respectively($P < 0.001$).Results of multivariate mixed logistic regression models indicated that students with remitted PLEs did not show significant association with suicidal ideation (OR: 1.87, 95% CI: 0.96-3.63), plan (OR: 1.52, 95% CI: 0.45-5.10), or suicide attempt (OR: 0.44, 95% CI: 0.05-3.77). But students with persistent or worsening PLEs showed significantly higher risk of suicidal ideation (OR: 2.93, 95% CI: 1.65-5.21), plan (OR: 3.23, 95% CI: 1.35-7.73), and suicide attempt (OR: 3.83, 95% CI: 1.37-10.70).

**Discussion:** Our findings indicate that students experiencing persistent or worsening PLEs are at a significantly higher risk of suicidal behavior. These results highlight the urgent need to early identification and suicide intervention. Regular assessment, using a simple but effective tools, is needed to track the dynamic trajectories of PLEs over time and identify high-risk population on time. suicide prevention and intervention strategies prioritize individuals with persistent or worsening PLEs.

## S16. A Psychological Autopsy Study of Participants With Psychosis who Died by Suicide

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**Background:** Suicide is among a leading cause of death for individuals with schizophrenia spectrum disorders (SSDs) with individuals having a 15 to 20 year decrease in average life expectancy in this population. Despite literature documenting associations between psychosis symptoms, suicide ideation, and attempt, less is known specifically in relation to suicide death. Given the lack of research among SSD suicide death samples, psychological autopsy is an innovative methodology, although underutilized, that has potential to inform suicide prevention efforts.
**Methods:** A psychological autopsy methodology was utilized among adults with psychosis symptoms who died between 1989 and 2017 in a Midwestern region of the United States. Causes of death were determined to be suicide (n=26), natural (n=26), and accidental (n=5). Psychological Autopsy data were collected from medical records of the deceased, as well as from interviews with next-of-kin for additional clinical and historical information. Data were collected in alignment with recommended procedures and under the leadership of the local county medical examiner's office, including data collection from medical records, legal records, medical examiner reports, and toxicology results of the deceased at time of death. Data were cleaned, coded, and analyzed in SPSS28.
**Results:** Those who died by suicide were most often younger, more educated, and more often employed than those who did not die by suicide. Those who died by suicide were also more likely to be in a first episode of psychosis, have diagnosis of schizoaffective disorder, and a history of suicide attempt and recurrent suicide ideation as compared to those who did not die by suicide. Further, the majority of those who died by suicide used a firearm. Additionally, several depressive symptoms, including low mood and anhedonia, were more prevalent amongst those who died by suicide than those who did not die by suicide.
**Discussion:** Findings align with existent literature on risk factors for suicide and highlight the role that both psychosis and depressive symptoms play in suicide risk. Study results point towards important clinical implications regarding the need for assessment and treatment for symptoms of depression among individuals with psychosis, greater emphasis on use of lethal means restriction, and better integration of suicide prevention efforts in early intervention programming.

## S17. Is it Possible to Predict Inpatient Suicide in Psychiatric Hospitals?

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**Background:** Rates of suicide in psychiatric inpatients are 50 times higher than in the general population, and psychiatrists are sometimes sued for negligence when a patient suicides while hospitalized. This study compared the electronic medical records (EMRs) of patients who died by suicide during psychiatric hospitalization with those of matched controls, to identify predictors of inpatient suicide.
**Methods:** The EMRs of 29 inpatients (cases) who died by suicide during hospitalization in three different psychiatric hospitals in Israel were identified. For each inpatient suicide, three

control inpatients matched for age, sex, and diagnosis were selected. After cases and controls were identified, all text identifying the subject as suicide or control were removed, so that raters were blinded to outcome. Attempts to differentiate between cases and controls were analyzed using three methods: 1) Narrative Analysis: searching for key phrases and themes 2) Machine Learning: using AI to develop a model predicting which inpatient would die by suicide 3) Expert Prediction: experienced attending psychiatrists read the EMRs and were asked to predict if the inpatient was a case or a control, and then to classify the risk for suicide on a scale of 1 (low risk) to 5 (high risk).
**Results:** In the narrative analysis, no clinically relevant variables were found to differentiate between cases and controls ($p > 0.05$). The senior psychiatrists classified 21%-24% of the patients who committed suicide in the top 20% likelihood of suicide, but the great majority of the patients were rated in the lowest 60% likelihood. The analysis using AI (Gemini) yielded a sensitivity of 0.66 and a specificity rate of 0.49.
**Discussion:** Three different means of analyzing EMRs were not able to retrospectively predict which inpatient in a psychiatric hospital will die by suicide. These data contradict claims of medical negligence in cases of inpatient suicide.

## S18. Relationship Between Cyberbullying and Psychotic Like Experiences in Adolescents

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**Background:** Traditionally, bullying has been shown to increase psychopathology in adolescents including the number of psychotic-like experiences (PLEs). With more access and time devoted to internet use, bullying has taken on a new look as different social media platforms are used to bully peers, known as Cyberbullying. Cyberbullying is dually impactful as it increases isolation and social exclusion, which are shown to increase psychosis severity. Like traditional bullying, cyberbullying is linked to higher rates of depression and anxiety, but the link between cyberbullying and PLEs is unclear. Moreover, it is unclear whether interventional targets, such as emotional regulation, may moderate the relationship between cyberbullying and PLEs. Past research suggests that cyberbullying victims engage in more rumination and have maladaptive emotion regulation strategies. Emotion regulation can be divided and thought of as either a positive strategy (reappraisal) or as a maladaptive strategy (suppression). Accordingly, we predicted that the experience of cyberbullying would be related to higher rates of PLEs and that both suppression and reappraisal would moderate this relationship.
**Methods:** Data from this study were derived from the Adolescent Brain and Cognitive Development (ABCD) study, a nationally representative longitudinal study of youth development across 21 sites. The current study used cross-sectional data from the 3-year follow-up (N=10,104, age 12-14). Assessments included the Cyberbullying Questionnaire (yes/no), Prodromal Questionnaire-Brief Child Version (PQ-BC) total distress, and the Emotion Regulation Questionnaire (ERQ) reappraisal and suppression sub scores. We conducted two independent moderation analyses, with cyberbullying as the predictor, PLEs as the outcome, and reappraisal or suppression as potential moderators. Models included age, sex, and race as covariates.
**Results:** Experience of cyberbullying was related to high endorsement of PLEs ($B=4.79$, $t=22.45$, $p < 0.001$). As expected, suppression served as a significant moderator between experiencing cyberbullying and PLEs ($B=0.40$, $t=4.99$, $p < 0.001$). Suppression had a positive

effect on PLEs where the relationship between cyberbullying and PLEs was amplified. Surprisingly, reappraisal was not a significant moderator between cyberbullying and PLEs (B=0.004, t=0.05, p=0.963).
**Discussion:** Findings suggest that poor emotional regulation (high suppression) strengthens the positive relationship between cyberbullying and PLEs. This modulatory role of emotion regulation strategies may not translate to reappraisal techniques because these skills are challenging to implement. Adolescents tend to reappraise by shifting blame or negative feelings onto their peers. This likely contributes to more isolation. Accordingly, future work will examine the role of other possible moderators or mediators, such as social support. Adolescents with significant social support may be able to shift their attention from the platform they are being bullied on to their peer connections. Our results highlight the importance of monitoring screen time and the potential harm of unmonitored social media use for adolescents. With more and more time dedicated to social media and other platforms, the way in which adolescents are connecting with each other is rapidly changing and the potential negative impacts of these changes need to be further investigated.

## S19. Exploring the Moderating Effects of Race and SES on Substance use and Psychiatric Symptom Severity in First-Episode Psychosis

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**Background:** Substance use disorders (SUD) are common in individuals with psychosis and can impact symptom severity and clinical outcomes. Research suggests that comorbid psychosis and SUD may contribute to prolonged symptoms and higher relapse rates, with substance use observed in up to 60% of psychiatric cases. In the U.S., 51.7% of first-episode psychosis patients have a lifetime history of alcohol or drug use disorders. Previous studies have identified associations between substance use and psychotic symptoms, particularly among males and White individuals. This secondary analysis explores how race moderates the relationship between substance use and psychiatric symptom severity in first-episode psychosis.
**Methods:** This secondary analysis used baseline data from 52 first-episode psychosis subjects in the Zucker Hillside Hospital Striatal Connectivity and Clinical Characteristics in Psychosis study (R01MH108654). Only participants with substance use data were included. Demographic information, including race and ethnicity, was collected. SES was assessed using the Hollingshead Two-Factor Index of Social Status, categorizing participants into five SES classes (I–V), with I being the lowest. Substance use over the six weeks before enrollment was measured using the Timeline Follow Back (TLFB) method, aggregated into a Total Substance Use variable including cannabis, cocaine, alcohol, stimulants, opioids, and other substances. Psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS), and functioning was assessed using the Global Assessment Scale (GAS). Moderation analyses were conducted using linear regression in R to examine race as a moderator of the relationship between psychiatric symptom severity (BPRS and GAS) and substance use, controlling for SES. Post hoc analysis (using emmeans) investigated within group racial disparities in substance use.
**Results:** No significant differences were found in BPRS ($p = 0.564$) or GAS ($p = 0.218$) scores across racial groups, with a mean BPRS score of 46.10 (SD = 6.96), and mean GAS score of 32.70 (SD = 5.96) for all groups. Black ($r = -0.38$, $p = 0.004$) and White ($r = -0.33$, $p = 0.008$) individuals reported lower substance use compared to Asian/Pacific Islander

individuals, but White participants reported significantly higher alcohol use compared to Black, Asian, and "Other" groups across all measures. Psychiatric severity ($r = -0.10$, $p = 0.324$) and global functioning ($r = 0.15$, $p = 0.201$) were not significantly associated with substance use in the six weeks preceding enrollment. No significant differences were observed within SES classes for Black, Other, or White racial groups. A significant negative correlation ($r = -0.45$, $p = 0.002$) was found between SES and substance use, with higher SES associated with lower substance use. The SES effects on substance use were strongest in Black individuals in Class V ($\beta = 155.54$, $p = 0.0056$) and White individuals in Class IV ($\beta = 190.96$, $p = 0.0031$). Pairwise comparisons showed differences in substance use between Class III and Class IV (estimate = 146.06, $p = 0.0205$, $r = -0.45$) and Class III and Class V (estimate = 175.46, $p = 0.0032$, $r = -0.45$) for the Asian or Pacific Islander group.
**Discussion:** In this secondary analysis, we explored how race moderates the relationship between substance use and psychiatric symptom severity in first-episode psychosis. Higher SES categories (Class IV and V) were associated with lower substance use among Black and White individuals. Symptom severity was not associated with substance use when controlling for race and SES, suggesting that socioeconomic and racial factors may have a more substantial impact. These findings underscore the importance of race and SES in understanding substance use behaviors in psychosis.

## S20. Associations of EEG-Based Event-Related Potentials With MRI-Based Structural Morphometry in Individuals at Clinical High-Risk for Psychosis: A Canonical Correlation Analysis of NAPLS2 Data

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**Background:** Electroencephalography (EEG) and magnetic resonance imaging (MRI) are common and complementary methods for assessing brain abnormalities in schizophrenia, and more recently, in individuals at clinical high-risk for psychosis (CHR-P). Whereas EEG-based event-related potentials (ERPs) and oscillations (EROs) assess task-related neuro-electrical activity with high temporal resolution, MRI assesses the brain's anatomical structure with high spatial resolution. Significant correlations between EEG-based ERPs/EROs and MRI-based structural morphometry measures in schizophrenia have been reported, suggesting that neuroanatomical and neuro-electric measures are related, at least partly due to their alterations being driven by the same underlying pathogenic processes.

However, their relationships have mostly been examined in a piecemeal fashion, with associations assessed between only one or a few ERP/ERO measures and brain structural morphometry measures. Such associations fail to consider the covariation among multiple ERP/ERO measures, and they are typically reported in small sample studies that lack the breadth of ERP/ERO measurements and statistical power to address multivariate associations. Taking advantage of the large sample 8-site North American Psychosis-Risk Longitudinal Study (NAPLS2) study of CHR-P individuals, we use canonical correlation analysis (CCA) to assess the multivariate relationships between a large battery of ERP/ERO measures and MRI brain morphometric measures.
**Methods:** CHR-P (N=368) individuals completed a baseline EEG and MRI session. CCA was conducted between 8 ERP and 4 structural morphometry measures. ERP measures included Mismatch Negativity (MMN) amplitude for duration-, pitch-, and double-deviants; Auditory and Visual Oddball P300 amplitudes for targets (P3b) and novels (P3a); 40-Hz Auditory Steady State Response inter-trial coherence (ITC). MRI measures included global cortical thickness and surface area, cortical white matter volume, and subcortical volume. Using extracted canonical variate scores, follow-up analyses examined whether correlations differed by CHR-P clinical outcome at 24-month follow-up (converters n=51, symptomatic n=106, remitters n=72).
**Results:** The first canonical variate was significant (canonical r=.30, $p < .001$, variance explained: 51.06%). The ERP side was dominated by MMN double-deviant, AOD target and novel, VOD novel, and 40-Hz ITC deficits, with small contributions from MMN duration-deviant deficits and slight contributions from MMN pitch-deviant and VOD target deficits. The MRI side showed deficits across all metrics, with strongest contributions from cortical thickness, followed by cortical surface area and subcortical volume deficits. Correlations for this canonical variate did not differ by CHR-P status (p=.173).
**Discussion:** CCA identified a significant (medium effect size) EEG and MRI relationship in CHR-P. These results highlight the utility of CCA in identifying complex, multivariate links between dysfunctional electrical brain activity and structural morphometric abnormalities. Moreover, results suggest that the joint use of EEG and MRI can provide important information on the cortical and subcortical structural substrates underlying ERP abnormalities in the CHR-P syndrome.

## S21. Impact of Childhood Trauma and Premorbid Stressors on the Development of Psychotic Symptoms

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**Background:** Previous studies have demonstrated that experiences of childhood trauma and premorbid stressors can increase the risk of developing psychotic symptoms, such as hallucinations and delusions. The Genomic Psychiatry Cohort (GPC) study aims to identify the genetic hallmarks that contribute to the development of neuropsychiatric disorders, such as schizophrenia (SCZ), schizoaffective disorder, bipolar disorder (BD), and obsessive-compulsive disorder (OCD), with an emphasis on diverse populations. The following study attempts to draw preliminary conclusions from existing GPC data, evaluating childhood trauma and premorbid stressors, and their impact on psychotic symptoms.
**Methods:** Using the Adverse Childhood Experiences (ACE) questionnaire and the Diagnostic Interview For Psychosis And Affective Disorders (DIPAD), two assessments that are completed with GPC study participants (n = 122), our research aims to investigate the

relationship between childhood trauma and the incidence of a premorbid stressor on psychotic symptoms. Participants were divided into four distinct categories by childhood trauma (ACE score > 3) and presence of premorbid stressor. A chi-square test was performed to compare the presence or absence of psychosis. Additional testing was conducted to characterize psychotic symptoms by dividing these symptoms into delusions, hallucinations, or both.
**Results:** Data collected from the ACE and DIPAD, mostly from psychiatric patients within the Mount Sinai Health System, shows a significant difference ($P < 0.05$) when statistically testing for the presence or lack of psychotic symptoms. However, testing performed by categorizing psychotic symptoms into their subtypes yielded no significant difference ($P > 0.05$).
**Discussion:** This preliminary study highlights the potential of examining adverse childhood experiences and premorbid stressors as markers for psychosis. Future studies with GPC data should aim to determine the type of adverse childhood experiences (ACEs) or premorbid stressors that are most likely to contribute to psychosis. ACEs and premorbid stressors could also be examined over time, in a longitudinal fashion, to better understand how these experiences contribute to the development of psychotic symptoms. In all future efforts, a greater number of participants should be included to allow for more accurate conclusions to be drawn; a limitation of the present study. A deeper understanding of ACEs and premorbid stressors, and their impact on the development of psychotic symptoms, could aid in the creation of better diagnostic tests and preventive measures, ultimately allowing at-risk individuals to receive care at an earlier stage.

## S22. Investigating the Best Structure to Conceptualize and Assess Multidimensional Schizotypy

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**Background:** Schizotypy offers a useful and unifying construct for understanding schizophrenia-spectrum psychopathology. Current conceptualizations and empirical findings support a 3-factor model of schizotypy consisting of positive, negative, and disorganized dimensions. However, recent studies have suggested 4- and 5-factor structures. The present study compared the factor structure of competing models of schizotypy and examined the extent to which they predicted relevant interview and questionnaire outcome measures in order to consider the best levels for understanding and assessing the dimensional structure of schizotypy.
**Methods:** The present study employed CFA and ESEM to compare the hypothesized 3-factor model of schizotypy with five competing models using the items from the Multidimensional Schizotypy Scale (MSS) in a sample of 10,814 young adults. We subsequently compared the supported models in terms of the prediction of interview and questionnaire assessed symptoms using hierarchical linear regressions.
**Results:** CFA and ESEM models indicated that the 3- and 4-factor models provided the best fit, with the 4-factor model providing slightly better fit. However, regression analyses indicated that the 4- and 5- factor models did not greatly improve the prediction of relevant

outcome measures and resulted in largely redundant, and in some cases less reliable, subfactors.
**Discussion:** The present findings, along with previous validation studies, support the use of the three MSS subscales. This does not rule out the pursuit of other schizotypy factors or consideration of an underlying facet structure. However, such investigations should ideally start with clear conceptual models that guide the development of psychometrically sound measures.

## S23. Protective Effect of Clozapine on Suicide

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**Background:** Schizophrenia is a devastating illness that affects up to 1% of the population and is associated with an elevated risk of suicide. Among antipsychotic medications used for schizophrenia, clozapine is the most efficacious and the only medication indicated for treatment-resistant schizophrenia. However, it is underutilized and its mechanism of action is still poorly understood. One aspect of its unique efficacy that requires further investigation is its effect on suicidality. A randomized controlled trial, the InterSePT study, yielded evidence that clozapine reduces suicidality more than olanzapine, after which it was approved for recurrent suicidal behavior in schizophrenia and schizoaffective disorder. We examined population mortality data to further elucidate the effect of clozapine on suicide.
**Methods:** We extracted data from autopsy records in Maryland, which is relatively unique in that virtually all unnatural deaths undergo full toxicology panels as part of autopsy, including postmortem blood levels of clozapine and olanzapine. We examined clozapine and olanzapine given that the latter has a chemical structure similar to that of clozapine, has relatively high efficacy among antipsychotics other than clozapine, and was used in the InterSePT study. Our analysis compared clozapine- and olanzapine-positive decedents across demographic, clinical, and manner-of-death outcomes using contingency table analysis and logistic regression.
**Results:** We analyzed records of Maryland's Office of the Chief Medical Examiner for all deaths by suicide, accident, or undetermined causes from 2003 to 2021. Of 53,144 decedents, 571 had olanzapine detected on autopsy while 50 had clozapine, with the two groups showing no significant sociodemographic differences. The odds of death by suicide in decedents with clozapine were < half the odds in decedents with olanzapine (odds ratio = 0.47; 95% C.I. 0.26-0.84; p = 0.011).
**Discussion:** Our study found that decedents with clozapine were significantly less likely to have died by suicide than by accident compared to those with olanzapine. To our understanding, this was the first study to use medical examiner records to examine the effect of clozapine or other psychiatric medications on suicide. It also highlights the utility of statewide autopsy records, an untapped resource for investigating the potential antisuicidal effects of psychiatric medications at a population level.

## S24. Investigation of the Relation Between Social Media Asociality and Negative Symptoms in Clinically High-Risk Populations

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**Background:** Negative symptoms are reductions in motivation, emotion, and expressive behaviour that are prominent in individuals with a schizophrenia spectrum disorder. Asociality is an important negative symptom referring to reduced interest in social interactions, arising prior to illness onset. An emerging challenge in understanding asociality in CHR-P individuals is that this population tends to be adolescents or young adults for whom using newer technologies is part of their daily social lives. Limited research has considered how asociality manifests in texting and social media usage. This is a significant gap in the literature as texting and social media use have increased substantially in the last decade. Observing specific social media applications and the way individuals use them could provide valuable insight into its impact on negative symptoms. This study aims to examine social media asociality through the Negative Symptom Inventory - Psychosis Risk (NSI-PR), an interview assessing negative symptoms in CHR-P individuals.

**Methods:** To examine this aim, we compared samples from the MAP and CAPR studies, which were assessed on different versions of the NSI-PR, and observed whether the interview prompts impacted the effectiveness of the social media asociality item. Both versions consisted of an asociality section measuring social media asociality (item 7, 4) and in person asociality (item 5, 3), rated on a scale of 1-5 (5 being severe asociality). MAP used an initial extended version of the NSI-PR (N = 182) and CAPR used a newer standard version (N = 549). For both samples, we conducted Pearson correlations to examine the relationship between social media asociality, in person asociality, the remainder of the NSI-PR, and the global functioning scale (GFS) to observe the effectiveness of the asociality items in predicting negative symptoms and social functioning. We also conducted qualitative analyses of interview notes to get information about the content reported (e.g., number of friends contacted) and conducted Pearson correlations between individual prompts, their item score, and the total NSI-PR score.

**Results:** For the MAP study, the results showed no significant difference between social media asociality ($r = 0.50$) and in person asociality ($r = 0.53$) when compared to total NSI-PR ($z = -0.51$). However, GFS scores for social media and in-person asociality showed social media asociality had a lower correlation (adj $r2 = 0.26$) than in-person asociality (adj $r2 = 0.33$). For the CAPR study, we found that in-person asociality had a significantly higher correlation with total NSI-PR ($r = 0.54$) as compared to social media asociality ($r = 0.37$) ($z = 4.55$). We also found a significant difference in social media asociality between the studies ($z = -1.854$). The GFS scores for social media asociality (adj $r2 = 0.22$) and in-person asociality (adj $r2 = 0.35$) showed similar correlations to the initial study.

**Discussion:** Based on the text analysis, we suggest that discrepancies in performance of the social media item in the revised NSI-PR relates to differences in weighting of prompts, indicating that this item might emphasize the quantity of communication via text and de-emphasize close personal communication. Further research is needed to determine the level of emphasis that should be placed on each prompt and the aspects of social media asociality being measured by the prompts. Additionally, it is critical to have tools that can meaningfully assess asociality in social media as we are focused on a population that is primarily adolescents and young adults.

In conclusion, this study showcases that we can substantially improve our assessments by characterizing social media usage features that are critical to broader negative symptoms and social functioning.

## S25. The Relationship Between Trauma Exposure and Non-Clinical Psychosis: A Meta-Analysis

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**Background:** Although robust evidence links trauma exposure to increased risk of clinically-relevant psychotic experiences, critical questions, which could elucidate mechanisms and potential intervention points, remain about how trauma exposure relates to psychotic-like experiences (non-clinical psychosis; PLEs). These questions include overall effect, whether different types of trauma affect risk differently, if there is a cumulative relationship and if the effect is moderated by methodological factors or sample characteristics.
**Methods:** A meta-analysis (following PRISMA guidelines) was conducted and studies were considered eligible if they reported on the relationship between childhood trauma exposure and PLEs. Each study was coded for effect size (converted to r-values), types of trauma (emotional, physical, or sexual abuse; emotional or physical neglect; bullying; discrimination), effect sizes by number of exposures, assessment methods for trauma and PLEs, number of male/female participants, and the race/ethnicity composition of the sample.
**Results:** 78 studies including 87 samples (174,660 individuals) were included with effect sizes between trauma exposure and PLEs ranging from r=-.05 to r=.609. The mean effect size was r=.226 and there was not evidence of publication bias, z=0.807, p=.420. Effect sizes by trauma type ranged from r=.193 (physical abuse) to r=.299 (emotional abuse). Notably, the effect size increased as number of trauma exposures increased.
**Discussion:** This meta-analysis highlights the importance of expanding assessment and reporting of trauma when examining risk factors for the development of clinical psychosis and PLEs, including the intensity and chronicity of trauma as well as exposures which have not often been considered such as bullying and discrimination.

## S26. In Utero Exposures to Psychotropics and the Risk of Developing Neurodevelopmental Disorders: A Population-Based Retrospective Birth Cohort Study

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**Background:** Continuation of psychotropics prescriptions to mothers with mental illnesses is effective in reducing relapse risk, but the effects of in-utero exposures to antipsychotics and other psychotropics on the future risk of developing neurodevelopmental disorders remain unclear. Previous population-based studies generally had short follow-up durations, and did not explore any possible difference between exposure happening different trimesters. We aimed to examine whether in-utero exposures to psychotropics would increase the risk of

developing neurodevelopmental disorders in offspring, using the population-based CDARS data in Hong Kong.

**Methods:** We retrieved all singleton birth episodes happened in government hospitals from 1 January 2004 to 31 December 2015. The CDARS data covered approximately two-third of all obstetric care in our locality. We collected the mothers' clinical data, including age at labor, psychiatric and medical history, obstetric complications, psychotropic prescriptions received two years prior to the date of labor. We also retrieved the offsprings' psychiatric history as of 31 December 2022, to ascertain the diagnosis of autism, attention-deficit hyper-activity disorder (ADHD), intellectual disability, conduct disorder, neurodevelopmental communication disorder, and learning disability based on ICD-10 codes. Kaplan–Meier curves for time-to-events (first diagnosis of neurodevelopmental disorders) were constructed. Adjusted Cox regression with variables having time-varying hazard was used. Exposures included four classes of psychotropics (antipsychotics, antidepressants, anticonvulsants, and benzodiazepines). Maternal age, sex of the offspring, winter conception (i.e. December-February), maternal diagnosis of severe mental illnesses (including schizophrenia, bipolar disorder and depression), obstetric and neonatal complications, mothers' Charlson Comorbidity Index during pregnancy, year of delivery, and the hospital were entered as covariates. Winter conceptions were calculated based on gestation weeks, and several studies had pointed out maternal infection during first trimester could be associated with developmental of ASD and schizophrenia. We included interaction terms between follow up years and delivery hospital as well as maternal age, to capture the demographic changes over time that might lead to substantial differences in hazard of neurodevelopmental disorders. Subgroup analyses were used to compare the effects of psychotropics prescribed in different trimesters on the offsprings' future risk of developing neurodevelopmental disorders. Negative control analysis further clarified any causal evidence for increased risk of neurodevelopmental disorders after in-utero exposure to psychotropics, by comparing the exposed group with mothers who had never been exposed to psychotropics two years prior to labor, and mothers who had discontinued psychotropics before conception.

**Results:** Among 370,380 newborns (given birth by 290,232 mothers), we found 1182, 2,854, 562 and 504 birth episodes with in-utero exposures to antipsychotics, antidepressants, anticonvulsants and benzodiazepines respectively. The cohort had a mean follow-up of 13.14 years. When subjects who had in-utero exposure to antipsychotics were compared with those without such exposure, the results showed non-significant associations between exposures and outcomes. However, we found significant associations between in-utero exposure to antidepressants and development of ADHD (aHR=1.26, 95%CI=1.06-1.49, p-value=0.009), and between in-utero exposure to anticonvulsants and intellectual disability (aHR=3.36, 95%CI=1.29-8.73, p-value=0.01). Unexpectedly, maternal history of severe mental illnesses was only significantly associated with ADHD, autism and conduct disorder, but not intellectual disability, learning disability, and neurodevelopmental communication disorder. The subgroup analysis results failed to support any difference in risk between mothers prescribed with the same psychotropics in different trimesters. In negative control analysis, individuals born to mothers who discontinued antidepressants prior to conception showed non-significant and reduced hazard to ADHD (aHR=1.19, 95%CI=0.93-1.52, p-value=0.17). Moreover, individuals born to mothers who discontinued anticonvulsants showed marginally non-significant and substantially reduced hazard of developing intellectual disability (aHR=2.35, 95%CI=0.94-5.89, p-value=0.07).

**Discussion:** Using a large-scale population-based retrospective birth cohort, our regression modelling results did not reveal that in-utero exposure to psychotropics would generally increase the risk of developing neurodevelopmental disorders. Nevertheless, the regression modelling and negative control analysis results suggested that in-utero exposure to

antidepressants and anticonvulsants may be associated with increased risk of developing ADHD and intellectual disabilities respectively. Our findings also support the safety of continuation of antipsychotics in pregnancy women with severe mental illnesses.

## S27. Exploring Protective and Risk Factors in the Perception of Ostracism in Adults Living With Schizophrenia

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**Background:** Persons living with schizophrenia (PWS) navigate a complex and challenging reality, contending with cognitive impairments, blunted emotional expression, and challenges with social functioning. These challenges are further compounded by ostracism, which plays a central role in experiences of separation, social isolation, and loss. Unfortunately, these experiences are all too familiar to individuals with schizophrenia, a condition that is consistently ranked among the most stigmatized of all psychiatric disorders. Ostracism not only reinforces the barriers to social engagement and community participation that PWS often face but also intensifies their sense of disconnection and social marginalization (Williams and Nida, 2022). Laboratory-based studies have found that 2 to 3 minutes of perceived social ostracism using a virtual ball toss game, Cyberball, is sufficient to threaten the fundamental needs of belonging, self-esteem, control, and meaningful existence and increase negative affect in children, adolescents, healthy adults, and vulnerable populations (i.e. borderline personality disorder, depressive disorder, and schizophrenia) (Gratz et al., 2013; Reddy et al., 2019; Tang et al., 2018; Williams, 1997, 2009; Zadro et al., 2004). The present study uses the Cyberball task to simulate social ostracism in a sample of adults with schizophrenia in order to explore psychological and individual difference factors that may influence the perception of social exclusion and ostracism in this special population.
**Methods:** Twenty-seven participants (Mage = 49.42 years, SD = 12.86, 17M and 10F) diagnosed with schizophrenia or schizoaffective disorder were enrolled from outpatient clinics at St. Joseph's Healthcare Hamilton. Participants were all treated with antipsychotic medications and were clinically stable. Participants completed a self-report survey measuring cognitive, emotional, and social factors in session one, followed by the Positive and Negative Symptom Scale (PANSS) and Cyberball task in session two. In the Cyberball paradigm participants believe they are playing with two other players whose profile matched that of the participants by age, gender and ethnicity and they are told a picture of them was taken so other players could see them in the game. Participants pass a ball with other players, but as the game progresses, they are excluded from ball tosses. After the game, participants complete self-report questionnaires assessing their experience of social inclusion/exclusion (e.g. In the game, what others thought of me did not bother me) and suspiciousness (e.g. I had to keep an eye out to stop the others from using me). Following the post-game questionnaire, participants were debriefed and informed of the experimental nature of the Cyberball task. Participants received coffee gift cards, and compensation for travel costs.
**Results:** The perception of ostracism will be examined using predictive modelling techniques, using demographics, PANSS scores and self-report measures. As an exploratory study, we anticipate identifying existing trends in the literature, such as a potential link between anxiety and perceived ostracism (Zadro et al., 2006); however, we remain open to uncovering novel relationships and factors that may contribute to the perception of ostracism in this population.

**Discussion:** By identifying protective and risk factors to ostracism in a schizophrenia population beyond psychotic symptoms, the findings may inform future research and clinical interventions to target internalized stigma and social isolation in this vulnerable population.

## S28. Patterns of Traits as Predispositions to Delusional Ideation

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**Background:** Delusional ideation (DI), a dimensional construct, refers to beliefs that are disconnected from reality and persistently held despite contradictory evidence. As a dimensional construct, DI ranges from subclinical unusual thoughts (e.g., suspiciousness) in the general population to overt delusions (e.g., superpower) observed in psychotic disorders. Importantly, DI can negatively impact an individuals' wellbeing and daily functioning. Given worsening subclinical DI has predicted transition to psychosis, identifying enduring risk factors for DI is important to aid prevention and intervention efforts targeting this trajectory. Certain trait-like characteristics may serve as predispositions that increase this risk for DI. For instance, measures related to neuroticism, impulsivity, and sensory responsivity have all separately been associated with DI in subclinical and diagnosed samples. However, there is a lack of longitudinal research examining how combined patterns of these traits predict DI over time. To address this critical gap, the current study will examine how these traits function together in a multivariate model to predict DI cross-sectionally, and moreover which predict DI longitudinally in an adult community sample.
**Methods:** We used an adult community sample (N=245, mean age=58yrs, female=67%, white=82%) from the Nathan Kline Institute Rockland Sample who completed the UPPS-P Impulsive Behavior Scale (UPPS), the NEO Five Factor Inventory (NEO) of personality, and the Adult Temperament Questionnaire (ATQ) which itself measures effortful control, positive and negative affectivity, plus orienting sensitivity to sensory stimuli. Critically, these self-report assessments have both conceptually overlapping and unique subscales. To identify data-driven construct communities for subsequent analysis, while respecting interrelatedness, all the subscales will be entered in a psychometric network analysis. To measure DI, we will use Peters et al. Delusions Inventory 21-item (PDI), a self-report scale designed for the general population, with elevated scores indexing risk for psychotic disorders. From a previous factor analysis of the PDI in this sample, we will investigate three DI subtypes (paranoia, grandiosity, and magical thinking) to enhance specificity. First, cross-sectional path models will investigate how these trait communities associate with DI subtypes. Second, longitudinal path models will test if trait communities at baseline predict DI a year later.
**Results:** For the network analysis, we hypothesize cross-assessment communities will represent constructs of inhibition, negative emotionality, positive emotionality, and openness to sensory experiences (OSE). For the cross-sectional model, we hypothesize constructs of inhibition, negative emotionality, and OSE will all be strongly associated with DI. For the longitudinal model, we hypothesize negative emotionality will be most predictive of DI a year later, given this trait reflects instability of negative emotions most relevant to symptom exacerbation.
**Discussion:** Assessing trait-like predispositions through a comprehensive approach is crucial for advancing the understanding of individual risk factors associated with developing DI. Furthermore, discerning how different traits play distinct roles in the complex manifestation of DI is critical to specifying the target for prevention and early intervention. For instance, assuming negative emotionality is the strongest predictor of future DI, clinicians may

prioritize teaching emotional awareness and regulation strategies to build resilience in individuals at risk for DI.

## S29. Mindfulness as an Adjunctive Intervention for Acute Psychotic Disorders: A Feasibility and Efficacy Pilot Study

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**Background:** Psychotic disorders, such as schizophrenia and schizoaffective disorder, disrupt cognition, perception, and behavior, leading to functional impairments (Bromet et al., 2002). While pharmacotherapy is effective in reducing positive symptoms, negative symptoms and cognitive deficits often persist (Kahn et al., 2015). Mindfulness, defined as "the ability to pay attention intentionally and nonjudgmentally to present-moment experience and to sustain that attention over time" (Miller et al., 1995), provides an evidence-based approach to address these residual impairments. This study explores the potential of mindfulness to enhance cognitive and emotional outcomes in hospitalized patients with psychotic disorders.

**Methods:** Participants

The study involved 62 patients aged 18–60 with psychotic disorders, requiring inpatient status and consent to mindfulness sessions over three intervention cycles.

Intervention

The T8SM-Crise program included eight sessions of short, guided mindfulness exercises tailored to the acute setting, with each session limited to 40 minutes.

Measures

Cognitive assessments included the Continuous Performance Test (CPT-II), Trail Making Test (TMT-A), Stroop Test, Digit Span (WMS-R), and Wechsler Abbreviated Scale of Intelligence (WASI). Pre- and post-intervention comparisons utilized paired t-tests and Cohen's d.

**Results:** Demographics

The study had 62 participants with an average age of 36.8 years. The majority were male (41 out of 62).

Educational levels varied from complete and incomplete elementary, middle, and high school education, to higher education.

Most participants were single (54 out of 62).

Diagnoses included schizophrenia (41 cases), bipolar disorder (TAB) (7 cases), autism spectrum disorder (TEA) (1 case), other diagnoses (9 cases), and other psychoses (4 cases).

Almost all hospitalizations were involuntary (61 out of 62).

For patients who completed cognitive tests:

21 patients with an average age of 33.52 years participated, most of whom were male (18 out of 21).

Their education ranged from incomplete middle school to complete higher education.

Of these, 20 were single.

Diagnoses included schizophrenia (12 cases), bipolar disorder (3 cases), autism spectrum disorder (1 case), and other diagnoses (5 cases), with no other psychoses noted.

20 out of 21 were involuntarily hospitalized.

Cognitive Outcomes

WASI scores were low compared to the general population, reflecting the expected intellectual functioning levels in this clinical sample.

TMT-A showed a 30% reduction in completion time, indicating improved cognitive flexibility (pre: 64.37 s; post: 45.00 s; Cohen's d = -0.36).

Stroop Test results showed enhanced inhibitory control with faster response times (T3 p=0.06; Errors 2 p=0.02).

CPT-II indicated improved sustained attention, with fewer omission and commission errors (e.g., omissions pre: 60.1; post: 53.4).

Working memory showed modest improvements on digit span tests.

**Discussion:** Mindfulness showed improvements in cognitive domains essential for functional recovery, even in acute psychiatric settings, underscoring its role alongside pharmacotherapy. Additionally, improved attention and inhibitory control hint at a greater capacity for managing impulsive emotional reactions.

Limitations

These findings are preliminary results from a controlled trial. The next phases, scheduled for the coming years, will include an active control group and a new intervention cycle of the T8SM-Crise program. While promising, the current results are limited in their generalizability due to the absence of a control group and the influence of variables, such as medication effects, which were not controlled.

Future Directions

Extending interventions into community settings will help assess the long-term impact on quality of life.

Conclusion

The T8SM-Crise mindfulness program is a viable adjunct for treating psychotic disorders in acute settings, promoting cognitive improvement and emotional regulation.

References

Bromet EJ, Dew MA, Eaton WW. (2002) Epidemiology of Psychosis with special reference to Schizophrenia. In Psychiatric Epidemiology, Second Edition, Edited by Ming T. Tsuang and Mauricio Tohen. ISBN 0-471-40974-X, John Wiley and Sons, Inc.

Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, Insel TR. (2015) Schizophrenia. Nature Reviews Disease Primers, Nov V12(1): 15067. DOI: 10.1038/nrdp.2015.67.

Miller JJ, Fletcher K, Kabat-Zinn J. (1995). Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. General Hospital Psychiatry, V17(3): 192-200. DOI:10.1016/0163-8343(95)00025-M.

Stübing, K.S., Russell, T.A., Cordás, T.A., Neto, F.L. (2021). A pilot intervention with mindfulness for inpatients with Eating Disorders. Academia Letters, Article 4247. https://doi.org/10.20935/AL4247.

## S30. Differential Patterns of Cognitive Effort-Based Decision Making in Schizophrenia vs Bipolar Disorder

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**Background:** Schizophrenia (SZ) and bipolar disorder (BD) both show abnormalities in goal-directed decision making, with SZ associated with diminished and BD elevated goal-directed activity. One component of decision-making, cost-benefit analysis, involves weighing a reward against the resources (time; physical or cognitive effort) to achieve the reward. Individuals with SZ are less willing to expend effort to gain rewards than controls, which may contribute to motivational and social functioning deficits. Studies of effort discounting in BD have yielded mixed and mood-dependent results. Few studies have compared cognitive effort-based decision making in SZ and BD samples, hindering our ability to draw conclusions about distinct mechanisms underlying opposing motivational profiles in these two disorders.
**Methods:** Eighty-four Veterans (mean age = 48.4, 80% male) were included (SZ: 31, euthymic BD: 22, control: 31). Participants completed the Role Functioning Scale and the MATRICS cognitive battery. Subjects completed an n-back task (n = 1 - 4). They then completed the Cognitive Effort Discounting Task in which they made decisions to either repeat a low effort (1-back) task for $1 or a higher effort n-back for a greater reward ($2 - $4). Rewards for the 1-back were titrated to an indifference point, where an individual was equally likely to choose the low effort or high effort task. Higher indifference points indicate more willingness to complete the high effort/high reward task. Nine indifference points were calculated for each condition of hard task offers: 3 n-back levels (effort) X 3 reward amounts (reward).
**Results:** In a mixed-effects ANOVA of indifference points, significant diagnostic group by reward ($p < .001$) and group by effort effects ($p = 0.041$) were found. Indifference points in the BD group were significantly higher than SZ and qualitatively higher than controls when the harder task option was the 2-back. Further, BD Veterans exhibited a steeper discounting curve than controls and SZ, such that willingness to choose the harder task fell rapidly as

required effort increased. Controls showed a moderate discounting rate, and SZ showed the flattest discounting curve. Further, willingness to exert effort for increasing rewards (the slope of indifference points across reward levels for 2-back decisions) was differentially associated with social cognition for BD and SZ Veterans (interaction p = 0.048), such that increased willingness had a trend negative association with social cognition in SZ but not in BD. There was also a trending group interaction in the association between this slope and social functioning. Indifference points across conditions were not associated with positive, negative, or manic symptoms.
**Discussion:** Distinct patterns of cognitive effort discounting of rewards were found in SZ and BD Veterans. Relative to SZ Veterans, Veterans with BD were more willing to select high effort, high reward tasks, particularly when the high effort option was relatively easy, but increases in the required task effort led to exaggerated discounting of reward. Conversely, SZ Veterans were less willing to choose the higher effort option overall, but increases in effort led to modest discounting effects. These results highlight opposing patterns of cognitive effort discounting in SZ and BD, with control Veterans falling between the patient groups in willingness to expend effort and discounting rate. Additionally, willingness to choose the higher effort option as reward increased was differentially associated with social cognition and (at a trend level) social functioning between BD and SZ Veterans. Further study of this relationship and the potential neural underpinnings are forthcoming.

## S31. Utilizing Adapted Cognitive Measures to Examine Cognitive Deficits in Low-Educated and Older Individuals With Schizophrenia in India and Nigeria: A Pilot Study

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**Background:** The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is considered the gold standard in the measurement of cognitive functions in schizophrenia. The MCCB has been translated into at least 24 languages, co-normed and validated in both high (HICs) and low- and middle-income countries (LMICs) and has been shown to have good psychometric properties in these settings. However, most of the co-norming and psychometric studies conducted in HICs and LMICs using the MCCB have enrolled mainly subjects with high level of education in urban centers and studies of its utility and validity among older, less educated subjects in rural areas in low- and middle-income countries are almost non-existent.
**Methods:** Following the method used by Stone et al (2020) in rural China, we adapted 5 tests of the MCCB (trail making, BACS symbol coding, Spatial span forward, Spatial span backward and Animal naming) (increasing the number of readings of instruction to up to six times and including a practice segment before the main test). The adapted measures were administered to 86 persons with schizophrenia (40 in Chennai, India and 46 in Ibadan, Nigeria) and 93 healthy control subjects (40 in Chennai and 53 in Ibadan) matched by age and level of education. Cases and control subjects were compared within sites and overall, on demographic and clinical variables, using $\chi 2$, t-test or Wilcoxon rank sum tests. We also compared cases and control subjects on cognitive test scores using a statistical test based on

the Spearman partial correlation coefficient for the association between cognitive outcome and group (patient group assigned a value of 1 and control group assigned a value of 0), controlled for age, gender, years of education and place of residence (rural vs urban). To ascertain the validity of the adapted measures in older and less educated individuals, we compared cognitive scores in cases and control subjects aged ≥ 60 years or with years of schooling < 5 years. Finally, we determined the demographic and clinical predictors of cognitive functions test scores using multiple linear regression analysis.
**Results:** The cases were not significantly different from the control subjects in terms of age, gender and years of education at both sites and overall (India: cases vs controls mean age 55.6□12.5 years vs 53.5□14.4years; % female 62.5 vs 70.0; mean years of education 7.5□6.4 vs 7.1□5.7; Nigeria cases vs controls mean age 55.□15.4 years vs 59.7□15.6years; % female 69.6 vs 56.6; mean years of education 8.8□6.8 vs 7.5□6.2). Mean age of onset of schizophrenia were similar in both site (Nigeria vs India 35.7□11.4 years vs 35.7□13.5 years) but mean Positive and Negative Syndrome Scale (PANSS) General Psychopathology scale score was higher in Nigeria compared to India (35.8□7.8 vs 29.6□9.4, t = 3.32, p = 0.001).
The proportion of all validly completed tests was 94.0% for cases and 97.4% for control subjects. Cases performed significantly worse than control subjects on Trail making (cases vs control mean score 136.1□88.2 seconds vs 110.9□73.3, Spearman ρ 0.25, p = 0.001), BACS symbol coding (cases vs control mean score 18.7□14.1 vs 21.1□16.3, Spearman ρ -0.27, p = 0.001) and animal naming (cases vs control mean score 9.8□4.8 vs 13.0□4.1, Spearman ρ -0.41, p < 0.001). With zero imputation of invalid test scores, cases performed worse than control subjects additionally on Spatial span backwards (cases vs control mean score 2.9□2.4 vs 3.5□2.4, Spearman ρ -0.16, p = 0.038). When analysis was restricted to subjects aged ≥ 60 years or with years of schooling < 5 years, the earlier mentioned tests were still able to distinguish between cases and control subjects. The predictors of cognitive functions test scores on the five tests in different sub-group analyses included case-control status, site, age, gender, education, place of residence and PANSS negative scale score. In several analyses, Spatial span forward did not distinguish between cases and control subjects at either site.
**Discussion:** Adapted cognitive measures showed largely acceptable utility and validity among older, less educated subjects in two LMIC settings.

## S32. Deficits in Reward-Based Learning are Linked to low Social Approach Motivation in Schizophrenia

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**Background:** Social isolation, defined as the lack of meaningful peer and family relationships and limited participation in community activities, is prevalent among individuals with schizophrenia and a subset of the general community. It has been proposed that social isolation in schizophrenia stems from deficits in processing social rewards, such as reduced sensitivity to reward and impaired reward-based learning. These deficits may reduce the pleasure derived from social interactions and diminish affiliative tendencies. This study

explores whether deficits in reward processing are specific to schizophrenia or if they are also present in socially isolated healthy individuals.
**Methods:** 59 individuals with schizophrenia (SZ), 84 socially isolated community participants (SIP), 40 healthy participants (HP), and 29 individuals with bipolar disorder (BP) completed a probabilistic implicit learning task, the One-Armed Bandit Task, to assess sensitivity to positive and negative outcomes in social (faces) and nonsocial (monetary) domains. Participants also completed a measure of inclination toward forming social connections and engaging in interpersonal interactions using a scale with established psychometric properties: The Affiliative Tendency Scale.
**Results:** Results of a 3-way repeated measures ANOVA examining outcome type (social vs. nonsocial) x valence (approaching positive outcomes vs. avoiding negative outcomes) x diagnostic group (SZ vs. SIP vs. HP vs. BP) revealed a main effect of group, with SZ individuals scoring lower optimal performance across trials than SIP and HP [$F(3,208)=6.03$, $p < .001$]. Furthermore, there was a main effect of outcome type, with higher optimal performance on nonsocial trials than social trials $F(1,208)=6.06$, $p < .05$. Similarly, there was a main effect of valence, with higher scores on avoiding negative outcomes [$F(1,208)=4.94$, $p < .05$] versus approaching positive ones. There was a significant two-way interaction between outcome type and valence [$F(1,208)=11.34$, $p < .001$], such that accuracy was higher for negative versus positive outcomes on nonsocial trials (Mdiff=0.090, SE = 0.020, $p < .001$, 95% CI [0.050, 0.131]) but not social trials (Mdiff=−0.024, SE=0.03, p=.34, 95% CI [-0.072, 0.025]). There were no significant interactions involving diagnostic group. Interestingly, in SZ, optimal performance on positive social outcomes was significantly positively correlated with affiliative tendency ($r=.28$, $p < .05$).
**Discussion:** In summary, although both SZ and a subset of community individuals are socially isolated, only the SZ individuals displayed deficits in both social nonsocial reward learning, and the association between social reward learning deficits and social approach motivation may be specific to schizophrenia. Future research should investigate why the association between social reward learning and affiliative tendencies is observed in individuals with SZ but not SIP or BP. One possibility is that, although SZ individuals experience generalized deficits in reward learning, their specific difficulties with social reward learning may reduce social approach motivation. In contrast, SIP and BP individuals may have social difficulties due to factors unrelated to reward learning deficits, such as environmental or other psychological influences.

## S33. The Effect of Processing Speed and Verbal Learning Ability on Self-Reported and Clinician-Rated Functioning

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**Background:** Cognitive impairments are well established in people with psychosis spectrum disorders and are present to an attenuated degree in people at clinical high-risk for psychosis (CHR). While the literature has been mixed about which cognitive domains are most predictive of transition to a psychotic disorder, several domains repeatedly stand out. In particular, processing speed and verbal learning have been observed to be impaired at an early age, can discriminate between people who do and do not transition to psychosis, and are included in the NAPLS risk calculator, which assesses psychosis vulnerability. However, little attention has been given to how cognitive impairment affects social and role functioning in the CHR population.

**Methods:** Using data from 943 participants (727 CHR, 216 controls) from the Accelerating Medicines Partnership – Schizophrenia (AMP SCZ), we examined the effect of processing speed and verbal learning abilities on social and role functioning using both self-reported and clinician-rated measures. Processing speed and verbal learning were measured by the Penn Computerized Neurocognitive Battery's Digit Symbol Test (DS) List Learning Test (LLT), respectively. Clinician ratings of functioning were measured by the Global Functioning Social and Role scales. Self-reported functioning was measured by ecological momentary assessment (EMA). A series of linear regressions were used to assess the interaction effects of group and either DS or LLT total correct scores on the functional outcomes listed above. When no interactions were present, models were reduced to examine the main effects. Mixed effects models will be used to assess how well cognition predicts future functioning.
**Results:** DS total score related to both clinician-rated social ($b = 0.019$, $t(723) = 4.411$, $p < 0.0001$) and role functioning ($b = 0.029$, $t(723) = 4.744$, $p < 0.00001$). Further, DS total score related to self-reports of how participants were able to function ($b = 0.022$, $t(161) = 2.073$, $p = 0.0397$) and how well participants could handle what came their way that day ($b = 0.027$, $t(161) = 2.523$, $p = 0.0126$). However, DS total score did not relate to how much time participants spent with others in person ($b = 0.022$, $t(161) = 1.691$, $p = 0.0928$) or online ($b = 0.011$, $t(161) = 0.890$, $p = 0.375$). LLT total score also related to both clinician-rated social ($b = 0.027$, $t(738) = 4.512$, $p < 0.00001$) and role functioning ($b = 0.042$, $t(738) = 5.005$, $p < 0.000001$). Further LLT total score related to how much time the participant spent with others in person ($b = 0.036$, $t(163) = 2.117$, $p = 0.0358$), but not how well they could function ($b = 0.023$, $t(163) = 1.664$, $p = 0.0981$), how well they could handle things ($b = 0.013$, $t(163) = 0.893$, $p = 0.373$), or how much time they spent with others online ($b = -0.014$, $t(163) = -0.872$, $p = 0.385$). No interactions with group were found.
**Discussion:** Both processing speed and verbal learning abilities related to clinician ratings of social and role functioning, while processing speed related to self-reports of role functioning and verbal learning related to self-reports of social functioning. Impending analyses will examine whether processing speed and verbal learning relate to functioning more than IQ and positive symptoms do, as well as examine if processing speed and verbal learning predict future functioning, or if the relationship is temporally bound.

## S34. Predictive Factors for Treatment Engagement in Individuals With Psychosis

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**Background:** Rates of treatment engagement for individuals with psychotic disorders has proven to be alarmingly low, considering the seriousness and persistence of symptoms (Fontanella et al., 2013). Prior research has shown that low cognitive functioning, often measured by IQ, is a good predictor of treatment engagement (Leeson et al., 2009). Additionally, certain at-risk, disadvantaged populations are less likely to engage in treatment because of an increase of barriers in accessing quality treatment (Fontanella et al., 2013). Thus, it is imperative to understand what variables impact treatment engagement in individuals with serious mental illness (SMI). This study tested three key hypotheses: 1) Higher IQ will correlate with higher rates of treatment engagement in individuals with psychotic disorders, and this relationship will be negatively mediated by treatment barriers; 2) Psychosis symptom severity will moderate the relationship between IQ and treatment engagement; 3) Demographic variables indicating specific disadvantages (e.g., socioeconomic status) will correlate with more treatment barriers.

**Methods:** Participants were a community sample, recruited online, and included 68 English-speaking adults who had psychotic diagnoses. IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI-II), and the Mini-International Neuropsychiatric Interview (M.I.N.I.) version 7.0.2 was used to confirm diagnoses. The Brief Psychiatric Rating Scale (BPRS) was used to measure symptom severity, across a variety of symptom profiles, and the Treatment History Interview (THI-4) was used to collect information regarding treatment engagement in the past month. Barriers were assessed by participants completing a self-report measure, with a checklist of possible treatment barriers as well as a free-response option.

**Results:** There was no significant correlation between IQ and treatment engagement ($r = -.035$, $p = .804$), no significant mediation of barriers in this relationship ($p = .866$), and no significant moderation of symptom severity in the correlation ($p = .373$). Additionally, there was no significant association between race, employment status, age, or education level with reported barriers ($p > .949$). However, independent sample t-tests indicated that participants who had diagnoses of an affective psychotic disorder (e.g., schizoaffective disorder, bipolar disorder with psychotic features) reported significantly more barriers to treatment than those whose diagnoses were non-affective ($t= 2.584$, $p = .012$), and individuals with affective diagnoses scored significantly higher on Full Scale IQ ($t= 2.193$, $p= .032$) and Verbal IQ measures ($t= 2.232$, $p= .029$).

**Discussion:** The lack of a relationship between IQ and treatment engagement may mean that cognitive abilities are not playing a role in how engaged an individual is in psychiatric care. This finding is important because it indicates that individuals with greater cognitive challenge are not less engaged in care than those with greater cognitive ability. However, given that previous literature suggests low engagement for individuals with SMI, it would be important to examine if interventions to increase engagement are equally effective across cognitive profiles. Additionally, the difference in IQ across the affective and non-affective diagnostic groups may offer one explanation behind the difference in reported barriers, as higher IQ may be associated with increased awareness of illness-related challenges. Conversely, this finding may also indicate that in this sample, the individuals with non-affective disorders may have greater cognitive challenges which may result in increased care facilitated by others. Future research should examine whether there is a relationship between IQ and treatment barriers, and whether this is associated with assistance by family or social support.

References

Fontanella, C. A., Guada, J., Phillips, G., Ranbom, L., and Fortney, J. C. (2013). Individual and contextual-level factors associated with continuity of care for adults with schizophrenia. Administration and Policy in Mental Health and Mental Health Services Research, 41(5), 572–587. https://doi.org/10.1007/s10488-013-0500-x

Leeson, V. C., Barnes, T. R. E., Hutton, S. B., Ron, M. A., and Joyce, E. M. (2009). IQ as a predictor of functional outcome in schizophrenia: A longitudinal, four-year study of first-episode psychosis. Schizophrenia Research, 107(1), 55–60. https://doi.org/10.1016/j.schres.2008.08.014

Linehan, M. M., and Heard, H. (1987). Treatment History Interview (THI). University of Washington, Seattle, WA.

Overall, J. E., and Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. Psychological Reports, 10, 799–812. https://doi.org/10.2466/pr0.1962.10.3.799

Sheehan, D. V. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry, 59, 22–33.

Wechsler, D., and Hsiao-pin, C. (2011). WASI-II: Wechsler Abbreviated Scale of Intelligence. 2nd. Psychological Corporation.

## S35. Investigation of the Effect of Different Stimuli on the Production and Valence of Emotional Words in Patients With Schizophrenia

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**Background:** Automated methods of speech analysis in patients with schizophrenia can aid in assessing symptoms and behavioral problems, even in regions with limited access to specialists. Preliminary findings have revealed distinct patterns of speech connectivity, analyzed using graph-based methods when compared to healthy controls or patients with other disorders. By converting speech into visual elements, speech graphs enable the observation of structural characteristics of speech. However, analyzing the content of speech presents a more significant challenge. Emotional, positive, and negative valence words provide valuable insights into patients' mental states. Despite this, few studies have explored this area, and none have yet compared the effects of different speech production stimulus protocols on the valence of emotional words.
**Methods:** This cross-sectional study included 37 patients with schizophrenia treated at the Center for Integrated Mental Health Care in São Paulo. Participants underwent an interview following the terms of the Discourse in Psychosis voice protocol, the largest collaborative network of automated methods in the study of thought and language disorders present in schizophrenia. In the study, five different stimuli were analyzed: 1) free conversational speech, 2) personal narrative, 3) health narrative, 4) picture descriptions, and 5) dream reports. The speech was recorded, transcribed, and submitted to Linguistic Inquiry and Word Count (LIWC) to analyze the count of emotional words, according to a previously validated Brazilian Portuguese dictionary, and positive and negative valence words. Statistical analyses used Friedman's and Wilcoxon tests with Bonferroni correction for multiple comparisons.
**Results:** The production of emotional words differed significantly across the stimulus protocols ($\chi^2$ = [410.44], df = 14, $p < 0.001$). This difference remained significant after applying the Bonferroni correction for multiple comparisons ($p < 0.0016$). For positive valence words, the "free conversational speech" protocol elicited significantly more positive words compared to the "dream reports" (Z = -3.896) and "picture descriptions" (Z = -4.383) protocols. Regarding negative valence words, the "health narrative" protocol elicited predominantly more negative words than all the other stimuli. The most significant differences were observed in comparison to "free conversational speech" (Z = -5.107) and "picture descriptions" (Z = -5.027), followed by "personal narrative" (Z = -4.458) and "dream reports" (Z = -3.598).
**Discussion:** The production of emotional words and the valence of discourse varied depending on the stimulus protocol used. Patients produced more words with positive connotations when discussing themselves and their favorite activities during their free time. In contrast, they used more negative words in medical contexts, reflecting their perception of

living with the illness as a challenging experience characterized by social stigma and a decline in functional abilities. Future studies should aim to include larger, more diverse samples from different cultural backgrounds and better address the potential effects of symptom severity. Our findings underscore the importance of standardizing stimulus protocols to enhance generalizability while demonstrating the significant potential of automated speech analysis tools to capture subtle emotional features with clinical relevance.

## S36. Discrepancies Between Subjective and Objective Cognitive Measures in Schizophrenia Spectrum Disorder: The Role of Anxiety

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**Background:** Cognitive deficits are common and impact the daily functioning of individuals with Schizophrenia Spectrum Disorder (SSD). Discordance between subjective and objective measures of cognition has been previously documented. Additionally, prior research has identified a relationship between anxiety and the underestimation of one's cognitive abilities. To build upon this existing literature, the present study addressed the following aims: 1. to examine the relationships between anxiety and subjective and objective cognition, 2. to explore the role of anxiety in the discordance between subjective and objective cognition, and 3. to explore subjective cognitive complaints at item level.
**Methods:** A sample of n = 51 individuals with a diagnosis of SSD were included in the analyses. Anxiety was assessed utilizing the State Trait Anxiety Inventory (STAI). Subjective cognition was assessed using the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS). Objective cognition was assessed with a battery of neurocognitive measures (Matrics Consensus Cognitive Battery (MCCB) and the d2 test of attention) assessing four domains: working memory, explicit memory, executive functioning (EF), and attention. Discrepancies between subjective and objective cognition were calculated by standardizing the objective and subjective scores on a scale of 1-10 and subtracting the subjective from the objective. Thus, discrepancy scores ranged from –10 to +10.
**Results:** Correlations between state/trait anxiety and standardized subjective scores revealed significant relationships with explicit memory, attention and executive functioning (p values ranging < .001 to .027). No objective cognitive domains had a significant relationship with anxiety. Simple linear regression models were used to examine state and trait anxiety as predictors of discrepancy scores. Anxiety predicted discrepancy scores for explicit memory, EF and attention ($R2 = 0.23$ to 0.09 and p-values between < .001 - .0371). Item and subdomain level correlations between subjective (SSTICS) items and objective domains found that a majority of SSTICS items did not significantly map onto their objective counterparts. Only one explicit memory item, $r(49) = -.29$, $p = .025$, and one working memory item, $r(49) = .31$, $p = .042$, had a significant relationship with objective measures. Finally, item level analysis between anxiety and subjective cognition (SSTICS) revealed weak to moderate associations between anxiety and questions pertaining to subjective perceptions of attention. explicit memory and EF.
**Discussion:** These findings suggest that anxiety has a relationship with subjective perception of cognition, namely an underestimation of cognitive performance relative to objective testing. Across a majority of cognitive domains, anxiety was significantly associated with subjective cognition. The lack of association between anxiety and objective cognition is consistent with prior research. Further, results of linear regressions suggest that anxiety

influences the discordance between subjective and objective measures across a majority of cognitive domains. Finally, our item level analyses further call into question the convergence between the subjective and objective measures. Item level analysis revealed weak to moderate relationships between anxiety and perceptions of EF and attention, yet the nature of this relationship remains unclear. These results highlight the importance of examining anxiety as a promising direction to better understand the discordance between objective testing and one's subjective cognitive experiences. Future research should incorporate additional measures and expand to experimental designs capable of examining causality.

## S37. Social Stress in Schizophrenia: Unique Contributions to Social Cognition and Social Functioning

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**Background:** Schizophrenia-spectrum disorders have been associated with heightened stress sensitivity, which can worsen prognosis, functioning, and quality of life. However, more research is needed to determine whether different types of stress impact specific functional domains.
**Methods:** This study used the Psychological Stress Index (PSI)—a self-report instrument designed and validated to measure perceived stress in psychosis—to delineate the unique contribution of social versus non-social stress to social functioning and social cognition. Fifty-nine participants with schizophrenia/schizoaffective disorder and fifty non-clinical controls completed the PSI and a battery of social functioning and social cognition measures. These social functioning/cognition measures included the Social Skills Performance Assessment (SSPA), UCSD Performance-Based Skills Assessment (UPSA) communication task, Reading the Mind in the Eyes Test (RMET), Penn Emotion Recognition Test (ER-40), and Global Functioning: Social (GFS) subscale.
**Results:** Elevated social stress predicted worse performance on an emotion recognition task (ER-40; $\Delta r^2=5.04\%$) and worse interviewer-rated social functioning (GFS; $\Delta r^2=3.29\%$), over-and-above non-social stress. Self-reported social stress explained significant amounts of variance ($\Delta r^2=4.80\%$) in social functioning over-and-above performance on the ER-40. Social stress also explained significant variance ($\Delta r^2=4.73\%$) in social functioning over-and-above performance on a theory-of-mind task (RMET).
**Discussion:** These results provide promising evidence that examining social stress separately from non-social stress provides unique information about social difficulties in schizophrenia-spectrum psychopathology. Examining social stress and other specific forms of stress may improve understanding of stress sensitivity in this population and better inform treatments aimed at improving functioning.

## S38. Apathy and Functioning in the General Population - A Latent Profile Analysis Approach

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**Background:** Apathy, characterized by diminished motivation, emotional engagement, and social interaction, is a core feature of schizophrenia spectrum disorders, and is also prevalent in milder forms in the general population. Despite its widespread occurrence, the heterogeneity of functional impairments associated with apathy is not well understood. This study aims to identify distinct profiles of apathy in the general population using a person-centered approach (latent profiles), focusing on the relationship between apathy dimensions, everyday functioning, anhedonia and psychotic symptoms.
**Methods:** A cross-sectional online study was conducted with the representative sample of the general population (N=1200; mean age=42.60, SD=12.48; 52% female). Apathy was assessed using Apathy Motivation Index (behavioral, social and emotional dimensions), and functioning was measured with the Specific Levels of Functioning Scale (Interpersonal Relationships, Social Acceptability, Activity, Work Skills) and WHO-DAS 2.0 (Understanding and communicating, and Getting along subscales). Psychopathology measures included the Community Assessment of Psychic Experiences (psychotic-like experiences) and the Temporal Experience of Pleasure Scale (anticipatory and consummatory pleasure). Latent profile analysis (LPA) was used to identify distinct apathy profiles, and associations with functioning and psychopathology were explored using Welch's t-test.
**Results:** Two clusters were identified. A profile characterized with higher behavioral and emotional apathy but low social apathy (N=206) showed significantly elevated positive psychotic symptoms (d=0.579), reduced anticipatory (d=-0.721) and consummatory pleasure (d=-0.864), better-perceived interpersonal relationships (d=0.508), lower-perceived socially acceptable behavior (d=-0.495), reduced participation in community and household activities (d=-0.372), and diminished work skills (d=-0.176). These findings indicate a dissociation between apathy dimensions and their impact on functioning within general population.
**Discussion:** Higher behavioral and emotional apathy appears to be linked to subclinical psychotic symptoms, diminished hedonic capacity, and deficits in vocational and daily functioning. In contrast, low social apathy may enable social interactions (in combination with higher behavioral and emotional apathy), but with limited depth or adherence to social norms. It might result from overestimations of quality/quantity of interpersonal relationships, potentially due to reduced emotional involvement or self-awareness. These results highlight the complexity of apathy's multidimensional nature and its relationships with psychosis, hedonic capacity, and social functioning.
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## S39. Structural Brain Complexity is Associated With Semantic Connectedness in the Schizophrenia Spectrum

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**Background:** Two separate traditions have long documented brain-structural along with language abnormalities in patients with first-episode psychosis (FEP), subjects at clinical high-risk of psychosis (CHR), and patients with schizophrenia (SCZ). A key question of current interest is whether language changes at the level of spontaneous speech might qualify as a potential behavioral readout of brain-structural changes, as has been previously documented for cortical thinning and gyrification. We used the Largest Lyapunov Exponent (lambda) as a measure of brain complexity. The present study aimed to employ nonlinear

analysis to identify differences in brain complexity of schizophrenia spectrum disorders (SSD) against HC, specifically targeting the lambda as a measure of structural brain complexity in FEP, CHR, and SCZ against healthy controls (HC). We hypothesized that changes in brain structure would be associated with language features that we previously reported to be related to brain-functional changes.
**Methods:** Structural MRI were acquired from 60 FEP, 16 CHR, 16 SCZ and 38 HC as part of the TOPSY study. Nonlinear analysis of the gray matter distribution was performed: First, the distances of each voxel from the center of mass in the gray matter image were calculated. Next, the distances multiplied by the voxel intensity were represented as a spatial-series, which then was analyzed by extracting the Largest-Lyapunov-Exponent (lambda), to generate brain maps depicting how gray matter topology changes. Two language models, FastText and BERT, were used to extract features of semantic structure and syntactic complexity from picture descriptions, and associated with brain complexity measures.
**Results:** Between-group comparisons of lambda brain maps resulted in statistically significant ($p < 0.05$) differences in FEP, CHR and SCZ compared to HC, with the highest brain complexity seen in HC group. Metrics of semantic connectedness, such as cluster coefficient and local semantic similarity, were significantly associated with the structural complexity in the cerebellum for all clinical groups, in the occipital lobe for FEP and SCZ, in the temporal for SCZ, and putamen for CHR.
**Discussion:** These results, reflecting a new analytical framework using spatial-series shows that groups are identifiable by these brain-complexity theoretic measures and that they relate to a behavioral readout obtainable computationally from spontaneous speech patterns. Findings of associations of the cerebellum with semantic language features in FEP, CHR, and SCZ support a model of alterations in the cerebellum (Biventral lobule, Tonsil, Flocculus and Crus) being associated with psychosis in the early course of illness9. Changes in the cerebellar volume of patients with schizophrenia have been linked to predominantly positive symptoms, which is in line with the fact that the cerebellum supports multiple cognitive functions such as emotion regulation, inhibiting impulsive decision making, attention, conceptual semantics, and working memory.

## S40. Trajectories of Cognitive Function in First-Episode Psychosis: Associations to Clinical Outcomes and Biomarkers

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**Background:** Cognitive dysfunction in psychotic disorders is common. At disorder onset, this impairment varies greatly between individuals, which may reflect different levels of decline compared to pre-morbid levels. Diverse trajectories in cognitive change prior to psychosis onset have been hypothesized to represent different underlying pathological processes. Our primary aim was to model cognitive change over time in a sample of individuals with first-episode psychosis (FEP) and controls. The secondary aim was to explore whether cognitive change was associated with clinical outcomes, and biological markers that have shown associations with disease progression.
**Methods:** Our sample consisted of 73 individuals with FEP who had undergone cognitive assessment at psychosis onset and 53 controls. Using school grades from registry data as a

proxy for pre-morbid cognitive ability, we modelled change in cognition using linear mixed-effects models. The resulting change scores were correlated to polygenic risk scores, cerebrospinal fluid levels of complement protein C4A and clinical outcomes.
**Results:** Groups did not differ in school performance prior to psychosis. Psychosis onset was associated with a large cognitive decline in FEP and thereafter they performed significantly worse than controls. Among FEP individuals, there was a large degree of variability in cognitive change leading up to psychosis onset. Degree of cognitive change was not associated to the selected biological variables but did predict worse clinical outcomes.
**Discussion:** The results indicate that individual cognitive trajectories may be a clinically relevant topic for further study, but given the exploratory nature of the analysis, replication in an independent sample is required.

## S41. Expert Consensus on Cognitive Assessment in Psychiatry: A Delphi Study

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**Background:** Many people diagnosed with psychiatric disorders (e.g., schizophrenia) experience cognitive dysfunction that can have a profound impact on their daily lives. Cognition is a broad term encompassing a range of mental processes including neurocognition (traditional cognitive domains, like memory and attention), social cognition (thought processes related to social situations, such as emotion recognition and theory of mind), and cognitive biases (tendencies to attend to, remember, and interpret information, such as when jumping to conclusions with little evidence). Research suggests broad cognitive impairments in many psychiatric disorders; however, there is a lack of consensus regarding measuring cognitive dysfunction in psychiatry, and previous consensus initiatives are out of date or limited in scope. We aimed to provide an updated and extended expert consensus on the domains, subdomains, and measures of cognitive dysfunction in psychiatric disorders as well as the ideal characteristics of such measures.
**Methods:** We employed the Delphi method, a systematic expert consensus technique that uses an iterative framework upon which consensus can be built. Participants (n = 20 in round 1) consisted of clinicians and researchers with expertise in cognition and psychiatry, with a graduate or professional degree in a relevant field (e.g., psychology, neuropsychology, psychiatry, cognitive neuro/science) and a minimum 3 years of training or academic contributions to the field. Experts were recruited through several avenues, including their academic publications on relevant topics, national and international academic societies (e.g., Canadian Network for Research in Schizophrenia and Psychoses, Schizophrenia International Research Society), the authors' professional networks, and the snowball method (potential participants recommended expert colleagues).
This ongoing study includes 3 consensus rounds, consisting of online questionnaires, with feedback on previous rounds provided to participants between rounds to gradually develop a consensus. Round 1 is complete, providing preliminary findings for the extended cognitive consensus. Round 1 served to generate content for the consensus (e.g., open-ended questions on cognitive domains, subdomains, and measures, as well as ideal characteristics for cognitive assessment batteries) and provide preliminary ratings for these aspects of cognitive

assessment (5-point scale: 1 = Not at all Important, 2 = Somewhat Important, 3 = Important, 4 = Very important, 5 = Essential).

**Results:** Twenty participants completed round 1 (47.1% response rate), with age ranging from 28-67 years old (mean = 42, SD = 9.53), and 55% of whom were assigned as females at birth. Half of the sample self-identified as a member of a minority group. 75% of the sample lived in Canada (Quebec, Ontario, British Columbia) and 25% were from outside Canada (France, Australia). Half of participants were professors of various ranks (assistant, associate, full), 39.3% were clinicians (neuropsychologist, psychologist, psychiatrist), with the remaining being trainees (PhD student, Postdoctoral researcher, research associate). Most (70%) endorsed expertise in young, middle, and older adulthood. Expertise in related research areas ranged from cognitive interventions (55%) to neurobiology (30%) and most respondents (90%) had expertise with severe mental illness (schizophrenia-spectrum disorders, psychosis, bipolar disorder).
The cognitive domains and subdomains that were rated as "essential" for cognitive assessment by 75% or more of the sample were: memory (95%, mean = 3.95), attention (90%, mean = 3.8), working memory (85%, mean = 3.85), executive function (85%, mean = 3.75), episodic memory (80%, mean = 3.65), processing speed (75%, mean = 3.6), and social cognition (75%, mean = 3.55). Language (mean = 3.15) and cognitive biases (mean = 3.55) were rated as essential by 40% of respondents. Motor function (mean = 1.8), perception (mean = 1.61), and sensation (mean = 1.54) were rated as essential by one or no participants. Additional subdomains that emerged from open-ended responses included: sustained attention, planning, inhibition, theory of mind, and verbal memory. The ideal characteristics most frequently endorsed for cognitive assessment were as follows: validated, repeatable, reliable, brief, digital, accessible, and normed. The ideal duration for a cognitive battery ranged from 20 to 180 minutes, with 30 minutes (15%), 60 minutes (15%) and 90 minutes (40%) receiving the greatest endorsement.

**Discussion:** Preliminary findings of this Delphi cognitive consensus indicated that traditional neurocognitive domains (memory – especially working and episodic, attention, executive function) and social cognition are essential for cognitive assessments in psychiatric disorders. However, there was variability in ratings as well as in the ideal battery duration, indicating that a flexible approach to cognitive assessment involving a modular battery may be most applicable to various settings. Future rounds of the Delphi study will refine these findings for an updated and extended cognitive consensus in psychiatry.

## S42. Sleep Problems and Cognitive Impairment in the Psychosis Spectrum: A Multi-Method Investigation

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**Background:** Cognitive impairment is prevalent in psychosis spectrum disorders, contributing to significant functional and occupational impairment (McCutcheon et al., 2023). Specifically, this group has consistently observed diminished executive functioning, processing speed, and impaired working memory (McCutcheon et al., 2023; Oomen et al., 2023). Preceding the onset of psychosis, individuals also experience disrupted cognitive

functioning associated with sleep disruption in ultra-high-risk samples (Waite et al., 2020). Sleep disruption also contributes to worse negative and positive symptoms, making it a potential target for treatment (Poe et al., 2017).
Recently, research has considered targeting sleep to reduce further cognitive decline in psychosis spectrum disorders and potentially improve specific cognitive areas (e.g., memory through sleep-dependent memory consolidation) (Manoach et al., 2021). In assessing sleep, it is important to consider that different methods (e.g., self-report and sleep actigraphy) may show poor convergence (e.g., Savage et al., 2021) and potentially have differential relations with cognitive functioning (Carruthers et al., 2021). Given this, the current study conducted a multimethod assessment of sleep using sleep diaries and sleep actigraphy to examine associations with cognitive impairment. We predicted that 1) Actigraphy-based measures of sleep (total sleep time, awake after sleep onset, and sleep latency) would relate to cognitive functioning, and 2) Sleep diary measures of total sleep time (TST), awake after sleep onset (WASO), and sleep latency (SL) will relate to cognitive impairment.

**Methods:** Data was collected from a transdiagnostic sample (N=79) of people with a psychosis spectrum disorder from the Baltimore and Washington D.C. area. The Brief Cognitive Assessment Tool (BCAT; Mansbach et al., 2012) was used to assess cognitive performance. The BCAT consists of a trial-making task (TMT), which assesses executive function and working memory; digit symbol (DS) substitution, which assesses processing speed, learning, and memory; and category fluency (CF), which assesses verbal fluency and language skills. The Consensus Sleep Diary (CSD; Carney et al., 2012) was administered across 7 days to assess daily sleep. Sleep actigraphy was also assessed for 7 days (Actiwatch Spectrum; Philips Respironics, Bend, OR).
**Results:** Examining agreement between the two sleep measures, analyses indicated that WASO by actigraphy was related to WASO by sleep diary ($r=.35$, $p < .01$); however, other sleep indices from the two measures were not related (ps > .05). Greater actigraphy-measured TST ($r=.34$, $p < .01$) and WASO ($r= .23$, $p < .05$) were related to slower (worse) performance on the TMT. Greater actigraphy-measured WASO was related to worse digit symbol performance ($r= -.23$, $p < .05$). Poorer performance on the trial making test was related to less sleep diary-measured TST ($r= -.29$, $p < .01$), greater SL ($r=.38$, $p < .001$) and greater WASO ($r=.28$, $p < .01$). Greater sleep diary measured SL was related to less correct DS ($r=.26$, $p < .01$). Neither sleep actigraphy nor sleep diary was related to category fluency.
**Discussion:** The two methods of assessing sleep showed only modest convergence. However, sleep indices from both actigraphy and sleep diary self-reports were related to poorer performance in cognitive domains primarily associated with executive function, working memory, and processing speed. These results confirm the relation between problematic sleep and cognitive impairment and emphasize the benefits of assessing sleep with a multimethod approach. Implication of these findings will be discussed at the time of the presentation.

## S43. OPEN BOARD

## S44. The Role of Facial Affect Recognition in the Increased Odds of First-Episode Psychosis in Ethnic Minority Populations: Findings From the EU-GEU Case-Control Study

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**Background:** Consistent evidence suggests increased rates of psychosis among various ethnic minority populations in high-income countries. However, the underlying psychological mechanism of this disparity is largely unknown. One possibility is that ethnic minorities have the tendency to mistakenly attribute neutral or positive facial expressions to negative emotions due to the exposure to threats in their environment. This study examined the role of facial affect recognition in the relation between ethnic minority status and odds of psychosis.
**Methods:** The study included a sample of 1035 cases with First-Episode Psychosis (FEP) and 1382 controls in six European countries and Brazil within the European Network of National Schizophrenia Networks studying Gene-Environment Interactions (EU-GEI) project. Ethnicity was classified in six categories; White, Black, Mixed, Asian, North African, other. First-episode ICD-10 psychotic disorders (F20–F33), non-affective disorders (F20-25) or affective psychotic disorders (F30-33) presented the outcome. The Degraded Facial Affect Recognition Task (DFAR) measured accuracy of facial affect recognition. Negativity bias was measured as the likelihood that neutral and happy faces were falsely interpreted as anxious or angry. Following imputation for missing data, a mediation analysis using natural effect models was conducted.
**Results:** Odds of psychosis were twice as high for ethnic minority groups than for the white majority (ORadj: 2.3, 95% CI [1.78, 2.97], $p < .001$), varying between 3.22 (95% CI 1.93-5.36) for the North African group and 2.32 for the Black group (95% CI 1.63 – 2.55). Adjusting for potential confounding, there was evidence that facial affect recognition mediated this relationship for the Black and Mixed ethnic group (proportion mediated: 55.3% and 30.9%, respectively). This was not the case for the North African, Asian and Other ethnic groups.
**Discussion:** Impaired facial affect recognition of ethnic majority faces may (partially) underlie the increased odds of psychosis among some ethnic minority groups. Social cognitive mechanisms represent promising targets for intervention in the early stages of psychosis, particularly among members of ethnic minority groups.

## S45. Egocentric Distance Estimation and Self-Other Boundary in Schizophrenia

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**Background:** A clear sense of self-other boundary that delimits one's personal space is disrupted in schizophrenia (SZ). Dysregulation of personal space is closely linked to clinical symptoms and social impairments in SZ but possible underlying perceptual mechanisms that may contribute to maladaptive self-other boundaries remain unspecified. To elucidate the relationship between spatial cognition and social behavior in SZ, we hypothesized that interpersonal space regulation may depend on accurate distance perception. We investigated the egocentric distance estimation, the certainty of those estimates, and their relationship to social functioning and symptom severity in SZ.
**Methods:** Individuals with schizophrenia and matched controls (CO) participated in an egocentric reachability task with objects placed on a table at specific locations on the z-axis. Each trial consisted of an object placed at a certain distance from the participant who were asked to decide whether they could reach the object or not. Participants' hands were hidden under a gown and were not allowed to use them. For all 'yes' responses, participants also gave a confidence rating. Moving from close to the body to farther away from the body, the estimated reachability boundary marks the point where participants begin to feel uncertain

about "yes" responses. For SZ group, clinical symptoms (SANS, SAPS) were obtained. For all participants, levels of loneliness (UCLA) and paranoia (RGPTS) were collected. Lastly, the length of the arm and the height were measured.
**Results:** SZ group had a larger estimated reachability boundary than CO, while having similar arm length to CO. Estimated reachability boundary was larger than arm length in SZ, while in CO they did not differ significantly. Arm length correlated with reachability boundary in SZ but not in CO. Calculating estimated distance and actual distance, SZ overestimated distance more than CO. In CO, larger differences between actual and perceived distance correlated with higher loneliness and paranoia levels. In SZ, no correlation was found between reachability estimates and symptoms, loneliness, or paranoia levels.
**Discussion:** In CO, their arm length, presumed to closely associated with peripersonal space, was matched to their own reachability estimates. In SZ, their arm lengths and reachability estimates diverged; they tended to overestimate reachability. These results suggest that egocentric distance estimation is impaired in SZ compared with CO. In CO, reachability estimates and paranoia as well as social isolation but in SZ, we did not observe a consistent relationship. However, a larger sample size is needed to elucidate the relationship between self-boundary and social functioning.

## S46. H-MRS Findings in Psychosis and Their Association With Cognition: A Systematic Review

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**Background:** There are several studies which analyzed the biological substrate of cognition in psychotic spectrum. However, there was no previous record of any literature review that includes the relationship of brain metabolites and cognitive development in these subjects. Exploring the possible relationship between metabolic alterations and the cognitive changes typical of Early Onset Psychosis, deficits in markers such as the Glutamate-Glutamine combination in the medial frontal cortex have been observed (Merritt et al., 2016), were associated with impairment in markers of cognition or global cognitive functioning (Bustillo et al. 2011). This supports the hypothesis that psychosis is associated with excess glutamatergic neurotransmission in several limbic areas, and indicates that compounds that reduce glutamatergic transmission may have therapeutic potential.

Regarding other brain metabolites, previous studies show reduced NAA levels in the dorsolateral prefrontal cortex, thalamus and hippocampus areas of subjects with psychosis (Frey et al., 2007; Steen et al., 2005; Zabala et al., 2007), areas related to cognitive functions.

Specifically, in individuals with first psychotic episodes, low levels of NAA are associated with a decreased ability to develop working and visual memory (Weinberger and Bermam, 1996), and verbal learning (Ohrmann et al., 2007); and poorer performance in executive functions (Galińska et al., 2007) and processing speed (Wang, et al. 2019).

In the Anterior Cingulate Cortex, a negative correlation of Glx/NAAx with working memory is observed among subjects with non-resistant schizophrenia. This study reinforces the idea that glutamatergic concentration in the ACC plays an important role in the classification of treatment resistance and cognition; it may become a potential biomarker of treatment prediction and response (Huang et al., 2023).

In the case of creatine, a relationship has also been found between reduced NAA/Cr ratio and cognitive deficits in subjects with schizophrenia (Bertolino et al., 2003; Callicott et al., 2000; Brugger et al., 2011; Huang et al., 2017; Steen et al., 2005). Creatinine may show a neuroprotective effect as higher amounts of this metabolite maintain cognitive functions (Turner et al., 2015).

Choline has also been shown to play an important role in cognitive function, as it is necessary for the synthesis of the neurotransmitter acetylcholine, phosphatidylcholine (essential for membrane integrity and maintaining brain structure and function) and betaine (contributes to DNA and histone methylation, modulating the expression of genes involved in brain function and structure) (Bekdash 2019).

On the other hand, there are studies with contrary results, in which no associations of brain metabolic levels with cognitive functions have been found in subjects with psychosis (Broeders et al., 2022, Borgan et al., 2019; Matsuzawa et al., 2008, Bartolomeo et al., 2019).

**Methods:** The systematic review was registered in PROSPERO: CRD42024567183. The databases PubMed/MEDLINE, EMBASE, PsycInfo, Web of Science and Scopus were searched by two researchers independently. The search strategy will incorporate terms related to the following concepts: 1) Cognition, 2) Brain magnetic resonance spectroscopy, and 3) Psychosis continuum population: At risk for psychosis and/or with a first episode/established psychosis and/or with affective psychosis. There will be no restrictions on publication dates, and only articles available in English will be included.
The study questions were:

1. Is there an association between metabolite levels assessed using MRS and neurocognitive function in individuals with psychosis?

2. Is this association different over the course of the disorder (i.e. between individuals at risk for psychosis, first episode psychosis or established psychosis)?

3. Does this association differ between affective and non-affective psychosis?

4. Is this association specific to psychosis and/or psychosis risk?

The inclusion criteria was: full text research articles investigating brain metabolite levels and neurocognition; measured using MRS in any brain region and a standardized or experimental neuropsychological test, respectively. Original empirical articles that included participants

under 65 years old with a first episode or a diagnosis of schizophrenia or other psychotic disorders, participants at clinical or familiar high-risk for psychosis.

**Results:** This review found 3333 studies: 845 from Embase, 773 PubMed, 721 Web of Science, 641 PsycINFO, 353 Scopus. 1639 of these were identified as duplicates and 1694 studies were screened against title and abstract.
In this screening, 1342 studies were excluded and 351 were assessed for full-text eligibility.

Of these studies 252 were excluded: 141 because they have a wrong study design, 62 wrong outcomes, 38 wrong patient population, 9 wrong intervention and 2 not available.

Finally, 99 studies were included and currently are in data extraction phase.

**Discussion:** Although the study is currently in progress, it will be entirely new and will fill a gap that has existed in the literature so far, allowing for a meta-analysis to be carried out.

## S47. Reductions in Positive and Negative Syndrome Scale Subscales With Xanomeline and Trospium Chloride in Adults With Schizophrenia: Pooled Post Hoc Analyses

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**Background:** Xanomeline and trospium chloride, formerly known as KarXT, was recently approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults. In contrast with most available antipsychotics, xanomeline is a dual M1/M4 muscarinic receptor agonist with no direct D2 dopamine receptor blocking activity. The efficacy and safety of xanomeline/trospium were demonstrated in the 5-week EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, in which xanomeline/trospium was associated with significant reductions from baseline to week 5 in Positive and Negative Syndrome Scale (PANSS) total score compared with placebo. Here we present analyses of xanomeline/trospium impacts on PANSS subscale scores.
**Methods:** The acute EMERGENT trials were randomized, double-blind, placebo-controlled, 5-week, inpatient trials of xanomeline/trospium in adults experiencing acute exacerbations of schizophrenia. EMERGENT-1 enrolled adults aged 18-60 years and EMERGENT-2 and EMERGENT-3 enrolled those aged 18-65 years. Participants were required to have recent worsening of symptoms warranting hospitalization, PANSS total score 80-120, a score of ≥4 on at least two PANSS positive scale items, and a Clinical Global Impression–Severity (CGI-S) score of ≥4. Eligible participants were randomized 1:1 to receive xanomeline/trospium or placebo. Dosing of xanomeline/trospium started at 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID. Efficacy was assessed in the pooled modified intention-to-treat population, defined as all participants who received ≥1 dose of trial medication and had 1 baseline and ≥1 postbaseline PANSS assessment. Change from baseline to week 5 in PANSS positive, negative, general psychopathology, and cognitive subscale scores was examined in post hoc analyses of data pooled from the 3 acute EMERGENT trials.
**Results:** The pooled efficacy population included 640 participants, including 314 in the xanomeline/trospium group and 326 in the placebo group. Previous results showed significant reductions from baseline to week 5 compared with placebo in PANSS total score (least squares mean [LSM] difference, -9.9; 95% confidence interval [CI], -12.4 to -7.3; $P < 0.0001$; Cohen's d effect size, 0.65). Scores also decreased from baseline to week 5 compared

with placebo across PANSS subscales, including PANSS positive (LSM difference, -3.2; 95% CI, -4.1 to 2.4; Cohen's d, 0.67), PANSS negative (LSM difference, -1.7; 95% CI, -2.4 to -1.0; Cohen's d, 0.40), PANSS general psychopathology (LSM difference, -5.0; 95% CI, -6.3 to -3.6; Cohen's d, 0.61), and PANSS cognitive (LSM difference, -1.4; 95% CI, -1.9 to -0.9; Cohen's d, 0.47) subscales ($P < 0.0001$ for all).
**Discussion:** In post hoc analysis of data pooled from the 5-week EMERGENT trials, xanomeline/trospium was associated with improvement across multiple symptom domains as assessed with PANSS positive, negative, general psychopathology, and cognitive subscales. These data corroborate previous results showing improvement in PANSS total scores in adults with schizophrenia and provide additional support for the efficacy of xanomeline/trospium as a novel treatment for psychosis based on muscarinic receptor agonism.

## S48. A Comparison of Psychotic and Mood Disorder Patients on Retinal Indices of Functional Impairment

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**Background:** As part of the central nervous system, characteristics of the retina serve as markers of overall brain health. Retinal neural layer thickness and blood flow correlate with cognitive functioning in adults, and in neurodegenerative disorder populations, retinal abnormalities have been found to predict later cognitive decline and disease progression. These associations illustrate the utility of the retina as a tool for understanding, predicting, and monitoring neural health.
Studies of patients with schizophrenia have reported that, relative to age-matched controls, this group has thinner retinal neural layers and reduced retinal microvasculature. There is evidence that patients with mood disorders exhibit similar retinal changes, but it is unknown which retinal markers, if any, are specific to schizophrenia and which are characteristic of psychopathology more broadly.

**Methods:** Participants were individuals with a psychotic disorder (schizophrenia or schizoaffective disorder; n = 26), mood disorder (major depressive or bipolar I disorder, n = 29), or no diagnosis of a serious mental illness (n = 22). Within the mood disorders group, seven people had a history of psychotic features. All participants were assessed with optical coherence tomography (OCT) and OCT angiography (OCTA), which respectively measure retinal neural layer thickness and blood flow within the retinal vasculature.
Statistical analyses were conducted in RStudio.

**Results:** Linear regressions showed that the psychotic disorders group had significantly greater optic nerve head (ONH) cup volume, lower macula central subfield macular cube thickness, and greater foveal avascular zone (FAZ) area, relative to the control group. While the mood disorder group did not significantly differ from the other groups, linear trend analyses demonstrate a consistent stepwise pattern on all measured retinal variables. Controls exhibited the most typical values (e.g., thicker neural layers, smaller FAZ area), followed by the mood disorders group with intermediate values, and the psychotic disorders group showed the most atypical values on all retinal indices.

Exploratory analyses were conducted to compare mood disorder participants who endorsed psychotic features to those with no psychotic symptoms. T tests revealed no significant differences between the two mood disorder subgroups on any of the retinal variables. Equivalence tests, conducted using the two one-sided tests (TOST) method, demonstrated that the groups were approximately equal in retinal neural layer thickness.

**Discussion:** These findings suggest that patients with psychotic disorders, compared to those with mood disorders and control participants, demonstrate greater retinal abnormalities associated with functional impairment and cognitive decline. The mood disorders group displayed an intermediate retinal profile, consistently falling between the control and psychotic disorders groups. This indicates there may be retinal markers of neurodegeneration and neuroinflammatory processes common to both psychotic and mood disorders, but these alterations are of a greater magnitude in patients with psychosis.

## S49. White Matter Micro-Structure Abnormalities in Medication-Naive First-Episode Psychosis Patients Evaluated With Normative Modelling of Fractional Anisotropy

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**Background:** Schizophrenia is a debilitating disease occurring in around 1% of the population. The underlying neuro-biology of Schizophrenia is still not entirely understood. Previous studies have shown abnormalities in white matter microstructure using diffusion weighted imaging (DWI). These studies used the measure fractional anisotropy (FA) derived from DWIs. Generally, they showed that fractional anisotropy (FA)---a measure used to estimate how aligned white matter fibers are---is lower in the white matter of patient populations when compared against healthy controls. These studies, however, use the standard case-controlled approach. Recently normative modelling has revolutionized neuroscience as it allows researchers to analyze deviation from the normal at the individual level. Additionally, normative modelling better accounts for differences caused by age and sex. Recently a normative model for the FA values of white matter tracts has been developed. In this abstract we show preliminary results for the first study to analyze FA in schizophrenia using normative modelling.

**Methods:** Diffusion weighted imaging data was collected on 257 volunteers consisting of 132 healthy controls and 125 first episode psychosis (FEP) patients at the University of Alabama at Birmingham. Diffusion-weighted image scanning parameters are a magnet strength of 3T with a TR/TE=3230ms/89.2ms, slice thickness=1.5mm, voxel-size 1.5x1.5 mm, 92 DWIs with 7 b=0s and the rest split across different b-values=1500,3000 s/mm2, a flip angle=84 and every DWI was measured with both AP and PA phase encoding.
DWI pre-processing consisted of DWI denoising and Gibbs ringing removal using MRTrix3. FSL was then used for: susceptibility distortion correction, eddy current correction, diffusion tensor (DT) model fitting and tract based spatial statistics (TBSS). For DT fitting, only the b=1500s/mm2 shell was used. From the TBSS skeleton we used the JHU-white-matter atlas

to extract average FA values for each tract (inline with how the values are extracted for normative modelling.

Quality checking was completed first checking for protocol adherence and then by visually checking the B0, masks, derived FA, registered FA and skeleton for every participant. After quality checking we are left with 110 healthy controls and 88 FEP patients.

For normative modelling we use the PCN-toolkit version 0.30. The FA data used is derived from 24 thousand participants across 19 sites [what should I cite here]. The 110 healthy controls in our study are used to adapt the normative models to our site. We then use the adapted normative models to estimate z values for every region of every FEP-participant.

**Results:** A region is characterized as positively deviated if the FA in that region is more than two standard deviations higher than the mean individual for their sex and age, and negatively deviated if the FA is < two standard deviations. The maximum number of deviations any participant can have is 48. In our results, more patients have over 5 negative deviations (10 patients) than over 5 positive deviations (5 patients).
We see that the maximum percentage of patients who share a negatively deviated region 10% and the maximum percentage of patients who share a positively deviated region is 7%. The area which is negatively deviated in the most patients is the corpus callosum.

**Discussion:** Negative deviations being more common than positive deviations agrees with the case-control approaches in the literature that generally show a lower FA in patients when compared against healthy volunteers.
The corpus callosum has previously been shown to have significantly lower FA in patients with schizophrenia than healthy controls. This agrees with our analysis.

## S50. Estrogen and Psychotic Symptoms Over the Menstrual Cycle in Perimenopausal Women at Clinical High Risk for Psychosis

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**Background:** Perimenopause, a female developmental phase between ages 40-55 marked by irregular menstrual cycles and declining fertility, is characterized by significant hormonal fluctuations and increased psychosis risk in some women. Hormonal changes are increasingly appreciated as potential contributors to the emergence of psychosis in susceptible individuals, and those in perimenopause offer a unique opportunity to understand this relationship. The dysregulation of sex hormone homeostasis through estrogen decline during perimenopause may lead to the onset or exacerbation of psychotic symptoms due to resulting neural system disruption. We hypothesized that perimenopausal women who are at clinical high risk for psychosis (CHR-P) would have lower levels of estrogen on days when they reported attenuated psychotic symptoms than on days when they did not experience these symptoms.
**Methods:** Women aged 40-55 who are CHR-P and have enrolled in the Predictors and Risk Evaluation of Menopause Associated Psychosis (PREMAP) study collected blood samples on days 1, 6, 8, 15, 20, and 22 following the onset of a period, as well as sharing information on psychotic symptom experiences like voice hearing and paranoia. Levels of estrogen are assayed for each blood sample and estrogen levels on days during which psychotic symptoms were present or absent were averaged.

**Results:** Preliminary analyses (n=2) are in line with the hypothesized difference, with lower estrogen levels being found on days during which voice hearing (3 days, estrogen = 20 pg/ml) and paranoia (2 days, estrogen = 32 pg/ml) were reported than on days when no symptoms were reported (7 days, Estrogen = 73pg/ml).
**Discussion:** Estrogen plays a crucial role in modulating dopamine and serotonin, which have been implicated in the pathophysiology of psychosis. Understanding the relationship between sex hormone fluctuations and attenuated psychotic symptom presentation may be key to uncovering the mechanism of action for psychosis emergence.

## S51. Dysconnectivity of Somatomotor and Visual Networks Clearly Emerges in the Functional but not Structural Connectome in Early Psychosis

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**Background:** Psychosis patients functionally exhibit thalamo-cortical hyperconnectivity and cortico-cortical hypoconnectivity in somatomotor and secondary visual (visual2) networks. These dysconnectivity patterns can be combined to form a "somato-visual" biomarker that is highly robust, reliable, and generalizable across samples (Keane et al., 2024, Mol. Psych.). Can traces of this biomarker be found in white matter?
**Methods:** To address this question, we leveraged diffusion MRI data from the Human Connectome Early Psychosis project, which included 33 healthy controls and 86 early psychosis patients. Diffusion data were preprocessed using QSIPrep. Tractography was performed using DSI Studio (see Peterson et al, 2023, BioRxiv). Structural connectomes (361x361) were derived from the thalamus (considered as a single region) plus 360 cortical parcels. Thalamo-cortical connectivity was computed by averaging streamline counts between the thalamus and visual2/somatomotor networks. Cortico-cortical connectivity was computed by averaging streamline counts between cortical parcels of the same two networks. To compute the structural variant of the biomarker, we normalized and subtracted the two averaged values (thalamo-cortical – cortico-cortical). To provide a comparison, we re-derived the functional variant of the biomarker from the same subjects in the same atlas space using already-published connectomes (Keane et al., 2024).
**Results:** Patients exhibited expectedly higher functional biomarker values ($p=5e-07$, Hedges' $g=1.0$) but non-significantly lower structural biomarker values ($p=.10$, $g=-.3$; $BF01=14.1$, one-tailed). The functional and structural biomarker variants were uncorrelated across patients and across all subjects (both $|r| < .06$, $p > .66$). The structural data passed numerous quality checks, suggesting that the null results cannot be attributed to noisy data. For example, using the 361 x 361 connectomes, the Fisher-z transformed structural/functional correlations were higher within- than between-subjects across all subjects ($p=9e-07$) and in each subject group (both $p < .01$). Moreover, the thalamo-cortical connectivity was higher in the primary versus secondary visual networks across all subjects ($p=6e-06$) and in each subject group (both $p < .05$).
**Discussion:** At the outset of psychotic illness, somato-visual functional dysconnectivity may emerge synaptically (e.g. due to pathology to the NMDA receptor) without corresponding large-scale changes in white matter.

## S52. Is Aberrant LTP-Like Plasticity Response to Cathodal TDCS a Biomarker for Illness Course and Cognitive Impairment in Schizophrenia?: A Double-Blind, Randomised, Sham-Controlled Study

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**Background:** Previous studies in schizophrenia demonstrated impaired LTD-like cortical plasticity to cathodal tDCS. None of these studies have considered the potential placebo effects of the perturbation technique or physiological response during serial cortical reactivity measures. Using a randomised, double-blind, sham-controlled, within-subject cross-over design, we examined the effect of cathodal tDCS (cathode left primary motor cortex [M1], anode right supraorbital) on LTD-like motor cortical plasticity, illness and cognitive correlates in schizophrenia patients (SZ) and age- and gender-matched healthy comparison subjects (HC).

**Methods:** Right-handed, SZ (DSM-5) (N=18; Age=32.7± 7.1; 13 males) and HC (N=18; Age=29.4±4.4; 13 males) were assessed for cortical reactivity using TMS-EMG. Thereafter, they received a single session of cathodal (2-mA; 20 minutes) and sham tDCS over the left M1 on two different days (inter-session interval for SZ - 3±1.2 days; HC - 3.5±2.1days) as per computer-generated randomisation sequence. Study participants and TMS administrator were blinded to the perturbation protocol. Motor evoked potentials (MEP) induced by 120%RMT (single TMS pulse) were reassessed at the 0, 10th, 20th and 30th minutes following the tDCS session. Comprehensive social and non-social cognitive functioning using Social cognition rating tool in Indian settings (SOCRATIS), A tool for recognition of emotions in neuropsychiatric disorders (TRENDS) and Brief cognitive assessment of Schizophrenia(BACS) were assessed in both SZ and HC; symptom severity was evaluated in SZ only.

**Results:** Blinding fidelity of TMS administrator X2(p)-1(1) and study subjects X2(p)-1(1) was satisfactory. Separate repeated measures ANOVA were performed for true and sham tDCS interventions using pre- and post-tDCS MEPs (T0, T10, T20, T30) as within-subjects factor and diagnosis status (SZ vs HC]) as between-subjects factor. We observed a significant diagnosis*time interaction effect for MEPs elicited by 120%RMT [F= 10.96; p =.002] in the true tDCS condition but not in the sham condition [F= 0.59; p = .45]. This indicated that the LTD-like plasticity effect, as elicited by true cathodal tDCS (and not sham), was poorer in SZ than in HC. Cathodal tDCS-induced LTP-like cortical plasticity had significant negative correlations with illness chronicity [spearman rho coefficient (ρ) = .43, p = .008], duration of untreated psychosis [ρ= .49, p = .003], history of cannabis misuse [t = 3.1,p = .004], degree of treatment resistance [ρ=.48, p = .003], impairment in 2nd order theory of mind [ρ=.44, p = .01], processing speed [ρ=.42, p = .01], executive function[ρ = 0.4, p=.002], verbal memory [ρ = 0.4, p=.001] and intracortical facilitation (ICF) amplitude [ρ = 0.4, p =.03].

**Discussion:** Aberrant LTP-like cortical plasticity response to Cathodal tDCS was found to be a potential diagnostic biomarker for SZ, and its correlation with several clinical, cognitive and SICI amplitude substantiates the glutamatergic pathogenesis in this disorder. Future theranostic studies could explore the validity of this perturbational biomarker for treatment outcomes.

## S53. Blood-Based Exosomal Inflammation From Brain Origins in First-Episode Psychosis: A Biomarker Discovery Study Considering the Multifactorial Context of Past Trauma

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**Background:** Due to its heterogeneous symptomatology, early diagnosis of first-episode psychosis (FEP) remains challenging for clinicians. Specific biomarkers of FEP diagnosis are needed. Moreover, how past psychotrauma contributes to the individual biosignature of patients is yet to be elucidated. Brain-derived exosomes may be a powerful and non-invasive tool for the identification of specific biomarkers, as they are produced by brain cells, cross the blood-brain barrier to release inflammatory cargo in the bloodstream. We aim to: (1) examine inflammatory content of several brain-derived exosomes in FEP vs healthy populations; and (2) determine the effect of past psychotrauma on the brain-derived exosomal content in FEP vs healthy biosignature.
**Methods:** 50 healthy controls, and 50 FEP individuals w/ or wo past trauma were recruited. Psychopathological measures (PANSS) and trauma history (CTQ; LEC-5). Exosomes from astrocytes, microglia and neurons were isolated and enriched from plasma samples by immunocapture with anti-GLAST, anti-TMEM119 and anti-CD171 antibodies, respectively. Inflammatory content of brain-derived exosomes was characterized using high-sensitivity multiplex essays. Pilot data from a subgroup of participants (n=10-12/group) have been generated for several immune markers (IL-10, IL-12p70, IL-17, IL-1β, IL-2, IL-4, IL-6, TNF-α and IFN-ɣ).
**Results:** FEP patients displayed high levels of astrocyte- and neuron-specific IL-2 ($p < 0.05$ vs healthy groups), regardless of past trauma exposure. FEP patients with history of past trauma had increased microglia-specific levels of IFN-ɣ and IL-10 ($p < 0.05$ vs healthy groups).
**Discussion:** Our findings highlight that: (1) psychotic context is associated to specific neuroimmune pathways; and (2) past trauma induces a distinct FEP biosignature. Our study strengthens the potential of brain-derived exosomes as accessible and non-invasive biomarkers reflecting neurological changes in humans.

## S54. Long-Term Follow-Up of Clinical High Risk Youth Reveals High Rates of Death, Suicide, Incarceration and Acts of Violence

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**Background:** Clinical High Risk (CHR) for psychosis research has provided important insights into risk factors for psychotic conversions and other adverse outcomes that occur within 2-3 years. The question of outcome after 5+ years has not been extensively studied.
**Methods:** In an ongoing project to perform long-term (5-20 year) diagnostic, symptom and functional assessments of up to 2000 individuals who previously met CHR criteria, we recontacted prior participants across 9 NAPLS sites. We assess all participants for adverse life events and history of violence and collect broad clinical data. In addition, we have obtained information on deaths and incarcerations from family interviews or public records.
**Results:** As of November 2024, N=584 prior CHR participants have been consented, N=441 interviewed and information about an additional N=57 individuals was obtained from family members or public records. Of those interviewed, N=36 (8.2%) of past CHR participants converted to psychosis within the original 2.5 year study and of the remaining 404 participants with long-term follow-up data, N=36 (8.9%) converted after 5 years or had in fact converted within 2.5 years but had dropped out of the original study. The total conversion rate of those interviewed so far is N=72/441 or 16.3%. According to public records, family interviews or brief interactions with past participants who were not formally interviewed (n=8), died (N=36) or were incarcerated (N=12) (N=57 total), we learned that an additional N=7 participants had converted to psychosis. Among the N=36 past participants who had died at follow-up, N=7 were confirmed to have died by suicide with another N=5 likely by suicide. The remainder of the deaths (N=23) were of unknown causes but many were young at the time of death (20s), suggesting suicide as a likely cause. Of the interviewed participants who converted to psychosis, 31% report suicidal ideation at the time of long-term follow-up. Within this group, suicidal ideation and behavior was significantly associated with a variety of clinical measures including depression, guilt, somatic concerns, hostility, hallucinations, bizarre behavior, and self-neglect (p's < .04 - < .001).
Of those interviewed, N=14 (17%) of past CHR participants reported a history of violent acts while N=106 (24%) reported a history of non-violent crimes. The mean age of first violent or non-violent act was 16 years and the majority were in treatment and not under the influence of substances at the time. From outside sources we also learned that an additional N=12 past participants were incarcerated for crimes such as rape, murder and assault per public records.

**Discussion:** The long-term follow-up of CHR participants will provide a wealth of information about later psychotic conversions, deaths, suicide and acts of violence, enabling robust prediction analyses using baseline clinical and biomarker data. This data will allow us to better understand and prevent adverse long-term outcomes in CHR youth.

## S55. Persistence of Psychotic-Like Experiences Through Adolescence and Their Relationship With Mental Health Problems and Brain Structure

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**Background:** Sub-clinical psychotic-like experiences are relatively common in the general population, and in young people they can be a risk factor for a wide range of mental health problems. Potential factors indicating whether psychotic-like experiences are clinically relevant could include distress, frequency, and whether they persist through adolescence. Interestingly, a recent study found reduced subcortical and cortical volumes in children reporting distressing and persistent psychotic-like experiences. We here investigated persistence of distressing and frequent psychotic-like experiences into later ages, and their association with mental health difficulties and brain structure in adolescence.
**Methods:** Adolescents completed three waves of yearly assessments (N=230, age range 11-14 at baseline). We assessed internalising and externalising difficulties with the Strength and Difficulties Questionnaire (SDQ) and psychotic-like experiences with the Adolescent Psychotic Symptom Screener, creating a weighted score of frequency and perceived distress. Adolescents with heightened scores (≥ 1 standard deviation) at ≥ 2 timepoints were classified as reporting persistent psychotic-like experiences. We acquired structural T1-weighted MRI and processed images with Freesurfer (v7.3.2), examining 18 subcortical and 62 cortical regions of interest. We used linear regressions to investigate the effect of persistent psychotic-like experiences on (1) SDQ internalising and externalising difficulties and (2) brain structure (subcortical volumes, cortical thickness, and surface area) at the final visit. We applied Holm correction and adjusted models for sex, age, and estimated Total Intracranial Volume (eTIV).
**Results:** A total of only 15 participants reported persistent psychotic-like experiences (n=12 female, $X2(1)= 4.71$, $p=.03$). They showed higher internalising and externalising difficulties at the final visit compared to those reporting no or transient psychotic-like experiences (internalising: $\beta=2.86$, 95%CI [1.05; 4.65], $p=.002$; externalising $\beta=4.82$, 95%CI [2.98; 6.65], $p < .001$). Differences in brain structure between those with and without persistent psychotic-like experiences did not survive multiple comparison correction and were not significant.
**Discussion:** In this adolescent sample, only few participants reported persistent psychotic-like experiences, with more females affected. Participants with persistent psychotic-like experiences also experienced higher internalising and externalising difficulties later in adolescence. In this small sample, perhaps not surprisingly we did not find differences in brain structure between this group and the group without persistent psychotic-like experiences. While this might well be related to insufficient power, it may also suggest that sustained psychotic-like experiences are not associated with brain structural alterations in

adolescence, even in the presence of psychopathology. Further research with larger or risk-enriched samples could help clarify whether brain structural alterations contribute to the persistence of these experiences and their link to broader mental health vulnerabilities.

## S56. The Evolving Schizophrenia Treatment Landscape in the United States: A Real-World Claims Analysis of Treatment Patterns and use of Long-Acting Injectable Antipsychotics

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**Background:** Schizophrenia, a mental disorder characterized by disordered thinking and episodes of psychosis, is estimated to affect > 3 million individuals in the United States. Antipsychotics, the mainstay of treatment for individuals with schizophrenia, are known to prolong the time to psychotic relapse and decrease the risk of hospitalization. However, individuals with schizophrenia have low adherence to oral antipsychotic treatment. Long-acting injectable antipsychotics (LAIs) were introduced to address the adherence challenges observed with oral antipsychotics, but LAIs remain underused despite documented benefits. Among the first LAIs developed, requirements for initiation regimens with oral supplementation or a loading dose before maintenance dosing are common. With the emergence of new LAIs with less complex initiation regimens, the use of LAIs for treatment of people with schizophrenia may have shifted. This retrospective study used administrative claims data in the United States to examine the treatment landscape for adult patients with schizophrenia and recent usage of LAIs by initiation characteristics.
**Methods:** Individuals aged ≥18 years with at least 1 claim with a schizophrenia diagnosis code in the EVERSANA open claims database from July 2018 to October 2023 were included. Individuals were grouped based on receipt of antipsychotics, antidepressants, and/or cholinesterase inhibitors/anticholinergics, and treatment not identified. Patients receiving antipsychotics were further categorized by route of administration: oral, injection, or "other" (eg, nasal, inhalant, topical). Those receiving LAIs were further grouped into cohorts receiving first-generation or second-generation antipsychotics. For patients initiated with second-generation LAIs on or after May 1, 2023 (after the latest approval for a schizophrenia LAI treatment at the time of this study), type of LAI initiation or loading requirement (ie, oral supplementation, LAI initiation regimen, LAI exposure prior to maintenance dose, and no loading or initiation) was evaluated.
**Results:** Among 1,444,283 adults with at least 1 claim for schizophrenia diagnosis (59% male, 26% aged 18–34 years), most received antipsychotics (68%) and/or antidepressants (52%), and 21% received cholinesterase inhibitors/anticholinergics; for 27% of patients, no treatment was identified. Of 976,380 patients with claims for antipsychotics, 94% (n=915,735) were for oral administration, 33% (n=321,651) for injectables, and 0.04% (n=415) for other routes of administration. Among those receiving injectables, 67% (n=215,389) had ≥1 claim for an LAI (second-generation, 77%; first-generation, 32%). Of 55,024 patients receiving second-generation LAIs after May 1, 2023, 56% (n=30,811) received an LAI with an initiation regimen, 27% (n=14,766) used an LAI requiring oral supplementation, 12% (n=6853) received an LAI that required LAI exposure prior to the maintenance dose, and 3% (n=1412) received an LAI with no loading or initiation required.

**Discussion:** In this real-world study, most individuals with schizophrenia received antipsychotic treatment, the vast majority of whom received oral antipsychotics and approximately one-fifth of whom received an LAI. Since May 2023 (the time period following the most recent approval of an LAI to treat schizophrenia), the most frequently prescribed second-generation LAIs required an LAI initiation regimen or supplementation with an oral antipsychotic. Newer LAIs that do not require oral supplementation or a loading dose may be easier to initiate, particularly in outpatient settings, but accounted for < 5% of second-generation LAI prescriptions.

## S57. Predictors of Response and Non-Response to Treatment for Schizophrenia: Machine Learning Analysis of Patients Treated With TV-46000 or Placebo in the Rise Study

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**Background:** Prevention of relapse is a key treatment goal for maintenance therapy in schizophrenia. In the RISE phase 3 randomized controlled trial in adults with schizophrenia in the US and Bulgaria, TV-46000—a long-acting, subcutaneous, antipsychotic agent—significantly reduced relapse risk in comparison with placebo. However, some placebo-randomized patients did not relapse, and a few TV-46000-treated patients relapsed during the study (patients with impending relapse: placebo, 53/181 [29%]; TV-46000 once monthly, 13/183 [7%]; TV-46000 once every 2 months, 23/179 [13%]). This post hoc analysis aimed to understand key predictors of relapse in patients treated with TV-46000 or placebo in the RISE study using machine learning (ML).
**Methods:** Adult patients with schizophrenia who were stabilized on oral risperidone (2–5 mg/day for 12 weeks) and then randomized to TV-46000 or placebo in the RISE study were included. The following potential predictors of relapse were included: baseline demographics and clinical characteristics prior to randomization, baseline adverse events of interest and total number of adverse events reported, abnormal movements, Personal and Social Performance (PSP) total and domain scores, severity of illness, Positive and Negative Symptom Scale (PANSS) total and subscale scores, EuroQol 5 Dimension (EQ-5D) scores, and the Drug Attitude Inventory scores. Three ML models were fitted to identify important predictors: Gradient Boosting Machine, Random Forest (RF), and Lasso. The final model was selected on the basis of the highest and most robust concordance index (C-index) in the validation set. Internal validation was conducted using 200 bootstrapping samples. In addition, hazard ratios (HRs) were calculated with univariate Cox regression analysis for the top 20 covariates. The False Discovery Rate method was used to adjust P values for multiple comparisons. Exploratory analyses were further conducted to identify trends of interactions among important predictors.
**Results:** Relapse data for 540 randomized adult patients (361 TV-46000; 179 placebo) in RISE were included. The RF model provided the best overall performance (mean [95% CI] internal validated C-index, 0.8 [0.75–0.84]) and was selected as the final model. There were no significant or clear trends in the relationship between baseline predictors related to the risk of relapse for TV-46000-treated patients. In placebo-treated patients, the top 8 predictive features strongly associated with lower risk of relapse in the ML models were location in the

US, no history of olanzapine use, higher body mass index (BMI), lower PANSS total and general psychopathology (GPSY) subscale scores, lower PSP domain 1 score, longer time since last relapse, and higher EQ-5D total scores. Univariate Cox regression analyses showed significant increases in relapse risk for those in a non-US location (HR [95% CI], 3.79 [1.97–7.29]), with a history of olanzapine use (2.82 [1.50–5.29]), with a PANSS GPSY subscale score increased by 5 (1.40 [1.11–1.76]), or without an EQ-5D total score increased by 10 (1.19 [1.04–1.37]). Higher BMI tended to be associated with a lower risk of relapse for patients without ongoing use of diabetes medications. Also, for patients without historical use of olanzapine, longer time since last relapse was associated with a lower risk of relapse.
**Discussion:** Among patients who received placebo in the RISE trial, some baseline characteristics (eg, treatment in the US, naïve to olanzapine, lower PANSS GPSY subscale score, higher EQ-5D total score) were associated with a lower risk of relapse. TV-46000 was effective in patients across baseline demographic and clinical characteristics in the RISE study.

## S58. Histological Effects of Nigella Sativa Oil on the Cerebellum of Paraquat-Induced Mice Models of Parkinson's Disease: Implications for Dopaminergic Dysfunction in Schizophrenia and Other Neurodegenerative Disorders

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**Background:** Parkinson's Disease (PD) and schizophrenia, while being distinct neuropsychiatric conditions, share overlapping pathophysiological mechanisms particularly in dopaminergic system dysregulation and neuroinflammation. PD is characterized by progressive loss of dopaminergic neurons often accompanied by oxidative stress and neuroinflammation while schizophrenia involves complex alterations in dopaminergic signaling potentially linked to oxidative damage. Paraquat, a wildly used herbicide, induces oxidative damage in animal models, mimicking PD like symptoms. Nigella sativa, commonly known as black seed, has demonstrated anti-inflammatory and antioxidative properties in various studies. Pramipexole, a dopamine agonist is a standard treatment for PD symptoms and has shown neuroprotective effects. This study investigates the histological effects of Nigella sativa oil on the cerebellum of paraquat-induced PD models shedding light on the brother relevance to schizophrenia and other neurodegenerative conditions.
**Methods:** Forty BALB/c mice were divided into four groups: a control group, a paraquat-induced group, a paraquat + pramipexole-treated group and a paraquat + Nigella sativa oil-treated group. Mice in the treatment groups received pramipexole or Nigella sativa oil concurrently with paraquat administration. After the experimental period, cerebella samples were harvested and subjected to histological analysis focusing on neuronal integrity, oxidative damage markers and inflammatory responses.
**Results:** Histological examination revealed significance neuronal loss, elevated oxidative stress markers, and increased inflammatory responses in the cerebellum of the paraquat only group compared to controls. Mice treated with Nigella sativa oil or pramipexole should improved neuronal preservation, reduce oxidative damage, and decreased markers of inflammation. The Nigella sativa oil group demonstrated effects comparable to those observed in the pramipexole-treated group, indicating its potential neuroprotective role.
**Discussion:** The findings suggest that Nigella sativa oil mitigates oxidative stress and inflammation in the cerebellum of paraquat-induced PD models, highlighting its neuroprotective potential. Considering the shared dopaminergic dysfunction and oxidative

stress mechanisms in PD and schizophrenia, these results extend relevance to schizophrenia where oxidative damage has been implicated in neuronal deficits and cognitive impairments. By reducing oxidative and inflammatory damage, Nigella sativa oil may have therapeutic potential across across neurodegenerative and neuropsychiatric disorders. Further research is warranted to elucidate the molecular pathways and clinical applicability of these findings, particularly in conditions like schizophrenia that involve dopaminergic dysregulation.

## S59. Which Psychological Intervention for Trauma Symptoms is Most Appropriate for Individuals who Have Psychosis? A Systematic Review and Meta-Analysis

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**Background:** Childhood trauma has been found to play a causal role in the development and maintenance of psychotic symptoms and informs the phenomenology of these symptoms. Higher rates of PTSD and CPTSD have also been found in those with a psychosis diagnosis compared to those without. This study aimed to systematically review randomised control trial's (RCT's) of trauma-focused therapy in participants across the psychosis spectrum, to allow for a clear comparison of clinical outcomes between different interventions. This could help us understand which approach may be more beneficial in this clinical group, and the potential factors that may affect this, like intervention and participant characteristics (e.g., stage of psychosis development).
**Methods:** We included any RCT using trauma-focused or trauma-informed psychological therapy for trauma-exposed individuals across the psychosis spectrum (those at clinically high risk to those with a schizophrenia spectrum disorder). Studies had to have outcome measures relating to clinical symptoms (psychosis and/or trauma), treatment accessibility, safety, feasibility, or cost effectiveness. The preliminary search was conducted using EMBASE, PsycINFO, MEDLINE, with secondary checks on Google Scholar.
**Results:** 11 RCT's were identified, comparing Eye Movement Desensitization and Reprocessing
(EMDR; n=8), Prolonged exposure (PE; n=4), trauma focused cognitive behaviour therapy (CBT; n=2), and trauma-focused acceptance and commitment therapy (ACT; n=1) with treatment as usual (TAU). 4 studies compared two different interventions vs TAU. RCT's of participants who had EMDR showed reduced PTSD symptoms (n=4), reduced general health difficulties (n=2), reduced positive (n=2) and negative (n=1) psychotic symptoms, more remission from schizophrenia (n=2), reduced depression (n=2) and anxiety (n=1) symptoms and increased self-esteem (n=1) compared to TAU. Participants who had EMDR were also less costly and had less adverse events and symptom exacerbation compared to those with TAU (n=1). One study did report no difference in psychosis, anxiety, or depression symptoms post treatment vs TAU. RCT's of participants who had PE showed reduced positive psychotic and PTSD symptoms (n=1), less symptom exacerbation and adverse events (n=1) and the intervention was less costly (n=1) vs TAU. RCT's of participants who had CBT vs TAU showed reduced PTSD symptoms (n=2) and RCT's of participants who had ACT vs TAU showed reduced overall psychiatric and anxiety symptoms and increased emotions acceptance and help seeking (n=1).

**Discussion:** This is the first systematic review of psychological therapies in individuals with psychotic experiences and trauma histories in six years, with multiple advances in interventions being made since then. Findings show that there is growing evidence of the effectiveness of EMDR for trauma-exposed individuals with psychosis, with promising evidence also for prolonged exposure therapy, trauma focused CBT and ACT in these individuals.

## S60. Onset, Duration, and Intensity of Procholinergic and Anticholinergic Adverse Events With Xanomeline and Trospium Chloride in the 52-Week, Open-Label Emergent-5 Trial

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**Background:** Xanomeline/trospium, formerly known as KarXT, comprises the dual M1/M4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride, and was recently approved for the treatment of schizophrenia in adults by the U.S. Food and Drug Administration. Efficacy and safety of xanomeline/trospium were assessed in the 5-week, randomized, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) clinical trials. In the 52-week, open-label EMERGENT-5 (NCT04820309) trial, efficacy of xanomeline/trospium was maintained, and no new safety concerns or tolerability issues emerged. Here we present results of post hoc analyses from the 52-week, open-label EMERGENT-5 trial to further characterize the long-term safety profile of xanomeline/trospium.
**Methods:** Eligible participants had a confirmed diagnosis of schizophrenia with stable symptoms, no prior exposure to xanomeline/trospium, a Positive and Negative Syndrome Scale score of ≤80, and Clinical Global Impression–Severity score ≤4. All participants initiated twice-daily oral doses of xanomeline 50 mg/trospium 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for 52 weeks. Analyses were performed on the safety population, defined as all participants who received ≥1 dose of trial medication. Treatment-emergent adverse events (TEAEs) were recorded at every visit and assessed for intensity (mild, moderate, or severe) and relatedness by the site investigator.
**Results:** The safety population comprised a total of 566 participants treated with xanomeline/trospium. Overall, 466 participants (82.3%) had ≥1 TEAE, 380 (67.1%) had ≥1 treatment-related TEAE, and 100 (17.7%) had a TEAE leading to study drug discontinuation. Treatment-related TEAEs occurring in ≥5% of participants were nausea (21.4%), vomiting (17.8%), constipation (16.8%), dry mouth (9.0%), dizziness (7.8%), diarrhea (6.7%), dyspepsia (6.5%), hypertension (6.5%), and somnolence (5.8%). Procholinergic and anticholinergic TEAEs, regardless of relatedness, were reported by 210 (37.1%) and 159 (28.1%) participants, respectively. The most common procholinergic TEAEs were nausea (23.1%), vomiting (20.3%), diarrhea (9.4%), and hyperhidrosis (5.1%). The most common anticholinergic TEAEs were constipation (18.0%), dry mouth (9.4%), and dyspepsia (7.2%). Procholinergic and anticholinergic TEAEs were generally transient and most likely to first occur within 2 weeks of initiating treatment. TEAEs leading to trial medication discontinuation that were possibly, probably, or definitely related to xanomeline/trospium were reported by 41, 23, and 11 participants, respectively.

**Discussion:** The safety and tolerability of xanomeline/trospium in the 52-week, open-label EMERGENT-5 trial were similar to those observed in the acute trials, and no new safety concerns were observed. Procholinergic and anticholinergic TEAEs observed during the trial were consistent with the known activity of xanomeline/trospium at muscarinic receptors, transient, and mild to moderate in intensity. Cholinergic TEAEs generally did not lead to treatment discontinuation.

## S61. Effectiveness of Pharmacological Treatments for Severe Agitation in Real-World Emergency Settings: Preliminary Results of an IPD Meta-Analysis

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**Background:** There are various pharmacological treatments for rapid tranquilization in severe psychomotor agitation and aggression. However, their comparison remains unclear, and previous reviews have been limited in scope, leading to inconsistencies in treatment guidelines.
**Methods:** To bridge this gap, we are conducting a systematic review and individual-participant-data network meta-analysis using data from randomized controlled trials (RCTs) examining various intramuscular or intravenous pharmacological interventions in adults experiencing severe psychomotor agitation or aggression in emergency settings. At least two independent reviewers screened records found in multiple electronic databases against predefined eligibility criteria. We requested and harmonized IPD from eligible trials, and two reviewers extracted also the aggregated data and assessed the risk of bias using the Risk of Bias 2 tool and the applicability using the RITES tool. The primary outcome is adequate sedation within 30 minutes after treatment, and secondary outcomes include the need for additional sedation and adverse events. We are conducting an IPD network meta-regression model within a Bayesian framework, incorporating study- and participant-level characteristics. The confidence in the evidence will be evaluated using the Confidence in Network Meta-analysis (CINeMA) approach. The protocol of the review was registered with PROSPERO (ID: CRD42023402365).
**Results:** After screening 4,684 titles/abstracts and 145 full-text articles, we identified 17 eligible RCTs, 13 of which provided IPD for 2,752 participants (mean age: 35.4 years; 56% men; 29% with substance or alcohol intoxication). These studies evaluated 12 different intramuscular or intravenous antipsychotics, benzodiazepines, and their combinations. Findings from preliminary pairwise meta-analyses based on aggregated data will be presented. The IPD meta-analysis is currently ongoing.
**Discussion:** This analysis can provide a fine-grained synthesis of the evidence that will be able to inform evidence-based treatment decisions regarding the selection of pharmacological treatments for this common yet heterogeneous emergency condition.

## S62. Patient and Caregiver Engagement to Support the Development of Clinical Trials in Adolescents Living With Schizophrenia

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**Background:** Enrollment of adolescents in clinical trials for schizophrenia (SCZ) treatments can be challenging. This work aimed to better understand the lived experiences of adolescents with SCZ and their caregivers and gain insight into their perceptions of clinical trials to inform patient-focused drug development.

**Methods:** This project included a survey of caregivers and 1:1 interviews of caregivers and adolescents with SCZ, schizoaffective disorder (SZA), schizophreniform disorder, or attenuated psychosis disorder (SCZ or related disorders). Schizophrenia and Psychosis Action Alliance recruited participants from their member network via email/social media and posted this opportunity on relevant websites. Caregivers of adolescents (aged 13–17 years) with SCZ or related disorders in the United States were eligible for the survey. Due to recruitment challenges, eligibility criteria for the interviews were broadened to include people diagnosed as adolescents but who are currently young adults (aged 18–22 years) and their caregivers. Following a pre-screening survey, eligible respondents consented to participate in a remote, 60-minute, 1:1 interview with a qualified researcher. Interviews were conducted using a semi-structured guide and were de-identified.

**Results:** In total, 69 caregivers completed the survey. Most adolescents described were male (65%), White (78%), and had a diagnosis of SCZ (70%). Regarding treatment, 67% had received counseling, 45% had tried medications, and 42% had inpatient treatment. Only 7% had experience with their adolescent participating in a clinical trial. The most common reasons for non-participation were not being offered the opportunity (39%) and concerns about taking an investigational medication (38%). When considering clinical trial participation, caregivers were “very worried” about losing their job/income (29%), hurting their relationship with their child (25%), and having their child take a medication that might not work (22%).

Interview participants included 2 adolescents with SZA, 3 young adults diagnosed with SCZ as adolescents, and 9 caregivers. Among the 5 participants with SZA/SCZ, the mean age at diagnosis was 15 years, and all were currently using antipsychotic medications (APs). Young adults reported trying several APs as adolescents before arriving at their current medication. Among caregivers, 2 had children with SZA and 7 had children with SCZ. Most children of interviewed caregivers were diagnosed in high school (mean age at diagnosis: 15 years). The interviewees noted the long duration between symptom onset and diagnosis/treatment and the initial fear about the potential impact on the future and quality of life.

No interviewee had clinical trial experience, and there were mixed views on the impact of clinical trial-related hospitalization. Most interviewees expressed concerns related to disrupting disease stability by discontinuing their current medication and clinical trial uncertainties such as the risk–benefit profile of the new medication, randomization to placebo vs active treatment, and drug availability after the study.

**Discussion:** This research provides insights into the experiences of adolescents with SCZ or related disorders and their caregivers that should be considered when planning clinical trials involving this patient population. The recruitment challenges in this work exemplify the difficulties that are faced when conducting clinical trials in this adolescent population. As adolescents with SCZ often have difficulties in receiving a definitive diagnosis during the early-disease stage, the diagnostic journey must also be considered.

## S63. Acute and Maintenance Treatment Effects of Olanzapine/Samidorphan on Negative Symptoms in Patients With Acute Schizophrenia: A Post Hoc Analysis

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**Background:** Addressing negative symptoms of schizophrenia can be a treatment challenge. This post hoc analysis examined the long-term effect of the combination of olanzapine and samidorphan (OLZ/SAM) on negative symptoms.
**Methods:** All adults who completed a 4-week OLZ/SAM study (olanzapine- and placebo-controlled) for the treatment of acute schizophrenia and who had ≥1 postbaseline visit in a 52-week open-label extension study were analyzed. The 4-week study OLZ/SAM, olanzapine, and placebo arms were combined for this analysis, and all patients received OLZ/SAM during the extension. Negative symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) Marder Negative Symptoms Factor score (Marder, 1997). Changes from the 4-week study baseline were evaluated overall, in a high baseline negative symptoms (Marder Negative Symptoms Factor score ≥24) subgroup, and in a high negative/low positive symptoms subgroup (Marder Negative Symptoms Factor score ≥24, PANSS Mohr [2004] positive symptoms factor score ≤19, and score of ≥4 on 2 of 3 PANSS blunted affect, passive/apathetic social withdrawal, or lack of spontaneity/flow of conversation items).
**Results:** Patients (n=281) had a mean (SD) PANSS Total score of 101.7 (11.1) and Marder Negative Symptoms Factor score of 25.2 (4.6) at baseline. The mean (SE) change from baseline in Marder Negative Symptoms Factor score at week 56 was (–8.5 [0.41], n=183). Among patients with a Marder Negative Symptoms Factor score ≥24 at baseline (mean, 27.7), the mean (SE) change in Marder Negative Symptoms Factor Score was –9.8 (0.50) at week 56 (n=124). A similar pattern of change was observed for the high negative symptoms/low positive symptoms subgroup (mean [SE] change at week 56, –8.9 [0.90], n=37).
**Discussion:** Results of this post hoc analysis suggest that OLZ/SAM provides a treatment benefit for negative symptoms of schizophrenia that is observable over long-term therapy.

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## S64. LB-102 (N-methyl Amisulpride) for Acute Schizophrenia in Adults: Efficacy and Safety From a Large Phase 2 Clinical Trial

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BACKGROUND: LB-102 (N-methyl amisulpride analogue) is a novel D2/D3/5HT7 antagonist under development for the treatment for schizophrenia. Preclinical assays showed receptor binding,

pharmacokinetics, and behavioral modification properties were similar between LB-102 and amisulpride, and a human dopamine receptor occupancy showed that LB-102 50 mg exhibited similar receptor occupancy as amisulpride 400 mg. A phase 1 clinical trial demonstrated an acceptable safety profile of LB-102 up to 150 mg/day in healthy volunteers. We report the primary results from a phase 2 clinical trial of LB-102 in adults with schizophrenia.

METHODS: This US-based, multicenter, randomized, double-blind, placebo-controlled trial (NCT06179108) comprised a 7–14-day inpatient screening period, 28-day inpatient treatment period, 5-day inpatient stabilization period, and outpatient safety follow-up visit ~2 weeks after the end of the treatment period. Eligible adults (18–55 yr) were diagnosed with schizophrenia (defined by DSM-5 and confirmed by MINI v7.0.2 for Schizophrenia and Psychotic Disorders Studies), required hospitalization or continued hospitalization for a current acute exacerbation of psychotic symptoms, and had Positive and Negative Syndrome Scale (PANSS) total score of 80–120, PANSS positive subscale item scores of ≥4 on at least two key items, and Clinical Global Impression of Severity (CGI-S) score of ≥4. MINI and PANSS screening assessments and PANSS at baseline and week 4 were reviewed by an independent central reviewer. Participants were randomized (3:3:3:1) to oral once-daily placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg, with the 100-mg dose considered exploratory. The primary efficacy endpoint was the change from baseline to week 4 in PANSS total score, with treatment differences between LB-102 and placebo analyzed using a two-sided 5% significance level with multiplicity adjusted for using the Hochberg procedure. Secondary endpoints included change from baseline in CGI-S score, changes from baseline in PANSS positive and negative subscale scores, and PANSS responder rates. Safety was assessed through treatment-emergent adverse events (TEAEs) and other assessments.

RESULTS: Of 359 participants randomized (and included in the safety and intent-to-treat populations: placebo, n=108; 50 mg, n=107; 75 mg, n=108; 100 mg, n=36), 261 (73%) completed the trial. Baseline PANSS total score was ~94 across arms. LB-102 met the primary endpoint, with 50 mg and 75 mg statistically superior to placebo using the Hochberg multiplicity correction; mean changes from baseline to week 4 in PANSS total score were -9.3 (placebo), -14.3 (50 mg, p=0.0009; effect size=0.61), -14.0 (75 mg, p=0.0022; effect size=0.41), and -16.1 (100 mg, nominal p=0.0017; effect size=0.83). All LB-102 doses demonstrated numerically and/or statistically greater improvements from baseline compared to placebo across secondary endpoints. TEAEs were reported in 56% (placebo), 69% (50 mg), 57% (75 mg), and 75% (100 mg) of participants. 10 participants reported TEAEs leading to withdrawal (placebo, n=2; 50 mg, n=2; 75 mg, n=3; 100 mg, n=3) and 5 reported serious TEAEs (placebo, n=2 [including 1 death]; each LB-102 arm, n=1). TEAEs in ≥5% of any arm included: insomnia, headache, anxiety, agitation, weight increase, hyperprolactinemia, blood creatine phosphokinase increase, alanine aminotransferase increase, somnolence, and constipation.

DISCUSSION: This phase 2 clinical trial provided rigorous evidence demonstrating the efficacy and safety of LB-102 for the treatment of adults with acute schizophrenia, which will inform the continued clinical development of LB-102 for schizophrenia treatment.

## S65. Monthly Olanzapine Extended-Release Injectable Suspension (TV-44749) for Subcutaneous use Leads to Early, Consistent Symptom Improvements Through Week 8 in Adults With Acute Exacerbation of Schizophrenia: Phase 3 Solaris Trial

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**Background:** Olanzapine is an extensively investigated and highly effective antipsychotic currently available in oral and intramuscular long-acting injectable (LAI) formulations; however, due to the risk of post-injection delirium/sedation syndrome (PDSS) and the associated Risk Evaluation and Mitigation Strategy (REMS), the use of intramuscular olanzapine LAI is limited. TV-44749 is a once-monthly, subcutaneous, extended-release injectable olanzapine based on an innovative copolymer delivery technology that ensures controlled release of olanzapine, designed to provide sustained efficacy over 1 month without PDSS risk. The Subcutaneous OLAnzapine extended-Release Injection Study (SOLARIS; NCT05693935) is an ongoing phase 3 study designed to assess the efficacy, safety, and tolerability of TV-44749 in adult patients with schizophrenia.

**Methods:** SOLARIS is a phase 3 trial in patients aged 18–64 years with schizophrenia, consisting of a randomized, double-blind, placebo-controlled 8-week acute treatment period (period 1) followed by an open-label safety period of up to 48 weeks (period 2). For period 1, patients with acute exacerbation of schizophrenia occurring ≤ 8 weeks before screening, who would benefit from hospitalization, were randomized 1:1:1:1 to receive once-monthly subcutaneous TV-44749 (318 mg, 425 mg, or 531 mg) or placebo. These selected TV-44749 doses correspond to 10, 15, and 20 mg/day of oral olanzapine, respectively. The period 1 primary endpoint was change from baseline to week 8 in the Positive and Negative Syndrome Scale (PANSS) total score while alpha-controlled key secondary endpoints were change in Clinical Global Impression-Severity (CGI-S) scale score and change in Personal and Social Performance (PSP) scale score from baseline to week 8. Secondary endpoints included change in Clinical Global Impression-Improvement (CGI-I) scale score from baseline to weeks 4 and 8 and change in Patient Global Impression-Improvement (PGI-I) scale score from baseline to weeks 2, 4, and 8.

**Results:** Overall, 675 patients were randomized (169 to each TV-44749 arm; 168 to placebo). Mean (SD) age was 44.6 (11.7) years; 75% (n=381) were male and 67% (n=341) were Black or African American. The primary endpoint was met; all three TV-44749 doses resulted in significantly greater change (95% confidence interval [CI]) from baseline to week 8 in PANSS total score versus placebo (318 mg: -9.69 [-13.52, -5.85]; 425 mg: -11.25 [-14.97, -7.52]; 531 mg: -9.71 [-13.44, -5.98]; all $P < 0.0001$). Key secondary endpoints were also met, demonstrating significantly greater change (95% CI) from baseline to week 8 for TV-44749 versus placebo for CGI-S scale score (318 mg: -0.53 [-0.75, -0.31]; 425 mg: -0.61 [-0.83, -0.40]; 531 mg: -0.47 [-0.69, -0.25]; all $P < 0.0001$) and for PSP score (318 mg: 4.63 [1.89, 7.38]; 425 mg: 3.15 [0.51, 5.80]; 531 mg: 4.93 [2.29, 7.56]; all $P < 0.05$). Analysis of secondary efficacy endpoints showed early and persistent changes across clinician- and patient-rated global illness scales. For PANSS total score, statistical significance versus placebo was met at week 2 for 318 mg and 425 mg and week 3 for 531 mg (all $P < 0.05$), which was maintained through week 8 for all doses. For change in CGI-S scale score, statistically significant change versus placebo was achieved at week 2 for 425 mg, week 3 for 318 mg, and week 4 for 531 mg ($P < 0.05$). All TV-44749 doses demonstrated superior change in CGI-I scale score at week 4 versus placebo ($P < 0.0001$). For change in PGI-I scale score, statistically significant improvement versus placebo was achieved at week 2 for 318 mg and 425 mg (both $P < 0.01$), and week 4 for all doses (all $P < 0.05$). Once statistically significant superiority was achieved with TV-44749 compared with placebo, it was maintained through week 8 across all respective scales. As of December 2024 (3485 active TV-44749 injections), no suspected or confirmed PDSS events were reported.

**Discussion:** TV-44749 is an innovative, once-monthly, subcutaneous, extended-release olanzapine injectable designed to provide sustained efficacy without the risk of PDSS. The SOLARIS trial met its primary endpoint and both key secondary endpoints by demonstrating that treatment with TV-44749 versus placebo resulted in significantly greater change from baseline to week 8 in PANSS total score, as well as in CGI-S and PSP total scores, respectively. Of clinical relevance, TV-44749 demonstrated consistent and early improvement that remained statistically significant through the 8-week period 1 of SOLARIS without a loading dose or complex initiation regimen. As of December 2024 (3485 active TV-44749 injections), no suspected or confirmed PDSS events were reported, and long-term safety, including the absence of PDSS risk with TV-44749, is currently being investigated in the long-term safety phase of SOLARIS (period 2).

## S66. Mechanisms and Correlates of Incentivized Response Inhibition in Schizophrenia and Bipolar Disorder

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**Background:** When healthy individuals are incentivized on response inhibition tasks (e.g., Stroop, Flanker), they recruit additional cognitive resources, enabling them to make faster, more accurate responses. Schizophrenia (SZ) and bipolar disorder (BP) are associated with poor response inhibition, but it remains unclear the degree to which incentives can effectively increase response inhibition in individuals with SZ versus BP. To investigate this, we examined the impact of incentives on response inhibition in SZ, BP, and healthy controls using a computational modeling approach to examining reaction time data from a Stroop-style response inhibition task with non-incentivized and incentivized trials.
**Methods:** Reaction time data from a Stroop-style task that included incentivized and non-incentivized trials were analyzed from 37 SZ, 26 BP, and 33 healthy controls. In addition to traditional mean reaction time analyses, we applied drift diffusion modeling, a computational modeling approach that allows for decomposition of reaction time data into subcomponents that can explain variation in response latencies. We focused on two drift diffusion parameters: the rate of information processing (i.e., drift rate) and the degree to which individuals prioritize speed over accuracy (i.e., response caution or boundary separation). We evaluated: 1) group differences in mean reaction time, 2) group differences in information processing rate and in response caution parameters derived from drift diffusion modeling, and 3) cognitive and clinical correlates of drift diffusion parameters in SZ and BP.
**Results:** There was a significant main effect of group on reaction time ($F(1,93)=5.50$, $p=.006$), with SZ showing significantly slower reaction time compared to healthy controls ($p=.001$). There was a significant group-by-incentive interaction effect on reaction time ($p=.016$), such that healthy controls and BP showed significantly faster response speed when incentives were introduced, but SZ did not show the same pattern of improvement as a function of incentives. Computational analyses indicated that groups did not significantly differ in response caution, but that healthy controls had significantly faster information processing rate compared to both SZ ($p=.015$) and BP ($p=.016$). In SZ, slow information processing was related to poor cognition ($p=.007$) and more severe negative symptoms ($p=.036$). Information processing rate was also related to positive symptoms in SZ ($p=.049$),

such that increased information processing rate was associated with positive symptom severity. There were no significant external correlates in BP.
**Discussion:** SZ may be distinguished from BP by a failure to enter an overall motivated state and decrease reaction time when incentivized. However, slow information processing rate may contribute to poor performance in both SZ and BP, whereas response caution is intact in both disorders. In SZ, better cognition may enable faster information processing. Additionally, information processing rate is related to positive and negative symptoms in SZ in opposite directions; this suggests distinct information processing deficits for core symptoms of the disorder. Future analyses will examine fMRI data collected while participants completed the response inhibition task. These analyses will include identifying group differences in the spatial distribution of activation within specific brain regions (e.g., dorsolateral prefrontal cortex, ventral striatum) during task completion, and examining whether differences in spatial distribution are related to within-group variability in response inhibition.

## S67. Predicting Auditory Verbal Hallucinations in the General Population and a Psychosis Sample From the UK Biobank

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**Background:** Auditory verbal hallucinations (AVH) in the form of hearing voices are defined as core symptoms of psychosis. AVHs are also experienced by members of the general population who have not been diagnosed with psychosis, where the prevalence of AVH ranges between 5% and 28%.
**Methods:** The current study aimed to identify the most important predictors of AVH from 9 sociodemographic, 11 environmental, 6 biological and 15 psychological and health features in two samples from the UK Biobank; a sample of individuals diagnosed with psychosis (n =305 voice-hearers and n = 637 non-voice-hearers) and a general population sample with no diagnosis of psychosis (n = 1,778 voice-hearers and n = 130,771 non-voice-hearers). A machine learning (ML) data-driven approach was applied using the XGBoost classification algorithm to develop a predictive model for AVH, which enabled us to compare the importance of the features using two metrics, gain (i.e., a decrease in node impurity) and the SHapley Additive exPlanations (SHAP).
**Results:** Passive suicidal ideation was the most important predictor of AVH in the general population, where other important predictors included the presence of mental distress, past trauma experience, the severity of post-traumatic stress disorder, the severity of depressive symptoms, and seeking professional help. Passive suicidal ideation and severity of anxiety symptoms were the most important predictors within the psychosis sample followed by the feeling of life being worthless, the severity of depressive symptoms, engagement in self-harm, post-traumatic stress disorder symptoms, and childhood trauma.
**Discussion:** This is the first ML-based analysis of predictors of AVHs in psychosis and general population samples where similar data is available for both, allowing cross-comparison. It shows that the most important features are largely consistent between the psychosis and general population samples. The high importance of traumatic experiences, psychological distress, and PTSD symptoms for predicting AVH in general population sample supports the hypothesis that AVH may be more appropriately understood as a

dissociative rather than a psychotic phenomenon. According to this hypothesis, dissociation may represent a post-traumatic lasting effect or a regulatory response to trauma by impairing the integration of traumatic experience with self-identity as internal dialog becomes disowned and perceived as unrelated and external to the self. The current findings indicate that AVH may be a valuable clinical marker and potentially a strong indicator of future suicidal tendencies and self-harm.

## S68. Linguistic Trajectories to a Bipolar Disorder Diagnosis: Evidence From a Social Media Cohort

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**Background:** Bipolar disorder (BD) is a severe mental disorder characterized by shifts between states of mania and depression. Recent evidence suggests that BD Results: in changes to the form of free-flowing speech. Additionally, it has been shown that these alterations might also manifest in social media posts. The goal of this study was to study changes to the content and form of posts as users move towards an impending BD diagnosis.
**Methods:** We utilize various techniques from the field of natural language processing (NLP) to data acquired from the popular social media platform Reddit. We compare a cohort healthy participants with a cohort of participants assumed to suffer from BD. Using linear mixed models, we compare changes from a pre-diagnosis to a post-diagnosis phase.
**Results:** We find various changes to the content and form of posts as BD users move towards a BD diagnosis. Changes were observed for the length of posts, coherence, the presence of certain syntax classes and illness- as well as non-illness related topics.
**Discussion:** Our study provides important insight into linguistic changes that announce the approach of a BD diagnosis. The linguistic features discovered here could, in the future, feed into social media-based health surveillance programs.

## S69. Speech Markers of Schizophrenia: Assessing the Role of Speech Task and the Association Between Acoustic and NLP Features

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**Background:** Promising speech and natural language processing (NLP) applications have shown great potential for identifying speech markers of schizophrenia (SZ) and developing systems to monitor patients' symptoms. However, speech production has generally been considered static and context-independent, and few studies have evaluated the role of contextual factors on voice production, such as the cognitive, social and affective constraints set by a specific task. Voice atypicalities may be limited to specific contexts, such as social interactions. Furthermore, previous speech-based applications in SCZ have used audio-only or text-only models, focusing on acoustic or textual data, respectively. However, both acoustic and language atypicalities represent crucial and only partially overlapping symptom dimensions. The aim of this study is to provide an account on how speech analysis

parameters relate to speaking task and clinical features and to investigate the mechanisms responsible for speech abnormalities. In addition, we aim to explore the relationship between acoustic and NLP features.

**Methods:** We aimed to collect a dataset of speech recordings of 30 individuals with SZ and 30 control subjects, using a comprehensive speech production task in which participants are required to produce speech in monologic and dialogic contexts: 1) reading aloud and recall; 2) narrative and autobiographical descriptions; 3) social interactions. The use of different tasks ensures two important advantages, i.e. to produce more robust results not specifically bound to a specific context, and to investigate the mechanisms and contextual factors responsible for voice abnormalities. For example, comparing monological vs. dialogical contexts enables investigation of the impact of socio-cognitive mechanisms on vocal production, often hypothesized to be impaired in neuropsychiatric disorders, while comparison of reading vs. narrative description allows testing for the impact of word search (alogia) and fine motor control of the vocal fold.

Voice recordings are automatically preprocessed to extract relevant features using consolidated signal processing algorithms (e.g. OpenSmile, Covarep). A large set of relevant acoustic and NLP features (e.g., pitch variability, pause duration, semantic coherence) is extracted using a speech and NLP pipeline (based on previous work). We ran multilevel regression models with speech and NLP measures as outcomes, and diagnosis (SZ, HC) and speech task as predictors, and varying effects by participant. Finally, we conducted a network analysis, i.e. a network of partial correlations, to examine the relationship between acoustic and text features.

**Results:** Preliminary results (n=15) show significant differences in acoustic and NLP features between patients with SCZ and controls, consistent with previous studies. Crucially, these differences are mediated by the specific speech task employed. For example, patients showed reduced pitch variability ($p < .01$) and increased pause duration ($p < .05$) only in conversational tasks and reduced voice quality measures also in reading and picture description tasks ($p < .05$).

In addition, the network analysis showed that speech and NLP features are associated. For example, reduced pitch variability was found to be associated with negative sentiment ($r = .32$), while reduced speech production (lower speaking rate, longer pauses) was associated with reduced lexical informativeness ($r = .37$).

**Discussion:** Our preliminary results suggest that speech and language abnormalities in schizophrenia do not manifest homogeneously across different contexts, but are largely mediated by the cognitive and social demands of a particular speech task. This confirms the importance of using comprehensive speech batteries when assessing speech production, which can also help to unveil the cognitive and social mechanisms responsible for the speech abnormalities. Furthermore, our results have shown that acoustic and NLP features are interrelated. Future studies may leverage on the possibility of using complementary information from different modalities (e.g., speech, text, but also video), e.g., by using large multimodal (speech + text) models, which would increase the capacity to capture speech-related clinical information closer to clinical needs.

## S70. Do Interpersonal and Non-Interpersonal Trauma Differentially Relate to Schizotypy Dimensions?

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**Background:** Trauma is a well-documented risk factor for psychosis. However, little work has examined how distinct trauma types may differently relate to the full spectrum of psychosis symptoms. In particular, interpersonal trauma (i.e., trauma inflicted by another person) may have specific relationships with psychosis spectrum symptoms revolving around social interactions and trust. To assess this gap for a broad range of psychosis spectrum symptoms, we utilize the four-factor structure of schizotypy dimensions from the Schizotypal Personality Questionnaire (SPQ): cognitive perceptual distortions, disorganization, restricted affect and relationships, and social anxiety. Thus, the current study aims to address the lack of specificity, by examining whether interpersonal trauma has unique relationships with certain schizotypy domains above and beyond non-interpersonal trauma.
**Methods:** Using a community sample recruited in central Indiana (N=180), participants completed the Stressful Life Events Screening Questionnaire (SLESQ) to assess a range of trauma experiences. Three trauma groups were identified (interpersonal trauma, non-interpersonal trauma, and no trauma) and matched for equal group size. All participants completed the brief revised version of the SPQ, and the Personality Inventory for the DSM-5 brief form (PID-5) as a measure of broad dimensional psychopathology. A preliminary analysis will test group differences in SPQ total and PID-5 total to characterize the sample. Primary analyses will look at differences across trauma groups on the four factors of the SPQ. Factors with significant differences will be further analyzed for specificity.
**Results:** Data analysis is currently underway. We hypothesize that interpersonal trauma will be characterized by higher total scores on SPQ and PID-5 compared to the other two groups. For primary analyses we hypothesize that interpersonal trauma will be associated with highest scores for cognitive perceptual distortions, restricted affect and relationships, and social anxiety compared to both non-interpersonal and no trauma groups. Finally, SPQ factors with significant differences will be explored further by looking at their subscales.
**Discussion:** The purpose of this research is to explore the specificity of trauma types and their relationship with schizotypy dimensions. This work could potentially advance our understanding of whether interpersonal trauma has a unique contribution for these dimensions. Such work is imperative to inform interventions for a person-centered approach in early psychosis programs.

## S71. Addressing the Validity of Schizoaffective Disorder Diagnosis

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**Background:** Schizoaffective disorder (SAD) has long been a controversial and debated diagnostic category in psychiatry. Characterized by a combination of mood disorder symptoms (either depressive or manic) and psychotic features (typically delusions or hallucinations), occupying a unique place in the diagnostic landscape. The validity and utility of a diagnosis in clinical practice and research rely heavily on its reliability. While Schizophrenia and mood disorders can be diagnosed with high reliability, there is poor diagnostic reliability for cases meeting the criteria for schizophrenia that also involve mood episodes, as well as the presence of psychotic symptoms over the time in the absence of

mood symptoms. For these reasons, the diagnostic validity of SAD has been questioned, particularly due to issues related to its definition, overlap with other psychiatric conditions, and inconsistent application in clinical practice.
The aim of this study is to analyze the stability of the initial diagnosis of SAD over the follow-up period for patients admitted to the Emergency Department of the Moyano Hospital between 1996-2022.

**Methods:** The Department database was analyzed to identify patients who, at the time of their first hospitalization, were diagnosed with schizoaffective disorder. These patients were followed up to evaluate whether their diagnosis changed over time, the time elapsed between the initial SAD diagnosis and the subsequent diagnostic change, and whether this change impacted on drugs received.
To describe our findings, measures of central tendency and dispersion were used. For quantitative variables, the mean and standard deviation were calculated, while qualitative variables were expressed as percentages. Statistical analysis was performed using SPSS Statistics 26. These results are preliminary data, as the study is ongoing, and we expect to analyze a larger sample to increase statistical power.

**Results:** A total of 44 patients were included. The mean age at the time of SAD diagnosis was 32.25 (±8.812) years. Of the total sample, only 18.8% retained the SAD diagnosis, while the majority experienced a change in diagnosis: bipolar disorder (50.0%), schizophrenia (6.7%) and others (brief psychotic episode, unspecified psychotic disorder, 12.5%). The mean follow-up period until de change in diagnosis was 72.18 (±57.810) months. Additionally, 60% of patients experienced modifications to their pharmacological treatment, with a trend toward the inclusion of mood stabilizers.
**Discussion:** Our main findings suggest that SAD is not a stable diagnosis over time. In our sample, more than 80% of patients experienced a change in diagnosis, most commonly to bipolar disorder. The average time to diagnosis change was 6 years. These findings raise significant concerns about the validity of the schizoaffective disorder diagnosis. Although SAD is conceptualized as a hybrid of psychotic and mood disorder symptoms, the observed diagnostic instability and frequent reclassification highlight significant challenges in reliably applying its criteria. This instability, combined with the observed adjustments in pharmacological treatments, often involving the addition of mood stabilizers, suggest that initial treatments based on the SAD diagnosis may be suboptimal, raising questions about the utility of SAD as a distinct diagnostic category in clinical practice and research.
These findings reinforce broader skepticism in psychiatry regarding the reliability of the SAD diagnosis, emphasizing the need for refined diagnostic frameworks or reconsideration of SAD as a standalone category

## S72. A Reliable Change Index to Inform Development of a Minimal Clinically Important Difference in Treatment Resistant Schizophrenia

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**Background:** Randomized controlled trials (RCT) are increasingly evaluated for clinical or "real world" importance. The reliable change index (RCI) is proposed to incorporate assessment of the reliability of ratings into evaluating change (Jacobson and Truax, J Consult Clin Psychol, 1991;59:12-19). A complementary concept, the minimum clinically important

difference (MCID) is defined as a measure of the minimum change in an objective score required to correspond to clinically significant change (Jaeschke et al., Control Clin Trials, 1989;10:407-415). These approaches differ from the widely applied, but increasingly criticized, 20% improvement in Positive and Negative Syndrome Scale (PANSS) score as denoting meaningful change.
An absolute increase of ≥12 points in total PANSS score is posited to indicate a clinically important relapse in schizophrenia (Siafis et al., Lancet Psychiatry 2024;11:36-46). To continue work in defining criteria for meaningful change in treatment resistant schizophrenia (TRS), our objectives were to 1) quantify a RCI for total PANSS score, 2) explore application to hospitalized patients, 3) compare findings with the original study of clozapine in TRS (Kane et al., Arch Gen Psychiatry 1986;45:789-796).

**Methods:** Using data from 68 participants from the Clozapine and Risperidone Enhancement (CARE) study (Honer et al., NEJM, 2006;354:472-482), PANSS ratings on day 1 and 7 (both under stable clozapine monotherapy) were used to calculate reliability using intraclass correlation, and derive a RCI for total PANSS score, and for PANSS-derived Brief Psychiatric Rating Scale (BPRS) total score (Evans et al., BMJ Men Health,1998;1:70-72). Patients hospitalized with TRS at the British Columbia Psychosis Program (BCPP, n=355) were included in an exploratory analysis. Mean age was 38 years, 26% female sex. PANSS scores were rated at admission, and at discharge (median length of stay of 5 months).

**Results:** CARE study total PANSS scores were 97.3 (SD 13.5) and 97.0 (SD 13.2) on days 1 and 7 respectively, with an intraclass correlation coefficient of 0.90 allowing calculation of an RCI of 11.8. Using the same data, an RCI for a PANSS-derived BPRS total score was determined to be 5.8.
Amongst BCPP patients, total PANSS scores at admission and discharge were 95.1 (SD 18.9) and 76.8 (SD 19.6) respectively. Mean change in score was 18.4 points (27% of baseline). Overall, 64% of patients improved by ≥20%. Similarly, 62% demonstrated a change of at least one RCI unit, with 30% changing between 1 and 2 units, and 32% improving by ≥2 units.

In the pivotal RCT of clozapine for TRS, study entry total BPRS score was 61, declining to 45 for clozapine-treated and 56 for chlorpromazine-treated patients. Using our PANSS-derived BPRS RCI of 5.8, mean changes represent 2.8 RCI units for clozapine, and 1.0 units for chlorpromazine. Interestingly, 30% of clozapine-treated patients were categorized as improved, similar to the 32% of BCPP patients achieving an RCI unit-change of 2 or more at discharge.

**Discussion:** The RCI for TRS in this analysis, a reduction of 11.8 total PANSS points, is remarkably similar to the 12-point increase in PANSS found to suggest illness relapse. Based on our data, an improvement of 1 RCI unit was associated with chlorpromazine treatment in the original Kane et al. RCT, compared with 2.8 units for clozapine. This, and the proportion of about 30% of TRS patients improving by 2 or more RCI units after a long hospitalization, suggests that a change of at least 2 RCI units (well over 20 points in total PANSS) may be needed to incorporate an RCI into developing an MCID for TRS. Ongoing analyses of changes in day-to-day function in hospitalized TRS patients may help incorporate the RCI approach into an acceptable MCID for clinical trial evaluation.

## S73. A Clinical Trial of a Behavioral Intervention to Reduce Violence by Young Adults With Early Psychosis Receiving Treatment in an Early Intervention Services Setting

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**Background:** Despite the public health impact of violence among young adults with psychosis, behavioral interventions to reduce the risk of engaging in violence remain rare. For young adults with early psychosis, cognitive behavioral therapy (CBT)-based psychotherapy has efficacy in reducing impairment and improving functioning. However, no CBT-based intervention to reduce violence has been formally adapted for young adults with early psychosis.

This presentation will describe the first clinical trial of a behavioral intervention to reduce violence for young adults with early psychosis. First, an existing CBT model called PICASSO (Psychological Intervention for Complex PTSD and Schizophrenia-Spectrum Disorder) was adapted through qualitative research. Next, the model was further refined through an open pilot trial.

**Methods:** All research occurred OnTrackNY, the largest early intervention services (EIS) program in the United States. First, qualitative interviews were conducted with EIS clinicians, EIS peer specialists, and EIS participants (patients) with recent violent ideation or behavior. These findings were used to adapt an existing model of CBT called PICASSO following the CDC Map of Adaptation. Finally, the intervention was tested in an open pilot trial with primary aims of feasibility and acceptability. During this open pilot trial, EIS participants completed 12 weeks of the PICASSO intervention with their EIS clinician. Quantitative measures (acceptability, feasibility) were collected on a weekly basis and qualitative interviews and surveys of the hypothesized mediators of the target were assessed at weeks 4, 8, and 12. All study procedures were approved by the Columbia University IRB and the study is registered with Clinicaltrials.gov (NCT05756855).

**Results:** Qualitative interviews were conducted with EIS clinicians (n=8), EIS peer specialists (n=5), and EIS participants with recent violence (n=6). These interviews generated themes regarding acceptability of PICASSO, including negative experiences of violence and the desire to control and minimize violence, as well as feasibility of PICASSO, including time constraints, consistency of participation in the intervention, and implementation issues in the context of stigma. Overall these interviews suggested a need for a behavioral intervention targeting violence behavior. Next, EIS clinicians (n=8) were recruited and trained in the delivery of the intervention. These EIS clinicians are recruiting EIS participants from their existing patient panel. Currently, 3 EIS participants are in the clinical trial with a target recruitment of 10-16 EIS participants total. Early results suggest high feasibility and acceptability of the PICASSO intervention, with EIS clinicians reporting they like the manual and EIS participants sharing they are finding the structured space in which to discuss violence useful. The trial is expected to end in early 2025 with preliminary results in March 2025.

**Discussion:** Because violent behavior causes interpersonal disruptions such as incarceration and increased caregiver burden, an innovative intervention to reduce violence risk could have broader health impact for this vulnerable population. Adapting the PICASSO intervention to the EIS setting will optimize its acceptability and feasibility by the intended target population in preparation for a large scale randomized trial.

## S74. One-Year Psychotic Symptom Control Disparities Among Black, White, and Latino Recent-Onset Schizophrenia Patients in a Coordinated Specialty Care Program

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**Background:** Due to systemic racism as well as ethnic difference in access to and acceptance of medical care, ethnoracial disparities are evident in psychiatric symptoms, treatment access, and treatment outcomes for Black and Latino Americans. To improve treatment outcomes for these groups, further understanding is needed of the efficacy of evidence-based interventions for Black and Latino first-episode patients. This study examines whether there were ethnoracial disparities in one-year psychotic symptom control in a sample of Black, Latino, and White first-episode patients in a coordinated specialty care program.
**Methods:** Participants were recruited from community clinics and hospitals and enrolled in a one-year 2x2 randomized controlled trial. Participants were randomly assigned to receive either an oral or long-acting injectable antipsychotic (LAI) medication. Participants were concurrently randomly assigned to either cognitive remediation or a healthy behavior psychoeducational group. Individual psychotherapy as well as individual placement and support were also provided to study participants. For the current analyses, Reality Distortion (mean of the BPRS items Unusual Thought Content and Hallucinations) was the primary outcome. Attitudes regarding antipsychotic medication were assessed with the Ratings of Medication Influences.
**Results:** Mixed general linear modeling revealed ethnoracial differences among the participants. Post-hoc contrasts showed that Latino American participants had disproportionally higher baseline Reality Distortion levels compared to Black participants (P=.02), which continued throughout the 12-month follow-through treatment period. White participants did not significantly differ from either Latino or Black participants in Reality Distortion levels. Latino patients in the oral antipsychotic group had the lower rates of medication adherence in contrast to Black (P=.03) and White (P=.001) participants. These disparities were not observed in the LAI group. Latino participants were more likely than White participants to need family support and supervision to maintain medication adherence for the oral medication group, but not the LAI group.
**Discussion:** These findings have the potential to enhance our understanding of the efficacy of evidence-based treatments for Black and Latino Americans. Long-acting injectable medications show promise in reducing these identified ethnoracial disparities.

## S75. Incidence of First-Episode Psychosis Across the COVID-19 Pandemic in South London: A Six-Year Pre-During-Post Analysis

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**Background:** The COVID-19 pandemic may have led to increased exposure to risk factors for psychosis.
Using a pre-during-post study design, we investigated changes in the incidence of first-episode psychosis (FEP) in South London. We hypothesised that FEP incidence rates increased during the pandemic and subsequently returned to pre-pandemic levels.

**Methods:** We used the Clinical Record Interactive Search (CRIS) system to identify individuals referred for FEP to Early Intervention Services for Psychosis (EISs) at the South London and Maudsley NHS Foundation Trust (SLaM) between 1 March 2018 and 29 February 2024.
Population data for the SLaM catchment area were obtained from the Office for National Statistics. Crude incidence rates were calculated, and Poisson regression models were used to estimate age-, sex-, and ethnicity-adjusted incidence rate ratios (IRRs) across the study years (March to February).

**Results:** A total of 3,752 individuals experienced FEP over 5,487,858 person-years at risk, accounting for a mean crude incidence rate of 68.4 per 100,000 person-years (95% CI, 66.2–70.6).
The Poisson regression model showed a departure from the mean during the peak of the COVID-19 pandemic (2020/21), with FEP rates rising to 77.5 per 100,000 person-years (95% CI, 71.1–83.2). Similar elevated rates were observed in 2021/22. Subsequently, FEP incidence returned to pre-pandemic levels.

Subgroup analysis showed the highest FEP increases among individuals of Black ethnicity, with an IRR of 1.45 (95% CI, 1.22–1.73) in 2020/21, sustained in 2021/22.

A notable increase was also observed among Asian individuals, with an IRR of 1.54 (95% CI, 1.20–1.88) in 2021/22.

**Discussion:** The incidence of FEP in South London increased during the peak of the COVID-19 pandemic, particularly among individuals of Black ethnicity.
These findings highlight the disproportionate impact of the pandemic on ethnic minorities and the need of targeted public health strategies for psychosis prevention.

## S76. Patterns of Model-Based and Model-Free Learning in Clinical High Risk for Psychosis, Major Depressive Disorder, and Healthy Controls

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**Background:** Prior research has found impaired reward-based decision-making abilities in both schizophrenia and major depressive disorder. Importantly, the nature of learning impairment across these syndromes may be distinct. Schizophrenia is associated with reduced rapid, explicit, or “model-based” learning, and depression with reduced gradual, implicit, or “model-free” learning, suggesting differential neural mechanisms and treatment implications. Despite the importance of early detection, no study to date has investigated (a) whether these patterns are evident among youth at clinical high-risk (CHR) for psychosis or (b) the extent to which learning impairments in this population are distinguishable from those seen in common depression.

**Methods:** A small ongoing pilot study is enrolling participants ages 14-30 who meet criteria for CHR syndrome, major depressive disorder (MDD), or no psychopathology (healthy controls, HCs). Participants complete a reinforcement learning task designed to distinguish model-based from model-free learning. Each trial consists of two phases. In the first, participants choose between two stimuli which lead to a common (70% probability) or rare (30% probability) transition to one of two "states" in phase two. In the phase two, participants choose between two stimuli which deliver reward on a gradually changing probability (20-80%). Purely model-free learners always repeat the same first-stage choice following a reward on the prior trial (main effect of reward). Model-based learners, however, consider the first-stage transition probability of the prior trial (reward-rarity interaction). To assess decision-making patterns, we examined the influence of previous-trial reward and transition rarity on first-stage choice (stay/shift) in the full sample and across clinical groups.
**Results:** 13 CHR, 8 MDD, and 5 HC have completed the task to date. Mixed models indicate a main effect of reward ($F = 30.7$, $p < .001$) and a reward-rarity interaction ($F = 48.9$, $p < .001$) in predicting first-stage choice, suggesting the presence of both model-free and model-based learning. The reward-rarity interaction was modified by group ($F = 4.6$, $p = .011$), indicating that model-based learning was not equally present across the groups. Follow-up analyses show that CHR youth were uniquely affected by a deficit in model-based learning relative to both HCs ($p = .068$) and MDD ($p = .019$). No evidence suggested reduced model-free learning in CHR or MDD.
**Discussion:** These early pilot results are consistent with findings from established schizophrenia suggesting a deficit in explicit or model-based learning. Our findings suggest that this deficit may be present in the high-risk stages even prior to illness onset. Moreover, the lack of impairment in model-based learning in MDD suggests that this deficit may not be a general marker of psychopathology but may have some specificity to the psychosis spectrum. Results will be presented with an updated dataset.

## S77. An Analysis of Symptoms of Psychosis on Symptoms of Anxiety and Depression Over Time

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**Background:** Coordinated specialty care (CSC) programs are designed to treat individuals who are experiencing a first-episode of psychosis (FEP). These models are considered the gold standard of treatment for reducing symptoms of psychosis and improving long-term outcomes for individuals, such as in employment, education, housing, and psychotic symptom management. While the purpose of these programs is to address the symptoms of psychosis the individual is experiencing, individuals often come into the program experiencing other clinically significant mental health concerns. This analysis reviewed how the treatment of other clinically significant symptoms such as depression as measured by the Patient Health Questionnaire – 9 (PHQ-9) and anxiety, as measured by the as measured by the Generalized Anxiety Disorder – 7 Item (GAD-7), impacted the reported symptoms of psychosis as measured by the CAPE-P15.
**Methods:** This study reviewed the measures completed in one CSC network in the Pacific Northwest. As a part of this networks model measures are delivered at regular intervals (monthly, quarterly, biyearly) to better assess symptoms and develop treatment plans. There were 869 individuals available for these analysis who completed measures between October

2015 and June 2024. Only individuals who reported experiencing clinically significant symptoms of depression (score of 10 or higher out of 27) (n=237) or clinically significant symptoms of anxiety (score of 10 or higher out of 21) (n=221) at intake to the program were included in the analysis. Scores of the CAPE-P15, which measures symptoms of psychosis, range between 0-3. A linear regression model was used for all analysis.
**Results:** Symptoms of depression and anxiety significantly predicted the symptoms of psychosis. For every one decrease on the total scores for the GAD-7 there was a .059 point decrease in the total scores of symptoms of psychosis ($\beta$ = -.059, CI: -.042 - -.077, $p \leq .001$) and for every one point increase in the total scores of the PHQ-9 there was a .042 point decrease in the scores of the CAPE-P15 ($\beta$ = -..042, CI: -.031 - -.054, $p \leq .001$).
**Discussion:** While the treatment models for CSC primarily focus on symptoms of psychosis, other clinically relevant symptoms can impact the reported symptoms of psychosis. Future work should use mediation analysis to review how impactful depression and anxiety are on the reduction of psychotic symptoms. CSC treatment models should continue to evolve as we better understand the comorbid effects that various mental health concerns have on the treatment process.

## S78. Comparative Efficacy and Tolerability of Antipsychotic Drugs in Early-Phase Psychosis: Systematic Review and Network Meta-Analysis of Western and Chinese Randomized Controlled Trials

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**Background:** Schizophrenia is one of the most common, burdensome, and costly psychiatric disorders worldwide. As of recent estimates, approximately 24 million people worldwide are affected by schizophrenia or 1 in 300 people worldwide (WHO Schizophrenia 2022). The onset of the condition typically occurs in early adulthood, most frequently in the early 20s, a period of significant individual development, social role formation and the initiation of a trajectory of accumulating disability (Anderson 2019). Several research studies demonstrated that adequate treatment during the early phase of psychosis can result in favourable treatment outcomes (Santesteban-Echarri O 2017). In addition to psychosocial interventions, drug therapy is the first-line treatment. The early course of psychotic disorders has been defined inconsistently, with the term "first episode" often applied broadly. Research commonly focuses on early-phase schizophrenia or recent-onset psychosis, typically limiting the duration of illness to 5 years at maximum.
The current evidence on drug treatments for early phase psychosis is limited to pairwise meta analyses that investigate long-acting injectable versus oral antipsychotics interventions (Correll 2024). Another network meta-analysis (NMA) restricted to first-episode patients only (Zhu 2017) has been conducted by our group but it is limited by the number of studies and participants included. Thus, the most efficacious and acceptable treatments for patients with schizophrenia in the early phase of the disorder are currently unclear. This underlines the need for a network meta-analysis to produce a comprehensive synthesis of all randomized evidence, focusing on this particular population.

**Methods:** Study design and participants

we included people with first-episode psychosis, first-episode schizophrenia, early-phase schizophrenia or recent-onset psychosis. Studies of early-phase schizophrenia or recent-onset psychosis we will accept when, by inclusion criteria, the duration of illness was 5 years at maximum. Participants must have acute symptoms of psychosis. We excluded studies in stable participants and in participants with predominantly negative symptoms; studies in other specific populations (e.g. wit comorbid drug abuse) were excluded in sensitivity analysis. Studies in which more than 50% of the participants were suffering for schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders) were acceptable. I.e. we accepted if studies include up to 50% of participants with psychosis due to other mental disorders because in first-episode/early phase of severe mental disorders diagnoses are not made definitely, yet and antipsychotics are used to treat psychosis in any case. We included the trials irrespective of the diagnostic criteria used. There were no restrictions in terms of age, sex or ethnicity.

Antipsychotics

We will include all 16 second-generation antipsychotic drugs available in Europe and/or the US and/or China (amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, olanzapine-samidorphan, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine) and placebo, and the second-generation antipsychotics blonanserine and perospirone which are only available in Japan and a few other Eastern Asian countries. Moreover, we will include the first-generation antipsychotics haloperidol, chlorpromazine, perphenazine and sulpiride. According to the Second International Consensus Study on Antipsychotic Dosing (ICSAD-2, DOI:10.1177/02698811231205688), antipsychotic dosing for patients experiencing early-phase or first-episode schizophrenia is generally recommended to be 25-30% lower than the doses used for patients with repeated episodes of psychosis. Therefore, we will also accept lower dose than those recommended for multiple episode patients in the Second International Consensus Study. We will exclude study arms whose dose range is completely above the maximum dose range recommended in the consensus. For analysis, we will pool different dose arms and different forms of administrations of the same compound.

Outcomes

Primary outcomes: Overall symptoms of schizophrenia as measured by rating scales such as the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS)

Secondary outcomes: Positive symptoms, negative symptoms, depressive symptoms, response to treatment, inefficacy or adverse events.

**Results:** We currently conducting data analysis.
**Discussion:** We currently conducting data analysis.

## S79. Pilot Examination of White Matter Changes in Cannabis-Using Females With First Episode Psychosis

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Candice Crocker

**Background:** Females with first episode psychosis (FEP) and substance misuse have been reported to have less favorable treatment responses than FEP males with substance misuse. This may be related to underlying neurobiological changes that occur with substance misuse, particularly with cannabis.
Despite being aware of the difficulties inherent in treating substance misusing female patients, research in this area has predominantly focused on the treatment outcomes in males and individuals who identify as men. Examination of the possible neurobiological underpinnings of the sex differences in response is even more sparse. This study aimed to examine whether neuroinflammation is a possible factor underlying treatment response in FEP females with cannabis use disorder, as measured by two types of diffusion tensor imaging aimed at attempting to discern if structural white matter abnormalities were present and if neuroinflammatory signals were also present.

**Methods:** Magnetic resonance imaging was conducted on a 3T GE MR750 scanner with a 32 channel head coil. Multi-shell imaging was employed to examine not only typical diffusion tensor variables but also diffusion kurtosis imaging (DKI) and Neurite Dispersion and Diffusion imaging (NODDI) were employed to examine the rostral region of the anterior cingulate cortex. The metrics of mean diffusivity (MD), mean kurtosis (MK) and orientation and dispersion index (ODI) were examined in conjunction with cannabis use data by Pearson's correlation. Pearson's correlations also were tested between amount of cannabis used and patient outcomes. Group comparisons were made by t-tests for three imaging variables representative of each imaging approach and relevant to our research question.
**Results:** 26 female patients with EPP were recruited. Of those with high quality imaging data, the final dataset was N= 13 cannabis using and N=11 without cannabis use. The cannabis using group was 5 moderate cannabis use disorder and 8 severe cannabis use disorder according to substance use module of the structured clinical interview for DSM5. ODI in the superior longitudinal fasciculus (SLF) and the Anterior cingulate cortex (ACC) were significantly correlated with clinical status as measured by the clinical global impression severity scale (CGI-S) ($p < 0.05$). Mean diffusivity (MD) correlated with functioning measures, the GAF and SOFAS ($p < 0.05$). While the ODI correlated to the MK value, there were only trend level results for correlations between clinical and functional measures to MK. Between group comparisons showed significant group differences were observed for MK, ODI and MD between cannabis users and non-cannabis users.
**Discussion:** These findings illustrate significant differences in imaging measures of brain white matter structural integrity. However, our initial supposition that neuroinflammation may be underlying the differences in treatment outcomes between the sexes is not supported. This is unfortunate as an understanding of the underlying poor treatment response in this patient subpopulation could help guide sex-specific treatment for these individuals.

## S80. Investigating Auditory Segmentation Deficiencies in the Cingulate Motor Area of First Episode Psychosis

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Jack Kavanagh

**Background:** Auditory Segmentation Potentials (ASPs) are event-related potentials (ERPs) that reflect the brain's classification of an acoustic pattern from multiple auditory stimuli. Previous EEG data from our lab has shown reduced ASPs in the Cingulate Motor Area for individuals within their first year of treatment since the onset of psychotic symptoms. (FEP). This present study aims to further investigate our previous EEG results by recording brain activity with Magnetoencephalography (MEG) while attending or ignoring to acoustic patterns.
**Methods:** Six FEPs and eight matched healthy comparison individuals (HC) completed two tasks and either ignored or attended to standard musical notes while watching a silent video. Stimuli consisted of 300 groups of three ascending notes (75dB, 50ms each, 5ms rise/fall times, SOA= 333ms), with deviations in the ascending note pattern and 1000 milliseconds separating each group. ASPs were recorded from standard groups, and measured from data filtered between 0.5-2 Hz, from 200ms to 600ms and 600-1000ms after onset of the first tone within CMA and bilateral Auditory cortex ROI's.
**Results:** Although not significant, statistical analysis of MEG data showed that in comparison to HCs, FEPs ignoring auditory patterns had diminished ASP activity within the Cingulate Motor Area with a large effect size (Cohen's D= 1.05, p=0.08).
**Discussion:** These results indicate diminished ASP within the FEP's CMA, an area that is well characterized as being diminished in schizophrenia. It is possible that the CMA's involvement in rhythm processing makes it an important biomarker for functional and clinical outcomes in schizophrenia.

## S81. Exploring the Role of Functional Capacity in Predicting Functional Outcome in Individuals at Clinical High-Risk for Psychosis

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Rui Ma

**Background:** Functional difficulties are a core feature of chronic psychotic disorders, particularly schizophrenia, and represent a significant health concern (Harvey, 2009, 2011). Functional capacity refers to underlying competencies and skills enabling individuals to perform real-world tasks (Harvey, 2009). While much of the research on functional capacity has focused on adults with chronic psychosis, there is a critical need to assess these factors earlier in the clinical high-risk for psychosis (CHR-P) population. The Map Task was specifically designed to fill this gap by providing an age-appropriate assessment for adolescents, focusing on cognitive planning and social interaction without requiring mastery of adult-level tasks (McLaughlin et al., 2016). This study aimed to determine whether performance on the Map Task predicts social and role functioning across multiple timepoints over 24 months.
**Methods:** Participants included 616 CHR-P young adults from NAPLS-3. At baseline, participants completed the Map Task, which measures cognitive planning and execution. Map Task performance was represented as a composite score combining task efficiency, errors, and completion time. Social and role functioning were assessed using GF:S and GF:R scales at baseline, 6, 12, and 24 months. Separate linear regressions were used to analyze the predictive value of Map Task performance on psychosocial functioning, adjusting for baseline functioning, age, and sex.
**Results:** The mean (SD) age of participants was 18.19 (4.06) years, and 45.6% were female. Linear regression showed that Map task performance was significantly associated with GF:R at baseline ($r=0.134$, $p < .001$) and predicted GF:R at 24 months ($B=0.765$, $t=3.03$, $SE=0.252$, $p=.003$). The effect at 12 months approached statistical significance ($B=0.351$, $t=1.93$, $SE=0.182$, $p=.055$). Map task performance was also significantly associated with GF:S at baseline ($r=0.196$, $p < .001$) and predicted GF:S at 6 months ($B=0.423$, $t=3.10$, $SE=0.137$, $p=.002$). However, it did not significantly predict GF:S at 12 months ($B=0.135$, $t=1.11$, $SE=0.121$, $p=.268$) or 24 months ($B=0.294$, $t=1.93$, $SE=0.152$, $p=.055$).
**Discussion:** Map Task performance was significantly associated with both social (GF:S) and role (GF:R) functioning at baseline, highlighting its relationship to concurrent psychosocial functioning. It also predicted short-term social functioning at 6 months and showed significant associations with role functioning at 24 months, demonstrating its relevance to functioning trajectories over time. These findings suggest that cognitive planning skills, as measured by the Map Task, play a role in both short- and long-term functional outcomes across social and role domains. Future research should explore these mechanisms, including how family environments and other contextual factors may provide opportunities to enhance cognitive functioning and improve adaptive outcomes in individuals at CHR-P.

## S82. Evaluation of Melodic and Rhythmic Perception in First-Episode Psychosis

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Dylan Seebold

**Background:** Schizophrenia and other psychotic disorders have been linked to deficits in auditory change detection, particularly for pitch, timing, and complex grouping. Additionally, complex melodic and rhythmic impairments, assessed via the Montreal Battery of Evaluation of Amusia (MBEA), are shown in chronic schizophrenia and are correlated with deficits in social cognition/functioning. Given overlapping characteristics between music and speech,

such as rhythm-prosody, accent-inflection, and pitch-intonation, the deficits indicated by the MBEA in chronic schizophrenia may be linked with deficits in social cognition driven by misinterpretation of speech, and its underlying emotional content, thus making it troublesome for maintaining social relationships. However, when these melodic-rhythmic deficits first occur, and whether they occur before, after, or concurrently with impairments in social cognition, has not been thoroughly studied. In this study we assess primary aspects of auditory perception (pitch, melody, and rhythmicity) using the MBEA in individuals within one-year of their first-episode of psychosis (FEP) and their associations with social cognition.
**Methods:** Auditory perception and musicality were assessed using the MBEA in 14 healthy controls (HC) and 7 FEP. The MBEA assesses 6 areas of musical ability (scale, contour, interval, rhythm, meter, and music memory) across 3 categories (melody, temporality, and working memory). Group differences were assessed with t-tests. Further comparison to social cognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB) and correlations done via Pearson's Correlation Coefficient.
**Results:** MBEA scores were generally reduced in FEP compared to HC, with the largest difference observed within the rhythm subtest ($p = 0.045$). FEP also showed a significant impairment in social cognition ($p = 0.03$) compared to HC. A positive correlation was identified between MBEA Temporality total score (rhythm and meter) with MCCB Social Cognition t-score ($r = 0.605$).
**Discussion:** Deficits in rhythmic processing in FEP identified here highlight not only auditory perception impairments, but potential impairments in the coordination between sensory and motor areas that process time-estimation, sequence learning, and rhythm perception such as the cortico-striatal-thalamo-cortical (CSTC) and cerebello-thalamo-cortical (CTC) circuits. Previous studies show that all six subtests of the MBEA are significantly impaired in chronic schizophrenia, whereas these data show that rhythmicity, and more generally timing/temporality, may be affected first in psychosis, and with significant impairment early in the course of illness. Social cognition impairment in the absence of the marked MBEA deficits shown in chronic schizophrenia points towards additional mediating factors having an impact on social cognition, and that melodic deficits may continue to increase as the illness progresses. Further neurophysiological investigation using EEG/MEG and MRI may shed more light on pinpointing where and when these rhythmicity deficits occur. Understanding rhythm processing deficits, and their associated brain regions, may provide new targets for directed treatment of psychosis early in its development, which may stave off the progression of melodic/rhythmicity impairment or ameliorate underlying symptoms of social cognitive dysfunction.

## S83. Differential Auditory Segmentation Potentials in First-Episode Psychosis: Active vs Passive Attention

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Hayley Rhorer

**Background:** Auditory segmentation potentials (ASPs) are event-related potentials (ERPs) that generate in response to segmented groups of auditory stimuli after a pattern is established. Past neurophysiological research showed significant reductions in mismatch negativity (MMN) and N100 in those with schizophrenia, pointing to perceivable dysfunction in auditory perception and emphasizing the importance of investigating auditory processing

in people with schizophrenia as a biomarker of the disease. Furthermore, our lab has previously demonstrated deficits in ASPs in people experiencing a first episode of psychosis (FEP), showing that FEPs had significantly reduced ASP amplitudes compared to the healthy comparison individuals (HC). This current study aims to replicate and expand upon these findings by investigating EEG recordings of ASPs in response to segmented acoustic precepts in FEPs, specifically during both active and passive attention.
**Methods:** Six FEP (within 1 year of first contact regarding psychotic symptoms) and six age-matched HC ignored and attended (two separate tasks) to tone groups while a silent nature video played concurrently. Stimuli consisted of 300 groups of ascending-pitch triplets (75 dB, 50 ms pips, 5 ms rise/fall times, SOA = 333ms), with occasional deviations in tone pitch/ascending pattern. During the attend task, participants are asked to respond when they notice a deviation in the triplet and during the ignore task, they disregard the tones and focus on the video. Groups were separated by 1000 ms ITI. Sustained potentials were measured from frontocentral ERPs filtered between 0.5-2 Hz, from 200ms to 900ms after onset of the first tone.
**Results:** ASP amplitudes in HCs were significantly larger during the active condition than the passive condition (MA = -2.31 μV, SD = 0.84 μV; MP = -1.19 μV, SD = 0.64 μV; n = 6; $p < 0.05$), compared to FEP amplitudes, which were not significantly different across both conditions (MA = -1.88 μV, SD = 0.67 μV; MP = -1.60 μV, SD = 0.82 μV; n = 6). Although not significant, ASP amplitudes during the active condition were larger in HCs than in FEPs, with a medium effect size (Cohen's d = 0.57), but during the passive condition, amplitudes were smaller in HCs than in FEPs, with a medium effect size (Cohen's d = 0.55).
**Discussion:** These preliminary results indicate that people experiencing first-episode psychosis may exhibit a reduced ability to establish/modulate pattern recognition to segmented acoustic stimuli, which might suggest that higher-order cognitive mechanisms that are crucial for auditory segmentation and processing are affected at an early stage in psychosis. This diminished differentiation observed in ASPs in FEPs between the active and passive emphasizes the importance of investigating auditory processing as a key marker for schizophrenia progression. Further research is needed to explore the mechanisms driving these deficits and to assess their potential utility as early diagnostic indicators.

## S84. Stigma Resistance, Recovery and Clinical Outcomes in the First Episode of Psychosis

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Katerina Konstas

**Background:** Although stigma is linked to a wide range of negative outcomes for individuals with psychosis, little is known about the process of resisting stigma, especially in the context of a first episode of psychosis. Stigma resistance (SR), the degree to which people actively rebuff stigma's negative effects, was measured among individuals in their first year of experiencing psychosis in order to understand the relationship between stigma resistance and a) recovery outcomes, b) clinical outcomes, and c) engagement in clinical services.
**Methods:** We examined baseline levels of SR and the relationship between SR and clinical variables of interest using the Stigma Resistance Scale (SRS) in an outpatient first-episode psychosis clinic. The SRS was included in a large core assessment battery administered to FEP clients every 6 months. The SRS is a 20-question self-report survey assessing five domains of SR: Self-Other Differentiation, Personal Identity, Personal Cognition, Peer

Stigma, and Public Stigma. Higher scores reflect greater SR. All measures were assessed at baseline and follow-up. The assessment collection period was from November 2023 to October 2024 totaling 72 records (58 unique individuals).

Recovery was measured using the Process of Recovery Questionnaire (QPR) and Lehman's Quality of Life Scale (QoL). Clinical outcomes were measured using the Colorado Symptom Index and COMPASS-10. Clinical engagement was measured by calculating duration in care and the number of clinical services utilized by the client.

**Results:** Recovery Outcomes

Individuals who presented with feelings of loneliness had lower levels of total stigma resistance ($p = .002$), self-other differentiation ($p > .001$), and public stigma resistance ($p = .02$) compared to individuals who expressed no feelings of loneliness. Stigma resistance was positively correlated with dimensions of recovery related to feeling part of society ($p < .001$), positive feelings towards their mental health ($p < .01$), engaging in pleasurable experiences ($p < .01$), acceptance of the past ($p = .02$), ability to assert oneself ($p = .01$), ability to develop positive relationships ($p < .001$), and quality of life ($p = .01$).

Clinical Outcomes

Individuals experiencing suicidal ideation had lower levels of total stigma resistance ($p < .01$), self-other differentiation ($p = .01$), personal cognition ($p = .02$), and peer stigma resistance ($p = .03$). No significant group differences were found between stigma resistance and clients with and without hallucinations, avolition, and asociality.

Clinical Engagement

Significant group differences were observed between stigma resistance and duration in care. Individuals who were in treatment for more than one year had lower total stigma resistance scores ($p = .01$), self-other differentiation ($p = .04$), and public stigma ($p < .01$). The number of services utilized by the client was positively correlated with public stigma resistance ($p = .02$) and peer stigma resistance ($p = .04$).

**Discussion:** These findings illuminate how first episode care may be a critical window for addressing stigma, especially given its relationship to recovery and clinical outcomes – particularly social isolation and suicidal ideation. Results also may have important implications regarding areas where treatment can further strengthen stigma resistance. All these findings can be beneficial in identifying treatment targets for coordinated specialty care.

## S85. Psychotic-Like Experiences Among Young Women: The Roles of Adverse Childhood Experiences, Premenstrual Distress, and Help-Seeking Stigma

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**Background:** Psychotic-like experiences (PLEs) are a transdiagnostic risk factor for mental health problems. Understanding the risk factors for PLEs can improve early identification and treatment efforts. Common risk factors for PLEs include depression, anxiety, and adverse childhood experiences (ACEs). PLEs are also more prevalent among women and young people, but risk and protective factors for these groups remain understudied. Emerging evidence suggests that severe premenstrual symptoms may be associated with PLEs, but there is limited research in this area. Better understanding PLEs among young women can facilitate more tailored early intervention services and potentially increase help-seeking and treatment engagement. The main objective of this study was to better understand the association between PLEs and premenstrual symptoms, controlling for known risk factors of PLEs. A secondary objective was to explore the potential protective nature of resilience, and a tertiary objective was to explore help-seeking stigma among this group.
**Methods:** College-aged women in the US (N = 131) were recruited online using census-matched sampling (CloudResearch). The sample was majority white (59%), senior class standing (28%), and in their early twenties (Mage = 21.1, SD = 2.18; range 18-28). Participants completed a 10-min survey measuring psychotic-like experiences/PLEs (PQ-16 total and distress scales), depression (PHQ-9), anxiety (GAD-7), ACEs (ACEs Aware), premenstrual distress symptoms (PSST), resilience (CD-RISC 10), and self-stigma of seeking help (SSOSH-3). Socio-demographics and data on past mental health service use were also collected.
**Results:** A majority of the sample (57%) reported being diagnosed with a mental health problem by a professional, and the mean number of PLEs reported was 4.86 (SD = 3.39). Overall, the regression model was significant, $F(5, 125) = 21.38$, $p < .001$, $R2adj = .44$) for total PLEs, predicted by ACEs ($p = .003$) and premenstrual distress symptoms (PSST; $p = .002$). Other covariates were not significant. This model and these predictors remained significant after controlling for PLE distress ratings, sexuality, race, and ethnicity. Resilience was not a significant variable in these models. In additional exploratory analyses, help-seeking stigma was significantly and positively associated ($p < .05$) with PLE total score, PLE distress, and premenstrual distress symptoms – but not other covariates.
**Discussion:** PLEs are more commonly found among women and young people, and more research is needed to better serve these groups. In this sample of college-aged women, it was found that adverse childhood experiences and premenstrual distress were particularly strong predictors of PLEs, even when controlling for other known risk factors and socio-demographics. Resilience did not emerge as a protective factor, while help-seeking stigma was uniquely associated with PLEs and premenstrual distress. Future investigations - longitudinal studies in particular - are needed to unpack these associations and identify risk and protective factors for young women experiencing PLEs and considering mental health services. Such future work will enhance efforts to translate this research into practice.

## S86. OASIS 1000: Real-World Clinical Outcomes in Individuals at Clinical High Risk for Psychosis (Chr-P) - An Electronic Health Record Cohort Study

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Andrea De Micheli

**Background:** Clinical High Risk for psychosis (CHR-P) is one of the most effective examples of primary indicated prevention in the field of psychiatry. OASIS clinic (Outreach and Support in South London) is the first CHR-P service in the United Kingdom, launched in 2001. This cohort study aims to overcome a core limitation of knowledge in the field as research has mostly focused on the prediction of transition to psychosis in the short-term. As a result, there is little understanding of long-term clinical outcomes of this clinical population beyond the transition to psychosis so preventive interventions and CHR-P services have targeted the short-term period. As a secondary outcome, our study will also explore predictors of long-term outcomes that are currently not completely determined.
**Methods:** Retrospective RECORD-compliant real-world Electronic Health Records (EHR) cohort study in secondary mental health care (OASIS clinic operating in South London and the Maudsley -SLaM- NHS Foundation Trust). All CHR-P patients accessing the CHR-P service in the period 2001-2024 were included. Baseline descriptive variables include sociodemographic (age, sex, ethnicity, marital status, employment status, accommodation status, SLaM borough) and clinical characteristics (severity of CHR-P symptoms, type of CHR-P subgroup, Duration of Untreated Attenuated Psychotic Symptoms; Social and Occupational Functioning Assessment Scale [SOFAS]; Health Of the Nation Outcome Scale [HoNOS]). The main outcomes were long-term cumulative risk of first: developing an ICD-10 psychotic disorder (primary outcome), receiving treatment with antipsychotic medication, benzodiazepines, other psychotropic medications, psychotherapy, receiving an informal or compulsory admission into a mental health hospital, and the time to these events; number of days spent in hospital and cumulative risk of death for any reason and age/gender Standardised Mortality Ratio (SMR). Data were extracted from the EHR and will be analyzed with Kaplan Meier failure functions, Cox, and zero-inflated negative binomial regressions.
**Results:** Data from the dataset are currently in preparation.

A previous publication from our cohort (now enlarged by 400 additional CHR-Ps) found a substantial long-term risk of developing psychotic disorders, being treated with medications, being admitted to mental health hospitals, and spending several days in hospitals. Some of the CHR-P subjects may be at risk of premature death in the long term. We also found that age, baseline symptoms severity, duration of untreated attenuated psychotic symptoms, ethnicity, and employment status are consistently associated with various long-term clinical outcomes in CHR-P individuals

**Discussion:** Our study demonstrated that the current short-term duration of care offered by specialized mental health services is unlikely to capture most real-world clinical outcomes presented by individuals at clinical high risk of psychosis. The available evidence indicated that specialized services for CHR-P individuals should extend the duration of the care offered.

## S87. Improvements in Physical and Psychological Health Domains After Participating in a CBT-Based Stigma Reduction Intervention for Early Psychosis

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Francesca Crump

**Background:** Individuals with early psychosis (EP) may be exposed to stigmatization due to stereotypes about mental health, which can lead to internalized stigma. Internalized stigma may increase depressed mood (Pyle et al., 2013), deplete self-esteem (Xu et al., 2016), decrease overall quality of life (Dengan et al., 2021), and lower engagement in healthy lifestyle behaviors (Carney et al., 2017). Prevention programs have been developed to improve course of illness; however, research shows that youth with EP tend to exhibit increased rates of obesity, premature cardiovascular disease, and death compared to peers their age without psychosis (Smith et al., 2020). A qualitative study (Carney et al., 2017) found that fear of judgment from others, the adoption of negative views about the self, and internalized stigma serve as barriers for healthy lifestyle behaviors (e.g., regular physical activity, nutritious diets, and avoiding substance use). Importantly, individuals with psychosis symptoms who exhibit stigma resistance (i.e., challenging and deflecting mental health stereotypes) tend to have better psychosocial outcomes (Thoits and Link, 2016) but the impact on physical health domains remains unknown. This study explored the impact of a CBT-based stigma intervention on both psychological and physical health outcomes.
**Methods:** This study piloted an 8-week, virtual group stigma intervention, called Resisting Internalized Stigma (RIS), that contained psychoeducation, CBT techniques to challenge stigmatizing thoughts, and anti-bullying strategies to diffuse confrontations. This study took place at the University of Pennsylvania's Psychosis Evaluation and Recovery Center (PERC) and a total of 9 individuals identified as EP participated in two groups. Assessments of psychological and physical health domains were administered at baseline and follow-up. Pearson correlations, paired sample t-tests, and change score analyses were performed.
**Results:** Paired sample t-tests demonstrated that RIS significantly decreased overall stigma ($p=0.044$) and improved positive emotions ($p=0.018$). At the trend level, self-esteem ($p=0.072$) and engagement in health and exercise ($p=0.073$) increased from baseline to follow-up. At baseline, correlations showed that higher shame was associated with increased depression ($p=0.013$), worse psychological health ($p=0.001$), poor nutrition ($p=0.019$), and decreased self-esteem ($p=0.002$). Experiences of discrimination were significantly related to worse depression ($p=0.009$) and less quality of life for physical health ($p=0.030$). At follow-up, most associations related to shame and discrimination became insignificant and were instead related to positive emotions. Correlations showed that positive emotions were related to less depression ($p=0.028$), improved quality of life for psychological health ($p=0.042$), and increased self-esteem ($p=0.006$). Trend findings demonstrated a positive relationship between positive emotions and increased health and exercise ($p=0.093$) and general health quality of life ($p=0.095$). Change score analyses showed that as shame increases, depression increases ($p=0.011$), psychological health decreases ($p=0.009$), substance use avoidance decreases ($p=0.013$), and healthy nutrition declines ($p=0.029$).
**Discussion:** This is the first study to examine the impact of stigma processes on physical health domains in addition to psychological outcomes in EP. Participants in RIS demonstrated improved mood, higher self-esteem, and better outcomes related to psychological and physical health domains, which suggests that stigma may be a factor in the engagement of healthy lifestyle behaviors. Incorporating stigma interventions, such as RIS, in early intervention programs may prove beneficial for individuals experiencing stigma, discrimination, and physical health problems related to their EP designation.

**S88. OPEN BOARD**

## S89. The Effect of Structured Missingness on the Research of Early Psychosis

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Barbora Rehak Buckova

**Background:** Integrating multi-site data is vital for advancing the research of early psychosis, enabling the exploration of larger, more diverse cohorts to uncover the mechanisms underlying the disorder. However, combining datasets often introduces structured missingness – a situation, where the results of test are systematically missing in a site, where they were not measured. If unadressed, a naïve imputation of such data can obscure clinically relevant findings and bias results, particularly in early psychosis studies, where heterogeneity in assessments and demographics is significant. Addressing these challenges requires tailored imputation strategies to harmonize data while preserving the variability critical for robust clinical insights and personalized care.

**Methods:** To assess the impact of structured missingness on imputation quality, we performed a simulation study. Simulated datasets incorporated demographic dependencies on age and site-specific effects to reflect variability in clinical assessments. We introduced three missingness mechanisms—random noise, blockwise missingness, and multivariate missingness with dependencies—to replicate common challenges in multi-site psychiatric research.

We evaluated imputation methods, including MICE, Extremely Randomized Trees, and AutoComplete, focusing on accuracy and preservation of data structure. Metrics included subject-specific coverage and width, variable-specific mean squared error and Jensen-Shannon divergence, and multivariate matrix similarity using the Frobenius norm. This comprehensive approach captured both individual and overall dataset performance.

We applied these methods to a real-world dataset of cognitive measures from healthy controls and individuals with early psychosis. Before the imputation process, we implemented Logical Harmonization, an approach that combines different cognitive tests through expert consensus. This step aimed to reduce the dimensionality of the dataset and improve the relationships between variables, ensuring the imputations remained clinically meaningful.

**Results:** In simulations, conventional imputation methods underestimated the variability present in multi-site psychiatric data, leading to poor imputation quality. Specifically, metrics like normalized square error worsened by an order of magnitude in blockwise missingness

scenarios compared to random noise, which was also accompanied by a very poor coverage, at cases below 50%.

Our tailored hierarchical MICE implementation, designed to account for site effects, demonstrated superior accuracy and robustness. It preserved variability and multivariate relationships essential for clinical modeling, outperforming other methods in maintaining the integrity of correlation matrices—a critical requirement for understanding cognitive and clinical outcomes.

In the real-world dataset, Logical Harmonization significantly improved imputation quality, reducing dimensionality while maintaining inter-variable relationships. This step proved indispensable for addressing site-specific discrepancies in cognitive measures. Our hierarchical MICE method, when combined with Logical Harmonization, delivered strong performance across healthy controls and early psychosis samples, effectively preserving clinically relevant variability.

**Discussion:** In an era of global collaboration, missingness in datasets is unavoidable, and the way it's addressed can significantly impact scientific analyses. This work evaluated how cognitive research in multi-site setups handles missing data, emphasizing the often-overlooked challenges of structured missingness. Our findings show that most state-of-the-art algorithms underperform significantly in such scenarios, failing to preserve variability and distributions essential for accurate analyses. However, tailored methods like hierarchical MICE effectively address some of these challenges, maintaining data structure and multivariate relationships.

Alongside methodological improvements, additional insight from our study is the need to integrate technical solutions with domain expertise. In practical settings, we highlight the pivotal role of Logical Harmonization that provides a foundation for imputations that are both accurate and clinically meaningful, ensuring that subsequent analyses remain robust and interpretable.

## S90. A Scoping Review of Service User Experiences of Iatrogenic Harm in Early Intervention in Psychosis Services in the UK

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Georgie Hudson

**Background:** Early intervention in psychosis (EIP) services were introduced to the NHS in 1999 and have been nationally mandated in England since 2001. People with psychosis have higher rates of both trauma and trauma-related diagnoses such as post-traumatic stress disorder than the general population. Trauma-informed care in psychosis is based on the knowledge and understanding of how trauma can affect people and includes principles such as an empathetic and non-judgmental environment, and adopting a person-centred approach. Trauma-informed care is associated with decreased rates of restraint and seclusion in acute mental health services, staff reporting a greater understanding of trauma, and service users

feeling trusted and cared for, however it is not routinely implemented in the UK. In part since EIP services do not routinely apply trauma-informed approaches, EIP service users remain at risk of retraumatisation and iatrogenic harm during their care. This scoping review aims to formally assess what is known about how service users can be harmed in EIP services in the UK.

**Methods:** We conducted a scoping review, systematically searching PsycINFO, Web of Science Core Collection, Scopus, Embase, CINAHL Plus, and Medline in October 2024 for qualitative studies published in peer-reviewed journals. Search terms related to four groups were used: qualitative, service user experiences, early intervention, and psychosis. Medical subject heading (MeSH) terms were used to include related terms. All qualitative studies investigating service user experiences of EIP services were searched for and included, but only data relating to harms were extracted. Inclusion criteria were: (1) Qualitative/mixed methods, empirical, primary research; (2) Original, peer-reviewed; (3) Looking at service user views and experiences of EIP; (4) Based in the UK; (5) Published 2000 – 2024; and (6) Written in English. Ten percent of titles/abstracts and full texts were double screened and inter-rater reliability was assessed. If inter-rater reliability met or exceeded Cohen's Kappa of 0.8, the remaining records were single screened. If Cohen's Kappa was below 0.8, a further 10% were double screened. This repeated until this cut off was reached. Qualitative data were extracted and thematically synthesised using framework analysis.

**Results:** Following de-duplication, 829 titles and abstracts were screened against inclusion and exclusion criteria. This led to full-text screening of 52 papers, with 14 meeting the criteria and being included in the review. Thirty percent of titles/abstracts were double screened to achieve a Cohen's Kappa of 0.87. Twenty percent of full texts were double screened with a Cohen's Kappa of 0.80. Preliminary categories of harm provided the initial framework for the synthesis: psychological harm, social harm, financial harm, physical harm, adverse medication effects, and future service use harm. Key themes were identified relating to relationships and communication with and between staff, stigma, and fragmented systems. A recurring theme was service users reporting a lack of staff continuity, resulting in them being forced to repeat their story many times and build up a new, trusting relationship, causing trauma. Staff members were seen to have a lack of knowledge and understanding of cultural and spiritual needs of their clients. Discharge into other services was seen by some as abrupt, with poor information sharing between the services. Impacts on service users as a result of these harms included stress, distress, and a feeling of helplessness.

**Discussion:** Few studies have investigated service users' experiences of EIP services in the UK, with none specifically focused on assessing negative experiences or harms caused by the services. Service users can experience social and psychological harms across relational, systemic and cultural levels. Many of the harms were caused by systemic problems, such as a lack of funding and training, however relational issues with staff and service users feeling stigmatised were also reported. Future work should focus on further assessing the impact of these harms, as well as developing specific practical recommendations for harm minimisation, via consultation with service users and staff.

## S91. Examining the Role of Antipsychotic Pharmacological Burden in Patterns of Substance use in Early Psychosis

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Samuel Murphy

**Background:** Substance use within early psychosis (EP) has emerged as an area of interest for clinical and psychiatric researchers, and has been linked to increases in symptomatic severity, decreased functioning, and legal/forensic involvement (Sheitman et al., 2024; Marino et al., 2020). This has in turn fostered development of interventions to reduce substance use in clinical settings such as coordinated specialty care (CSC; Marino et al., 2022). Most attempts to understand predictors of substance use in CSC neglect to explore the impacts of antipsychotic prescription on substance use, despite the demonstrated negative effects of anticholinergic cognitive burden, mental clouding, and sedation on service user's wellbeing and quality of life (Tandon et al., 2020; Seale et al., 2007). This study sought to further investigate potential compensatory patterns of substance use by examining associations between adverse psychiatric medication effects and substance use in EP.
**Methods:** Participants were selected from the EPINET national database, a multi-site study assessing EP clients across more than 100 CSC clinics in 17 states. Assessments of substance use, medication, symptomatology, and other clinical characteristics were collected at six-month intervals over the first twelve months of enrollment in CSC. Using field standard measures (Boustani et al., 2008), participants were grouped by presence of clinically relevant anticholinergic cognitive burden, and analyses of substance use patterns and frequency were conducted. Logistic regressions were conducted to examine associations between presence of anticholinergic medication burden and substance use at intake.
**Results:** Analysis of substance use patterns over the first 12 months of program enrollment showed higher rates of nicotine, alcohol, and opioid use, and lower rates of THC use in participants experiencing clinically relevant ACB (all significant $p < .05$). Substance use and medication data assessed within 2 months of intake into CSC program were retained, labeled as "baseline", and incorporated into logistic regression models. Odds ratios were calculated from regression models and indicate that increased anticholinergic burden at intake is associated with higher likelihood of nicotine use ($OR = 1.14$, $p < .001$), alcohol use ($OR = 1.11$, $p = .001$), and opioid use ($OR = 1.31$, $p > .001$).
**Discussion:** Findings indicate that substance use in early psychosis is multidimensional and may potentially manifest as compensatory behavior responding to adverse side effects of treatment, namely pharmacotherapy. Interventions to reduce anticholinergic burden and other associated side effects of antipsychotic medication could allow for early intervention programs to more effectively improve youth and young adult experiences and promote sustained clinical and personal recovery.

References

Boustani, M., Campbell, N., Munger, S., Maidment, I., and Fox, C. (2008). Impact of anticholinergics on the aging brain: a review and practical application. Aging health, 4(3), 311-320.

Marino, L., Scodes, J., Richkin, T., Alves-Bradford, J. M., Nossel, I., Wall, M., and Dixon, L. (2020). Persistent cannabis use among young adults with early psychosis receiving coordinated specialty care in the United States. Schizophrenia research, 222, 274-282.

Marino, L., Jankowski, S. E., Kent, R., Birnbaum, M. L., Nossel, I., Alves-Bradford, J. M., and Dixon, L. (2022). Developing a theoretical framework for persistent cannabis use among young adults with first episode psychosis. Early intervention in psychiatry, 16(4), 371-379.

Seale, C., Chaplin, R., Lelliott, P., and Quirk, A. (2007). Antipsychotic medication, sedation and mental clouding: an observational study of psychiatric consultations. Social Science and Medicine, 65(4), 698-711.

Sheitman, A., Bello, I., Montague, E., Scodes, J., Dambreville, R., Wall, M., ... and Dixon, L. (2024). Observed Trajectories of Cannabis Use and Concurrent Longitudinal Outcomes in Youth and Young Adults Receiving Coordinated Specialty Care for Early Psychosis. Schizophrenia Research, 267, 313-321.

Tandon, R., Lenderking, W. R., Weiss, C., Shalhoub, H., Barbosa, C. D., Chen, J., ... and Castle, D. (2020). The impact on functioning of second-generation antipsychotic medication side effects for patients with schizophrenia: a worldwide, cross-sectional, web-based survey. Annals of general psychiatry, 19, 1-11.

## S92. Baseline Insight and its Trajectory: Predicting the Risk of Psychiatric Hospitalizations Among First-Episode Psychosis (FEP) Individuals During the First Year of Coordinated Specialty Care (CSC)

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Hadar Hazan

**Background:** This study aimed to examine how baseline insight and its trajectory predict the risk for the number and length of psychiatric hospitalizations among individuals with first-episode psychosis (FEP; N = 186) during their first year in Coordinated Specialty Care (CSC).

**Methods:** Data were collected from FEP individuals enrolled in the CSC program for Specialized Treatment Early in Psychosis (STEP) between 2014 and 2019. Insight was assessed using the G12 item of the Positive and Negative Syndrome Scale (PANSS), with participants classified into low (G12 > 4) or high (G12 ≤ 4) insight groups at baseline, 6 months, and 12 months. Insight trajectory was determined across these three time points, resulting in six patterns: stable high, stable low, declining, increasing, and inconsistent (high-low-high or low-high-low) insight trajectory. The number and length of stay (LOS) in psychiatric hospitals were recorded for each participant before and during the first year of enrollment at the STEP clinic.

**Results:** The high baseline insight group showed a significantly greater relative risk reduction in hospitalizations compared to the low baseline insight group (RRR = 1.95, p = 0.002), indicating a 95% greater reduction in hospitalizations for the high insight group post-admission. A similar trend was observed for the LOS, with the high insight group demonstrating a greater relative risk reduction (RRR = 1.77, p = 0.10), though this result did not reach statistical significance. Longitudinally, stable high insight demonstrated the most substantial risk reductions in the number of hospitalizations (RR = 0.12, p < 0.001) and LOS (RR = 0.04, p < 0.001), outperforming the stable low and fluctuating (low-high-low/high-low-high) insight groups. Sustained improvements in insight were observed over time, with

the proportion of individuals with high insight significantly increasing from 54.9% at admission to 64.0% at 12 months ($p < 0.05$).
**Discussion:** This study underscores the pivotal role of insight in predicting the risk for hospitalization in FEP patients. Whether low insight is considered a state measured at baseline or a trait measured longitudinally, is associated with less favorable clinical outcomes among FEP in the first year of care.

## S93. Exploring Polygenic Risk Groups as Tools for Predicting Health and Behavioural Outcomes in Psychosis and Bipolar Disorder

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Miryam Schattner

**Background:** Current methods for risk prediction of psychosis and related disorders rely heavily on sociodemographic factors and symptom occurrence, with several limitations such as cognitive biases, poor understanding of risk factors' roles in disorder onset, and a lack of effective prevention or early screening tools. This study explores the potential application of polygenic scores (PGS) as a complementary tool to address these gaps. Using stratified PGS risk groups for schizophrenia (SCZ), bipolar disorder (BP), major depressive disorder (MDD), anorexia nervosa (AN), and attention-deficit/hyperactivity disorder (ADHD) we analysed whether high or low genetic liability to these disorders influences mood, risk-taking behaviours, sleep and health variables, and sociodemographic factors.
**Methods:** Participants included individuals of European ancestry from the UK Biobank without psychosis (N=380,776), and UK BioBank (N= 3238) and GLAD participants (N=5,579) with self-reported diagnoses of BP, SCZ, and related disorders. PGS for SCZ, BP, MDD, ADHD and AN were calculated and standardized against the 1000 Genomes Project reference panel using the automated Genopred pipeline. Population stratification was accounted for by regressing raw PGS on the first six principal components derived from the reference panel. Genetic risk groups were classified as low (≤1 SD below the mean), high (≥1 SD above the mean), and average (within ±1 SD). Behavioural phenotypes included mood, sleep, health, risk behaviours, and socioeconomic factors. Statistical models (logistic, ordinal, and linear) were adjusted for age and sex, with Bonferroni correction for multiple testing.
**Results:** In our healthy population, high SCZ, BP, ADHD and MDD PGS risk groups were associated with lower mood, poorer health outcomes, and increased risk-taking behaviours, whereas AN PGS was also associated with lower mood but better health outcomes and reduced risk-taking behaviours. Notably, in the clinical cohorts PGS risk was only significant for mood variables in the BP cohorts, not the psychosis cohorts. Associations were found between high PGS risk for MDD and lower mood, but high PGS risk for BP and low risk for ADHD with better mood. Similarly, in the same BP group, low ADHD but high BP risk was associated with greater sense of meaning and purpose in life whereas high MDD risk was associated with less ($p < 0.05$ after Bonferroni correction). In both individuals with self-reported BP or psychosis, higher AN PGS appeared protective against behaviours such as smoking. In the healthy population, higher SCZ PGS was associated with lower chance of being overweight, a finding that contrasts with the clinical trend of higher BMI in schizophrenia. In the clinical cohort of bipolar disorder, lower SCZ PGS was linked to reduced odds of being diagnosed as overweight between ages 20–30, coinciding with the

typical age of SCZ/BP onset. However, it remains unclear whether weight gain is a risk factor or a consequence of psychosis. All high PGS risk groups in the general population were associated with reported disability while this was only true for MDD PGS risk groups in the clinical cohorts. Interestingly, variables relating to cognitive functions typically affected in the present conditions such as memory were not predicted by BP, and SCZ PGS risk groups, but rather by ADHD and MDD PGS risk groups.
**Discussion:** These findings suggest that PGS risk stratification may be valuable for predicting certain behaviours in both the general population and individuals with diagnoses of psychosis or bipolar disorder. Interestingly, effects observed in the general population often did not translate to the clinical cohort, supporting the hypothesis that these factors may represent true risk factors. Further research is needed to disentangle these effects and to explore the clinical utility of PGS-based risk stratification.

## S94. OPEN BOARD

## S95. Immune Polygenic Risk Scores and Gene Expression in Schizophrenia: Links to Clinical Characteristics

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Kosar Teymouri

**Background:** Schizophrenia (SCZ) is a complex and heterogeneous disorder. The most recent genome-wide association studies (GWAS) identified 287 loci associated with SCZ risk. An extensive body of research has demonstrated the significant role of the immune system in the pathophysiology of SCZ; however, the underlying mechanism remains poorly understood. This study investigates the role of immune genes in SCZ by examining their expression profiles and associations with treatment-resistant schizophrenia (TRS), age of onset (AO), Global Assessment of Functioning (GAF) score, and number of hospitalizations (NOH).
**Methods:** We identified 1227 immune genes across 22 KEGG immune pathways and annotated SNPs to genes using SCZ GWAS summary statistics and MAGMA. Immune-specific genes significantly associated with SCZ (N=77; $p < 4.47e-05$, Bonferroni-corrected) were analyzed using FUMA Gene2Func to assess tissue expression profiles. SNPs corresponding to significant immune genes were used to calculate immune-polygenic risk scores (immune-PRS) with PRSice. We used our Toronto Schizophrenia sample (N=157) as the target cohort, comprising patients over 18 years old diagnosed with schizophrenia or schizoaffective disorder. Associations between immune-PRS and TRS (using clozapine use as a proxy), AO, GAF, and NOH were assessed. Sex, age, and five principal components were included as covariates.
**Results:** We identified 77 immune genes associated with SCZ risk. FUMA analysis demonstrated that a subset of these immune genes were enriched in brain tissues and their expression was downregulated in three brain regions (e. g. anterior cingulate cortex), linking immune processes to neural substrates in SCZ. Furthermore, immune-PRS was significantly associated with AO ($R^2$=0.066, P=0.047) and GAF scores ($R^2$=0.054, P = 0.004) but not TRS or NOH.

**Discussion:** This study is the first to examine schizophrenia subtypes using immune-specific PRS and gene expression profiles. Our results highlight the differential expression profiles of the immune genes in the brain and emphasize the significant role of the immune system in the pathophysiology of SCZ. However, further research using larger datasets is required to validate these results.

## S96. Genetic Contributions to Treatment Resistant Schizophrenia: A Scoping Review

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Hayley Riel

**Background:** Individuals with schizophrenia display significant heterogeneity in symptoms and treatment responses. Approximately 30% of those with schizophrenia develop treatment-resistance (TRS), characterized by a non-response to two or more antipsychotic medications of adequate dose and duration. TRS is associated with higher disability, poor prognosis, and increased mortality. Despite advancements in genetics, the genetic architecture of TRS is unknown. Like schizophrenia, TRS is heritable, but most recent SNP heritability estimates have pointed it to be much lower at ~1-4%. This scoping review aimed to identify and synthesize the available evidence on the genetics of TRS, exploring both common and rare genetic variation, and gene expression studies.
**Methods:** A scoping review was conducted to explore genetic factors related to TRS using COVIDENCE. Articles were collected through PubMed in January 2024 and were included if they reported on the genetics of TRS, had participants aged 18+, and were in English language. Review articles, grey literature, theses/dissertations, case reports, and non-article publications were excluded. The articles were first screened by title and abstract by two independent reviewers, then full text screened by two independent reviewers for final inclusion or exclusion. Discrepancies were assessed by a third independent reviewer. To ensure reliability of the included studies, the same screening method was used.
**Results:** The search identified 525 articles, with 94 meeting the inclusion criteria. The studies were published between 1998 and 2024, and the majority ( > 90%) were cross-sectional in design. Most studies examined TRS, and ~5% of studies addressed ultra-resistant schizophrenia. There were some inconsistencies across studies in defining TRS (i.e., terms used, clinical and functioning scales, medication history). The studies included mostly individuals of European genetic ancestry (n=32), followed by East Asian (n=23), African (n=8), Middle Eastern (n=5), South Asian (n=4), and other ancestries (n=6), with 8 studies including more than one ancestry. Three main categories emerged: (1) Common genetic variation (n=70), which was further divided into candidate gene, genome-wide, or polygenic score approaches; (2) Rare variants (exome sequencing) or copy number variant studies (n=8), one study included both rare and common genetic variation, and (3) Other, which included epigenetics or RNA-based studies (n=17).
**Discussion:** The majority of studies focused on TRS, with a small subset addressing ultra-resistant schizophrenia. Inconsistent TRS definitions across studies emphasize the need for a well-defined characterization of TRS. Current data on the genetics of TRS are predominantly from European populations, emphasizing the lack of generalizability across ancestries. Most of the studies explored specific genetic variants associated with TRS. A fulsome examination of the entire genome and the functional role of specific variants in TRS is still needed.

## S97. An Investigation of Gene Expression Changes in Schizophrenia: RNA-Seq Analysis of Whole-Blood Samples Pre- and Post-Stress Test

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Derek Morris

**Background:** Schizophrenia (SZ) is a highly heritable psychiatric disorder that is clinically and genetically heterogeneous. RNA-sequencing (RNA-seq) measures the presence and quantity of RNA molecules in a sample and has been used in neuropsychiatric research to reveal gene expression patterns linked to psychiatric disorders. Stress is a risk factor for SZ. Here we sought to investigate the time-related changes in gene expression that occur in SZ patients and healthy controls pre- and post- a stress test.
**Methods:** We performed RNA-seq analysis on whole blood samples collected from SZ patients (n=50) and healthy controls (n=50) enrolled in the Immune Response and Social Cognition in Schizophrenia (iRELATE) study and matched by age and sex. Each individual completed the Trier stress test and blood samples were collected at two time-points (pre- and post-stress test) for each individual. Whole blood samples were collected and prepared using PaxGene tubes to stabilise RNA, followed by RNA isolation with PaxGene kits. Quality control (QC) was performed on the extracted RNA and samples with yields > 2µg were sent to Azenta to perform RNA-Seq using polyA selection for library preparation. RNA-seq bioinformatics analysis began with sample QC using FastQC and adaptor trimming using Trimmomatic to remove low-quality reads and adaptors. Sequence alignment was performed using HISAT2, which aligned to the human reference genome GRCh37. Post-alignment QC was performed using SAMtools for sorting, converting, indexing, and further QC of the aligned data. Read counting and normalisation were carried out using FeatureCounts, and differential expression analysis was performed with DESeq2. Cellular deconvolution using bMIND was employed to impute gene expression profiles from single cell reference data.
**Results:** Differential expression analysis identified significantly altered expression (p-adj < 0.05) at baseline in 2,545 genes, which were associated with the case-control status of the individual. Notably, genes involved in the TLR and IL pathways showed altered expression in SZ patients compared to controls, suggesting an immune component in the disorder's pathophysiology. Timepoint analysis identified 770 genes that showed significant gene expression alterations pre- and post- stress test. Cellular deconvolution analysis identified a significant proportional difference between cases and controls for CD4 naive T-cells.
**Discussion:** Our results reveal that there are significant gene expression alterations in blood associated with SZ and with response to stress. Functional analysis of individual genes, pathways and cell types points to altered immune function.

## S98. Contact With Health Services for Adverse Childhood Experiences and Subsequent Risk of Non-Affective Psychotic Disorder: Population-Based Evidence From Ontario, Canada

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Kelly Anderson

**Background:** Adverse childhood experiences (ACEs) are stressful or traumatic events that occur during childhood, and they have been shown to increase the risk of psychotic disorders later in life. Many of the prior studies on ACEs and psychotic disorders have relied on small convenience samples, or samples recruited from specialized clinical settings, with a notable lack of population-based research. Our objective was to estimate the association between indicators of health service contact for ACEs and the risk of psychotic disorders during adolescence and early adulthood using population-based health administrative data.
**Methods:** We accessed a retrospective birth cohort constructed using data from the universal Ontario health care system. This birth cohort included children born in Ontario between 1992 and 1996, linked to maternal health records, and followed to age 27-31 years within the databases to identify incident cases of non-affective psychotic disorder. We conducted a scoping review to identify codes indicative of health service contact for ACEs, which were used to identify ACE-related visits prior to age 12 years, including indicators of abuse, neglect, and household dysfunction. We used a validated algorithm to identify incident cases of non-affective disorder occurring after age 12 years. Modified Poisson regression models were estimated to obtain incidence rate ratios (IRR) and 95% confidence intervals (CI) for the association between ACEs and non-affective psychotic disorder. Estimates were adjusted for sex, birth year, rurality, neighbourhood marginalization indicators, maternal migrant status, and maternal psychotic disorders.
**Results:** In our analytic sample of 559,073 children, 24.1% (n=134,763) had a health service contact related to household dysfunction, 1.4% (n=7,817) had a contact related to abuse or neglect, and 1.6% (n=9,077) had service contacts for both household dysfunction and abuse/neglect. Our findings suggest that the risk of non-affective psychotic disorders was 51% higher for those with a contact for household dysfunction (IRR=1.51;95%CI=1.45,1.58), 78% higher for those with a contact for abuse/neglect (IRR=1.78;95%CI=1.58,2.01), and nearly three-fold higher among those who had health service contacts for both household dysfunction and abuse/neglect (IRR=2.61;95%CI=2.38,2.85), relative to those with no ACE related contacts. Furthermore, we found a gradient in risk with a greater number of ACE subtypes – people who had a health service contact for 4+ ACE subtypes had more than a four-fold greater risk of non-affective psychotic disorder (IRR=4.04;95%CI=3.26,5.01), relative to those with no health service contacts for ACEs.
**Discussion:** Our findings add population-based evidence to the growing body of literature showing the detrimental effects of ACEs on serious mental disorders, and highlight the utility of administrative databases for advancing research in this field. Linkages of other administrative databases, such as from child protective services or criminal justice agencies, would further enable ascertainment of ACEs in large administrative datasets.

## S99. Healthcare Professionals' Attitudes Toward use of Long-Acting Injectable Antipsychotics for Schizophrenia Treatment Differ Among Settings of Care: Advance Survey Results

Kelli R. Franzenburg[1], Rolf T. Hansen[1], Mark Suett[2], Ayelet Yaari*[3], Aviva Peyser Levin[4], Martin Sergerie[5], Sigal Kaplan[4], Alma Gonzalez[1], Kameron Sedigh[6], Stephan Heres[7], Martha Sajatovic[8]

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Ayelet Yaari

**Background:** Long-acting injectable antipsychotics (LAIs) are underused despite known benefits in the treatment of schizophrenia (SCZ). In patients with SCZ, LAIs improve adherence and reduce relapses, but LAI use by healthcare professionals (HCPs) may vary based on factors related to the healthcare system and setting of care. This analysis from the novel, multinational survey study Attitudes DriVing regional differences in long-acting injectable ANtipsychotic utilization for SCZ among HCPs, patients, and CaregivErs (ADVANCE) evaluated the influence of setting of care and associated factors on LAI initiation.

**Methods:** HCPs enrolled in ADVANCE were psychiatrists or nonphysicians who specialized in psychiatry, spent ≥25% of their time providing direct patient care, managed adult patients, of whom ≥10% were diagnosed with SCZ, and reported treating patients with second-generation LAIs. Eligible HCPs from Australia, Canada, China, Germany, Israel, South Korea, Spain, or the United States (US) completed an online survey that included questions related to the HCP's setting of care and their experience managing and treating individuals with SCZ, including the role of LAIs in their treatment.

**Results:** Psychiatrists and psychiatric nonphysicians (N=791) practiced in inpatient (IP) psychiatric wards (n=260; 32.9%), community/psychiatric outpatient (OP) clinics (n=227; 28.7%), hospital-based OP clinics (n=174; 22.0%), independent practice (n=107; 13.5%), or other settings (eg, long-term care facilities; n=23; 2.9%). HCPs in independent practice reported managing the highest numbers of patients per month (mean [SD]=55.9 [110.1]), while HCPs in an IP psychiatric ward reported managing the lowest number of patients (mean [SD]=41.7 [48.6]). Compared with HCPs in other settings, those in independent practice reported the lowest rates of support for managing patients with SCZ from a nurse (81.3% vs 85.5–94.2%), psychologist (72.9% vs 81.9–85.0%), case manager (36.5% vs 48.1–58.6%), or pharmacist (28.0% vs 36.6–58.9%). HCPs in independent practice were less likely to initiate an LAI (1=never, 5=very likely; mean [SD]=3.8 [0.9]) compared with HCPs in a hospital-based OP clinic (4.1 [0.8]), a community/psychiatric OP clinic (4.2 [0.9]), or an IP psychiatric ward (4.2 [0.8]). When ranking treatment objectives, HCPs in independent practice prioritized improved recovery and patient quality of life, HCPs in an IP psychiatric ward prioritized management of positive symptoms, and HCPs in community psychiatric OP clinics or hospital-based OP clinics prioritized preventing nonadherence/relapse/hospitalization. Fewer LAIs were available to HCPs in independent practice (mean [SD]=4.7 [2.9]) compared with those in a hospital-based OP clinic (5.1 [2.5]), IP psychiatric ward (5.2 [2.5]), or community/psychiatric OP clinic (5.9 [2.3]). HCPs in independent practice or a hospital-based OP clinic reported patients with higher levels of social stigma, illness insight, and motivation to be treated vs the other settings of care (mean of ratings from 1 [none] to 5 [very high]: 3.35–3.48 vs 2.89–3.39).

**Discussion:** Independent-practice HCPs were less likely to initiate an LAI for the treatment of SCZ and reported managing a higher number of patients with SCZ compared with HCPs in other care settings, despite having the lowest levels of support staff. Limited LAI access, variation in care team member support, patient type, and focus on different primary treatment objectives (eg, recovery and patient quality of life, preventing nonadherence/relapse/hospitalization) are some factors that may account for the differences in LAI use across care settings.

## S100. Understanding Drug Efficacy in Psychiatric and General Medicine: Insights From an International Online Survey of Doctors and Laypeople

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**Background:** Psychiatric and internal medicine treatments are integral to modern healthcare, addressing distinct aspects of human health. Psychiatric medications, which include antidepressants, antipsychotics, and mood stabilizers, aim to treat mental health conditions like depression disorder, schizophrenia, and bipolar disorder by modulating neurotransmitter levels. In contrast, internal medicine drugs focus on physical health conditions such as hypertension, diabetes, and cardiovascular diseases, targeting physiological functions. Despite their critical role in treatment, psychotropic medications often face skepticism, with many questioning their efficacy relative to placebos. This has contributed to growing mistrust in psychiatric treatments among clinicians, patients, and the public. Therefore, we will investigate how doctors from various specialties and laypeople perceive drug efficacy compared to placebo in an international survey, covering a range of medical and psychiatric disorders.

**Methods:** Participants

We will recruit a broad range of medical professionals and laypeople. Eligible medical professionals will include doctors from different specialties and training levels, as well as medical students. Meanwhile, we will include laypeople from various professions, such as lawyers, teachers, etc. Participants will be required to have sufficient English proficiency. Recruitment process will be sent via email invitations through hospital mailing lists, doctors' networks, and personal contacts for medical participants, while lay participants will be recruited via the Prolific platform.

Questionnaire

A digital questionnaire will be designed using SoSci-Survey (V.3.3.13) to enhance accessibility. To ensure clarity, the survey is primarily in English, with introductory explanations provided in local languages where necessary. The survey will ensure complete anonymity, with no tracking of IP addresses, and will adhere to strict data protection protocols, utilizing secure internet communication to safeguard participants' information. Participants will be informed about the data processing protocols in advance.

The questionnaire will consist of two sections: participants' demographics and response rates. Participants will estimate their perceptions of drug and placebo efficacy for specific disorders, based on the top 20 causes for Disability-Adjusted Life Years (DALYs) from the 2021 Global Health Estimates by the World Health Organization, as well as DSM-5 or ICD-10/11 criteria. These will include medical disorders (e.g., hypertension, myocardial infarction, etc) and psychiatric disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder, etc).

Statistical analysis

We will include only fully completed and returned questionnaires in the analysis. Descriptive statistics will be used to calculate means, medians, and standard deviations for response rate estimates across disorders, grouped by participant type and country. Inferential tests, such as independent t-tests, ANOVA, and Chi-square tests, will compare response rates between groups and regions. Bland-Altman plots will compare survey results with a published meta-

analysis, and paired t-tests will identify significant deviations. Correlation analysis will explore relationships between demographic factors and response deviations. Analyses will be conducted using SPSS or R, with $p < 0.05$ and Bonferroni correction applied.

**Results:** Preliminary findings from this ongoing survey targeting 1,000 participants across more than 10 countries (e.g., Germany, France, UK, Japan, and China) will provide insights into perceptions of drug and placebo efficacy. Results will include detailed comparisons across psychiatric (e.g., schizophrenia, depressive disorder) and medical conditions (e.g., hypertension, myocardial infarction). Descriptive statistics will highlight central tendencies and variability, while inferential analyses (e.g., t-tests, ANOVA) will uncover significant group-specific trends. Cross-national and professional background comparisons will reveal cultural and role-based differences, deepening our understanding of global perspectives on drug efficacy.

**Discussion:** The discussion will interpret the findings, focusing on how estimates align with actual drug efficacy as reported in clinical trials. Potential implications include addressing gaps in understanding among doctors and laypeople, fostering informed decision-making, and promoting accurate communication about treatment outcomes. Cross-cultural differences will be examined to identify areas for targeted educational interventions. In the end, we expect to bridge understanding between psychiatry and general medicine by highlighting perceptions of drug efficacy and foster better treatment awareness and communication.

## S101. Combining Social Media and a Live In-Person Interactive Event to Promote Mental Health Awareness for Tunisian Youth

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**Background:** Stigmatization of young people with mental health issues is a global phenomenon that
significantly hinders help-seeking behaviors, treatment adherence, and overall quality of life. Tunisian youth are no exception, as cultural and societal attitudes contribute to the stigma surrounding mental health. Studies indicate that negative stereotypes about mental health persist not only among the general public but also within primary care providers and mental health professionals in Tunisia. Addressing these issues requires educational initiatives that are culturally tailored to both the public and professionals within school and university settings. Mental health conditions such as depression affect approximately 5% of adolescents globally, making it a leading cause of disability (WHO). In Tunisia, research reveals that one-third of individuals with mental illness initially seek help from traditional healers, often delaying access to critical care due to limited awareness of mental health symptoms. Therefore, stigma reduction and awareness campaigns are essential for improving access to early intervention and care.

**Methods:** To combat these challenges, the Clinical High-Risk Program (CHiRP) at Razi University
Hospital organized a mental health awareness day on November 27, 2024, at the Faculty of Sciences, University of Tunis. The primary goal of the event was to raise awareness, reduce stigma, and promote early intervention among university students. A media campaign, “Psybettounsi,” launched on Instagram and Facebook a week prior to the event, engaged the audience through posts and stories. The event consisted of two main sessions. The morning session featured five theme-based informational stands, each dedicated to a different mental health condition such as depression, anxiety, and addiction. At each stand, informational flyers were distributed, and interactive quizzes encouraged learning, with awards for top scorers. Mental health specialists, including psychologists and psychiatrists, were available to answer questions and provide insights. The afternoon session took place in an auditorium, where talks by medical professionals and social media influencers addressed the biological, psychological, and social aspects of mental illness, including emerging theories such as epigenetics. This session also included activities aimed at debunking myths and misconceptions surrounding mental health, culminating in a recovery story shared by a social media influencer, which emphasized hope and resilience. The event concluded with information on accessing CHiRP’s mental health services and pathways for care.

**Results:** The event successfully combined both online and in-person engagement to achieve significant
reach. On social media, the Instagram campaign gained 925 new followers, with posts reaching over 3,000 accounts. Stories shared by content creators reached 4,512 views and resulted in five individuals seeking help for mental health concerns. On Facebook, event posts
reached 3,499 accounts and generated high levels of engagement. In terms of in-person participation, over 325 students engaged with the outdoor activities and quizzes, while approximately 200 students attended the indoor sessions. These interactive activities, which

included quizzes and myth-busting discussions, encouraged active learning and promoted deeper understanding among participants.

**Discussion:** The initiative effectively addressed mental health stigma among Tunisian youth by combining
cultural sensitivity, professional expertise, and innovative digital outreach strategies. The social media campaign, amplified by influencers, significantly increased engagement and broadened the reach of the event. On-campus activities facilitated meaningful dialogue, allowing participants to directly engage with mental health professionals. The myth-busting activities and personal stories of recovery played a crucial role in challenging cultural misconceptions and promoting a scientific understanding of mental health. Moving forward,

there is a need to expand the program nationwide and include training for educators and primary care providers to identify early signs of mental health issues. Sustained efforts, including workshops and peer-led initiatives, are essential for ensuring long-term impact. This
event highlights the effectiveness of integrating digital influence, cultural relevance, and professional expertise to combat stigma and raise mental health awareness.
This model demonstrates the potential of culturally sensitive and inclusive strategies
in fostering engagement and promoting access to mental health resources, paving the way for future efforts to address mental health challenges in Tunisia and beyond.

## S102. Country-Specific Factors Influencing Patients' Willingness to use a Long-Acting Injectable Antipsychotic to Treat Schizophrenia: Patient and Caregiver Advance Survey Results

Kelli R. Franzenburg[1], Rolf T. Hansen[1], Mark Suett[2], Ayelet Yaari[3], Aviva Levin*[3], Martin Sergerie[4], Sigal Kaplan[3], Alma Gonzalez[1], Kameron Sedigh[5], Stephan Heres[6], Martha Sajatovic[7]

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**Background:** Long-acting injectable antipsychotics (LAIs) are associated with improved adherence and reduced relapse compared with oral antipsychotics (OAPs) in patients with schizophrenia (SCZ), yet LAIs are underutilized globally. This analysis from the Attitudes DriVing regional differences in long-acting injectable ANtipsychotic utilization for SCZ among healthcare professionals, patients, and CaregivErs (ADVANCE), evaluated perceptions of LAIs expressed by patients with SCZ and caregivers of people with SCZ to understand country-specific factors that may affect patients' willingness to use LAIs.
**Methods:** ADVANCE included patients living with SCZ, aged ≥18 years, from Australia, Canada, China, Germany, Israel, South Korea, Spain, or the United States (US), who were being treated with or had been recommended an LAI. Caregivers of adults living with SCZ who had tried or been recommended an LAI were also included. Enrolled patients and caregivers completed a survey through computer-assisted telephone interviewing. Participants answered questions regarding reasons for accepting or declining an LAI.
**Results:** 447 patients with SCZ and 375 caregivers of people living with SCZ completed the survey. 70% (n=313) of patients were male and had a mean age of 33.1 (SD, 6.6) years. Caregivers had been providing care for a person with SCZ for a mean of 4.1 (SD, 2.2) years. The perception that LAIs work better for improving the condition was the most common reason patients identified for accepting an LAI in South Korea (86%, n=36/42), Germany (69%, n=27/39), and Canada (66%, n=23/35). Patients in China most commonly reported accepting an LAI because they felt that LAIs work better for improving their condition (81%, n=42/52) and injections were easier than pills (81%, n=42/52). The doctor's recommendation was the top patient-reported reason for accepting an LAI in Australia (78%, n=31/40), the US (73%, n=61/84), and Spain (71%, n=24/34). Among caregivers, the perception that injections

are easier than pills was the most common reason for LAI acceptance in Australia (87%, n=26/30), the US (87%, n=39/45), Canada (78%, n=18/23), and China (75%, n=27/36). In Spain, the top caregiver-reported reasons for accepting LAIs were that injections are easier than pills (72%, n=21/29) and that LAI use may reduce hospitalizations (72%, n=21/29); in Germany, reducing hospitalizations (76%, n=22/29) and the belief that LAIs have fewer side effects than OAPs (76%, n=22/29) were top reasons for accepting LAIs. The top caregiver-reported reason for LAI acceptance in South Korea was doctor's recommendation (73%, n=27/37).

The primary reason patients reported declining an LAI across all countries was concern about side effects (range: 58% [n=14/24] in Spain to 100% [n=10/10] in South Korea). In Spain, 58% (n=14/24) of patients also reported that they did not have enough information about LAIs. Caregiver-reported most common reasons for patients declining LAI therapy were concern regarding potential side effects (Spain, 85%, n=11/13; China, 73%, n=8/11; Canada, 62%, n=16/26; Germany, 55%, n=11/20), fear of drug in the body (South Korea, 91%, n=10/11; Australia, 61%, n=11/18), fear of physical pain (US, 73%, n=22/30), and fear of losing control (US, 73%, n=22/30; Canada, 62%, n=16/26).

**Discussion:** Top reported reasons for LAI acceptance may differ by country and for patients versus caregivers. Across all countries, the most commonly reported reason for patients to decline an LAI was concern regarding side effects. The primary reasons cited by caregivers for patients' declination of LAIs varied across countries. In 4 of the 8 countries, the principal reason reported by caregivers was consistent with that reported by patients.

## S103. Height, Month and Season of Birth in Schizophrenia Patients

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**Background:** Schizophrenia is a psychiatric disorder associated with different physical outcomes, such as reduced height, increased medical comorbidity, and reduced life expectancy.

Schizophrenia is believed to arise from a gene and environmental factors combination, being season of birth a widely replicated one. Winter birth is associated with an increased risk of

developing mental health diagnoses at earlier ages of onset with severe symptomatology. We aim to describe the association between winter birth and height in schizophrenia.

**Methods:** 15181 individuals diagnosed with schizophrenia and with recorded height and date of birth, comprising 7414 males and 7767 females from the Chang Gung Research Database

from Taiwan were included.

**Results:** Patients born in winter displayed the shortest height, and such seasonal effect remained significant after adjusting for sex and age (161.9 ± 8.8; 2.3; p = 0.020). The same pattern also applied in female patients, however, the seasonal effect after adjusting for age only

showed a trend towards significance. February-born schizophrenia patients displayed the shortest height (161.5 ± 8.8), but such a monthly effect did not reach significance after adjusting

for sex and age. No significant effect was detected in male patients about the season/month of birth.

**Discussion:** Our results revealed a sexual dimorphism pattern in schizophrenia patients, with female patients displaying reduced height by season of birth (winter) and month of birth (February). Our results suggest that winter birth is not only a risk factor for schizophrenia but also affects other outcomes such as height in terms of an epiphenomena.

## S104. Advancing the Study of Ketogenic Diets in Schizophrenia: Results of a Change.org Support Petition

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**Background:** Schizophrenia and related disorders (SRD) are serious mental conditions with heterogenous presentation, lack of clear understanding of pathophysiology, and only partially effective available treatments. New treatments are urgently needed as many people continue to suffer from persistent positive or negative symptoms with antipsychotic treatment. Recent data suggests that targeting the gut brain axis with dietary interventions is a promising avenue for improving mental health symptoms in individuals with SRD.

One such approach is the medical ketogenic diet which consists of low-carbohydrate, adequate protein, and high fat intake inducing a state in which ketone bodies in the blood provide energy to cells. In rodent models of schizophrenia, a ketogenic diet regimen resulted in complete restoration of normal behaviors, independent of strict caloric restriction. In humans, in addition to at least 7 published case reports, an open-label ketogenic diet study,

retrospective study and recent prospective clinical trial found significant improvement in SRD symptoms.

**Methods:** Our research team was conducting the first US-based randomized controlled single blind inpatient clinical trial testing a medical ketogenic diet vs. regular diet for psychiatric symptom improvement in SRD (ClinicalTrials.gov NCT05968638). This rigorously controlled environment provided round-the-clock oversight and allowed for an optimal setting to manage fat and macronutrient ratios, examine safety, and collect stool samples for microbiome evaluation. This IRB-approved study was being conducted specifically on a long-standing 35-year State-University collaborative research unit which permitted inpatients, including those with court ordered status, to voluntarily participate with physician recommendation, informed consent, evaluation of capacity to sign consent, and chance for open label trial for all participants. In April of 2024, this ongoing study was halted prematurely by the Maryland Department of Health, stating they were implementing a new policy to permit only federally funded studies to be conducted, thus prohibiting studies supported from research foundations, philanthropy, or research enterprises. This unprecedented move created an outcry at the state, national, and international levels. More concerningly, the study stoppage interrupted patients' autonomy and ability to receive groundbreaking care, and participants who completed no longer had the benefit of contributing to published science, as detailed in the consent. Broad scale implications include science setbacks with eliminating philanthropic funding sources in Maryland and a precedent of government intervening without checks and balances.

Among many public attempts to bring attention to this unexpected decision, a petition was started on a public site, Change.org, by Dr. Christopher Palmer from Harvard Medical School. This petition and site allowed the public to sign anonymously or publicly and also leave a public comment. We received IRB waiver of research for the project and present results consisting of the thematic content of the comments and rationale for commenting.

**Results:** As of 10/24/2024 (14 weeks), there were 21,037 verified signatures supporting the continuation of the halted medical ketogenic diet study. To date, 1,097 people supplied a public comment or video representing 37 countries (77% from the US (N=834), 7% (n=77) from Australia/New Zealand, and 16% from other countries). 187 of the videos and comments noted direct observations that a ketogenic diet had substantial positive impacts, including 137 commenters who self-identified as benefiting from a ketogenic diet. Of the reasons people listed for signing, 554 said they were advocates of the research. Others proposed ulterior motives, including 65 who suggested political reasons and 51 who suspected conflicts of interest with pharmaceutical companies.

**Discussion:** This is the first open data collection tool to our knowledge regarding public comments of a scientific study shutdown by government without cause. While there are limitations to the aggregate of open-source data, the large number of responders allow us to see that public support of dietary interventions is substantial as supported by over 21,000 signatures and over 1,000 people leaving comments from around the globe. Additionally, this study provides evidence that the majority of the public who signed does not agree with halting science. This implies public support for implementing protections against unapproved governmental intervention of science in other health care settings when administrators have opinions or agendas that may deviate from sound, safe, and IRB-approved scientific endeavors. Lastly, the number of testimonials detailing positive impact for self, family/friends, and providers may be the largest reported to date, demonstrating support for increasing scientific and clinical resources on this evidence-based medical ketogenic diet.

These comments advocating for this work highlight the need to continue investigating emerging research data surrounding this potentially life-changing intervention, which should rightfully receive much future attention.

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## S105. Lessons Learned From a Mixed Methods Evaluation of Value-Based Care Implementation in a Safety Net Psychosis Program

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**Background:** Over the last decade, health systems have faced pressure to move from fee-for-service to value-based care (VBC) payment models. Safety net systems (SNS) have been slow to adopt these models due to insufficient resources to support the transition. To address this challenge, Massachusetts Medicaid offered incentive funding to SNS to facilitate delivery system reform. In our diverse urban SNS, the Psychiatry Department was responsible for performance on 11 quality metrics. One of these metrics was the Care Plan Completion Rate (CPCR), defined as the proportion of patients in a 300-person ambulatory chronic psychosis clinic with active "care plans" at the end of the calendar year. Of note, care plans were required to be documented in a special note type, separate from the visit note, in the electronic health record (EHR). CPCR was chosen as a metric in part because it could be completed by the provider without input from the patient, making it distinct from the other 10 metrics.
**Methods:** In this mixed methods evaluation, we measured performance on the Care Plan Completion Rate (CPCR) metric selected for an ambulatory psychosis program and synthesized data from administrative records to estimate clinician time costs. We then elicited feedback on CPCR trends from the program's clinical leaders to identify potential barriers to reliable performance.
**Results:** CPCR rose from 52% (Jul. 2023) to 85% (Dec. 2023), before falling to 41% (May 2024). An estimated 124 hours of non-billable clinician time were spent addressing performance gaps. Feedback from clinician-leaders revealed three major challenges to consistent performance. First, VBC targets may have been selected for perceived attainability rather than clinical utility. Though decision-makers believed the target would be easily met because care plans could be completed without patient involvement, clinicians perceived care plan creation as limited in clinical relevance and challenging to integrate into existing workflows. Second, timely and accurate performance data was not always available to the clinicians responsible for meeting the target. The existence of multiple reports with discrepant, outdated CPCR data presented strategic challenges to clinician-leaders tasked with course-correcting performance dips. Finally, metric-specific information often flowed through multiple stakeholders, which made it difficult to know who to approach with CPCR-related questions.
**Discussion:** The shift to VBC, while well-intentioned, may be ushered forward before input is gathered from critical stakeholders. While the perceived urgency may be necessary given financial strain facing SNS, leaders can save time long-term by: (1) partnering with clinicians to select clinically-relevant, easy-to-implement metrics; (2) partnering with IT to ensure adequate staffing to generate reliable reports; and (3) designating a single individual through whom metric-specific information flows.

## S106. Evaluating Accelerated Retinal Decline in Mental Disorders Through Normative Modeling: A UK Biobank Study

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**Background:** Several studies have found thinner retinal tissue in mental disorders compared to healthy controls. Because the retina is part of the human brain, this suggests that informative brain structure readouts can be obtained efficiently through retinal imaging. Instead of focusing on group-level case-control differences, we used normative modeling to estimate age-related decline of the human retina (and its expected variation) and compared it to the decline seen in schizophrenia (SZ), bipolar disorder (BD), and major depression (MDD). We hypothesized accelerated retinal decline in mental disorders compared to controls, with SZ being most affected, followed by BD, then MDD.
**Methods:** Using UK Biobank data, we estimated age-related retinal decline in healthy controls (HC, N = 56,545) for total macular thickness (including coronal subfields) and two sublayers (retinal nerve fiber layer; RNFL; and ganglion cell-inner plexiform layer; GC-IPL). We then compared the decline in SZ (N = 171), BD (N = 256), and MDD (N = 102) to the normative decline in HC.
**Results:** For HC, the pattern of age-related decline for total macular thickness, RNFL, and GC-IPL was curve-like rather than linear and more pronounced in males compared to females. For mental disorders, the decline-pattern was generally faster, driven by SZ and disorder-specific macular subfields. There was also an enrichment of individuals with extremely low (infranormal) values. These results were confirmed in robustness checks that ruled out unspecific confounders.
**Discussion:** These findings suggest that mental disorders, particularly SZ, involve accelerated neurodegenerative decline that can be detected in the human retina.

## S107. Mapping the Schizophrenia Interactome

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**Background:** Signaling pathways are composed of interacting molecules working in concert to control neurophysiology. These macromolecular interactions can be broadly placed into three categories: input, signaling, and output, with interactions spanning molecular classes. Genetic risk for schizophrenia (Sz) is distributed across each level, including receptors and channels (e.g., GRIN2A and CACNA1C), signaling proteins such as TRIO and MAPK3, and SETD1A and DMN3 at the output level, implicating interactions between different signaling modalities including protein phosphorylation, small molecules, and lipids. This level of complexity demands an integrated assessment of multiple "-omes" composing the "interactome." To accomplish this, we characterized the proteome, phosphoproteome, lipidome, and metabolome in dorsal postmortem anterior cingular cortex (dACC) grey matter from 56 schizophrenia patients and matched controls to provide novel insights into the disease.

**Methods:** dACC grey matter was dissected from 56 schizophrenia and control subjects matched for sex, age, and postmortem interval (PMI), previously included in Common Mind cohorts. For proteomics and phosphoproteomics, tissue was homogenized and digested on S-Traps. Samples were randomized into 8 groups containing 14 samples and two pooled controls and labeled with TMTpro. Phosphopeptides were enriched using FeIMAC, and both fractions were analyzed by LC-MS/MS with offline fractionation. Methanol chloroform extraction was used to isolate lipids and metabolites, followed by untargeted quantification of both classes by LC-MS/MS. Peptides and phosphopeptides, lipids and small molecules were identified and quantified in Proteome Discoverer (v2.5), Lipid Search (v5.1) and Compound Discoverer (v3.3), respectively. Each data tranche was individually imputed, followed by mixed linear modeling accounting for clinical co-variants and performing case-control statistics. Dysregulated features in each tranche were characterized with KEGG, Lipid Ontology, and Metabolanalyst. Biologically directed multiomics analysis utilizing defined interactions extracted from KSEA, STRING and STITCH were segregated into multiomics communities utilizing k-core clustering and biologically characterized with KEGG.
**Results:** Following quality control, statistical analyses were performed on 4,282 proteins, 11,177 phosphorylation sites mapping to 3,631 proteins, 8,347 lipid features, and 1,472 metabolite features. Overrepresentation analysis was individually performed on each tranche of upregulated ($q < 0.05$, $FC > 0$) and downregulated ($q < 0.05$, $FC < 0$) features. Upregulated protein features are collectively mapped to extracellular matrix organization (q=5.7E-10), while downregulated proteins are mapped to mitochondrial translation (q=3.1E-29), consistent with Sz literature. Altered metabolite features indicated upregulation in carbon metabolism (q=3.1E-25) and downregulation in amino acid biosynthesis (q=7.4E-5). Upregulated lipid features mapped to ceramides (q=4.3E-19), while downregulated features mapped to phosphatidylcholines (q=2.9E-26). Proteins with upregulated phosphorylation mapped to GTPase signaling molecules (q=9.5E-5), conversely proteins with downregulated phosphorylation mapped to ion transporter and NMDA receptors (q= 4.8E-3). Our multiomics analysis identified 14,285 total macromolecular interactions, separated into 23 communities by k-core clustering, each with unique biological functions. 3 of the 23 communities were significantly enriched for dysregulated features; the top 3 most connected nodes from these communities included the Sz risk gene MAPK3.
**Discussion:** We can assemble a biological network of macromolecular interactions that segregate into discrete communities with defined biological functions grounded in genetic risk for Sz.

## S108. Is Reduced Heart Rate Variability Associated With Increased Task-Related Suspiciousness in the Psychosis Spectrum?

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**Background:** Paranoia is a core feature across the psychosis spectrum that presents along a continuum across community individuals, high-risk states, and fully manifested psychotic disorders. Suspiciousness (SUS) sits at the milder end of the paranoia continuum, and while this phenomenological experience is proposed to be shaped by thoughts and physiological arousal, the objective evidence linking these levels of analysis is scant. Objective physiological indices of increased arousal include reduced heart rate variability (HRV) and can provide mechanistic insight during states of heightened SUS and paranoia. Traditionally, assessments of SUS and paranoia rely on self-reports, which are subject to biases. However,

the Minnesota Trust Game (MTG) provides an objective task-based measure that isolates SUS mistrust from rational mistrust (RMT) and risk aversion; thus, providing a task-based metric of SUS to complement self-report scores. The current study will be the first to specifically investigate relationships between task-based SUS and physiological arousal. This study aims to answer three key questions: (1) Do individuals with higher levels of task-based SUS exhibit lower HRV during interpersonal mistrust conditions? (2) Do individuals with higher levels of task-based SUS exhibit lower HRV also during risk aversion condition and resting-state? (3) How do these physiological arousal and task-based SUS metrics relate to self-reported measures of paranoia?
**Methods:** A community sample of 20 adults with elevated scores on the Prodromal Questionnaire Brief, thus enriched for psychosis risk, completed the study. Participants played the Other Player condition of the MTG measuring interpersonal mistrust (SUS + RMT), and the Coin condition measuring risk aversion. HRV was measured during resting baseline, MTG risk aversion condition, and MTG interpersonal trust condition. For each of the three conditions root mean square successive difference (RMSSD) values were calculated for HRV. Self-reported paranoia was assessed using the Revised Green Paranoia Thought Scale (GPTS). Analyses will primarily examine correlations between RMSSD values, task-based SUS, and GPTS scores, with a focus on how elevated physiological arousal (reflected as lower RMSSD) relates to SUS across modalities.
**Results:** Participants will be divided into high and low SUS groups using a median split of GPTS scores. We hypothesize GPTS scores will be correlated with task-based SUS but will not be related to task-based RMT or risk aversion. We hypothesize that high SUS participants will exhibit lower RMSSD during risk aversion and resting-state compared to low SUS participants, but will specifically show more drastic reductions in RMSSD during the Other Player condition as a function of evoking interpersonal mistrust. We hypothesize RMSSD in the interpersonal mistrust condition will be most correlated with task-based SUS and will be negatively correlated with GPTS scores.
**Discussion:** This study will address critical gaps in understanding the physiological mechanisms underlying paranoia across the psychosis spectrum. By linking HRV during MTG to both task-based SUS and self-reported paranoia, the findings will provide insights into whether arousal influences interpersonal mistrust. These results could inform early identification of individuals at risk for psychosis and guide future interventions, such as biofeedback, to improve self-regulation and reduce paranoia.

## S109. Resting-State Functional Connectivity Within Social Brain Networks Show Differential Associations With Negative Symptom Domains in Schizophrenia

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**Background:** Negative symptoms—reductions in goal-directed activity, social behavior, pleasure, and emotional expression or speech—strongly predict functional impairment in schizophrenia (SZ). Factor analyses support a hierarchical structure of negative symptoms with two broad dimensions (motivation/pleasure vs. expressivity) and a 5-factor structure (anhedonia, avolition, asociality, blunted affect, alogia). Support for the latent structure of negative symptoms highlights the need to identify neurobiological correlates at both the broader dimension and individual domain levels. The current study assessed the validity of this latent structure at the neural level by analyzing associations between the two

dimensions/five domains and resting-state functional connectivity (RS-FC) in five brain networks critical for social behavior.
**Methods:** 125 early psychosis patients (SZ) and 58 healthy controls (CN) participated in clinical symptom ratings and resting-state MRI for the Human Connectome Project-Early Psychosis project (HCP-EP). RS-FC analyses assessed the synchrony of five social brain networks important for social behavior: aversion, affiliative, perception, mentalizing, and mirror networks.
**Results:** Findings revealed that individuals with SZ had reduced RS-FC in social brain networks compared to CN with no specific network driving the effect. Certain negative symptom domains exhibited unique correlations with RS-FC networks that were masked when data were examined at the broader dimension level, while other domains traveled together at the dimension level.
**Discussion:** Findings support previous evidence that broad negative symptom dimensions and specific domains capture unique mechanistic variance. Unique correlations among negative symptom domains emphasize the need for updated diagnostic procedures and mechanistic treatment targets.

## S110. Evaluating Harmonisation Methods for Multi-Site Psychosis MRI Data: Insights From the Psy-Shared Resource

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**Background:** Neuroanatomical research in psychosis populations using MRI often struggles with challenges due to limited sample sizes, recruitment difficulties, and a lack of diversity in patient populations. The Psychosis MRI Shared Data Resource (Psy-ShareD) was established to address these gaps, providing an open access global repository of multi-site T1-weighted MRI data acquired in individuals with schizophrenia spectrum disorders, psychosis risk and healthy controls. However, differences in scanner hardware and acquisition protocols across sites and datasets introduce variability that can obscure true biological effects. Harmonisation methods have been developed to address these challenges, and reduce the impact of site-related variability. To validate our harmonisation pipelines, we run analyses to compare classification and prediction results using original (unharmonised) images with three harmonisation approaches: HACA3 (Zuo et al., 2023), IGUANe (Roca et al., 2025), neuroCombat (Fortin et al., 2018).
**Methods:** We used T1w MRI scans from seven datasets collected in the UK, Italy, and Japan, acquired in individuals with schizophrenia (n = 287) and healthy controls (n = 267). The images were processed with FreeSurfer (surfer.nmr.mgh.harvard.edu) to extract cortical and surface measures for this analysis. Two analytical frameworks were used to evaluate the harmonisation methods: (1) an Support Vector Machine (SVM) classifier to differentiate

schizophrenia from control populations and (2) regression models to predict clinical scores on the Positive and Negative Syndrome Scale (PANSS) subscales. Each method was assessed for its impact on classification accuracy and predictive performance relative to the unharmonised images. All models were cross-validated by training with the data from six sites and testing with the remaining one. Pairwise t-tests were conducted to determine the statistical significance of differences between methods.
**Results:** All harmonisation methods generally performed at least as well as the classification models using original images, with variations across methods and tasks. For classification, original images (55.8% ± 5.6) had a statistically significant lower classification accuracy than HACA3 (58.3% ± 7.4; $p < 0.001$) and IGUANe (57.9% ± 6.0; $p < 0.001$), but not neuroCombat (55.9% ± 5.9; $p = 0.089$). For PANSS score prediction, HACA3 and IGUANe achieved mean absolute errors (MAEs) with no significant difference to original images across subscales, while neuroCombat showed higher MAEs, particularly for PANSS negative and general.
**Discussion:** Harmonisation methods generally preserved or enhanced performance, particularly in classification tasks, underscoring their utility in mitigating site-related variability. Significant differences between harmonisation methods suggest task-specific advantages, with HACA3 and IGUANe showing the most consistent results. Whilst classification accuracies are at the lower range of those previously reported (~60%; Filippis et al 2019), we have shown that the harmonisation pipelines do not reduce this accuracy and actually significantly improve accuracy for HACA3 and IGUANe. Future improvements in model accuracy may be achieved by optimising feature selection and the model's hyperparameters. By combining Psy-ShareD with robust harmonisation techniques, researchers can improve the reliability and interpretability of multi-site psychosis studies and facilitate insights into this complex condition across larger and more diverse samples.

## S111. Spatial Working Memory Predicts Psychosis-Risk for Women in Menopause

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**Background:** Men and women experience psychosis-risk differently. While both sexes have a typical age of onset in early adulthood, women are uniquely at risk during midlife. Women over 40 are admitted to the hospital for a first-episode of psychosis twice as often as men over 40. While an extensive body of research has identified risk factors for the onset of psychosis, this research has been almost exclusively done in adolescents and young adults. Little is known about individual risk factors for psychosis-onset during midlife.
Midlife risk for psychosis onset in women has been largely attributed to the changes in ovarian hormones that characterize the menopausal transition. Perimenopause, the transition from premenopause to postmenopause—is considered the menopausal stage with the highest risk for physical, neurological, and psychiatric symptoms due to rapid and marked fluctuations in estrogen levels. Perimenopausal women experience myriad symptoms across physical, psychological, and cognitive domains. Hot flashes, headaches low mood, brain fog, and memory concerns are all commonly reported perimenopausal symptoms, which are more severe in women with greater ovarian hormone sensitivity. Individual variability in ovarian hormone sensitivity is revealed across menopausal stages, for example via premenstrual and postpartum symptoms, as well as perimenopausal symptoms.

Cognitive dysfunction is a robust risk factor for psychosis and psychotic-like features. Indeed, spatial working memory—the ability to hold information online—is one of the few factors that predicts transition to psychosis in clinically high-risk youth. It is also associated with psychotic-like experiences in the general population. The goal of the current study is to investigate whether spatial working memory is also a risk factor for psychosis and psychotic-like symptoms during women in midlife, whether this putative relationship is stronger during perimenopause, and ovarian hormone sensitivity moderates the relationship between spatial working memory and PLEs in perimenopausal women.

**Methods:** The current sample consists of 202 women in midlife at various stages of menopause - 85 (42.1%) premenopausal women, 79 (34.2%) perimenopausal women, and 38 (18.8%) postmenopausal women. Participants are recruited via a population-based registry. Menopausal stage was determined according to criteria set by the Stages of Reproductive Aging Workshop (STRAW +10) based on responses to the Menopause Questionnaire (MQ). Average menopausal symptoms over a 35-day measurement period, assessed using the Green Climacteric Scale (GSC), were used as a proxy of ovarian hormone sensitivity (excluding items related to psychological symptoms). Spatial working memory was assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB) Token Test and psychotic-like experiences were assed with the Community Assessment of Psychiatric Experience – 15 Item (CAPE – P15). Since distressing PLEs are the best predictor of transition to psychosis in high-risk samples, we used the maximum level of distress associated with all PLEs as our dependent measure of interest.
**Results:** Within the whole sample of midlife women, spatial working memory did not predict psychotic-like experiences from a linear regression model controlling for age ($\beta$ = -0.001, 95% CI [-0.008, 0.006], p = .813). Working memory also did not predict psychotic-like experiences in any of the menopausal groups separately (premenopause: $\beta$ = -0.002, 95% CI [-0.010, 0.006], p = .667; perimenopause: $\beta$ = 0.004, 95% CI [-0.012, 0.020], p = .611; postmenopause: $\beta$ = -0.003, 95% CI [-0.021, 0.016], p = .765) . Importantly, however, ovarian hormone sensitivity moderated the relationship between spatial working memory and PLEs in the perimenopause group while controlling for age. More severe PLE-related distress was predicted by worse performance during a spatial working memory token-search task, but only for perimenopausal women with higher levels of ovarian hormone sensitivity ($\beta$ = 0.008, 95% CI [0.001, 0.015], p = .023).
**Discussion:** These results highlight that psychosis risk (i.e., PLE-related distress) is predicted by spatial working memory abilities in women during midlife –consistent with findings in early adulthood—but only for women in perimenopause with higher hormone sensitivity. Taken together, the findings suggest that at women sensitive to hormone shifts may be uniquely at-risk for severe mental illness during perimenopause.

## S112. Associating Mood Symptom Severity With Subcortical Brain Volumes in Bipolar Disorder and Major Depressive Disorder Using an Item Response Theory Model

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**Background:** Mood rating scales are widely used to assess the severity in Bipolar Disorder (BD) and Major Depressive Disorder (MDD), but the diversity of these scales complicates multisite data aggregation and replication. This study aimed to capture the common signatures of mood symptom severity across scales, and relate item-level variance to subcortical brain volumes in a global transdiagnostic dataset.
**Methods:** The study included 9,625 individuals from 49 independent study sites (5,355 controls, 2,804 BD, 894 MDD) from the ENIGMA MDD and BD working groups. Depression was assessed using the Hamilton Depression Rating Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), or Beck Depression Inventory (BDI). A graded item response theory (IRT) model was used to calculate trait-level parameters for response categories and discrimination parameters for each item (mirt package, R). T1-weighted brain images were segmented using FreeSurfer, and subcortical volumes were harmonized using ComBat.
**Results:** Transdiagnostic discriminative items were sadness, suicidal thoughts, and reductions in work and activities ($\alpha > 0.3$), while sleep and appetite were less informative. Total- and IRT-scores correlated highly ($r > 0.83$). IRT scores captured more significant variability overall ($\Delta > 8\%$) and showed significant associations with subcortical volumes. Expected volumetric differences were found in MDD and BD relative to CN and lower volumes between MDD and BD in reward-related structures (e.g., accumbens, putamen) and higher ventricular and thalamic volumes ($pFDR < 0.05$). IRT-derived scores were associated with subcortical regions (MDD r range=-0.099;-0.249, BD r range= -0.069; -0.143) with cross-disorder differences in the accumbens (MDD > BD), hippocampus (BD > MDD) and ventricles (MDD > BD).
**Discussion:** IRT scores provide an efficient and sensitive method to measure symptom severity and reveal distinct brain volume differences. Lower volumes in reward-related regions and larger thalamic and ventricular volumes in BD, provide further insight into the neurobiological distinctions between BD and MDD by taking into account the relative associations between individual symptoms of depression severity.

## S113. Investigating Clozapine-Induced Brain Structure and Connectivity Changes Using Multi-Modal Imaging: An 18-Week Longitudinal Study in Patients With Treatment-Resistant Schizophrenia

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**Background:** Clozapine is the only effective antipsychotic for patients exhibiting inadequate response to treatment, suggesting its unique mechanism of action and potentially distinct underlying pathophysiology. We investigated the longitudinal effects of clozapine treatment on brain structure and connectivity, exploring potential associations with other clinical and functional variables.

**Methods:** TRS patients intending to initiate clozapine treatment and non-TRS (NTRS) patients were recruited. T1-weighted and resting-state fMRI data were obtained at baseline and after 18 weeks of clozapine treatment. Longitudinal analyses were conducted to evaluate changes in gray matter and functional connectivity within both cohorts. Additionally, potential relationships between structural and connectivity changes were explored.
**Results:** Following 18 weeks of clozapine treatment, TRS patients exhibited significant reductions in gray matter volume in bilateral frontotemporal gyrus and limbic areas, while no such changes were observed in the NTRS control group. Furthermore, a significant decrease in functional connectivity was observed specifically in TRS patients, involving the frontal and superior temporal gyrus. Notably, reductions in gray matter volume were correlated with decreased functional connectivity.
**Discussion:** Clozapine treatment is associated with cortical/subcortical volume reductions and decrease in frontotemporal connectivity, correlated with clinical and cognitive outcomes. Importantly, these TRS-specific brain alterations emphasize the distinct impact of clozapine, independent of disease progression or other medications, enriching our understanding of its unique neurobiological effects in TRS. Furthermore, the observed relationship between structural and functional changes emphasizes the interdependence between brain structure and function.

## S114. Basolateral Amygdala Surface Deformations are Associated With Clinical Ratings of Aggression in Chronic Schizophrenia

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**Background:** Schizophrenia increases the risk of aggression due to factors that are characteristic of the disorder, such as aberrations in brain structure, psychotic symptoms (delusions and hallucinations) and cognitive impairments. Regarding brain structure, studies have previously shown that violent individuals with schizophrenia have reduced volumes within the amygdala and hippocampus, providing insight into the neurobiological profile of aggression in schizophrenia in its most severe form. However, these studies have utilized gross volumetric data to make these characterizations, and no work has been done to localize relationships with aggression by leveraging deep brain morphology. Given these gaps, the aim of this study was to utilize high-dimensional brain mapping to determine mediating relationships between subcortical neuromorphometry, cognitive impairments, and aggression in schizophrenia. Due to the exploratory nature of the study, it was hypothesized that aggression would be predicted by impaired cognition and that this relationship would be partially mediated by morphologic deformation in the basal ganglia, thalamus, hippocampus, and amygdala.
**Methods:** Using cognitive, clinical, and neuroimaging data collected from four sites derived from the SchizConnect database, estimates of executive function, learning and memory, language, and processing were used as covariates for clinical ratings of aggression, creating a sample that only included chronic schizophrenia participants (N = 316). Deep brain surface mapping of the basal ganglia (caudate, putamen, globus pallidus, nucleus accumbens),

thalamus, hippocampus, and amygdala was accomplished using Large Deformation Diffeomorphic Metric Mapping procedures derived from T1-weighted MR scans. Statistical analyses included: zero-order bivariate correlations between aggression, all clinical data, and cognitive data, mediated ordinal logistic regression models with clinically rated aggression (harmonized scores from P7 of the PANSS and B3 of the SAPS) as the outcome variable, the cognitive domains as the predictor variables, and deep brain morphology as the mediating variable. General linear models between rank-transformed aggression ratings and shape deformation in deep brain regions were conducted and corrected for multiple comparisons using random-field theory.
**Results:** No cognitive domains significantly correlated with aggression. Modest positive spearman's correlations between aggression and clinical features were present, namely positive symptoms ($r(314) = 0.21$, $p < .001$) and disorganization ($r(314) = 0.29$, $p < .001$). RFT-corrected deep brain surface maps revealed a negative relationship between a deformity in the basolateral complex of the left amygdala and aggression. A follow up spearman correlation was then conducted between aggression ratings and mean deformation estimates within the basolateral complex cluster, which demonstrated a modest inverse relationship ($r(314) = -0.22$, $p < .001$). When controlling for age and sex, mean estimates of these deformities within each subject were a significant negative predictor of aggression, with a satisfactory model fit (OR [95%] = 0.14 [.04, .42], AIC = 517 .08). Additionally, confidence interval calculations indicated that this inverse relationship was robust, 95% CI [-3.13, -0.88], independent of sex (OR [95%] = .93 [-0.71, 0.53]) and age (OR [95%] = .99 [-0.04, 0.01]).
**Discussion:** The findings of this study are consistent with those of prior studies examining the neurobiological substrates of aggression in psychotic disorders, particularly within subcortical regions. Our results showed that decreases in amygdalar shape deformation are associated with higher aggression ratings, providing a potential anatomical substrate for aggressive behavior in chronic schizophrenia. Prior studies have found that violent offenders with schizophrenia demonstrate decreased volumes in subfields of the amygdala when compared to schizophrenia patients with no history of violent offending. Our study provides preliminary evidence that specific amygdala markers may predict aggressive behavior in a chronic non-violent population.

## S115. The Influence of Prior Knowledge in Detecting Speech in Schizophrenia With and Without Auditory Hallucinations

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**Background:** Many individuals with schizophrenia (SZ) who experience distressing auditory hallucinations (AH) do not respond adequately to antipsychotic medications and/or experience adverse side effects from these treatments. Thus, there is an urgent need to better understand AH pathophysiology to inform the development of novel, targeted interventions. Recent mechanistic models of psychosis suggest that AH may result from a pathological overweighting of expectations relative to bottom-up sensory signals during perception, and that lower-level sensory processing impairments in SZ may contribute to this pathology.
**Methods:** To investigate these potential AH mechanisms, we are leveraging recent advances in the use of electroencephalography (EEG) to index the hierarchical processing of natural speech and the effects of prior knowledge on this processing in SZ subjects with and without

AH (AH+ / AH-) and in matched healthy controls (HC). Subjects listen to speech segments of an audiobook and clips of acoustically degraded speech while EEG is recorded. Before each degraded speech clip, subjects are presented with text of a sentence on a computer screen that matches the content of the degraded speech clip in 50% of the trials. Following each degraded speech clip, subjects rate how many words they detected and understood. EEG responses to the audiobook and degraded speech clips are modeled to derive indices of acoustic and phonetic feature encoding of speech. Using data from the degraded speech task, the change in EEG measures of speech processing and in speech intelligibility ratings associated with the addition of prior exposure to the speech content (i.e., match-mismatch change scores) are calculated to provide neural and perceptual indices of the effects of prior knowledge. Symptom severity in SZ is measured with the Brief Psychiatric Rating Scale, and self-reported perceptual disturbances in all subjects are assessed with the Audio-Visual Abnormalities Questionnaire (AVAQ).

**Results:** We have assessed 22 SZ (10 AH+, 12 AH-) and 15 HC thus far. As expected, all 3 groups (AH+, AH-, HC) displayed a perceptual pop-out effect when provided with prior knowledge regarding the content of degraded speech, i.e., subjects indicated understanding significantly more words in the match v. mismatch condition of the degraded speech task. However, examination of group differences indicated that the AH+ group experienced the smallest pop-out effect of the 3 groups (AH+ < HC, p=.009, Cohen's d effect size [ES]=1.18). This group difference appeared to be driven primarily by higher mismatch intelligibility ratings among AH+; in other words, AH+ subjects tended to indicate that they understood more words in the mismatch condition than did AH- or HC (AH+ > HC, p=.108, ES=0.73). In the total SZ sample, higher mismatch intelligibility ratings were significantly associated with more severe positive symptoms (r=.533, p=.011; hallucinations: r=.317, p=.150; unusual thought content: r=.406, p=.061) and more self-reported auditory perceptual disturbances (r=.495, p=.019). Notably, higher mismatch intelligibility ratings were also significantly related to self-reported perceptual disturbances in HC (auditory: r=.553, p=.050; visual: r=.588, p=.034; total AVAQ scores: r=.592, p=.033). In contrast to these behavioral results, preliminary EEG analyses with a subset of subjects (4 AH+, 5 AH-, 7 HC) indicate a larger change in phonetic feature encoding of degraded speech between the match and mismatch conditions in AH+ relative to AH- (AH+ > AH-, ES=0.76).

**Discussion:** Contrary to expectations, behavioral results from a degraded speech paradigm did not yield any evidence of stronger top-down effects based on recently presented information on the perception of degraded speech in SZ with AH. Instead, AH+ group status, and more severe positive symptoms and self-reported perceptual abnormalities, were associated with the tendency to detect more words in degraded speech clips in the mismatch condition, suggesting a greater influence of previously acquired speech priors in those with hallucinations and related symptoms. On the other hand, EEG results suggest stronger top-down effects based on recently presented information in AH+ and HC relative to AH-. Our behavioral results are consistent with several prior findings suggesting that hallucinations in SZ (Vercammen et al., 2008), and hallucination proneness in the general population (Alderson-Day et al., 2022), are associated with the "spontaneous" tendency to perceive speech in ambiguous auditory stimuli, i.e., when not primed with prior information. Similarly, based on findings in the non-clinical literature (Sohoglu et al., 2016), we interpret the preliminary EEG results as suggesting stronger top-down effects in AH+ compared to AH-, likely due to the reduction in prediction error that resulted from the provision of prior knowledge in the match condition. Overall, these results suggest that the behavioral and neural indices from this degraded speech paradigm may yield information on different aspects of predictive processing alterations in SZ with AH.

Of note, this presentation will include EEG results for all subjects, along with additional subjects who complete the study prior to March 2025.

## S116. In Vivo Measurements of Glutamate and Glutathione Using Dante-Press at 7T in Patients With Schizophrenia

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**Background:** Schizophrenia is a complex psychiatric disorder where wherein abnormalities in neurotransmission influences positive, negative, and/or cognitive symptoms.
Several studies have suggested that glutamatergic dysfunction has been associated with the pathophysiology of schizophrenia and target for potential therapeutic interventions. The glutamatergic models suggest that high levels of glutamate lead to glutamate excitotoxicity in relation to hypofunction of the N-methyl D aspartate receptor (NMDAR). However, antioxidants such as glutathione play a therapeutic role in moderating glutamate-levels from the glutathione cycle.

Single-voxel proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive in vivo imaging technique used to quantify the concentration of human brain metabolites. We will be using an novel multi-metabolite-selective sequence known as double-Delays-Alternating-Nutation-Tailored-Excitation Point-RESolved-Spectroscopy (DANTE-PRESS). This sequence will only preserve the signal of two metabolites of interest while suppressing unwanted signals through a narrow-band frequency-selective refocusing pulse. This is a cross-sectional study that observed glutamate and glutathione differences between healthy controls and patients living with schizophrenia using double DANTE-PRESS at 7 Tesla.

**Methods:** For this study, we are aiming to scan 20 patients living with schizophrenia and 20 healthy controls. The healthy controls were group-matched for gender, age, parental socio-economic status, no personal history to mental illness and family history of psychotic disorder. Patient volunteers were recruited from the referrals received by the Prevention and Early Intervention for Psychosis Program at London Health Sciences Center and all patients had been diagnosed by psychiatrists based on the DSM-5 criteria. Participants underwent screening to exclude head injury, medical illness, and MRI contraindications. Participants were also provided with written, informed consent according to the Human Research Ethics Board for Health Sciences at Western University, London, Ontario.
All scans were performed on a 7T MR scanner (Siemens MAGNETOM 7T Plus, Erlangen, Germany) with an 8 transmit channel head-only radiofrequency coil and 32 channel receive coil at the Centre for Functional and Metabolic Mapping (CFMM) at Robarts Research Institute in London, Ontario. For T1-weighted anatomical images, the vendor-provided MP2RAGE sequence (works-in-progress package 925B) was used, featuring Compressed Sensing (CS) acceleration [1] and dynamic parallel-transmission (pTx) RF pulses [2] (FOV: 246x246x168 mm, sagittal orientation, 0.70 mm iso-volume voxels, CS acceleration: 4, flip-angle: 4/5 degrees, TI: 860/2700 ms, TR: 6000 ms). The voxel (2.0x2.0x2.0cm3) was placed

at isocentre in phantom and at the dorsal anterior cingulate cortex (dACC) in vivo. Voxel placement was based on positioning the posterior end of the voxel coinciding with the precentral gyrus and the caudal face of the voxel coinciding with the most caudal positioning that was not part of the corpus callosum. Voxel angle was set to be tangential to the corpus callosum.

A water unsuppressed spectrum was acquired using Point RESolved Spectroscopy (PRESS) for absolute quantification (TR/TE/AVG/BW=3000ms/96ms/8avg/3000Hz). A water suppressed double DANTE-PRESS was centred on glutamate's 2.35ppm multiplet and glutathione 3.77ppm to achieve metabolite selectivity (TR/TE/AVG/BW/DANTE pulse FWHM=3000ms/96ms/64avg/3000Hz/56Hz). Metabolite positions were determined relative to N-acetylaspartate (NAA) singlets observed in our water-suppressed PRESS sequence and used for fine power and chemical shift adjustment loops of the DANTE pulse.

Spectra visualization and metabolite fitting was done using an in-house post-processing software known as FitMangui. FitMangui is a time-domain fitting algorithm that uses a non-linear, iterative Levenberg-Marquardt minimizing technique to estimate metabolite chemical shift, concentration, linewidth and phase (0th and 1st order). The advantage of DANTE-PRESS is being able to obtain simple spectra only refocusing the signal from our metabolites of interest (inside the DANTE pulse passbands).

**Results:** Glutamate and glutathione levels were 8% and 12% higher in patients living with schizophrenia compared to healthy controls. We have scanned 6 healthy controls and 6 patients living with schizophrenia. The mean inter-individual Cramer Rao Lower Bounds (CRLB) were < 9% and 12% for glutamate and glutathione respectively in patients and healthy controls.

**Discussion:** Our finding of glutamate and glutathione levels being 8% and 12% higher in patient volunteers is consistent with Jeon et al., who reported an increase in glutamate and GSH levels in patients diagnosed with first episode schizophrenia relative to group-matched healthy volunteers. In contrast, Kumar et al., reported a reduction in glutathione and glutamate levels in patients with residual schizophrenia relative to group-matched healthy volunteers suggesting glutamatergic dysfunction via glutamate excitotoxicity in first episode has downstream effects that may present with lower metabolite levels.

## S117. The Hidden Complexity: Exploring Resting State EEG Dynamics in Schizophrenia and Ketamine's Neural Landscape

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**Background:** Schizophrenia involves a complex interplay of neurobiological alterations, notably glutamatergic dysfunction leading to an excitatory-inhibitory (E/I) imbalance. N-Methyl-D-Aspartate Receptor (NMDAR) hypofunction appears to be a key factor, modeled in healthy individuals using NMDAR antagonists like ketamine. However, interindividual variability exists, and robust assessment methods are lacking. The aperiodic slope of EEG power spectra has been proposed as a marker of E/I balance, complemented by novel EEG

complexity measures. Yet, the relationship between these markers and NMDAR hypofunction in the ketamine model of schizophrenia remains unexamined.
**Methods:** Forty-five healthy volunteers participated in two sessions, receiving S-ketamine (5 mg bolus plus 0.006 mg/kg/min infusion) and placebo in a randomized, double-blind, crossover design. Five-minute eyes-closed resting-state EEGs were recorded during each session. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). EEG data underwent automated preprocessing, including filtering, artifact rejection, and independent component analysis. Power spectra (1–45 Hz) were obtained via fast Fourier transform and decomposed into periodic and aperiodic components. Geometric complexity was analyzed using Eigen-Time-Delay embedding, and cross-parameter coupling was assessed with Convergent Cross-Mapping. Statistical analyses included parametric tests (aperiodic, complexity, and coupling parameters) and cluster-based permutation tests (periodic spectra).
**Results:** S-ketamine administration increased all symptom domains measured by PANSS in healthy volunteers. Compared to placebo, ketamine significantly reduced periodic activity in slower frequency bands ( < 30 Hz, $p < 0.01$) and flattened the aperiodic slope ($p < 0.01$). Traditional broadband increases in the gamma range ( > 30 Hz) were observed when not controlling for the aperiodic parameter ($p < 0.01$); however, these differences were no longer detectable after accounting for it. Ketamine also induced increases in high-frequency (beta, $p < 0.01$; gamma, $p < 0.01$) and aperiodic ($p = 0.043$) complexity as modeled by Eigen-Time-Delay embedding, while cross-parameter coupling significantly decreased between most parameters after ketamine administration.
**Discussion:** Our findings suggest that the uniform flattening of the aperiodic slope following ketamine reflects increased neuronal excitation, and potentially explains previously reported ketamine-induced broadband high-frequency increases in the resting state EEG. The association between shifts in the aperiodic component, increased EEG complexity accompanied by cross-frequency decoupling, and NMDAR hypofunction warrants further investigation, possibly using glutamatergic agents acting as NMDAR co-agonists. Establishing a relationship to glutamatergic neurotransmission and responsiveness to targeted interventions could position these EEG parameters as potential biomarkers for NMDAR hypofunction.

## S118. Differences Between Patients With Schizophrenia and Healthy Participants Regarding the Relationship Between AMPA Receptor Density and Intraregional/Interregional Functional Centrality

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**Background:** Neurobiological factors that determine the degree or strength of functional connectivity measured with resting-state functional MRI (rsfMRI) remain unknown. To address these challenges, we utilized [11C]K-2 PET that was developed to visualize AMPA receptors in the living humans since these receptors have been identified as integral to the pathology of psychiatric disorders in animal studies. Concurrently, we applied local functional connectivity density (lFCD) and global functional connectivity density (gFCD)-

lFCD metrics, representing brain intraregional and interregional functional centrality, respectively. The aim of this study was to test the hypothesis that an increase in AMPA receptor density corresponds to higher lFCD and gFCD-lFCD not only in HP but also in patients with schizophrenia (Sz). Additionally, we explored the difference in the relationship between AMPA receptor density and these indices in both healthy participants (HP) and those with schizophrenia.
**Methods:** [11C]K-2 PET (AMPA receptor PET) and rsfMRI were performed in 31 HP and 14 Sz. Standard Uptake Value Ratio (SUVR) with the white matter as the reference region was used as an index of AMPA receptor density, and SUVR images and lFCD and gFCD-lFCD values derived from rsfMRI data, were extracted from the whole brain, Yeo's 7 network Atlas regions, and 83 regions in the Hammers atlas. The correlation between SUVR and In one lFCD image, each voxel (a starting voxel) value represents the number of voxels in each cluster that satisfy the following two conditions: i) have significant connectivity with the starting voxel, and ii) are spatially adjacent to each other in each cluster. Conversely, in one gFCD image, each voxel value means the number of voxels that meet i), and iii) are not spatially adjacent to each other. lFCD (l-correlation) and the correlation between SUVR and gFCD-lFCD (g-correlation) were calculated with the Spearman's rank correlation coefficient test in a voxel-wise manner. Next, using the Hammers atlas, SUVR, lFCD, and gFCD-lFCD images of both groups were averaged, and ROI-wise l- and g-correlations were extracted across the whole brain in both groups and were compared between the two groups. The l- and g-correlations in the anterior cingulate cortex (ACC), which was the main region where SUVR was lower in the Sz group than that in the HP group in our previous study, were also compared between the two groups.
**Results:** In the voxel-wise analyses, the mean l-correlation coefficients were 0.46 and 0.40 in the HP and Sz groups, respectively, for the whole brain. The mean g-correlation coefficients were 0.46 and 0.39 for the HP and Sz groups, respectively. The mean l- and g- correlations showed positive correlations in many brain regions and most functional networks in both groups. In the HP group, both the l-correlation ($r=0.33$, $p=0.0022$) and g-correlation ($r=0.33$, $p=0.0025$) showed positive correlations across the whole brain. On the other hand, in Sz, a positive correlation was observed only for the l-correlation ($r=0.35$, $p=0.0015$) across the whole brain, while no significant correlation was observed for the g-correlation. Furthermore, in the ACC, the Sz group showed a significantly smaller correlation in the l-correlation than the HP group ($t=2.5$, $p=0.021$), while no significant difference was found in the g-correlation between the Sz and HP group ($t=1.8$, $p=0.080$).
**Discussion:** In both the HP and Sz groups, AMPA receptor density was positively correlated with intraregional and interregional functional centrality in the whole brain, many brain regions, and most functional networks. Furthermore, the g-correlation was disrupted in the Sz group compared to the HC group in the whole brain, and the l-correlation in the ACC was significantly smaller in the Sz group than that in the HP group.

## S119. Information Processing Differences Between Schizophrenia and Bipolar Disorder as Measured by Alpha Oscillations

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**Background:** Schizophrenia (SCZ) and bipolar disorder (BD) are serious mental illnesses that are characterized by information processing abnormalities that impact cognition and functioning. These disorders have genetic overlap but different clinical presentations. Hence, it is not clear whether the same brain mechanisms are driving information processing impairments in these two disorders. Alpha oscillations have been linked to a variety of information processing functions in healthy adults and can be studied in SCZ and BD to better understand differences in clinical presentations. Here we examined how alpha oscillations may differentiate BD and SCZ by focusing on two different phenomena: peak alpha frequency (PAF) and frontal alpha asymmetry (FAA).
**Methods:** Data from two large datasets that recorded brain activity during resting-state electroencephalography (EEG) were examined. The first study examined PAF as an index of visual information processing that is also correlated with cognition. We assessed whether PAF was slower in SCZ (n = 90) and BD (n = 62) relative to healthy controls (n = 69), and whether there were associations between PAF, visual information processing, and cognition within each group. In the second study, alpha oscillations were studied in terms of FAA, the difference in alpha activity over right vs left frontal hemispheres of the brain. Increased activity in the left hemisphere has been linked to information processing that drives approach motivation (right-sided FAA), whereas increased activity in the right hemisphere has been linked to avoidance motivation (left-sided FAA). We examined group differences in FAA between SCZ (n = 58), BD (n = 32), and healthy controls (n = 130).
**Results:** First, we found that PAF was reduced in SCZ compared with BD and healthy controls (t's > 3.72, p's < .001), and was comparable between BD and healthy controls. Reduced PAF was correlated with poorer visual information processing in SCZ (r = -.31, p < .03), but not in BD. Further, reduced PAF was associated with poorer overall cognition in SCZ (r = .30, p < .03), but not in BD. Specifically, PAF was associated with speed of processing in SCZ and BD groups (r's = .22 - .31, p's < .05), but was only associated with reduced attention/vigilance and social cognition in SCZ (r's = .24 - .34, p < .001). Second, for FAA we found that BD showed more right-sided FAA than SCZ and healthy controls (t's > 2.07, p's < .05). FAA was not correlated with symptoms in any group.
**Discussion:** We observed unique patterns of alpha effects across illness types. Slower alpha oscillations (i.e., reduced PAF) characterize SCZ but not BD. Further, individual differences in PAF relate to abnormalities in visual information processing and cognition in SCZ but not BD. In a separate large dataset, SCZ and BD groups showed different patterns of hemispheric alpha activation. BD showed more right-sided FAA compared with SCZ, suggesting a sensitivity for approach motivation and the behavioral activation system in BD. These differential findings are intriguing given the genetic overlap between the two disorders.

## S120. White Matter Integrity in Familial High Risk for Psychosis, Ultra-High Risk for Psychosis and First-Episode Psychosis

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**Background:** White matter microstructure abnormalities are commonly observed in individuals diagnosed with psychosis, including schizophrenia. This study aimed to investigate differences in fractional anisotropy (FA) measures between individuals with first

episode psychosis (FEP), those at ultra-high risk for psychosis (UHR-P), and those at familial high risk for psychosis (FHR-P).
**Methods:** Thirty individuals with FEP, 31 individuals with UHR-P, 18 individuals with FHR-P, and 19 HCs participated in this study. Participants underwent a comprehensive clinical interview and MRI scanning, with diffusion-tensor imaging (DTI) acquired on a 3T MRI scanner to measure fractional anisotropy (FA). Diffusion data were analyzed using FSL's Tract-Based Spatial Statistics (TBSS). Group comparisons were conducted using the randomise tool with 5.000 permutations, applying threshold-free cluster enhancement (TFCE) to correct for multiple comparisons. Statistical significance was set at $p < 0.05$. Age and gender were included as covariates in all analyses.
**Results:** Compared to healthy controls, individuals with FEP and FHR-P showed decreased FA values in the superior longitudinal fasciculus in both hemispheres. Additionally, the FHR-P group exhibited lower FA values in the left superior longitudinal fasciculus compared to the UHR-P group.
**Discussion:** These findings suggest that the integrity of white matter fibers is disrupted in individuals with early psychosis and those at risk for developing this mental disorder. Further studies with larger samples, incorporating changes in structural connectivity within these populations, may provide a better understanding of the neurobiology of psychosis.

## S121. Modeling the Early Exposome: Impact of Positive and Negative Childhood Experiences on Psychotic and Affective Features

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**Background:** Early childhood represents a critical period of heightened sensitivity to environmental factors, during which early experiences play a pivotal role in shaping vulnerability to mental illness including subclinical psychotic symptoms. However, while much research has focused on the detrimental effects of early adversity, fewer studies have explored the protective potential role of positive early experiences, particularly in fostering resilience among at-risk or affected individuals. The exposome paradigm provides a comprehensive framework to model the full range, positive and negative, of early environmental exposures, and has shown promise in predicting psychosis-spectrum disorders. This study aimed to (i) develop an Early Exposome, incorporating both positive and negative experiences and, (ii) explore its associations with subclinical psychotic features and affective symptoms.
**Methods:** The sample is part of the Barcelona Longitudinal Investigation of Sensitivity and Schizotypy (BLISS 2) study, consisting of 1,181 non-clinical young adults (mean age = 22.8; SD = 6.5; 76% female). Participants completed a comprehensive battery of self-reported measures including schizotypy dimensions (Multidimensional Schizotypy Scale Brief), anxiety (Beck's Anxiety Inventory) and depression symptoms (Beck's Depression Inventory-II). To assess early environmental experiences, a total of 145 items from subscales capturing both positive and negative early experiences were included. We conducted a data reduction process to optimize the modeling of environmental variables and identify their underlying structure. This included iterative factor analyses and a final Bifactor Confirmatory Factor Analysis. Linear regression analyses were conducted to test the association of the Early Exposome and its dimensions with psychotic and affective features.

**Results:** The analysis yielded a general Early Exposome score, along with four specific factors: Positive Experiences, Paternal Adversity, Maternal Adversity, and Role Reversal. The general Exposome score, with higher scores reflecting more adversity exposure, was positively associated with all outcome variables, with the strongest impact on depression. Positive Experiences demonstrated a similar but inverse pattern of associations, albeit with weaker effect sizes. Maternal Adversity showed significant positive associations with paranoia as well as positive and disorganized schizotypy while Paternal Adversity did not exhibit any associations. Role Reversal was only associated with positive schizotypy.
**Discussion:** To our knowledge, this is the first study to incorporate both positive and adverse childhood experiences within a multifactorial exposome framework and to examine their impact on psychotic and affective features in a non-clinical sample. The general Early Exposome broadly correlates with increased psychotic and affective symptoms while Positive Experiences is associated with reduced symptomatology, underscoring the protective role of early positive experiences in mitigating risk for subclinical transyndromic manifestations. The differentiation of experiences by parental figure and their differing pattern of associations highlights the need for further investigation into how paternal and maternal dynamics separately influence offspring's risk and resilience to mental health. These findings emphasize the complexity of relational contexts and the co-existence of protective and adverse influences. Further exposome research may inform prevention and intervention strategies targeting modifiable childhood risk and protective factors to lower the population-level incidence of psychosis.

## S122. Neural Correlates of Peripheral Inflammation in Individuals With First-Episode Schizophrenia: A Functional Magnetic Resonance Imaging Study

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**Background:** Evidence from animal and human studies has consistently reported alterations in inflammatory processes in schizophrenia (SCZ), including increased C-reactive protein (CRP) and dysregulation of cytokines. Importantly, functional magnetic resonance imaging (fMRI) research has shown that inflammation affect resting-state brain functional connectivity (FC). In line with evidence in affective disorders revealing alterations in prefronto-striatal FC in association with inflammation, we investigated striatal FC in individuals with first-episode schizophrenia (FES) stratified according to their peripheral inflammation levels, and its correlation with negative symptoms and cognitive performance.
**Methods:** We included 132 individuals with FES (26.9 ± 5.3 years) who underwent resting-state fMRI on 3T scanners as part of the Benefit of Minocycline on negative symptoms of

schizophrenia (BeneMin) trial. Subgroup membership of FES individuals based on inflammatory patterns was predicted by applying a support vector machine model. A seed-based functional connectivity analysis was conducted using bilateral basal ganglia nuclei as seeds. We evaluated psychotic symptoms with the Positive and Negative Syndrome Scale (PANSS) and cognitive performance using the Digit Symbol Substitution Test (DSST).
**Results:** Two main clusters were detected: low inflammation cluster (n = 97) and elevated CRP cluster (n = 30). Compared to the low inflammation cluster, individuals with FES in the elevated CRP cluster presented higher FC between the right accumbens and the left middle frontal gyrus and between the right pallidum and the left precentral gyrus/middle frontal gyrus. Age, sex, body mass index and antipsychotics dose did not influence the FC differences. We found a higher positive correlation between right accumbens – left superior and middle frontal gyri FC and PANSS negative scores in the CRP cluster relative to the low inflammation cluster. The DSST scaled scores presented a higher positive correlation with the FC between the right accumbens and two clusters in the left orbitofrontal cortex and in the left middle temporal gyrus, as well as a negative correlation with the FC between the right accumbens and the bilateral supramarginal gyrus in the CRP cluster relative to the low inflammation cluster. Furthermore, the DSST scaled scores showed a higher positive correlation with the FC between the right pallidum and the left orbitofrontal cortex in the CRP cluster relative to the low inflammation cluster.
**Discussion:** This study represents the first step towards achieving a better understanding of the interplay between inflammation, functional connectivity, negative symptoms and cognitive impairment in FES. Inflammation-related fronto-striatal dysconnectivity may serve as a potential target for novel therapeutic strategies that inhibit inflammation or reverse its effects on dopamine or other neurotransmitter systems.

## S123. Medication Exposure and Mortality in Patients With Schizophrenia

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**Background:** The use of antipsychotics, antidepressants, and benzodiazepines may influence the risk of mortality in people with schizophrenia. However, many observational studies have not accounted for immortal time bias (ITB), which occurs when there is a period during which patients in the exposed group are necessarily alive and misclassified as exposed (the period between start of follow-up and initiation of drug). Ignoring ITB may lead to misinterpretation of the association between these drugs and mortality.
**Methods:** The aims are to examine whether the cumulative dose of antipsychotics, antidepressants, and benzodiazepines is associated with mortality risk in patients with schizophrenia and discuss the potential impacts of ignoring ITB.This cohort study used administrative data from Québec, Canada, including patients aged 17 to 64 years diagnosed with schizophrenia between January 1, 2002, and December 31, 2012. Data analysis was

performed from June 22, 2022, to September 30, 2024. The primary outcome was all-cause mortality, with follow-up from January 1, 2013, to December 31, 2017, or until death. Mortality risk was assessed for low, moderate, and high exposure to antipsychotics, antidepressants, and benzodiazepines. Cox proportional hazards regression models with time-fixed exposure (not controlling for ITB) and time-dependent exposure (controlling for ITB) were performed.
**Results:** The cohort included 32 240 patients (mean [SD] age, 46.1 [11.6] years; 19 776 [61.3%] men), of whom 1941 (6.0%) died during follow-up. No dose-response association was found for antipsychotics with mortality using the time-fixed method. However, high-dose antipsychotic use was associated with increased mortality after correcting for ITB (adjusted hazard ratio [AHR], 1.28; 95% CI, 1.07-1.55; P = .008). Antidepressants showed a reduced mortality risk using the time-fixed method, but only at high doses when correcting for ITB (AHR, 0.86; 95% CI, 0.74-1.00; P = .047). Benzodiazepines were associated with increased mortality risk regardless of the method.
**Discussion:** The findings of this study do not dispute the known efficacy of antipsychotics in schizophrenia, but they call into question the magnitude of long-term mortality benefits.

## S124. Nigella Sativa Oil Modulates Hippocampal Glutamate Levels, Mglur-Ii Expression, and Astrogliosis in a Mouse Model of Dizocilpine-Induced Schizophrenia

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**Background:** Schizophrenia is a complex neuropsychiatric disorder characterized by positive, negative, and cognitive symptoms. Despite extensive research, effective therapies remain elusive. Nigella sativa oil (NSO), a medicinal plant known for its dietary, neuroprotective, and anti-inflammatory properties, may offer potential benefits in treating schizophrenia. However, there is limited research on its neuroprotective effects in this context. This study investigates the modulatory effects of NSO on the hippocampus in a dizocilpine-induced mouse model of schizophrenia.
**Methods:** Sixty 14-week-old male BALB/c mice (23-25g) were divided into five groups (n=12): control (normal saline, 1 mL/kg), NSO (1 mL/kg), dizocilpine-control (0.5 mg/kg), NSO-preventive (NSO for 7 days followed by dizocilpine for another 7 days), and NSO-reversal (dizocilpine for 7 days followed by NSO for another 7 days). Dizocilpine was administered intraperitoneally, and NSO orally. Behavioral tests included the open field test for stereotypic behavior, elevated plus maze for anxiety, and novel object recognition for memory. After behavioral studies, animals were euthanized, brains harvested, and hippocampal glutamate levels were measured spectrophotometrically. Neuronal arrangement, size, and density were assessed using H and E stain, and dendritic arborization was analyzed using Golgi stain. Immunohistochemical analyses were performed to evaluate mGluR-II and GFAP expression. Statistical analysis was conducted using ANOVA at $\alpha$=0.05.
**Results:** Stereotypic behavior was observed in the dizocilpine-control group but was absent in both NSO-treated groups. NSO significantly increased the open arm entry and exploration indices in the preventive and reversal groups compared to the dizocilpine-control group. Novel object recognition performance was also improved in NSO-treated groups relative to dizocilpine-control. Relative brain weight and hippocampal glutamate levels were higher in the NSO-reversal group compared to dizocilpine-control. Neuronal density was modulated by NSO in both the preventive and reversal groups. NSO inhibited the significant neuronal de-arborization seen in the dizocilpine-control group. mGluR-II expression increased in NSO-

treated groups, while GFAP expression, indicating reduced astrogliosis, was significantly lower in NSO-treated groups compared to dizocilpine-control.
**Discussion:** Nigella sativa oil demonstrated neuroprotective effects in a dizocilpine-induced model of schizophrenia, mitigating schizophrenic symptoms through modulation of hippocampal glutamate levels, mGluR-II upregulation, inhibition of astrogliosis, and preservation of neuronal integrity. These findings suggest that NSO may have therapeutic potential in schizophrenia management.

## S125. Comparative Activity of Muscarinic Agonists Ml-007 and Xanomeline in Preclinical Models of Schizophrenia and Cognitive Impairment

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**Background:** Muscarinic activators represent a potential new class of treatments for schizophrenia with a distinctly different mechanism of action than atypical antipsychotics. Based on the pattern of expression in human brain circuitry, M1 and M4 receptors have been considered relevant for the treatment of psychosis and cognitive deficits. Here we characterize a novel investigational M1/M4 agonist, ML-007, that is under development for schizophrenia and Alzheimer's disease psychosis. We present a comparative study with xanomeline, the first-in-class muscarinic to receive approval for schizophrenia.
**Methods:** In vitro assays were used to measure the level of G-protein activation following ligand binding to M1 and M4 receptors. Amphetamine-induced hyperlocomotion, PCP-induced hyperlocomotion, and conditioned avoidance response were used to assess potential antipsychotic activity of muscarinic agonists. M1 and M4 knockout mice were used to assess the contribution of these receptors to activity in the amphetamine-induced hyperlocomotion assay. Improvements in cognition after muscarinic agonist treatment were assessed in the Tg2576 mouse line, a transgenic mouse model of Alzheimer's disease.
**Results:** GTPgammaS assays demonstrated that ML-007 has stronger intrinsic agonist activity at both M1 and M4 receptors compared to xanomeline. Both xanomeline and ML-007 showed robust antipsychotic activity across a range of preclinical models for schizophrenia. However, dose-response experiments in M1 and M4 knockout mice revealed that at low doses, the activity of xanomeline is more sensitive to loss of M4 receptors, whereas ML-007 is more sensitive to loss of M1 receptors. Importantly, in Tg2576 mice, we find that ML-007, but not xanomeline, improved spatial memory and social memory task performance.
**Discussion:** Taken together, our data suggest that both M1 and M4 receptors contribute to antipsychotic activity in preclinical rodent models of schizophrenia, whereas strong agonism at M1 receptors may be required for treating cognitive impairment.

## S126. Positive and Negative Symptoms Changes in Schizophrenia Patients on Antipsychotic Treatment: A Systematic Review and Dose-Response Meta-Analysis

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**Background:** Positive and negative symptoms are critical aspects of schizophrenia. Changes in these symptoms serve as key indicators for measuring the effectiveness of antipsychotic treatment. Our study aimed to explore the relationship between antipsychotic doses and changes in positive/negative symptoms.
**Methods:** We reviewed the Cochrane Schizophrenia Group register (most recently updated on 24th January 2024) and prior systematic reviews to identify fixed-dose randomized controlled trials (RCTs) that assessed the monotherapy effects of 19 antipsychotic drugs in patients with acute schizophrenia. The primary outcome measure was the average change in positive and negative symptoms from the studys' baseline to endpoint, calculated using standard mean differences (SMD) as the effect size metric. To model dose-response relationships, we employed random-effects meta-analyses utilizing the restricted cubic spline approach.
**Results:** We screened 1297 references and identified 155 studies. 110 studies with 370 dose arms (22940 participants) reported on positive/negative symptoms and were evaluated in meta-analyses. Of these, 95% had a duration of < 3 months, 91% of the studies used oral formulations and 32% of the participants were female. Participants in 3 study were experiencing their first episode, while the other studies also included participants with an acute exacerbation of their chronic condition.
The dose-response curves showed that most antipsychotics exhibited comparatively parallel lines, with the negative symptom curve positioned above and the positive symptom curve below, both declining until reaching an inflection point, after which they plateaued.

**Discussion:** The tendencies of positive and negative symptoms changes of one antipsychotic are always the same. This information can help clinicians to titrate and adapt antipsychotic dose.

## S127. Comparative Analysis of Clinical Outcome in Patients Treated With Lai Aripiprazole and Lai Paliperidone Based on 14-Year EMR Data

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**Background:** Long-acting injectable antipsychotics (LAIs) are an effective treatment option for schizophrenia and other severe mental illnesses. Over the last decade, new formulations with extended dosing intervals have been approved worldwide, providing greater flexibility and adherence potential. Prescribing of LAIs has increased in South Korea as well, but real-world data on their usage remain sparse, and the clinical outcomes from LAIs are not well-defined. This study aimed to compare current use and clinical outcomes in patients treated with LAI aripiprazole and LAI paliperidone, which are the most widely used LAI antipsychotics in South Korea.
**Methods:** This retrospective cohort study analyzed electronic medical records (EMR) of patients prescribed LAI aripiprazole and LAI paliperidone at Seoul National University Bundang Hospital from January 2011 to June 2024. Patients with comorbid autism spectrum disorder, intellectual disability, or substance use disorder were excluded. The study compares demographic and clinical characteristics, including LAI prescribing patterns, relapse rates, and changes in concurrent medication use, between patients treated with LAI aripiprazole and LAI paliperidone.
**Results:** A total of 13,232 prescriptions from 521 patients (LAI aripiprazole = 236 patients, LAI paliperidone = 302 patients) were identified. Preliminary analysis shows notable

differences between the two groups. Females accounted for the majority of recipients in both groups, with gender distribution showing significant variation ($p < 0.001$). The average age for LAI aripiprazole recipients was 35.6 years, significantly younger than 40.9 years for LAI paliperidone recipients ($p < 0.001$). Age distributions spanned from 14 to 83 years across all types. The mean (±SD) prescription duration was approximately 51.2 (±46.0) months for aripiprazole and 53.4 (±50.6) months for paliperidone. Additionally, the prescribing pattern differed by location, with specific LAI types dominating certain clinical settings ($p < 0.001$). Relapse rates and concurrent medication changes are under further evaluation.
**Discussion:** By leveraging long-term real-world data from a university hospital, this study highlights significant demographic and clinical differences between recipients of LAI aripiprazole and LAI paliperidone. These findings contribute to the growing body of evidence guiding LAI antipsychotic selection in clinical practice, with the ultimate goal of optimizing individualized treatment strategies and improving patient outcomes. Final analyses will further elucidate these differences and their implications for clinical decision making.

## S128. Long Acting Injectable Antipsychotics Predict Treatment Response to Electroconvulsive Therapy in Patients With Psychosis

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**Background:** Electroconvulsive therapy (ECT) has been reported to have effectiveness in combination with antipsychotic medication in schizophrenia. Patents with schizophrenia treated with long acting injection (LAI) of antipsychotics have been found to have better adherence to treatment than patients treated with oral antipsychotic drugs. To date, there are few established results of treatment response of ECT with LAI in patients with psychosis. The objective of this study is to evaluate clinical outcomes for LAI use group and non-use group with psychosis patients treated with ECT. The study aimed to investigate predictors of treatment response.
**Methods:** The study conducted a retrospective chart review of patients with psychosis who received ECT at Nowon Eulji Medical center, Eulji university, South Korea. Electroconvulsive therapy included both acute ECT and maintenance ECT. The clinical outcomes were defined as decrease in the Clinical Global Impression - Severity scale scores. $\chi 2$ test was used to compare treatment response to ECT with LAI and without LAI. Multivariate logistic regression was employed to identify risk factors.
**Results:** In total, 64 subjects with psychosis underwent ECT during the study period and 48.5% of patients were treated concurrently with both ECT and LAI. Among LAI user group, 26% of patients were injected Aripiprazole, 71% used Paliperidone, and 3% used both. There was no difference in CGI-S scores between the two groups at baseline. Factors associated with a better response to ECT were LAI (67.8% vs 42.4%, P=0.04) and history of ECT (36.4% vs 15.4%, P=0.02), and factors not associated with treatment response included age, diagnosis, use of Clozapine, and history of hospitalization. LAI and history of ECT were identified as significant features for predicting response following ECT.

**Discussion:** In this study, LAI and history of ECT are associated with treatment response among patients treated by ECT. The LAI reliably predicts the treatment response in patients who are psychosis with ECT.

## S129. Risk of Major Adverse Cardiovascular Events With Aripiprazole Versus Olanzapine, Quetiapine, and Risperidone in Severe Mental Illness: A Target Trial Emulation

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**Background:** Antipsychotics, the mainstay of treatment in severe mental illness, can cause cardiovascular adverse reactions which contribute to morbidity and premature mortality. A prescribing strategy which aims to minimise cardiovascular risk might therefore prevent or delay incident major adverse cardiovascular events (MACEs). Evidence suggests that aripiprazole compares favourably to other frequently prescribed antipsychotics on parameters such as weight gain and blood pressure, but there is limited comparative evidence for the longer-term risk of MACE.
**Methods:** Using data from Clinical Practice Research Datalink - we emulated a pragmatic, head-to-head trial of aripiprazole versus olanzapine, quetiapine, and risperidone as antipsychotic monotherapy in UK primary care 2005-2014, with follow-up to 2019. Patient eligibility included: diagnosis of bipolar disorder, schizophrenia, or other non-organic psychoses; age 40-99; and no history of stroke, myocardial infarction, or dementia. The primary outcome was the five-year risk of MACE (a composite of hospitalisation for non-fatal acute myocardial infarction or stroke and cardiovascular death). We used multiple imputation for missing covariates, overlap weighting to minimise confounding, and estimated risks using a weighted pooled logistic model following intention-to-treat and per-protocol approaches.
**Results:** We included 20,404 eligible patients initiating new antipsychotic monotherapy in primary care (aripiprazole, n=1,807, olanzapine, n=7,965, quetiapine, n=5,613, risperidone, n=5,019). The overall mean age was 54 years, with 57% female, 86% white ethnicity, and 41% diagnosed with bipolar disorder. Following imputation and weighting, patients initiating aripiprazole monotherapy had similar five-year risks of MACE as those initiating olanzapine (risk ratio [RR], 1.03, 95% confidence interval [CI], 0.78 to 1.32), quetiapine (RR, 1.02, 95% CI, 0.72 to 1.32), and risperidone (RR, 0.88, 95% CI, 0.67 to 1.17). The five-year risk of MACE was lower among patients initiating and continuing to be prescribed aripiprazole versus risperidone (RR, 0.58, 95% CI, 0.39 to 0.84), but similar for those initiating and continuing olanzapine (RR, 0.77, 95% CI, 0.51 to 1.10) and quetiapine (RR, 0.90, 95% CI, 0.53 to 1.24).
**Discussion:** Initiation of aripiprazole, as compared to olanzapine, quetiapine, and risperidone, did not have a differential average effect on the five-year risk of MACE; but initiation and continued prescription of aripiprazole reduced the risk when compared to continued prescription of risperidone. Caution should be taken when prescribing risperidone on a long-term basis to patients at risk of cardiovascular morbidity. Further research with larger samples is needed to identify the optimal treatment strategies for individual patients and to understand the mechanisms by which continued risperidone use might contribute to a greater risk of MACE compared to aripiprazole.

## S130. Feasibility of Applying a Precision Medicine Approach to Ketogenic Diet Intervention in Serious Mental Illness

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**Background:** The ketogenic diet (KD), long used to treat epilepsy, is now gaining attention as an adjunctive therapy to enhance mood stabilization and alleviate symptoms in serious mental illnesses (SMI) like schizophrenia and schizoaffective disorder. However, the behavioral change associated with KD can be challenging for individuals with SMI. Amae Health's comprehensive outpatient psychiatric care prioritizes physical alongside mental health through precision medicine approaches, positioning it to address these challenges. While clinical trials have begun to investigate the KD in psychiatric populations, the feasibility, acceptability, and impact of implementing the KD in a SMI outpatient setting that emphasizes comprehensive and personalized care remain underexplored.
**Methods:** 10 participants diagnosed with SMI, focusing on a history of psychosis, will be recruited and follow a KD. After a 2-week baseline, participants will undergo a 4 month KD intervention, transitioning from full meal support of 3 meals per day in month 1, to 2 meals per day in month 2, 1 meal per day in month 3, to fully self-prepared KD meals in month 4. Participants will have weekly sessions with Amae's registered dietitian for support in diet adoption and preparing keto-friendly meals. Data collected will include daily blood ketone levels, monthly metabolic markers, Oura ring biometrics (sleep patterns, activity, heart rate data), monthly assessments using the Computerized Adaptive Testing for Mental Health (CAT-MH), Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), Global Assessment of Functioning (GAF), and Quality of Life Scale (QOLS), and monthly acceptability data. Preliminary analyses are based on data from the first 5 participants.
**Results:** The clinical profile of participants and outpatient study setting have impacted the feasibility of the intervention and data collection in early stages. Scheduling external lab visits was difficult alongside care at Amae. 2 participants struggled with maintaining and operating wearable devices, such as charging Oura rings and syncing them reliably. No safety issues in physical health or adverse events have been reported.
Regarding tolerability and acceptability, all participants enjoyed the convenience of prepared meals but felt restricted by the limited variety. 1 participant found the Oura ring uncomfortable and 2 participants felt burdened by finger-pricks for ketone tracking.

Despite these challenges, all participants achieved ketosis (ketone levels of 1–3 mmol/L). Improvements were observed in psychiatric symptoms, mood, quality of life, and functioning. CAT-MH module scores decreased by 25% for psychosis, 55% for depression, and 22% for anxiety. Sleep efficiency improved by 12%, average REM sleep increased by 19%, and resting heart rate decreased by 6%. Qualitatively, participants reported mood stabilization, increased energy, weight loss and clearer skin.

Data collection is ongoing, and comprehensive results on feasibility (e.g., adherence, tolerability), acceptability, and outcomes will be evaluated upon study completion.

**Discussion:** Preliminary results support the feasibility and acceptability of implementing the KD in a comprehensive outpatient setting for patients with SMI. Initial data indicate potential benefits in psychiatric symptoms and health-related biomarkers. Further research with larger cohorts and randomized controlled trials is necessary to confirm these results and evaluate the diet's effectiveness in outpatient care. Clinicians observed that adherence to the KD enhanced overall treatment adherence and served as an effective model for implementing broader behavioral interventions. Funding for the study was generously provided by the Baszucki Group and Metabolic Mind.

## S131. Impact of Nutritional Interventions on the Quality of Life in Schizophrenia Spectrum Disorders – A Scoping Review

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**Background:** Schizophrenia is a chronic condition that requires long-term management. Quality of life is an important outcome measure for individuals diagnosed with schizophrenia, allowing to track changes over time and evaluate whether interventions lead to sustainable improvements. Nutrition and dietary interventions are an underutilized treatment for tackling the metabolic consequences of mental illness, which is now recognized as having increased importance in the management of schizophrenia. This study examines the impact of nutrition and dietary interventions on quality of life outcomes for those with schizophrenia.
**Methods:** A systematic review of the literature was conducted, assessing the impact of nutritional interventions on quality of life outcomes in individuals with a diagnosis of schizophrenia.
**Results:** A total of 982 articles were screened, of which nine articles met the inclusion criteria. Quality of life measures varied across studies, which made comparison across studies challenging. Previous studies had relatively small sample sizes and did not have long follow-up durations. Some of the studies found that dietary intervention such as counselling, weight management programs, as well as food diaries and nutritional education improved quality of life whereas others did not detect any effect.
**Discussion:** The review provides preliminary evidence that nutrition and dietary interventions may benefit quality of life among individuals with schizophrenia. There were however substantial limitations in studies highlighting the need for further research. The paper also highlights the need to standardize assessment tools for future quality-of-life research.

## S132. Social Cognition and Cognitive Flexibility Sustaining the Neurodevelopmental Hypothesis in Schizophrenia: A Rehabase French Cohort Study

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**Background:** the REHABase cohort is a French national initiative aimed at improving understanding and care for individuals with severe and persistent mental health disorders particularly schizophrenia. it is a prospective, multi center cohort of volunteer participants from 22 psychosocial rehabilitation centers located across France. a wide range of sociodemographic clinical, functional and cognitive evaluation data enables ongoing

monitoring of individuals participating in psychosocial rehabilitation care. we focused cognitive flexibility and social cognition according to the neurodevelopment hypothesis of schizophrenia.
**Methods:** we selected 427 patients diagnosed with schizophrenia from REHABase. we present a descriptive analysis of the cohort. these patients were tested for cognitive flexibility (international commission test ICT) and social cognition (MASC). we study the correlation and the variance of these cognitive data through the criteria of the age of onset of the illness and the duration of the disorders.
**Results:** we describe 427 patients from the REHABase cohort. we show a positive correlation between cognitive flexibility and the age of onset. the variance of cognitive flexibility and social cognition is explained by the age of onset.
**Discussion:** the link between early onset and cognitive flexibility sustains the neurodevelopemental hypothesis suggesting that early neurodevelopemental anomalies contribute to long term impairments in cognitive flexibility and increase vulnerability to schizophrenia. This motivates the involvement of clinicians in the implementation of databases that capture real world data in routine care for schizophrenia.

## S133. We Like to Move it! Determinants of Increased Metabolic Health Risk Related to Antipsychotic Medication in Schizophrenia Spectrum Disorders

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**Background:** Unwanted weight gain represents a major side effect of the treatment with second-generation antipsychotics posing a significant factor for increased health risk in patients with schizophrenia spectrum disorders (SSD). Indeed, counteracting health risk factors to reduce increased mortality is gaining more and more attention in the treatment of SSD. Besides antipsychotic-induced weight gain, modifiable lifestyle factors, such as unhealthy dietary habits and reduced physical activity in daily life may also contribute to increased health risks in this patient group. In this ongoing longitudinal study (goal N=100) we are specifically interested in the identification of determinants for metabolic health risk in SSD to develop therapeutic approaches for risk reduction. One such approach includes exercise therapy as a complementary intervention, which may additionally result in improvement of cognitive and psychosocial functions.
**Methods:** Inclusion criteria comprise indication for antipsychotic treatment for at least six months due to a diagnosis of SSD. Health risk is assessed via blood analysis including cholesterol (LDL,- HDL-Chol) and HbA1c, waist circumference (given as percent of reference value), body mass index (BMI) and body composition, i.e. fat mass and fat free mass. Participants complete an incremental stepwise exercise test on a bicycle to determine objective physical fitness defined by workload (per kg body weight) at aerobic-anaerobic threshold (AT) together with perceived exertion, lactate levels, and heart rate at AT. Furthermore, hand grip strength is assessed. Dietary habits, weekly physical and sport activity, and subjective fitness levels on a visual analogue scale from 0-100% are also assessed as modifiable predictors of health risk factors. Moreover, disease-related data including current symptom expression and level of self-efficacy, illness duration, number of different antipsychotic agents (AP) and current medication are recorded.
**Results:** Preliminary cross-sectional analyses of baseline data from 20 participants (10 females, 32.1 ± 19 years (mean ± SD), BMI 31.5 ± 1.5, WC 112.7 ± 4.0%, Olanzapine

equivalents 14.1 ± 2.4, number of AP 3.3 ± 0.35, subjective fitness level 43.9 ± 5.3%) suggest that BMI and waist circumference are best predicted by subjective estimates of fitness levels ($R^2$=-0.283; β=-0.544; p=0.007 and $R^2$=0.254; β=-0.511; p=0.004, resp.) and the number of previously taken antipsychotics ($R^2$=0.196; β=0.454; p=0.018 and $R^2$=0.374; β=0.612; $p < 0.001$, resp.). These two factors explain 47.9% of variance in BMI and 61.8% of variance in waist circumference. Furthermore, higher waist circumference is associated with lower self-efficacy ($R^2$=0.565; β=-0.761; p=0.002). HDL cholesterol levels are predicted by the dietary score ($R^2$=0.225; β=0.515; p=0.020), while the workload at AT predicts 32.6% of the variance in HbA1c ($R^2$=0.326; β=-0.609; p=0.012) and 21.6% of the variance in LDL cholesterol ($R^2$=0.216; β=-0.515; p=0.034). No further associations are yet observed.
**Discussion:** Preliminary analysis suggests that primary determinants of health risk factors include the number of previously taken antipsychotic agents, individual estimates of subjective fitness levels and self-efficacy, and dietary score. Additionally, our findings confirm the notion that objective fitness in SSD treated with antipsychotics is directly related to health risk factors such as HbA1c and LDL-cholesterol. This constellation of findings underlines the importance of subjective fitness estimates for predicting individual health risk. Treatment strategies for increasing self-efficacy may help patients to engage more in personalized exercise training meeting their preferences.

## S134. Identifying Patients With Tardive Dyskinesia Using Schooler-Kane Criteria and Diagnostic Codes in Real-World Data

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**Background:** Tardive dyskinesia is a severe and often irreversible movement disorder most frequently associated with antipsychotic treatment. Timely assessment, recognition, and diagnosis of TD remain significant barriers to treatment. The Abnormal Involuntary Movements Scale (AIMS) is a structured assessment tool typically used to diagnose TD. However, usage of the AIMS may vary in clinical practice and frequency of ICD diagnosis alongside or following a positive AIMS assessment is unknown. The study analysed electronic health records (EHRs) to investigate the prevalence of ICD diagnoses among patients with AIMS records.
**Methods:** This is a retrospective analysis of de-identified EHR data. Data were collected during provision of routine healthcare across multiple institutions in the United States (US) throughout years 1999–2024 (NeuroBlu v24r5). Study population included patients with at least one AIMS record. Within the population, the proportion of patients with evidence of TD was estimated using Schooler-Kane criteria: i) cumulative exposure to an antipsychotic for at least 3 months, ii) no other lifetime diagnosis associated with abnormal movements (Huntington's, Parkinson's, Wilson's, tic disorders, or dystonias), and iii) at least moderate dyskinetic movements in one body area (≥ 3 on AIMS) or mild dyskinetic movements in two body areas (≥ 2 on AIMS). Diagnosed TD was defined as an ICD-10 code of G24.01. The proportion of patients with evidence of TD via the AIMS that also had a recorded ICD diagnosis of TD was calculated.
**Results:** Overall, 95,108 patients with a complete AIMS record were identified. Of those, 1,507 (1.6%) met Schooler-Kane criteria for evidence of TD in the AIMS. ICD diagnoses of TD were relatively infrequent, such that 190 (12.6%) of patients who met the Schooler-Kane criteria also had an ICD diagnosis of TD at any point in the EHR record. The ICD TD diagnosis was recorded after an AIMS positive measurement in 161 (84.7%) of patients. In

these patients, the median (IQR) time between the first AIMS assessment positive for TD and first recorded ICD diagnosis of TD was 134 days (0, 904).
**Discussion:** Our findings further suggest a potential underdiagnosis of tardive dyskinesia (TD) in routine clinical practice. A methodological strength of this investigation is the implementation of the Schooler-Kane criteria, which provides a standardized diagnostic framework that, while validated, is not typically employed in routine clinical assessments. Our analysis identified an approximately four-month interval between initial positive AIMS assessments and subsequent ICD diagnosis of TD, potentially indicating a delay in diagnosis. The potential delay in diagnoses may result in lower or delayed TD treatments.

## S135. Impact of Mental Health Training on Knowledge, Attitude and Practices on Traditional and Faith Healers and Community Health Workers in Ibadan, Nigeria

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**Background:** Help-seeking for serious mental illness (SMI) in low-and-middle-income countries (LMICs) is pluralistic, with traditional and faith healers (TFHs) often being the initial, sometimes the only sources of help or the preferred first contact for mental disorders. In this study, we explore TFHs and community health worker's (CHWs) knowledge, attitudes and practices (KAP) towards mental health, and their perceptions of collaboration with biomedical services. Additionally, considering the challenge of limited access to biomedical services and the reliance on TFHs in slum communities in LMICs, we sought to evaluate the impact of an intervention training workshop on KAP of TFHs and CHWs.

**Methods:** This mixed methods study was carried out in Ibadan, Nigeria. Qualitative data was collected from focus group discussions, while quantitative data was obtained through surveys, both administered at two time points: directly before (pre-) and after (post-) a 3-day intervention workshop training.
The training included seven didactic and interactive sessions on collaborating with biomedical teams, overview of mental health, mental health services, human rights, common and serious mental disorders, and referrals.

Participants were clustered into groups of 25 based on their respective models of practice. Six facilitators, who were mental health professional and people with lived experience, conducted the sessions.

Participants were asked to complete a KAP questionnaire which assessed their views on the following themes: knowledge and attitude assessment, signs and symptoms, aetiology, shame and stigma, treatment/intervention, and referral. Questions were binary choices (true/false) from which we calculated the percent change of true responses. Qualitative data was analysed using thematic analysis.

**Results:** 137 participants took part (n=62 TFHs, Mage=47.8±11.75; n=75 CHWs, Mage=38.7 ±10.3).
Knowledge and attitude towards mental health improved post training by 11% for TFHs and 16% CHWs, as did knowledge regarding signs and symptoms by 3% for TFHs and 5% for CHWs, and aetiology by 15% for TFHs and 6% for CHWs.

Attitudes towards shame and stigma worsened post training in TFHs by 2% and improved by 9% for CHWs suggesting that beliefs around stigma and behavioural changes may take longer to shift particularly for TFHs.

Knowledge towards treatment/intervention post intervention improved by 4% in TFHs and by 6% in CHWs. For referral knowledge, TFHs improved by 5% in contrast to CHWs who improved by 1%.

Qualitatively, participants reported learning the importance of collaboration between TFHs and biomedical services and overall gained knowledge about mental illnesses. Post training, participants reported that mental illness can affect anyone, are treatable, not a sign of weakness, and that shame and stigma are unhelpful. In their practice, participants reported that they would listen actively, with empathy, without judgment, would refer patients to biomedical practitioners and would cease harmful practices.

**Discussion:** The interactive training delivered in this study led to increased knowledge, challenged preconceived notions, and more positive practices among both TFHs and CHWs. The improvements in knowledge, attitudes and practice achieved in this study indicates that there is window of opportunity for future collaborative activities between traditional healthcare providers and biomedical providers, despite there still being work to do to ensure proper collaboration and trust building.

## S136. Psychotic-Like Experiences of First-Generation Migrants From Pakistan

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**Background:** Epidemiological studies have highlighted an established association between migration and psychosis. It is also well known that this risk is not the same across all migrant groups. Notably, Black migrants are at significantly higher risk than other ethnic groups. However, the evidence is less clear in other groups and it is unclear why this risk may differ. Sample sizes and statistical methods limit our ability to understand this therefore we used qualitative methods to begin to explore what the experiences of psychosis are in Pakistani migrants.
**Methods:** We used interpretative phenomenological analysis (IPA) to explore Pakistani migrants experiences of psychosis. We interviewed six first-generation Pakistani migrants (four female, two male) living in the UK who had experienced psychosis. Participants were recruited in the community using existing networks and third-sector community organisations.
**Results:** Six general experiential themes were identified into two distinct time periods.

The lead up to and during first-episode psychosis: The three themes identified were: 1. BREAKDOWN OF SIGNIFICANT CLOSE RELATIONSHIP AND COMMUNITY ISOLATION EVOKES EMOTIONAL TURMOIL; 2. PSYCHOTIC-LIKE EXPERIENCES ARE CONCOMITANT WITH DETACHMENT FROM SELF, LACK OF CONTROL AND DISCONNECTED RELATIONSHIPS; 3) NAVIGATING SOCIAL STIGMA: STRUGGLING WITH DISCLOSURE, OWNERSHIP OF EXPERIENCE AND FEAR OF SHAME

Living with and navigating managing life with psychosis: 1) ADAPTING TO NEW LIFE: DEVELOPING ACCEPTANCE AND RECONNECTION WITH SELF AND SURROUNDINGS; 2) TRANSFORMING SOCIAL WORLD: NEGOTIATING FRACTURED FAMILY RELATIONSHIPS AND FINDING SOLACE IN SHARED EXPERIENCE; 3) RECENTRING FAITH: RECONNECTION AND RECLAIMING PRACTISE ENABLES SENSE OF STRENGTH AND ROUTINE

**Discussion:** This analysis is still in progress but will be complete at the time of the conference.

## S137. Creating Shared Realities in Psychosis Treatment: An Ethnographic Study of the Psychiatrist-Patient Relationship

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**Background:** Creating shared realities between psychiatrists and patients is a complex task, particularly for patients experiencing the altered reality of psychosis. Advocates for patient-centered care have long critiqued the Western psychiatric system for the perceived authoritarianism in medical care, and for the failure of clinicians to explore patients' subjective realities. Despite the rise of patient-centered care and shared decision-making models, both clinicians and service users report difficulties in developing mutual understandings within the clinical encounter and translating this into effective care practices. Thus, it is unclear what role the subjective perspective of the patient plays compared to the perspective of the psychiatrist in the treatment encounter, and if or how the patient's subjectivity is used to create a shared reality during psychiatric treatment. The concept of intersubjectivity offers a conceptual framework to explore how the realities of psychiatrists and patients may intersect, and how shared realities may be constructed within the psychiatric treatment setting. However, limited work to date has explored how psychiatrists and patients construct shared, intersubjective realities during psychosis treatment.
**Methods:** This study involved 9 months of ethnographic fieldwork within a major healthcare system that offers specialty psychosis care in the southeastern United States. Fieldwork involved observations of two specialty psychosis clinics and one general psychiatry clinic. Specifically, observations involved studying the real-time dynamics between psychiatrists and patients during treatment visits, and examined how shared understandings developed or failed to develop over the course of treatment. In addition to clinical observations, this study included in-depth interviews with fieldwork participants and other key informants, including 25 interviews of psychiatrists treating patients with psychosis, and 23 interviews of patients receiving psychosis treatment.
**Results:** Results revealed that the development of a shared reality or understanding between psychiatrists and patients in the context of a treatment relationship for psychosis is a complex, arduous, and often subtle process. Both interview and ethnographic data revealed that psychiatrists and patients often markedly differed in their definition and conceptualization of how to create a shared understanding or joint reality in the treatment space, and only occasionally overlapped in the manner in which their own subjective perspectives conceptualized the meaning of the illness, the treatment encounter, and the most effective relational dynamics. For example, while many psychiatrists focused on developing goals of care with patients, and felt that a shared understanding could be forged through

understanding the patient's goals, patients often noted that they hoped a shared reality would instead involve the psychiatrist understanding their emotions, their broader worldview, or in some cases, the experiential components of the psychosis itself. Given the often highly disparate subjectivities and varying views on how to bridge the subjectivities, treatment relationships varied significantly in whose subjectivity, the psychiatrist's or the patient's, delineated the contours and boundaries of the shared reality. In many psychiatrist-patient dyads, patients conformed to the psychiatrist's subjective reality, while in others, the psychiatrist demonstrated more flexibility and harmonization towards the patient's reality. For example, a patient conforming to the psychiatrist's reality may have presented as letting the psychiatrist lead a discussion on goals of care, while making only minimal mention of the content of the psychosis itself, despite the patient privately hoping for a sense of understanding of those experiences from the psychiatrist, instead of discussing goals of care. In contrast, the psychiatrist conforming to the patient's subjectivity often involved a more open-minded attunement to what was important to the patient, and creating time and opportunities for that to develop. Often, these encounters built upon each other over time, and led to more extreme disconnects or overlaps with time. Finally, findings revealed the fundamental impact of power and trust on this process, as many patients reported feeling coerced to conform to the psychiatrist's viewpoint, even in the absence of overt, forced treatment. Despite the complexity of the process, during times in which a shared understanding did emerge, participants reported that it was highly rewarding for both parties, and was often described by patients as the means to effective treatment.
**Discussion:** The findings indicate important implications for psychiatric care for those experiencing psychosis, and suggest possible paths forward for a deeper understanding of shared meaning in psychiatric treatment. The ramifications of intersubjective engagement may be significant, as patients with psychosis stand to greatly benefit from more attuned and engaged clinicians. Given the complexity of these processes, these findings underscore the need for further exploration of the process of intersubjectivity during psychosis treatment.

## S138. Transcranial Direct Current Stimulation (TDCS) Combined With Computer-Based Cognitive Training to Reduce Food Cravings and Binge Eating in Individuals Taking Antipsychotic Medication

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**Background:** People with schizophrenia have high rates of weight and metabolic disorders induced by antipsychotic medication which may increase appetite, food cravings and binge eating. The ENTER study evaluated the feasibility of combining real versus sham transcranial direct current stimulation (tDCS) with approach bias modification training (ABM) to reduce food cravings and binge eating in those taking antipsychotics.
**Methods:** This double-blind, parallel-group, sham-controlled trial included adults diagnosed with schizophrenia or schizoaffective disorder, prescribed a stable dose of antipsychotics. Participants were randomly allocated to receive five sessions of ABM with real or sham bilateral tDCS (anode over the right/cathode over the left) to the dorsolateral prefrontal cortex over 3 weeks. Primary outcomes were changes in food craving and binge eating from baseline (T0) to post-treatment (T1) and 2-week follow-up (T2). Food craving was assessed with the Food Craving Questionnaire-Trait (FCQ-T), and bingeing with the Eating Disorder Examination Questionnaire (EDE-Q). Secondary outcomes were changes in body mass index

(BMI), psychopathology and approach bias to food. Symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS), cognition with the Montreal Cognitive Assessment (MoCA), impulsivity with the Barratt Impulsiveness Scale (BIS-11) and mood with the Depression, Anxiety, and Stress Scale (DASS-21). Approach bias towards food was assessed by the Food Approach-Avoidance Task (F-AAT) and the Stimulus-Response Compatibility Task (SRCT).
**Results:** 28 patients were randomised. Baseline characteristics were similar in both groups: on average participants were 46.8years old (SD = 9.3), had an illness duration of 12.9 years (SD = 8.8), mild symptoms of schizophrenia (PANSS-6: M=12.7, SD=4.9), and mild cognitive impairment (MoCA: M = 23.5, SD = 3.5). Participants had an average BMI of 32.5 kg/m² (SD = 6.4), 6.3 binge eating episodes/28 days (SD = 10.7) and scored 52.3/90 (SD = 18.9) in the FCQ-T. Completion rates were high (T1=85.7% and T2=78.6%); blinding accuracy was 46.4%. Between-group effect-size analyses were not significant. Small-to-medium effect sizes in binge eating (T2-T0) favored ABM + real tDCS (real: M= -6.5, SD = 13.9; sham: M = -2.4, SD = 6.2; d' = 0.4, 95% CI -1.1, 0.4), and changes in food craving scores favored ABM + sham tDCS (real: M=-4.3, SD=16.9; sham: M = -8.1, SD = 13.7; d' = -0.25, 95% CI -0.5, 1.0). However, within-group analyses showed the real tDCS group had significant reductions in SRCT approach bias to food (M = -345.6 ms, SD = 449.7, p = 0.003) and SRCT approach-avoidance bias to food (M= -21.7 ms, SD = 43.5, p = 0.002), with significant medium-to-large and large effect sizes, respectively (d' = -0.769 and -0.887). Significant reductions in change scores between T2-T0 were observed in binge eating (M = -6.7, SD = 9.3, p = 0.049), and DASS total score (M = -1.7, SD = 19.4, p = 0.0016), with moderate and large effect sizes, respectively (d' = -0.718 and d' = -0.933). In the sham group, significant reductions were only seen in DASS total scores (M = -16.8, SD = 26.2, p < 0.001; d' = -1.48) and DASS anxiety scores (M = -5.8, SD = 8.8, p = 0.014; d' = -0.75), with large and moderate effect sizes.
**Discussion:** Combining tDCS with ABM may be a promising intervention for mitigating weight-related side effects of antipsychotics. In the real tDCS group, reduced attention bias to food, followed by mood improvement and less binge eating, suggests there are synergistic effects between tDCS and cognitive training in this population. A larger randomised controlled trial is required to validate the findings and confirm their consistency in between-group comparisons.

## S139. Metformin for the Prevention of Antipsychotic-Induced Weight Gain: Guideline Development and Consensus Validation

Aoife Carolan*[1], Caroline Hynes-Ryan[1], Faye Carrington[2], Sri Mahavir Agarwal[3], Rita Bourke[4], Walter Cullen[2], Fiona Gaughran[5], Margaret Hahn[6], Amir Krivoy[7], John Lally[5], Stefan Leucht[8], John Paul Lyne[9], Robert McCutcheon[10], Michael Norton[9], Karen O'Connor[11], Benjamin Perry[12], Toby Pillinger[5], David Shiers[13], Dan Siskind[14], Andrew Thompson[15], Donal O'Shea[16], Dolores Keating[1], Brian O'Donoghue[17]

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**Background:** Overweight and obesity are highly prevalent in people with severe mental illness. Antipsychotic-induced weight gain (AIWG) is one of the most commonly reported and distressing side effects of treatment and people living with severe mental illness (SMI) place a high value on the avoidance of this side effect. Metformin is the most effective pharmacological intervention studied for the prevention of AIWG yet clear guidelines are lacking and evidence has not translated into practice.

The aim of this research was to develop a guideline for the use of metformin for prevention of AIWG using a validated framework for guideline development.

**Methods:** The appraisal of guidelines for research and evaluation II instrument (AGREE II) was followed for guideline development. Literature was reviewed to address key health questions. The certainty of evidence was evaluated using GRADE methodology and an evidence-to-decision framework informed the strength of the recommendations. A consensus meeting was held where the algorithm and strength of recommendations were agreed. Independent external reviews were conducted involving experts in the area of metabolic psychiatry, general medicine and patient and public partners.

The guideline was retrospectively applied to a dataset of young adults with first episode psychosis to estimate eligibility for metformin.

**Results:** Metformin is the only pharmacological agent that has demonstrated efficacy for preventing AIWG. Co-commencement with antipsychotic medicines can reduce the extent of weight gain by 4.03kg (95% CI -5.78kg to -2.28kg) compared to controls. A guideline for the use of metformin for prevention of AIWG was developed with specific recommendations for co-commencement of metformin at initiation with an antipsychotic or commencement if certain criteria are present. Core recommendations were graded as strong by consensus agreement.

Retrospective application of the guideline to a dataset of 77 young adults, aged 15-24 years, with first episode psychosis revealed that 43% (n= 33) met criteria to co-commence metformin and 26% (n= 20) met criteria to commence metformin within the first year of treatment with an antipsychotic.

**Discussion:** This is the first published evidence-based guideline using the AGREE II framework and GRADE methods for the use of metformin to prevent AIWG incorporating recommendations for co-commencement. Implementation and evaluation of the guideline will be supported by a shared decision-making package and assessment of barriers and facilitators to implementation.

## S140. Psychological Interventions for Persons With Co-Occurring Psychotic and Trauma Symptoms: A Systematic Review and Meta-Analysis of Symptom Outcomes, Attrition, and Tolerability

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**Background:** Persons diagnosed with primary psychotic disorders (PPDs) commonly report traumatic experiences and resulting symptoms, which are associated with increased symptom severity, perseverance, and worsened treatment outcomes. Approaching trauma in the context of psychosis was initially feared to lead to exacerbation of psychotic symptoms and relapse, especially when including elements of exposure. Recently, psychological interventions have increasingly targeted these co-occurring symptoms. However, information on the efficacy, tolerability, and acceptability of these interventions is limited in this evolving field. To address this gap, we conducted a systematic review and meta-analysis of relevant trials.
**Methods:** In July 2024, CINAHL, Embase, PubMed, PsycINFO, ClinicalTrials.gov, and the Web of Science Core Collection were systematically searched for randomized controlled trials (RCTs) of psychological interventions for persons aged 16+ with co-occurring psychotic and trauma symptoms. Following preregistration (CRD42024553934), the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed where possible, and bias was assessed with A Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB-2). The primary outcomes were psychotic and trauma symptoms, secondary outcomes were depressive and anxiety symptoms, social functioning and quality of life, as well as adverse events, symptom exacerbations, and attrition rates. A minimum of five effect sizes were required to perform random-effects meta-analysis and ten for mixed-effects meta-regression.
**Results:** 10 RCTs with 559 participants were included, eight of which showed at least some concerns of bias. Samples varied in symptom severity, whereas interventions varied in duration,
treatment focus, setting, measured symptoms, and intervention approach. All interventions approached trauma symptoms, while psychotic symptoms were not explicitly targeted in the majority of studies. Two distinct approaches could be made out: Primary exposure-based trauma-focused approaches (eye movement desensitization and reprocessing [EMDR], prolonged exposure [PE], and written exposure) and non-exposure-based approaches (acceptance and commitment therapy [ACT], cognitive behavioral therapy [CBT], and cognitive therapy). Compared to usual treatment and active control groups, effect sizes did not significantly favor overall interventions at reducing total psychotic (g = 0.26, 95% CI [–0.17, 0.70]), positive (0.21, [–0.02, 0.44]), and negative (–0.03, [–0.50, 0.45]) symptoms at post-treatment as well as at follow-up. Notably, the small significant effect on trauma symptoms at post-treatment favoring the intervention groups (0.33, [0.08, 0.57]) was attributable to the medium effect of the exposure-based trauma-focused interventions (0.65, [0.39, 0.91]), rather than those not employing exposure (0.06, [–0.21, 0.33]), while the small significant effect at follow-up (0.34, [0.12, 0.56]) was not differentially attributable. Anxiety (0.24, [−0.21, 0.68]) and depressive (g = 0.26, [−0.01, 0.53]) symptoms were not improved significantly at post-treatment, while a small significant effect favored intervention groups concerning the reduction of anxiety symptoms (0.39, [0.02, 0.76]) at follow-up. Functional

outcomes did not significantly favor either group. Treatment dropout was similar in proportion (17%) to typical treatments for trauma and psychosis. Exposure-based interventions had a slightly higher aggregated treatment dropout rate (19%). Dropout effect sizes were highly heterogeneous and may have been higher due to evidence of publication bias. The majority of studies reporting on tolerability (4/5) were exposure-based and narrative synthesis showed the scarcity of adverse events, which tended to be unrelated to treatment, although some to-be-expected and transient trauma symptom exacerbations occurred during two exposure treatments.

**Discussion:** Findings suggest that psychological interventions for persons with psychotic and trauma symptoms are safe, tolerable, and efficacious at treating trauma symptoms when employing exposure. These findings challenge commonly held fears of symptom exacerbation with exposure-based interventions in psychosis and could help to implement them for persons currently in need. Considering the substantial risk of bias, small number of studies, non-significant results for other clinical and functional outcomes, and heterogeneity between studies not accounted for in this analyses, further research is needed. This study did not rely on funding and has no conflicts of interest to declare.

## S141. Obstacles and Facilitators of Intimate Relationships: An Exploratory Study in Schizophrenia and the General Population

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**Background:** Persons with lived experience of schizophrenia (PWLES) frequently report difficulties in their intimate relationships compared to the general population. Literature regarding the factors influencing these relationships remains scarce, especially concerning their relative importance and the role of environmental factors. This study aimed to characterize the relevance and impact of environmental, personal and impairment-related factors on intimate relationships in PWLES and the general population.
**Methods:** On the basis of the International Classification of Functioning, an online questionnaire was developed to explore the relevance (whether the factor is relevant for the participant) and the impact (obstacle, facilitator, or having no influence) of 17 factors. Descriptive analyses were performed on responses from 65 PWLES and 444 participants from the general population.
**Results:** The great majority of barriers and facilitators of intimate relationships are shared by both groups. However, because they are reported far more frequently by PWLES, some obstacles appear more specific to this group (traumatic experiences, discrimination, cognitive difficulties, pharmacological treatment). Conversely, some facilitators are more frequently reported by the general population (housing intimacy, social support, sexual self-esteem). The findings highlight the significant impact of personal, environmental, and impairment-related factors on intimate relationships of both PWLES and the general population.
**Discussion:** This study provides insights into understanding the disparities in social participation between these groups, and underscores the potential of health professionals to provide valuable support in this domain, by identifying barriers and facilitators that PWLES may face in daily life.

## S142. Incorporating a Resilience-Based Model to Predict Successful Transition of Schizophrenia Patients From ICM to Shared Care

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**Background:** Schizophrenia (SCZ) spectrum disorder is one of the most debilitating psychiatric illnesses. SCZ patients are often referred to intensive case management (ICM) services; a high-intensity treatment model characterized by small caseloads and frequent contact for more targeted care. In Canada, ICM services are limited in capacity and inaccessible to many markedly ill patients who would benefit from this intervention. To accommodate new SCZ patients, eligible individuals must be transitioned from ICM to less intensive shared care models, which involve collaboration between family physicians and consulting psychiatrists to provide accessible mental health care. However, there is a limited understanding of which ICM patients are best suited for successfully transitioning to shared care. In this study, we aim to develop a prognostic prediction tool to identify SCZ patients eligible for a successful transition from ICM to shared care. The prognostic tool will use key clinical variables to predict which SCZ patients are most likely to remain clinically stable post-transition to shared care. In addition, we intend to identify the most sensitive standardized clinical rating scales with a focus on functioning, recovery, and symptom severity to further optimize the prediction tool.

**Methods:** In this cross-sectional pilot study, we recruited SCZ patients treated in ICM clinics (n=11) and shared care clinics after one year post-ICM transition (n=8) from St. Michael's Hospital. Quantitative data, on symptom severity and functioning, were collected as distal (available at ICM discharge) and proximal (measured at study entry) predictors using standardized clinical scales. Distal predictors include clinical and sociodemographic variables such as age at onset and lifetime history of substance use disorder. Proximal predictors include symptom severity, functioning and recovery, and insight and therapeutic alliance variables, which will reflect the patient's status at study entry. Initially, a prognostic algorithm was developed to predict a successful transition to shared care using only distal predictors. Subsequently, a logistic regression model with proximal predictors was applied to identify key variables that could improve the accuracy of the prognostic tool.

**Results:** Distal predictors showed no significant differences between ICM and shared care patients. However, on average ICM patients had a slightly earlier illness onset (ICM= 27 years, SC= 28 years), more childhood trauma exposure based on the Childhood Trauma Questionnaire (ICM= 65, SC= 58), and a higher prevalence of suicide attempts (ICM= 50%, SC= 14.3%) compared to the shared care group. The proximal predictors were not statistically significant but revealed a notable trend in drug severity scores, with the Drug Abuse Screening Test approaching significance (p= 0.19). Additionally, the shared care group exhibited slightly higher levels of perceived stress (ICM= 28.5, SC=31.7) and stressful life events (ICM=125, SC=182), as well as a marginally smaller resilience index to stress.

**Discussion:** Our prediction tool revealed no significant differences in symptom severity or recovery between patients in ICM and those in shared care. This suggests that transitioning patients with SCZ from ICM to shared care does not adversely affect their stability or symptom management. However, our measures of stress suggest an increase in the shared care group, indicating that additional support may be needed to help patients manage stressful life events after transitioning to shared care. Developing a robust prognostic prediction tool for transitioning patients with SCZ to shared care will enable safer, more successful discharges, ultimately enhancing the capacity and efficiency of ICM services.

## S143. Subjective Well-Being in Early-Phase Schizophrenia Patients Using Long-Acting Injectable vs Oral Antipsychotic Drugs: Data From the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST)

Anna - Theresa Schulze[1], Franziska Tutzer*[1], Timo Schurr[1], Fabienne Post[1], Beatrice Frajo-Apor[1], W. Wolfgang Fleischhacker[1], Alex Hofer[1]

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**Background:** This study aimed to evaluate potential differences in subjective well-being among patients with schizophrenia (SZ) randomly allocated to either long-acting injectable (LAI) or oral antipsychotic medication, as well as the impact of symptomatology, pharmacological side effects, and demographic characteristics on subjective well-being.
**Methods:** Patients aged ≥ 18 years and meeting DSM-IV criteria for SZ were recruited and followed
up for up to 19 months as part of the "European Long-acting Antipsychotics in Schizophrenia Trial"

(EULAST) trial. Subjective well-being was assessed using the Subjective Well-being under Neuroleptic Treatment scale (SWN) and possible differences between the type of formulation of antipsychotic drugs regarding subjective well-being were analysed by a linear mixed-effects analysis

approach. Multivariable and comprehensive models were implemented to investigate the potential

effects of age, sex, symptomatology (Positive and Negative Syndrome Scale [PANSS]), and side

effects of medication (Systematic Monitoring of Adverse events Related to TreatmentS [SMARTS],

St. Hans Rating Scale for Extrapyramidal Syndromes [SHRS]) on SWN change.

**Results:** There was no significant difference in SWN change in 364 patients undergoing LAI or oral
antipsychotic treatment ($p = 0.2780$) over time. PANSS dimensions (p values $< 0.0001$), SMARTS (p

$< 0.0001$) and several SHRS subscales (subjective ($p = 0.0035$) and objective ($p = 0.049$) akathisia,

parkinsonism ($p < 0.0001$)) showed a significant inverse relationship with SWN scores.

**Discussion:** These findings indicate comparable subjective well-being in SZ patients treated with
either LAI or oral antipsychotic medication, while symptomatology and medication side-effects work as reliable predictors in this context. These results highlight the importance of patient-centred approaches tailoring antipsychotic treatment to the individual, focusing on effective symptom reduction, and considering the side effects of medication to minimize their impact on subjective well- being.

## S144 Clozapine Induced Delirium; A Gold Standard Gone Wrong

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**Background:** Clozapine, an atypical antipsychotic, is the gold standard medication and drug of choice in refractory schizoaffective and schizophrenia disorder1. Among many of its fatal side effects, delirium is less reported and inconsistently recognized by clinicians. Delirium is a clinical syndrome characterized by an acute change in mental functioning, including attention, awareness, cognitive function, and perception. Symptoms tend to fluctuate in presence, duration, and severity2. Limited literature is available when researching delirium and clozapine, so here we present a case of delirium onset following clozapine initiation in a 55-year-old male with schizoaffective disorder.

**Methods:** 49 papers were reviewed from sources like Jama, Science direct and PubMed. Of those, 44 were excluded due to treatment not being Clozapine, or articles were deemed "paid to read".

**Results:** The patient, a 55-year-old male with a longstanding diagnosis of schizoaffective disorder, was admitted to the psychiatric inpatient unit for exacerbation of psychotic symptoms, including auditory hallucinations and paranoid delusions. Despite previous trials of multiple antipsychotic medications, his symptoms remained poorly controlled. Consequently, the treatment team initiated clozapine at a low dose of 12.5 mg daily, with plans for gradual titration. (See Titration Schedule)

Within 72 hours of clozapine initiation, the patient exhibited a rapid onset of delirium characterized by fluctuating levels of consciousness, disorientation, and visual hallucinations. He displayed agitation, restlessness, and difficulty maintaining attention during clinical assessments. Physical examination revealed tachycardia, diaphoresis, and mydriasis, consistent with autonomic hyperactivity associated with delirium.

Clozapine-induced delirium was suspected as a potential etiology, given the temporal relationship between medication initiation and symptom onset, as well as the absence of alternative precipitating factors. Clozapine was promptly discontinued, and supportive measures, including hydration and close monitoring, were initiated. The patient's delirium gradually and quickly improved over the subsequent days, with resolution of visual hallucinations, stabilization of vital signs, and restoration of orientation and cognitive function.

1 week timeline image is added in this section.

**Discussion:** Delirium is a serious and potentially life-threatening complication associated with clozapine use, necessitating prompt recognition and intervention. Several mechanisms have been proposed to underlie clozapine-induced delirium, including cholinergic dysregulation, central anticholinergic effects, and dopaminergic hypersensitivity3,4.

This case underscores the importance of vigilant monitoring for adverse effects following clozapine initiation, particularly in patients with preexisting risk factors for delirium5, such as advanced age and cognitive impairment. Healthcare providers should maintain a high index of suspicion for clozapine-induced delirium and promptly intervene to mitigate potential complications.

## S145. An Investigation of Differential Outcomes Between Women and Men With Schizophrenia Spectrum Disorders

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**Background:** Schizophrenia Spectrum Disorders (SSDs) are linked to reduced quality of life and personal recovery, and impairments in social and occupational functioning. Several socioenvironmental factors have been linked to outcomes for individuals with SSDs, including social support and internalized stigma. While some evidence suggests women with SSDs have better outcomes, there are mixed findings for gender-based differences in quality of life, personal recovery, and community functioning. This study sought to examine differences in recovery, quality of life, and community functioning between women and men with SSDs. Additionally, we also sought to examine gender-based differences in perceived social support and internalized stigma in this population given their linkages with outcomes.
**Methods:** Study participants included individuals 16 years of age and older with a schizophrenia spectrum or related psychotic disorder, receiving care at the Centre for Addiction and Mental Health in Toronto, Canada, who were participating in a longitudinal clinical cohort study examining outcome trajectories in psychotic disorders. Participants completed symptom evaluation with the Brief Psychiatric Rating Scale (BPRS), and outcome evaluations with the Recovery Assessment Scale (RAS) to assess personal recovery, the WHO Quality of Life Brief Version (WHOQOL-BREF), and the Personal and Social Performance Scale (PSP) to assess social and occupational functioning. Participants were also administered the Internalized Stigma of Mental Illness Scale (ISMI) and the Multidimensional Scale of Perceived Social Support (MSPSS). Statistical analyses consisted of t-tests to examine gender differences in personal recovery, quality of life, and community functioning, as well as internalized stigma and perceived social support.
**Results:** The study sample consisted of 184 participants with SSDs, with a mean age of 41.5 (12.9), 44% identifying as women, and a mean BPRS total score of 39.4 (11.7). There were no differences between women and men in age, or BPRS total scores. Group comparisons revealed a significant difference in community functioning (PSP) score ($t=3.3$, $p=.006$, Cohen's $d = 0.42$), with women exhibiting better community functioning compared to men (mean PSP total score 59.5 (19.7) vs 52.1 (16.3)). There were no significant differences, however, between women and men in RAS or WHOQOL
**Discussion:** This study sought to examine gender differences in outcomes for individuals with SSDs. We found that women with SSDs exhibited significantly better community functioning compared to men, with no differences in other key outcomes including personal recovery or quality of life, nor in internalized stigma and social support. These findings provide additional insights regarding areas of differential and similar outcomes for women and men with SSDs. Additional studies needed to more comprehensively examine differential longitudinal outcome trajectories and their predictors that may help inform gender-specific approaches to enhancing outcomes for affected individuals.

## S146. Long-Term Efficacy of Xanomeline and Trospium Chloride in Schizophrenia: Responder Analyses From the 52-Week, Open-Label Emergent-5 Trial

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**Background:** Xanomeline and trospium chloride (formerly known as KarXT), an agent comprising the M1/M4 preferring muscarinic receptor agonist xanomeline and peripherally restricted muscarinic receptor antagonist trospium chloride, was recently approved for the treatment of schizophrenia in adults. In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium improved symptoms and was generally well tolerated in people with schizophrenia experiencing acute psychosis. Xanomeline/trospium was associated with continued symptom improvement over 52 weeks in the open-label, long-term EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials. We further characterize the efficacy seen in EMERGENT-5 by performing a responder analysis of the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression–Severity (CGI-S) scores.
**Methods:** EMERGENT-5 was a 52-week, open-label phase 3 trial enrolling participants with schizophrenia, a PANSS score ≤80, a CGI-S score ≤4, and no prior xanomeline/trospium exposure. Participants received twice-daily oral dosing of xanomeline 50 mg/trospium chloride 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium chloride 30 mg for 52 weeks. Efficacy analyses were performed in the modified intent-to-treat (mITT) population (participants receiving ≥1 dose of xanomeline/trospium and with ≥1 postbaseline PANSS assessment). Efficacy measures included change from baseline to week 52 in PANSS total, PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores. Responder analyses were performed by assessing the proportion of participants with ≥30% reduction in floor-adjusted PANSS total score, ≥1-point improvement in CGI-S score, and CGI-S score ≤3.
**Results:** A total of 558 participants were included in the mITT population. After initiating treatment with xanomeline/trospium, improvements in all efficacy measures were seen as early as 2 weeks (earliest measured time point) and were maintained through week 52. The proportion of participants who were PANSS responders increased over the course of the trial. By week 52, 30% of completers achieved ≥30% improvement in PANSS total score from baseline. Other PANSS responder thresholds will be analyzed and presented. At baseline, 50% of participants had CGI-S scores ≤3, representing ratings of "mildly ill," "borderline ill," or "not at all ill." By week 52, the percentage of completers who had CGI-S scores of ≤3 increased to 78.5%.
**Discussion:** Treatment with xanomeline/trospium led to continued, durable improvements in PANSS total, CGI-S, PANSS positive subscale, and PANSS negative subscale scores over 52 weeks. These results were paralleled in responder analyses showing nearly 30% of participants achieved ≥30% improvement in PANSS total score from baseline and 78.5% had disease regarded as "mild, borderline, or normal" using the CGI-S after 52 weeks of treatment.

## S147. Co-Designing a Peer-Support Approach to Foster Work Participation for Individuals Living With Schizophrenia Spectrum Disorders

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**Background:** This project was instigated by a local community organization – Société Québécoise de la Schizophrénie et des psychoses apparentées (SQS) – whose mission is to improve quality of life of individuals living schizophrenia-spectrum disorders (SSD). The SQS wished to scientifically evaluate of their new peer-support program dedicated to creating bridges between individuals living with SSD and local employability services. While the benefits of peer-support has been well demonstrated for clinical recovery, it has not yet been examined in the context of employability. Further, only a small proportion of individuals living with SSD succesfully maintain employment (about 20%) despite a large majority wishing and being able to work. Employment being one of the social determinants of health, this highlights the urgent need to develop innovative person-centered approaches.
Through a meaningful collaboration, a team of researchers, SQS staff, and peer-support workers have partnered to co-design this research project. Together, we aimed to unravel factors contributing to successful professional trajectories of individuals living with SSD who received specialized peer support. The objective of this presentation is to describe the process used to co-design this project and highlight how the unique expertise of peer workers can be central to study development.

**Methods:** We adopted a community-based participatory approach, in which we built the project based on stakeholders' perspectives. This translated into multiple meetings, draft sharing and shared decision-making to iteratively co-design all project material, such as funding application, study protocol, ethics submission, data collection tools, data analysis framework, and knowledge mobilization activities. Qualitative approaches (i.e. focus groups) was collaboratively identified as a feasible, acceptable and useful methodology for the project. Interview guides have been co-designed with SQS staff and peer-workers and will be use with 3 participant categories: (1) individuals living with SSD who received peer support to reach their professional objectives, (2) peer support workers who provided these specialized services, and (3) employability counselors who are on the other end of the bridge built by peer workers to reach individuals living with SSD.
**Results:** The research funding we were able to secure and the meaningful relationship that was established is an example of successful clinical-research partnerships that we hope can inspire other teams. Our approach has allowed us so far to highlight the importance of flexibility and involvement of peer workers in program development. Their insights, influenced by lived experience and unique capacity to engage with individuals living with SSD, has been essential in adequately tailoring the program so that it can meet the needs of both the individuals and the organizations.
**Discussion:** Community-based participatory approaches that unify clinical and research perspectives is a powerful tool to develop and implement useful, safe, and engaging programs. Peer workers bring essential knowledge to this process in all steps of research development that can increase projects' relevance, acceptability, and feasibility.

## S148. Prediction of Relapse in Early Psychosis: A 12-Year Follow-Up of the Randomized-Controlled Trial on Extended Early Intervention in Hong Kong

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**Background:** Psychotic disorders are a group of severe mental illness characterized with potentially chronic course with relapse and remitting patterns. While existing research has attempted to improve relapse prediction in first-episode psychosis (FEP) to facilitate early intervention and relapse prevention, most studies are limited by their short follow-up period. This study aimed to examine the rate and predictors of relapse, as well as to clarify the relationship between between-episode intervals and number of prior relapses in early psychosis patients within the context of 12-year follow-up of a randomized-controlled trial (RCT) comparing 1-year extension of early intervention (EI) with step-down psychiatric care for FEP in Hong Kong

**Methods:** One-hundred-sixty Chinese patients were recruited from specialized EI program (EASY) for FEP in Hong Kong after they had completed this 2-year EI service, and underwent 1-year RCT (i.e., Extended EI trial) as well as 2-year post-RCT follow-up (i.e., 3-year follow-up). Clinical interview reassessment and systematic medical record review spanning the subsequent follow-up period was conducted 12 years after the RCT commencement. Assessments on premorbid adjustment, onset profile, psychopathology, functioning and treatment characteristics were performed. Relapse, which occurred between 3-12 years of follow-up (with data available for 147 patients), was operationalized as the exacerbation of positive symptoms following partial or full remission (measured by CGI score), necessitating psychiatric hospitalization and/or antipsychotic medication change (dose increase or medication switch). Multivariate cox regression analysis was conducted to identify early-stage (baseline to 3 years of follow-up of extended EI study) predictors of relapse.

**Results:** A total of 78 patients (53.1%) relapsed during 3-12 years of follow-up. A history of substance use (HR=7.41, p=0.01), past self-harm behaviors (HR=15.00, p=0.02), more serve disorganized symptoms (PANSS disorganization dimension score) (HR=1.12, p=0.02), and poorer insight (SUMD score) (HR=1.51, p=0.04) in the early-stage period independently predicted subsequent relapse in early psychosis patients. Additional analyses further revealed that the mean between-episode time-interval decreased with increasing number of prior relapse ($F(1,6)=57.3$, $p < 0.001$), and an increased number of prior relapse significantly associated with an increased risk of subsequent relapse (HR=1.39, $p < 0.001$).

**Discussion:** This 12-year follow-up study indicated that early psychosis patients with a history of prior relapses had significantly elevated risk of further relapse, and with progressively shorter between-episode intervals. More severe early-stage disorganization symptoms, poorer insight, and past history of self-harm and substance abuse represent important determinants of relapse, and hence critical therapeutic targets in early psychosis intervention for effective relapse prevention to facilitate long-term clinical remission and functional recovery in patients with psychotic disorders.

## S149. Prediction of Functional Remission in First-Episode Psychosis: 12-Year Follow-Up of the Randomized-Controlled Trial on Extended Early Intervention in Hong Kong

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**Background:** Existing data have indicated improvement in both short-term and long-term outcomes in specialized early intervention (EI) program although the magnitude for long-term benefits was diminished. Past studies suggested extending the duration of EI program to promote better long-term outcomes. Functional remission is important indicator for long-term outcomes in psychotic disorders. This study aimed to evaluate long-term functional remission of extended EI program.
**Methods:** This study was a 12-year follow-up of a single-blind RCT comparing a 1-year extension of specialized EI (a 3-year EI service) with a step-down care (a 2-year EI service) in patients who completed a 2-year EASY program for first-episode psychosis (FEP). EASY program is a publicly funded, territory-wide service providing early assessment and intervention for individuals aged 15 to 25 years with FEP in Hong Kong. Assessments on premorbid adjustment and personality, clinical profiles, functioning, and treatment characteristics were conducted. Patients were regarded as functionally-remitted if they attained: (1) Social and Occupational Functioning Assessment Scale score > 60, Role Functioning Scale (RFS) independent living and immediate social network scores > 5, and RFS work productivity and extended social network > 4 at 12-year follow up; and sustained employment (full-time or part-time work or full-time study) over the last 12 months of 12-year follow up. We used LASSO-penalized logistic regression to construct our predictive model.
**Results:** Of the initial cohort (n = 160), 106 participants (Extended EI: n=53; standard care (SC): n=53) completed 12-year follow-up assessment. Of 106 participants, 49.1% were female. The mean age of the sample at study intake was 23.1 years (SD = 3.3) and the median duration of untreated psychosis was 17 weeks (mean = 12.8, SD = 0.07). At 12-year follow-up, 26 patients (24.5%) achieved functional remission. The LASSO logistic prediction model identified five variables in predicting functional remission. Patients with male sex (OR=1.138), lower level of premorbid schizoid-schizotypal traits (OR=0.502), lower levels of amotivation at 3-year follow-up (OR=0.679), lower levels of depressive symptom at baseline (OR=0.832), better global functioning at 3-year follow-up (OR=2.244) and better role functioning at 3-year follow-up (OR=1.586) were more likely to achieve functional remission at 12-year follow-up. The in-sample AUC was 0.827 and the Brier score was 0.147, suggesting moderate prediction accuracy of our prediction model. The bootstrapping internal validation procedure with 1000 iterations produced an optimism-adjusted AUC of 0.733 for our model.
**Discussion:** In our study, we found that 24.5% of participants achieved functional remission at the end of 12-year follow-up. This was slightly higher than our previous follow-up. Predictors with better premorbid adjustment, lower levels of symptoms and better functioning for functional remission were broadly consistent with other FEP studies. Findings for sex were mixed in other studies. Effect of extended EI in functional remission was not sustained at 12-year follow-up.

## S150. Social Disconnection and Psychotic-Like Experiences in the General Population: A Longitudinal Study

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**Background:** Psychotic - like experiences (PLEs) are present in the general population and are associated with similar factors as symptoms observed in individuals with schizophrenia. Previous studies have demonstrated that social disconnection, encompassing the quality and quantity of social relationships and loneliness, is robustly associated with psychotic symptoms across the continuum from healthy to mental illness. This longitudinal study aimed to investigate the relationship between social disconnection and PLEs in the general population using data collected via an online panel.
**Methods:** Psychotic experiences were measured using the Community Assessment of Psychic Experiences (CAPE-42). Social disconnection was assessed with the UCLA Loneliness Scale (UCLA-3) and the "Getting Along with Others" subscale of the WHO Disability Assessment Schedule (WHO-DAS 2.0). Data were collected at two time points: November 2023 and November 2024. The first wave included 1,200 participants representative of the general adult population regarding age, gender, and education. At retest, 795 participants (mean age = 52.35, SD = 14.74) completed follow-up assessments. Linear regression analyses included age, gender, and history of mental illness included as covariates.
**Results:** Age, gender, history of mental illness, baseline depression severity, baseline CAPE-42 psychotic experiences, and social disconnection at baseline were used as predictors, while follow-up psychotic experiences (CAPE-42 scores) served as the dependent variable. The overall model explained 47% of the variance ($F = 101.074$, $p < 0.001$). Significant predictors included age, baseline CAPE-42 scores, history of mental illness, and scores on the "Getting Along with Others" subscale of the WHO-DAS 2.0 ($B = 0.123$, $SE = 0.059$, $Beta = 0.066$, $p = 0.038$).
**Discussion:** The findings showed that social disconnection, precisely interpersonal difficulties, prospectively predicts the severity of PLEs in the general population, even after accounting for relevant covariates. These results emphasize the importance of interpersonal functioning and social processes as critical risk factors for the development of psychotic experiences.
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## S151. Effects of Chronic Stressors on Symptomatology Severity Among Asian Americans Diagnosed With Schizophrenia Spectrum Disorder

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**Background:** Research has advanced our understanding of social stressors' impact on the etiology and trajectory of schizophrenia, but some conceptual limitations in existing studies are worth noting. Notably, most of the research conducted on stress in schizophrenia has focused on the adverse effects of stressful life events. A less researched category of social stressors is chronic strains, non-acute but persistent stressors. Exposure to such stressors is common among individuals with schizophrenia, yet inadequate attention has been given to studying its effects on symptomatology. This descriptive study examined the relationship between chronic strains and the severity of different symptom dimensions in Asian Americans diagnosed with schizophrenia spectrum disorder (SSD). Informed by the neural diathesis-stress model (Walker et al., 2008), we expected symptomatology would rise with the levels of chronic stress.

**Methods:** This study utilized data gathered cross-sectionally from clients receiving services at urban community mental health centers. Participants, recruited using a nonprobability sampling method, were aged 18 or older; received a chart diagnosis of SSD; self-identified as Asian or Asian American; could speak and read English or an Asian language; and received services at one of the participating sites during the recruitment period between February 2016 and February 2017. Participants' symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). A five-factor PANSS model guided the ratings' computation and interpretation (Wallwork et al., 2012). The scores of the Positive, Negative, Disorganized, Excited, and Depressed factors formed the primary outcome measures of this study. Chronic strain was measured with a 16-item inventory developed by Wheaton (1994). Ordinary least-squares linear regression models were fit to estimate the effects of chronic stress on the different symptom dimensions in schizophrenia while adjusting for the control variables of age, biological sex, age at onset of illness, acute stressors, and history of childhood adversities.
**Results:** Ninety-three Asian American clients were referred, and 75 were enrolled and completed the research interview. However, we analyzed data from only participants who reported using antipsychotic medication continuously for the past six months (n = 68; 90.61%). The study sample featured 45 participants diagnosed with schizophrenia (66.17%) and 23 with schizoaffective disorder (33.82%). Participants were Asian Americans from different origin groups. Their ages ranged from 19 to 66 years (M = 43.1; SD = 12.4). Men (55.88%) and women (44.12%) were of comparable distribution. The mean factor scores indicate the average participant was not acutely ill at study entry. Participants encountered stressors at different stages of development, varying in type, origin, and duration. However, participants experienced more chronic, non-acute stressors compared to other types of social stressors. Bivariate analyses revealed that none of the examined control variables exerted a confounding effect. Accordingly, simple linear regression models were estimated. Chronic stress was not statistically significantly associated with any factors except the Depressed factor, $b = 1.23$, $t(65) = 4.67$, $p < .001$. Due to the interconnectedness among different stressors, it was necessary to partial out the impact of acute stressors to evaluate the specific effect of chronic strains on symptoms. This was achieved using nested regression. Controlling for acute stressors did not change the results of the simple regression analyses. However, acute stressors showed a statistically significant association with the Depressed factor, $b = 0.62$, $t(64) = 4.31$, $p < .01$. Acute stressors alone explained 15.88% of the variance in the Depressed factor score. Adding chronic strains increased the explained variance by 16.19%, which was statistically significant.
**Discussion:** This study contributed to the literature by examining the variation in the severity of different symptom dimensions as a function of chronic strains among Asian Americans diagnosed with SSD. It featured a more diverse assessment of social stressors to disaggregate the effects of acute stressors and continuous chronic strains. The data were mainly incongruent with our hypothesis. In this group of medicated non-first episode participants, chronic stress levels were not associated with statistically significant or meaningful changes in the severity of positive or negative symptoms, cognitive disorganization, and excitement-related symptoms. However, it showed a statistically significant association with affective symptoms. Similarly, acute stressors showed a statistically significant association with affective symptoms. Although both forms of stressors had a moderate relationship with affective symptoms, chronic strains better predicted affective symptom severity. One plausible explanation for the null findings is that individuals farther along the illness trajectory may not undergo stress sensitization and, therefore, exhibit reduced psychotic reactivity to stressful activities compared to those experiencing early psychosis.

## S152. Understanding the Anatomy of Schizophrenia - A Multimodal Meta-Analysis of Structural and Functional Brain Changes in Schizophrenic Patients

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**Background:** Schizophrenia is a complex neuropsychiatric disorder characterized by both structural and functional brain alterations. While previous studies have used various neuroimaging techniques to investigate neurobiological changes associated with schizophrenia, results have often been inconsistent or modality specific. This meta-analysis employs a multimodal coordinate-based approach integrating seven neuroimaging modalities, to provide a comprehensive comparison of structural and functional brain alterations in individuals with schizophrenia versus healthy controls.
**Methods:** This multimodal meta-analysis examined brain alterations in schizophrenia across seven neuroimaging modalities: VBM, cortical thickness, gyrification, ALFF, ReHo, ASL, and FDG-PET. A coordinate-based approach was applied to whole-brain studies comparing schizophrenia patients with healthy controls. A systematic literature search was conducted on the PubMed database up to November 2024 in accordance with PRISMA guidelines to identify relevant studies. The coordinates of the peak regions and the corresponding t-values were extracted and included in the analysis. A meta-analysis was conducted using SDM-PSI software, resulting in effect-size maps for each modality. Sensitivity analyses, heterogeneity, and publication bias were assessed using jackknife methods, $I^2$ statistics, and funnel plots.
**Results:** A total of 301 studies, including 17,221 patients with schizophrenia and 16,635 controls, were analysed across seven neuroimaging modalities: 42 studies on ALFF, 29 on ReHo, 13 on ASL, 6 on FDG-PET, 12 on gyrification, 23 on cortical thickness, and 176 on VBM. Significant alterations were found in multiple brain regions. ALFF and ReHo increased in the striatum and caudate, while activity decreased in the postcentral gyrus and the orbitofrontal area. ASL showed increased blood flow in the left striatum and reduced activity in the anterior prefrontal cortex and the dorsal anterior cingulate cortex. FDG-PET revealed increased glucose metabolism in the left cerebellum and decreased metabolism in the ventral anterior cingulate cortex. Gyrification was higher in the orbitofrontal area and the ventral anterior cingulate cortex, while cortical thickness was reduced in the retrosubicular area and the anterior cingulate cortex. VBM identified reduced grey matter volume in the retrosubicular area and the right cerebellum.
**Discussion:** The results reveal widespread brain alterations in schizophrenia, consistent with previous findings of disturbances in key regions. All modalities demonstrated abnormalities, with a notable increase in ALFF and ReHo in the striatum and caudate, indicating dysregulated network activity. Reduced cortical thickness and grey matter volume align with known atrophy in schizophrenia. These findings highlight robust neural disruptions, particularly in areas related to cognition, sensory processing, and executive function. The convergence across imaging techniques provides a comprehensive understanding of the neurobiological basis of schizophrenia, warranting further research into the causal mechanisms behind these alterations.

## S153. Self-Prioritization Effect Alterations in Mood Disorders and Schizophrenia

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**Background:** The ability to prioritize self-relevant information is a fundamental aspect of human cognition, shaping how we perceive, interact with, and respond to the world. Disruptions in self-processing in psychiatric conditions can lead to social and cognitive impairments. Previous research has shown that the self-association task (SAT) is an effective tool for capturing the self-prioritization effect (SPE). This study explores alterations in the SPE among patients with schizophrenia and mood disorders to enhance our understanding of self-processing across different psychiatric disorders.

**Methods:** We recruited 204 patients with depressive disorder (MDD), 188 with bipolar disorder (BD)—148 without psychosis and 40 with psychosis—and 118 patients with paranoid schizophrenia (SCZ). Participants completed the SAT, requiring them to match personal identity labels (self, friend, stranger) to neutral geometric shapes quickly and accurately. We recorded reaction times (RT) and accuracy, calculating efficiency (RT/accuracy) to evaluate task performance. ANCOVA was conducted to examine the effect of personal identity on efficiency, while GLM assessed the impact of mental disorders on efficiency across identities. Age, sex, education level, inpatient/outpatient status, and first-episode status were included as covariates in all analyses.

**Results:** No significant differences in efficiency across identities were found for BD with psychosis [$F(2, 98) = 1.39$, $p = .25$] and SCZ [$F(2, 347) = 2.42$, $p = .09$]. In contrast, significant differences emerged in MDD [$F(2, 534) = 5.21$, $p < .01$, partial $\eta^2 = .019$] and BD without psychosis [$F(2, 408) = 3.49$, $p < .05$, partial $\eta^2 = .017$]. Specifically, MDD exhibited higher efficiency for self compared to both friend and stranger identities ($p < .05$ and $p < .01$, respectively), with no significant difference between friend and stranger ($p = 1.00$). BD without psychosis showed greater efficiency for self compared to stranger ($p < .05$) but not friend ($p = .37$), with no significant difference between friend and stranger ($p = .83$). Significant between-group differences in self-identity efficiency were observed [Wald $\chi^2(3) = 7.99$, $p < .05$]. SCZ showed significantly lower efficiency than both BD without psychosis and MDD (ps < .001) but did not differ significantly from BD with psychosis ($p = .50$). Efficiency in BD without psychosis was significantly lower than in MDD ($p < .05$) but similar to BD with psychosis ($p = 1.00$). BD with psychosis also demonstrated significantly lower efficiency than MDD ($p < .05$). Although the main effects of mental disorders on efficiency were not significant for friend and stranger identities, post-hoc comparisons revealed that SCZ patients had lower efficiency in associating with friend and stranger identities compared to both BD without psychosis and MDD (ps < .05). No significant differences in efficiency were observed based on sex. Efficiency was lower among older participants across all mental disorders, and among those with lower levels of education specifically in MDD and BD.

**Discussion:** This study constructs a psychopathological profile of self-related disorders in mood disorders and schizophrenia. The findings reveal distinct patterns and suggest a continuum of impairments in self-relevant processing and social cognition across psychiatric disorders, underscoring the significance of SPE alterations for early diagnosis and personalized intervention within precision psychiatry.

## S154. Treatment Patterns and Healthcare Resource Utilization Following Initiation of Aripiprazole Lauroxil Using a 1-Day Initiation Regimen

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**Background:** Initiation of the long-acting injectable antipsychotic aripiprazole lauroxil (AL) using a one-time injection of a NanoCrystal Dispersion formulation of AL (ALNCD) and a 30 mg dose of oral aripiprazole significantly improved symptoms of schizophrenia in a phase 3 study. The current analysis examined treatment patterns and healthcare resource utilization (HCRU) among patients with schizophrenia initiating AL using ALNCD in a real-world setting.
**Methods:** This retrospective analysis used administrative claims data from January 1, 2018, to December 31, 2022. Adult patients with schizophrenia and continuous plan enrollment ≥6 months before (baseline) and after (follow-up) AL initiation using ALNCD (index date) were eligible. Treatment patterns were evaluated during and after initiation. Inpatient admissions, emergency department (ED) visits, and outpatient visits were compared between the baseline and follow-up periods.
**Results:** Included patients (N=1152) had a mean age of 38.4 years; 36% were female. Most patients received AL 1064 mg (39%) or 882 mg (37%); 90.3% initiated treatment with ALNCD and their first AL injection on the same day, and 78% received a second AL dose. Proportions of patients with all-cause, mental health (MH)-related, and schizophrenia-related inpatient admissions and ED visits significantly decreased between baseline and follow-up (all $P < 0.001$), whereas the proportions of patients with all-cause, MH-related, or schizophrenia-related outpatient visits were similar between baseline and follow-up.
**Discussion:** Findings from this first real-world study suggest that initiating AL using ALNCD may result in clinically meaningful reductions in patient burden and healthcare costs, as evidenced by significant declines in inpatient and ED HCRU.

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## S155. Brilaroxazine Phase 3 Recover 52-Week Open-Label Evaluation of Efficacy and Safety Over 12 Months in Stable Schizophrenia Participants

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**Background:** Brilaroxazine (RP5063), a multimodal, serotonin-dopamine neurotransmitter signaling modulator, possesses high affinity (Ki, □6nM) and selectivity for key serotonin receptors 5-HT1A/2A/2B/7 along with partial agonist functional activities for serotonin 5-HT1A/2A and dopamine D2/4 receptors. Phase 1 study in patients with stable schizophrenia

established its safety and initial efficacy profile. Its phase 3 trial (RECOVER, NCT05184335) reinforced prior phase 2 (REFRESH, NCT14900086) observations by demonstrating significant broad-spectrum efficacy at 50 mg and activity at 15 mg versus placebo for total PANSS and multiple symptom domains in acute schizophrenia while showing excellent tolerability and low treatment-related discontinuation rates. It has reduced proinflammatory cytokines, an underlying disease driver producing neuroinflammation.

**Methods:** To evaluate brilaroxazine's longer-term efficacy, safety, and persistency effects in participants with stable schizophrenia, a 12-month, global, multi-center open-label extension (OLE) followed the initial 4-week double-blind pivotal study. The evaluation involved 435 enrolled participants undergoing treatment at flexible doses (Dose: 139 [15 mg], 155 [30 mg], and 141 [50 mg]). The treatment population included 156 participants from the double-blind (rollover) and 279 newly enrolled individuals (de novo). Evaluation occurred at baseline, followed by weeks 2 and 4 in the first month, then every four weeks thereafter until Week 52. Efficacy endpoints included total PANSS and subdomains. Safety evaluation included treatment-related adverse events (TRAEs), along with monthly laboratory tests and vital sign examinations. Patient adherence and persistency assessment involved tracking participant discontinuation from the trial due to treatment and non-treatment factors.

**Results:** For all completed patients (N=113), initial findings showed sustained dose-dependent efficacy. The 15, 30, and 50 mg doses showed total PANSS significant ($p<0.0001$) reductions from baseline to Week 52 of -15.2, -18.6, and -20.8 points, respectively. PANSS total score decrease in double-blind rollover patients included >30-point in 86.76%, >40-point in 64.70%, and >50-point in 33.82%. Pooled data (all doses) showed clinically meaningful, sustained, and significant ($p<0.0001$) reductions across PANSS Total scores (-18.6), positive symptoms (-5.2), and negative symptoms (-4.5). Safety evaluation (N=435) found that 15.2% of participants experienced at least one TRAEs, mostly mild (12.2%) or moderate (3%) in severity and transient. The most common TRAEs were weight increase (3.2%), insomnia (1.8%), and somnolence (1.6%). The discontinuation rate was 35%, primarily due to consent withdrawal (22%), then lost to follow-up (7%).TREAs accounted for a small portion of discontinuations (1.6%).

**Discussion:** Overall, findings from the brilaroxazine phase 3 OLE part of the study reinforce the initial safety and efficacy results from the double-blind part of the phase 3 trial (RECOVER), emphasizing a dose-dependent effect. Furthermore, they highlight the sustainability of brilaroxazine's significant, broad-spectrum efficacy on Total PANSS, along with Positive and Negative components, and that patients tolerated this treatment well, as evidenced by low TREAs and high adherence to therapy. Collectively, these findings strengthen the overall efficacy, safety, and treatment adherence profile of brilaroxazine.

## S156. A Phase 2 Randomized Controlled Trial of Luvadaxistat in Treatment of Adults With Cognitive Impairment Associated With Schizophrenia: Results From the Erudite Study

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**Background:** Deficits in glutamatergic signalling is hypothesized to play an important role in cognitive impairment associated with schizophrenia (CIAS). Luvadaxistat, an inhibitor of D-amino acid oxidase, can modulate glutamatergic neurotransmission by elevating the levels of D-serine, one of the obligatory NMDA receptor co-agonists. In a prior phase 2 INTERACT study (NCT03382639) of luvadaxistat in negative symptoms of schizophrenia, daily luvadaxistat 50 mg showed a nominally significant improvement in cognitive test performance in adults with schizophrenia (Murthy et.al., 2024). This phase 2 ERUDITE study (NCT05182476) was conducted to find out if the results from the INTERACT study were replicable.

**Methods:** ERUDITE was a randomized, double-blind, placebo-controlled, parallel group study that included participants with schizophrenia who were receiving background antipsychotic therapy, comprising a 28-day screening period, 14-day double-blind placebo lead-in period and a 12-week double-blind treatment period. The primary endpoint was the 14-week change from baseline (CFB) in the Brief Assessment of Cognition (BAC) in Schizophrenia composite score. Secondary endpoints included the CFB to Week 14 in the Schizophrenia Cognition Rating Scale (SCoRS) score and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). Safety endpoints included assessment of treatment-emergent adverse events (TEAEs).

**Results:** Of 203 participants randomized 2:1:1 to receive placebo, luvadaxistat 20 mg or 50 mg, respectively, 177 (87.2%) completed the double-blind treatment period. In the efficacy analysis dataset placebo, luvadaxistat 20 mg and 50 mg groups, respectively, mean age was 36, 37 and 38 years, 58%, 71% and 70% were male, mean (SD) baseline BAC composite score was 32.8 (13.0), 34.1 (15.3) and 36.0 (12.2) and mean (SD) baseline SCoRS interviewer total score was 33.3 (8.7), 34.5 (9), 37 (9.7).

There were no significant improvements in BAC composite score versus placebo with luvadaxistat 20 mg or 50 mg at Week 14 ($p = 0.75$ and $p = 0.69$, respectively). The least squares (LS) mean CFB to Week 14 in BAC were 2.6 (95% confidence interval [CI]: 1.4, 3.8), 1.9 (0.1, 3.7) and 2.1 (0.3, 3.8) with placebo, luvadaxistat 20 mg and 50 mg, respectively.

There were no significant improvements in SCoRS interviewer total score versus placebo with luvadaxistat 20 mg or 50 mg at Week 14 ($p = 0.52$ and $p = 0.2$, respectively). For the SCoRS interviewer total score, LS mean CFB to Week 14 were –2.2 (CI: –3.3, –1.0), –2.1 (–3.8, –0.4) and –3.0 (–4.6, –1.4) with placebo, luvadaxistat 20 mg and 50 mg, respectively.

There were also no significant improvements in VRFCAT score versus placebo with luvadaxistat 20 mg or 50 mg at Week 14 ($p = 0.88$ and $p = 0.63$, respectively). For VRFCAT

score, LS mean CFB to Week 14 were 1.92 (CI: –0.87, 4.71), 2.30 (–1.86, 6.45) and 3.12 (–0.90, 7.13) with placebo, luvadaxistat 20 mg and 50 mg, respectively.

Overall, 32 (31.7%) participants receiving placebo and 29 (28.7%) receiving luvadaxistat had at least 1 treatment-emergent adverse event (TEAE). TEAEs occurring in ≥3 participants (headache, anxiety, back pain, infection) occurred at similar frequencies with placebo and luvadaxistat. TEAEs leading to drug discontinuation occurred four participants receiving placebo and one receiving luvadaxistat.

**Discussion:** The ERUDITE study did not meet its primary or secondary endpoints. Luvadaxistat did not significantly improve cognitive performance or cognitive functional test results versus placebo. Results may be confounded by variability in cognition measures across the studied population and BAC baseline differences between arms. CIAS remains an important unmet therapeutic need.

Study funded by Neurocrine Biosciences, Inc.

## S157. Glutamate Modulation Benefits Patients Who Are Inadequate Responders to Second-Generation Antipsychotics: Results With Evenamide as an Add-On From an International, Randomized, Double-Blind, Placebo-Controlled Study

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**Background:** The NMDA receptor hypofunction hypothesis has dominated development of new drugs for schizophrenia for 20-30 years [Javitt and Zukin, 1991]. The reduced activity of NMDARs on GABAergic interneurons in the ventral hippocampus would result in disinhibition and consequent hyperexcitability of pyramidal neurons, leading to increased glutamate release and firing of DA neurons in the ventral tegmental area [Coyle et al, 2010]. This hypothesis explains the neural basis, not only of positive, but also of cognitive and negative symptoms.

The need to explore this novel line of research is supported by the high proportion of patients discontinuing their second-generation antipsychotic (SGA) [Lieberman et al, 2005]. However, a recent meta-analysis including 40 placebo-controlled studies with NMDA modulators (e.g. bitopertin, D-cycloserine, sodium benzoate) used as add-on to antipsychotics (AP) shows that no randomized well-controlled study with adequate power has demonstrated efficacy in improving symptoms of schizophrenia [Goh et al, 2021].

Reasons for failure of new chemical entities (NCE) include inappropriate dose or treatment duration, high placebo response, insensitive efficacy measures, incorrect patient selection, etc. [Marder et al, 2017], however, it is difficult to exclude that failure may be due to inefficacy.

Here we report on the first potentially pivotal study with evenamide demonstrating improvement in inadequate responders to SGAs. Evenamide, a NCE, structurally unrelated to any AP, and devoid of biological activity at >150 CNS targets, is reducing excessive glutamate release without affecting its basal level by selectively targeting sodium channels.**Methods:** Study 008A was a 4-week, randomized, double-blind, placebo-controlled, study evaluating the safety, tolerability, and efficacy of oral doses of evenamide 30 mg bid as add-on in patients with schizophrenia on a stable therapeutic dose of a SGA. Outpatients aged ≥18 years, both males and females, with a diagnosis of schizophrenia (DSM-V), who had been receiving AP for ≥2 years , but were still symptomatic (PANSS 70-85, CGI-S 4-6, predominant positive symptoms), were eligible. In addition, only patients with AP plasma levels consistent with a therapeutic concentration were included. After a 21-day screening period, patients were randomised 1:1 to evenamide 30 mg or placebo, bid. Efficacy (PANSS, CGI-S/C) was assessed weekly, with the primary endpoint at Day 29.

**Results:** A total of 428 patients were screened, of whom 291 were randomized. Overall, 11 (3.8%) patients discontinued prematurely, only 3 (1.0%) due to adverse events (AEs). Evenamide add-on to an SGA was well tolerated, with a similar incidence of treatment-emergent AEs between evenamide and placebo (~25%); no pattern of abnormalities in any safety measure (vital signs, labs, ECG, EEG, etc) was noted.

Add-on treatment with evenamide was associated with a statistically significant ($p<0.05$) improvement compared to placebo at Day 29 on the PANSS (primary endpoint, treatment difference = -2.5) and CGI-S (key secondary endpoint, treatment difference = -0.16), and clinically meaningful benefit compared to placebo based on the responder rates (PANSS ≥20% improvement from baseline/CGI-C “any improvement” or “at least much improved”). In addition, the robustness of these findings was confirmed by multiple sensitivity analyses (Anand et al, 2024).

**Discussion:** The demonstration of efficacy through glutamate modulation with evenamide in patients with schizophrenia responding inadequately to an SGA is remarkable and suggests that it may be of value in the treatment of this population, as well as patients with treatment-resistant schizophrenia, to be determined in a potentially pivotal phase 3 trial.

## S158. Efficacy and Safety of Iclepertin for Cognitive Impairment Associated With Schizophrenia in 1835 Patients: Results From Three Phase III Randomized Controlled Trials (CONNEX Program)

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**Background:** Although cognitive impairment is a core feature of schizophrenia and is associated with poor functional outcomes, no pharmacotherapies have received regulatory approval for its treatment. In a Phase II study (NCT02832037), iclepertin, a glycine transporter-1 inhibitor, demonstrated a pro-cognitive effect in patients with cognitive impairment associated with schizophrenia (CIAS). Following these findings, a multinational clinical trial program comprising three Phase III trials (CONNEX-1, CONNEX-2, CONNEX-3) investigated the efficacy and safety of iclepertin 10 mg for the treatment of CIAS.

**Methods:** CONNEX-1 (NCT04846868), CONNEX-2 (NCT04846881), and CONNEX-3 (NCT04860830) were Phase III, double-blind, placebo-controlled, 26-week trials conducted across 338 sites in 41 countries. Eligible adults (18–50 years of age) with schizophrenia and on a stable dose of 1–2 antipsychotic medications were randomized 1:1 to receive oral iclepertin 10 mg once daily or placebo for 26 weeks (in combination with standard-of-care therapy). The primary efficacy endpoint was the change from baseline in the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) overall composite T-score at 26 weeks. Key secondary endpoints included the change from baseline in Schizophrenia Cognition Rating Scale (SCoRS) total score and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) adjusted total time T-score. Safety and tolerability were assessed.

**Results:** Of 1835 patients who received ≥1 dose of trial medication (918 randomized to iclepertin and 917 to placebo), 1602 completed the treatment period. The number of patients who prematurely discontinued study medication for any cause was low (iclepertin: n=114, 12.4%; placebo: n=119, 12.9%). Patients had a mean (standard deviation [SD]) age of 34.7 (8.8) years, were mostly male (65.7%), White (49.2%) or Asian (30.4%), and from Latin America (32.8%), Europe (23.5%), or Asia (29.2%). The mean (SD) time since first diagnosis was 10.6 (7.9) years. At 26 weeks, the adjusted mean change from baseline in MCCB overall composite T-score, SCoRS total score, and VRFCAT adjusted total time T-score were similar between treatment groups (adjusted mean difference for iclepertin versus placebo for MCCB overall composite T-score was 0.13, 95% CI: -0.40, 0.65, p=0.63; for

SCoRS total score was 0.62, 95% CI: -0.03, 1.27; p=0.06, and for VRFCAT adjusted total time T-score was -0.45, 95% CI: -1.69, 0.80, p=0.48). The safety profile of iclepertin was favorable and consistent with Phase II findings.

**Discussion:** The multinational CONNEX program investigating iclepertin for the treatment of CIAS demonstrated no significant efficacy compared with placebo. Iclepertin was well tolerated by patients, with a safety profile comparable to placebo. There remains a significant unmet need within this patient population, underscoring the importance of continued research and development of effective therapeutic options for the treatment of CIAS.

Funding: Boehringer Ingelheim.

## S159. Adapting the Optimal Health Program for Youth at Clinical High Risk for Psychosis: A Participatory Approach

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**Background:** The Optimal Health Program (OHP) is a comprehensive, evidence-based, psychosocial self-efficacy program with proven efficacy in reducing psychiatric symptoms and improving quality of life in adults with chronic physical and mental health conditions. While OHP shows promise as an early intervention for clinical high risk (CHR) for psychosis youth, it required adaptation to the unique needs of CHR individuals before pilot testing. We set out to adapt OHP for CHR youth through a structured process, engaging youth with lived experience.
**Methods:** A six-member advisory group consisting of youth with lived experience of psychosis spectrum disorders was formed. Led by Youth Engagement Specialists, the group met weekly to review and adapt the OHP workbook. The youth advisors provided feedback on each module of the intervention. The adaptation process adhered to the Patient Engagement in Research (PEIR) framework and best practices for engaging youth, emphasizing accessibility, flexibility, mutual respect, positive team interactions, inclusivity, training and support, adequate compensation, and recognizing the value of youth contributions. A total of 9 engagement sessions were conducted from April to July 2023.
**Results:** Key adaptations to the OHP included: 1) Simplifying language to be more accessible and hopeful for youth; 2) Customizing content to address the specific needs of CHR youth, such as providing information on psychiatric medications; 3) Incorporating personal stories to foster connection and reduce feelings of isolation; 4) Emphasizing individualized recovery goals; 5) Adding guided activities with clear instructions and examples; 6) Enhancing visual elements to improve engagement. The advisory group responded positively to the adapted workbook, noting that their feedback was effectively integrated. An evaluation of the engagement process indicated that youth involvement was

meaningful and impactful, resulting in content that closely aligned with the unique needs and priorities of CHR youth.
**Discussion:** The adaptation of OHP for CHR youth through continuous engagement with youth advisors underscores the importance of involving individuals with lived experience in developing mental health interventions. The adapted OHP is expected to better align with the needs and priorities of CHR youth, enhancing engagement and potentially improving mental health outcomes. We are currently in the process of evaluating the feasibility, acceptability, and preliminary efficacy of delivering the adapted OHP intervention to CHR youth.

## S160. Validation and Measurement Invariance of the Cape-15 For the Assessment of Psychotic-Like Experiences in an Italian Sample: The Role of Anxiety, Mood, and Schizotypal Symptoms in the C.A.T.C.H. In. HE.AD. Study

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**Background:** Measuring psychotic-like experiences (PLEs) in non-psychotic individuals poses both a significant challenge and an essential opportunity. These assessments play a pivotal role in early screening to identify individuals potentially at risk for developing psychotic disorders. Among the available tools, the Community Assessment of Psychic Experiences (CAPE-15) has gained recognition as one of the most widely used instruments. However, despite its popularity, further evidence supporting its validity is required to enhance its psychometric validity across diverse samples (e.g., gender and age).
**Methods:** A total of 469 Italian non-clinical individuals (28.84±14.1 years old, 57.6% female) completed a psychometric test battery, including the Community Assessment of Psychic Experiences (CAPE-15), the 16-item Prodromal Questionnaire (PQ-16), the DSM-SCID questionnaire for schizotypal personality (SCID-SP), and depression, anxiety and stress scales from the Depression Anxiety Stress Scales (DASS-21). While all measures had been previously validated in Italian and thus were used in this study, the CAPE-15 underwent a rigorous back-translation process before administration. The research in which this study is embedded was approved by the Ethics Committee.
**Results:** Confirmatory factor analyses conducted on the overall sample clearly supported the original three factor structure (i.e., persecutory ideation, bizarre experiences, and perceptual abnormalities). Moreover, this factor structure was substantially invariant in terms of factor loadings, thresholds, and residual variances across gender (males vs. females) and age groups (emerging adults vs. adults). Persecutory ideation and bizarre experiences were consistently associated with PQ-16 scores (respectively, r=.52 and r=.53) and with SCID-SP scores (respectively, r=.53 and r=.63), while perceptual abnormalities displayed lower associations with both PQ-16 (r=.32) and SCID-SP (r=.39). Finally, persecutory ideation and bizarre experiences were associated with all DASS-21 scales with rs > .40, while the latter were associated consistently lower with perceptual abnormalities (rs around .20). All correlations discussed in this section were significant for $p < .001$
**Discussion:** The findings of this study provide robust evidence supporting the validity and applicability of the Community Assessment of Psychic Experiences (CAPE-15) in a non-clinical Italian sample. Importantly, this structure showed substantial invariance across gender and age, suggesting that the CAPE-15 appropriately assesses PLEs regardless of these demographic variables. Findings from convergent and criterion validity analyses carry significant implications for the screening and monitoring of individuals at potential risk for psychotic disorders. However, the differential associations across the PLE dimensions also

suggest that further refinement of the CAPE-15 may enhance its sensitivity to specific risk profiles rather than to a single overarching pattern of impairment.

## S161. The Role of Auditory Excitability on Anomalous Visual Excitability

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**Background:** Detecting schizophrenia before the onset of psychosis is critical. We are focusing on non-clinical individuals with a high number of schizophrenia-like traits (schizotypy) to assess the effects of symptom load without clinical confounds such as medication. Our recent work identified perturbations in a behavioral measure of visual processing (more illusions in the Pattern Glare Test) that correlated with increased schizotypy symptom load (N= 913). More illusions on the Pattern Glare Test suggest greater cortical hyper-excitability. Investigating the schizotypy subfactors (cognitive-perceptual, interpersonal, disorganized) revealed that only the disorganized traits predicted more illusions. We conducted two studies to further investigate the effects of disorganized traits on other biomarkers of schizophrenia.
**Methods:** For the first study, we recruited 54 undergraduate students who completed the Schizotypal Personality Questionnaire-Brief Revised (SPQ-BR) and a visual retro-cue task consisting of items with easy and hard conditions. For the second study, we recruited 56 subjects who completed the SPQ-BR and an auditory oddball task consisting of standard (1046.5 Hz, 80%) and infrequent pitch-deviant tones (1108.73 Hz, 20%) while we recorded electroencephalography (EEG).
**Results:** For the first study, more disorganized schizotypy traits were associated with faster reaction times during both easy ($p=.01$) and hard ($p=.04$) trials in the visual retro-cue. For the second study, only disorganized schizotypy traits were associated with reduced N1 amplitudes to standard ($p=.03$) and deviant ($p=.02$) tones but not with MMN amplitudes ($p=.60$).
**Discussion:** Overall, individuals with a high number of disorganized schizotypy traits show neural hypo-excitability when detecting auditory stimuli, consistent with the auditory impairment observed in schizophrenia. However, they are hyperresponsive in behavioral measures of visual sensitivity and visual working memory speed. Together, this suggests impairments in non-clinical disorganized schizotypy that may be linked to the sensory and cognitive perturbations in schizophrenia-spectrum disorders (SSD). Focusing on disorganized schizotypy traits instead of total scores shows potential for gauging SSD risk.

## S162. Identification of Robust Speech-Based Markers of Negative Symptom Severity in Schizophrenia Spectrum Disorders

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**Background:** Digital assessment technologies have the potential to enhance the assessment of negative symptoms in schizophrenia spectrum disorders (SSD). For example, automated speech analysis has been used to quantify the speech and language changes associated with negative symptom severity in SSD. However, the large number of available speech features

and variability in results across studies make it difficult to determine the features with the greatest clinical utility. The goal of the current analysis was to identify the most robust speech-based markers of negative symptom severity by evaluating their reliability and validity in a sample of participants with SSD.
**Methods:** Data were analyzed from 62 inpatient participants with a SSD who completed a longitudinal cohort study of acute psychosis, including a baseline visit during inpatient admission and a follow-up visit upon discharge. Clinical assessments included the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS). Speech was recorded while participants completed several tasks using the Winterlight Labs iOS app – tasks included in this analysis were 2 picture description and 2 journaling tasks. A set of 25 speech features relevant to negative symptoms and quantifying the acoustic and linguistic properties of speech were extracted for each participant from speech recordings and their transcripts. Speech features were evaluated for: 1) associations with negative symptom severity (SANS Total) at the baseline visit (Spearman partial correlations adjusted for age and biological sex); 2) acceptable or higher test-retest reliability when comparing the 2 stimuli within tasks at the baseline visit (intraclass correlation [ICC] ≥ 0.50); 3) replicability of significant associations with negative symptoms and within-visit test-retest reliability at the follow-up visit; 4) convergent validity (associations with BPRS Negative symptom score), discriminant validity (no association with BPRS Positive), and specificity for negative symptom severity (no association with BPRS Total); and 5) interrelationships among identified speech features.
**Results:** At the baseline visit, 7 speech features from the picture description task and 5 features from the journaling task were significantly correlated with SANS Total ($r = |0.30\text{-}0.44|$) and additionally demonstrated ICC ≥ 0.50 for separate stimuli within tasks. At the follow-up visit, findings were replicated for 4 features from picture description (mean pause duration, phonation rate, speech rate, unfilled pauses) and 3 features from journaling (phonation rate, speech rate, unfilled pauses). Convergent validity with BPRS Negative scores was consistently demonstrated across visits for speech rate (picture description, journaling) and unfilled pauses (picture description), and these features were not associated with BPRS Positive (discriminant validity) or BPRS Total (specificity for negative symptoms). Speech rate and unfilled pauses were highly intercorrelated ($r > -0.80$) for each task and visit, suggesting they may be providing similar information.
**Discussion:** Of the examined speech features, 3 features related to rate of speech demonstrated consistent associations with negative symptom severity and acceptable or higher within-visit test-retest reliability across tasks and visits: phonation rate, speech rate, and unfilled pauses. Of these, speech rate further consistently demonstrated convergent validity, discriminant validity, and specificity to negative symptom severity. Results suggest that speech rate may serve as a robust speech-based marker of negative symptom severity to complement existing measures in SSD.

## S163. Automated Assessment of Language Concreteness in Clinical High-Risk and Healthy Control Speech Using Large Language Models

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**Background:** Language disturbances are key indicators of altered thought processes and serve as reliable markers for emerging psychotic disorders, making them a crucial target for early detection and intervention. Research has shown that individuals with schizophrenia tend

to use more concrete language and have difficulty processing abstract concepts. Examining concreteness in individuals at clinical high risk (CHR) for psychosis can reflect changes and deficits in abstract thinking, as increased reliance on concrete language frequently precedes the onset of full psychotic symptoms. These deficits may be more attenuated in CHR, yielding more subjective and labor-intensive assessments using manual rating tools. The development of automated tools using large language models offers a novel approach to quantifying these linguistic features objectively and at scale, potentially advancing our ability to detect early warning signs of psychosis.
**Methods:** Participants: The study included 79 CHR and 24 matched healthy controls (HC) from the Accelerating Medicines Partnership® in Schizophrenia (AMP® SCZ) dataset. All participants underwent a clinical interview at their baseline visit. These interviews were transcribed and used for subsequent language analysis. Analysis: Interviewee speech was extracted. Within each sentence, the Stanza natural language processing tool identified all content words (nouns, verbs, adjectives) and sequentially occluded them one at a time. For each occluded word, Llama-3 generated ten alternative predictions (the "contrast set") based on the three preceding sentences of context. The model then compared the occluded word to each suggestion in the contrast set, assigning a value of 1 if the suggestion was more concrete and 0 if it was more abstract. These ratings were averaged for each occluded word, and the averages were further aggregated across all occluded words in the sentence to calculate a sentence-level concreteness rating, and finally averaged across all sentences in the transcript to generate a concreteness score for each individual.
**Results:** A visual examination of the data reveals a bimodal distribution in the CHR group. Variability analysis revealed that HC patients exhibited an average between-participant standard deviation of 0.045 whereas CHR had an average between-participant standard deviation of 0.075, indicating a greater spread of concreteness scores within the CHR group. Only two of 24 HC participants (8%) received a concreteness above .55 while 23 of 79 CHR (29%) received a score above .55. This indicates that there is a subset of CHR with higher levels of concrete speech, which may be a useful subtype in understanding cognitive deficits and predicting conversion to psychosis in longitudinal analysis.
**Discussion:** Our novel methodological approach leverages Llama-3 to provide a more reliable and scalable alternative to manual concreteness ratings. By generating and comparing contextually-appropriate word alternatives, this approach offers a nuanced assessment, capturing subtle linguistic differences that may characterize early psychosis risk. Future research will explore longitudinal changes in concreteness in CHR, with particular attention to those who convert to psychosis, as these individuals may exhibit heightened concrete language use that could serve as a predictive marker. Additionally, investigating the relationship between automated concreteness measures and other cognitive markers could help elucidate the heterogeneity of specific deficits in the psychosis spectrum.

## S164. Semantic Similarity in Verbal Fluency: A Predictor of Negative Symptoms Beyond Cognition

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**Background:** Key clinical features of schizophrenia (SZ) include diminished language coherence (i.e., "formal thought disorder") and conceptual disorganization. Recent advances have enabled computational modeling of semantic verbal fluency (SVF) data to quantify the semantic similarity between items and the semantic structure of responses. This has facilitated the investigation of semantic sampling patterns across the psychosis spectrum. However, as there is evidence that SVF performance in SZ patients correlates with cognitive performance in working memory (WM) and inhibition tasks, it is not clear whether the semantic similarity merely reflects cognitive performance or provides additional information on semantically guided sampling. In this study, we hypothesized that semantic similarity correlates with cognitive outcomes, namely WM and negative inhibition across the psychosis spectrum. We also aimed to determine the semantic structure of responses by examining their deviation from random semantic transitions (i.e., their divergence from randomness [DFR]). Compared to healthy controls (HC), we expected patients' responses to show reduced DFR. Lastly, we tested whether semantic similarity and DFR improve model fit in predicting negative psychosis symptoms beyond cognitive factors and classical fluency (i.e., the number of non-duplicate items produced). We hypothesized that models incorporating semantic similarity and DFR show better fit than control models containing only cognitive factors and classical fluency.
**Methods:** Our sample was derived from a cross-sectional study and comprised 80 HC (40 with low schizotypy, 40 with high schizotypy), and 40 individuals with early psychosis. Participants completed three SVF tasks (animals, clothes, and food items). Item lists from the SVF task were converted to lists of word vectors using fastText word embeddings. We calculated similarity-2 (average semantic similarity of consecutive item pairs), similarity-8 (average local similarity of subsets of 8 proximate items), and DFR (actual semantic distance z-scored against 1000 random permutations, averaged across all windows). Classical fluency was derived from the item list. WM and negative inhibition were assessed with cognitive tests. Symptom severity was estimated with the Positive and Negative Syndrome Scale (PANSS).
**Results:** Similarity-2 ($r(118) = -0.33$, $p < .001$) and similarity-8 ($r(118) = -0.27$, $p = .003$) were significantly associated with WM, but not with negative inhibition. An ANOVA revealed no significant differences between patients and HC in DFR, $F(1, 118) = 0.18$, $p = 0.669$. A likelihood ratio test indicated that the model including similarity-2 showed a significant improvement in fit compared to the control model, $\chi^2(1) = 5.70$, $p = .017$, when predicting negative psychosis symptoms. Bayesian Information Criterion (BIC) values also slightly favored the model including similarity-2 ($BIC_{control} = 735.02$, $BIC_{similarity\text{-}2} = 734.11$). However, adding similarity-8 and, subsequently, DFR as predictors did not result in further significant improvements.
**Discussion:** Our results provide evidence that semantic similarity in SVF task responses is more related to maintaining and integrating information than inhibiting irrelevant responses. The lack of significant differences in DFR between patients and HC indicates that both groups exhibit a comparable level of structured responses. Additionally, our findings highlight the potential of consecutive semantic similarity for identifying and monitoring negative psychosis symptom severity.

## S165. Exploring Risk Pathways to Psychosis Conversion for U.S. Latine Youth at Clinical High Risk for Psychosis

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**Background:** In the U.S., Latine individuals endorse greater rates of subclinical psychotic experiences (13.6%) compared to non-Latine White individuals (9.7%; Cohen and Marino, 2013). Research examining whether these ethnoracial differences extend to the clinical high risk for psychosis (CHR-P) period is limited. Alderman and colleagues (2015) found that negative symptom severity and social functioning decline predicted later conversion to overt psychosis in a sample of Latine youth at CHR-P. The present study extends this prior work by examining ethnoracial differences in symptom and functioning predictors of conversion in a large North American sample of Latine and non-Latine White youth at CHR-P.
**Methods:** We combined NAPLS 2 (Addington et al., 2012) and NAPLS 3 (Addington et al., 2022) consortium data, which prospectively followed youth at CHR-P for two years across multiple sites in the U.S. and Canada. Primary measures included the Structured Interview for Psychosis Risk Syndromes (SIPS; Miller et al., 2003) to assess CHR-P symptom severity and conversion to psychosis, and the Global Functioning: Social and Role Scales (Cornblatt et al., 2007).

Participants included 733 non-Latine White (Mage = 18.27, SD = 5.54) and 280 Latine (Mage = 17.63, SD = 3.86) youth at CHR-P. Independent samples t-tests and chi-square analyses were used to compare symptom and functioning variables as well as conversion rates between Latine and White youth at CHR-P. Logistic regression analyses with ethnicity as a moderator examined symptom and functioning predictors of conversion. Latine and non-Latine White participants with data at baseline were included in the analyses.

**Results:** The proportion of participants who converted to psychosis during the 24-month study period did not differ between Latine (8.6%) and White (9.7%) youth, $X2 (1, 1013) = .30$, $p = .63$. The number of days between baseline to conversion also did not significantly differ between Latine (M = 228.04, SD = 334.06) and White youth (M = 284.75, SD = 257.79).

Despite having comparable positive and negative CHR-P symptom and social and role functioning levels at baseline, Latine youth endorsed more severe negative symptoms and poorer social functioning at conversion compared to White youth, $t(81) = -4.72$, $p < .05$ and $t(82) = 3.67$, $p < .001$, respectively.

We identified a significant interaction between the effects of baseline negative symptom severity and ethnicity ($B = 0.11$, $p < .05$) on conversion to psychosis when controlling for baseline social and role functioning and positive CHR-P symptoms with an overall significant model, $X2 (6, 986) = 35.36$, $p < .001$. Specifically, greater baseline negative

symptom severity predicted conversion for Latine ($b = 0.09$, $SE = 0.04$, $t = 2.12$, $p < .05$) but not White youth.

**Discussion:** Latine youth at CHR-P demonstrate comparable rates of conversion to psychosis relative to White youth at CHR-P, however they report worse clinical and functional outcomes at the time of conversion. Negative symptom severity may be a helpful prognostic factor for Latine youth at CHR-P. Bolstering early intervention efforts focused on addressing negative psychotic symptoms and social skills training may be particularly important for Latine youth at CHR-P.

## S166. Evaluating Language Models and Preprocessing Strategies for Detecting Psychosis-Related Language Disturbances

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**Background:** Language models show promise in detecting psychosis-related language disturbances from speech samples. Semantic similarities derived from text embeddings quantify the "distance" between speech units, a method linked to psychosis in multiple studies. However, no standardized approach exists for model selection or preprocessing. Static models, which generate word embeddings independent of context (GloVe, LSA, word2vec), and contextual models, including Large Language Models (LLMs) that incorporate semantic/grammatical context (GPT-2, RoBERTa, LLaMA), have not been systematically evaluated. This study compares these six models across three preprocessing levels—verbatim (Level 1), removal of disfluencies/repetitions (Level 2), and additional stopword removal (Level 3)—using established semantic similarity metrics. Clinical correlates include categorical SSD diagnosis and severity of three language disturbance dimensions: impaired expressivity, inefficient speech, and incoherence.

**Methods:** Participants with schizophrenia spectrum disorder (SSD; n=153) and healthy volunteers (HV; n=76) were recruited from three studies at Zucker Hillside Hospital, Northwell Health, NY. Speech samples were collected in response to open-ended prompts, and three language disturbance dimensions were quantified based on previously published work from clinical ratings on the Scale for the Assessment of Thought Language and Communication. Three preprocessing strategies were compared. For each method, 15 validated semantic similarity measures were extracted, including k-interword distances (comparing word similarity at 0–10 word intervals), moving window (average similarity within a 5- or 10-word window), and first- and second-order sentence similarity. Statistical descriptors (5th percentile, median, 95th percentile, interquartile range) were calculated, yielding 68 features per level, per model. Features were compared across SSD vs HV groups using the Mann-Whitney U test with effect sizes reported as Cohen's D (CD). Correlations were calculated with Spearman's rho for associations with language disturbance dimensions within SSD.

**Results:** Across models, preprocessing levels 1, 2, and 3 respectively generated 181, 173, and 131 significant associations ($p < 0.05$) between semantic similarity features and SSD diagnosis, with mean absolute CD of 0.40, 0.36, and 0.39. At Level 1, RoBERTa generated the most significant features (67, mean CD=0.40), followed by word2vec (36; 0.41), GloVe (33; 0.39), LSA (23; 0.36), LLaMA (14; 0.28), and GPT-2 (8; 0.32). RoBERTa remained the top performer across Levels, and consistently produced high-performing features across k-

interword, moving window, and sentence similarity measures, with a maximum CD of 0.70 for 95th percentile of k3 interword similarity.

For dimensional relationships with speech and language disturbance, RoBERTa showed the strongest association with impaired expressivity (61 significant correlations), followed by GloVe (14), GPT-2 (12), word2vec (9), LLaMA (7), and LSA (4) at Level 1. However, RoBERTa performed the worst for incoherence and ranked second to last for inefficient speech, where LLaMA and GloVe outperformed other models, respectively. Overall, language models demonstrated similar performance across language disturbance dimensions, with max and mean absolute rho values of 0.32 and 0.21 for inefficient speech, 0.32 and 0.20 for incoherence, and 0.30 and 0.21 for impaired expressivity.

**Discussion:** Our findings suggest that Level 1 (verbatim) preprocessing and RoBERTa outperform their counterparts in SSD classification. Dimensionally, the effectiveness of RoBERTa was primarily limited to impaired expressivity, with poor performance in detecting incoherence and inefficient speech. Notably, there was no categorical advantage for contextual or larger models applied to semantic similarity comparisons, as static models demonstrated comparable performance across various evaluation metrics.

## S167. Protective Effects of N-Acetylcysteine Against Schizophrenia-Related Behavioral Deficits and Impairments in Parvalbumin Interneurons Induced by Adolescent Stress

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Felipe Gomes

**Background:** Adolescent stress is a critical risk factor for the development of psychiatric disorders, including schizophrenia. Previous studies from our group indicate that applying a stress protocol to rats during a period corresponding to adolescence results in schizophrenia-like impairments in adulthood, such as an increase in the activity of the dopamine system in the ventral tegmental area (VTA). These changes were associated with dysfunction in the excitatory-inhibitory (E/I) balance in the ventral hippocampus (vHip), linked to a functional loss of GABAergic interneurons expressing the calcium-binding protein parvalbumin (PV) and their associated perineuronal nets (PNN), with the presence of a redox imbalance in the vHip. Therefore, we propose that antioxidant drugs could potentially "protect" PV interneurons/PNN from adolescent stress-induced damage and, consequently, attenuate behavioral and electrophysiological impairments caused by stress. Aims: We evaluated whether the treatment with the antioxidant N-acetylcysteine during the exposure to an adolescent stress protocol would prevent the long-lasting stress-induced behavioral, electrophysiological, and deficits in PV and PNN expression in the vHip in adult rats. We evaluated whether the treatment with the antioxidant N-acetylcysteine during the exposure to an adolescent stress protocol would prevent the long-lasting stress-induced behavioral, electrophysiological, and deficits in PV and PNN expression in the vHip in adult rats.
**Methods:** Male Sprague-Dawley rats were subjected to a stress protocol consisting of a combination of stressors: daily sessions of footshock (25 shocks of 1mA - 20 ± 60s) between postnatal days (PD) 31 to 40 and restraint stress for one hour on PD 31, 32, and 40. Throughout the stress protocol, the experimental groups – stress vs. naïve (non-stressed; n=10-12/group) – were treated with vehicle or N-acetylcysteine (900mg/L) in drinking water.

In adulthood (from PD 60), rats underwent behavioral tests to assess anxiety-like responses (Elevated Plus-Maze - EPM and Light-Dark Box - LDB), sociability (Social Interaction test - SI), and cognitive function (Novel Object Recognition - NOR test). On PD 66, some animals underwent in vivo electrophysiological recordings of VTA dopamine neurons. For other animals, their brains were perfused and collected for immunofluorescence staining of parvalbumin (PV), PNNs using Wisteria floribunda agglutinin (WFA), and 8-Oxo-DG (a marker of DNA damage caused by oxidative stress) in the vHip (CA1-Subiculum).
**Results:** Adolescent stress resulted in anxiety-like behavior in adulthood in the LDB ($F(1,45)= 9.33$, $p=0.007$), decreased sociability ($F(1,45)= 3.74$, $p=0.002$), and impairments in novel object recognition memory in the NOR test ($F(1,45)= 9.32$, $p=0.004$). The treatment with N-acetylcysteine attenuated these behavioral changes. Additionally, adolescent stress caused the animals to present an increased number of spontaneously active VTA dopamine neurons ($F(1,20)= 16.74$, $p=0.0006$). N-acetylcysteine prevented this change. In the vHip, a reduction in the number of PV+ ($F(1,20)= 18.82$, $p=0.0003$) and PV+/PNN+ cells ($F(1,20)= 13.82$, $p=0.001$), along with an increase in 8-Oxo-DG labeling ($F(1,20)= 3.28$, $p=0.046$), were observed in adult rats subjected to adolescent stress. N-acetylcysteine also prevented these impairments.
**Discussion:** Our findings indicate that the treatment with N-acetylcysteine during the stress protocol prevented the long-lasting changes related to schizophrenia in adult rats caused by adolescent stress.

## S168. Estimated Head Motion Explains Considerable Variance in Case-Control Magnetic Resonance Imaging Morphometry Comparisons

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**Background:** Morphological alterations in estimated gray matter volumes have been reported in patients with schizophrenia (SCZ) compared to neurotypical controls (NC). However, volumetric estimates are highly sensitive to confounding factors, particularly head motion during MRI scans. Previous research has primarily addressed it in small methodological studies, with limited attention to its impact on group comparisons in psychiatry. To address this gap, we analyzed gray matter volume differences in SCZ (N=330) and NC (N=1,149) across three independent cohorts, leveraging motion-related information derived from contextually collected functional MRI scans.
**Methods:** We used principal component analysis (PCA) on twenty-four motion parameters extracted from individual functional scans, identifying five principal components (PCs) that explained over 80% of the total variance. Motion patterns were consistent across cohorts and fMRI tasks, including resting state, emotion recognition, and working memory. Standard and motion-corrected linear models, which included the motion PCs as covariates, were conducted using voxel-based morphometry (VBM) and region of interest (ROI) approaches, covering both cortical and subcortical regions.

**Results:** VBM analyses showed reduced gray matter volume in SCZ (vs. NC), with motion correction reducing the spatial extent of observed differences by approximately 40%. ROI-based analyses in cortical and subcortical regions confirmed previously reported volume reductions in SCZ, particularly in the insular cortex, temporal-parietal and prefrontal cortices, as well as in the hippocampus, amygdala, and thalamus; however, motion correction still affected the magnitude of group differences ($pFDR < 0.05$). A systematic decrease in effect sizes across cortical networks and reduced significance of group differences were found in subcortical volumes when motion was accounted for. Motion correction affected the magnitude of group differences also in an additional validation cohort of 50 patients with bipolar disorder type I and II (BD), indicating that these effects may be related to motion traits associated with psychiatric patients rather than being diagnosis-specific.
**Discussion:** Our findings indicate that the widely reported volumetric differences between patients and healthy controls may be overestimated. The implications of this study likely extend beyond psychiatric populations, including lifespan research, where groups with inherently higher motion estimates, such as children, may also be affected.

## S169. Neurophysiology of Striatal and Cerebellar Timing Systems in First Episode Psychosis

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**Background:** Discoordination of sensory and cognitive processes may be a fundamental pathology that underlies many cognitive and behavioral impairments in psychosis. Impairments in perceptual processes that rely on the coordination of sensory, cognitive, and motor systems, such as time estimation, sequence learning, and rhythmic stimulus processing, have been linked to dysfunction in cortico-striatal-thalamo-cortical (CSTC) and cerebellar-thalamo-cortical (CTC) systems, which are integral to the internal representation of temporal patterns. Here, we investigated the degree to which beta-band (13-30 Hz) phase synchronization precedes tone onset in these systems during metric rhythm perception and when attention is directed to auditory timing in a rhythmic finger tapping task.
**Methods:** Magnetoencephalography (MEG) data was analyzed in 6 individuals with first-episode psychosis (FEP) and 7 healthy controls (HC). Participants performed a 2Hz rhythmic finger tapping task, where they first listened to, then tapped along with an auditory tone (1000 Hz, 50ms duration). Participants then continued tapping for 30 repetitions after the tone stopped. Beta-band power was measured as the average over 100ms preceding stimulus onset in source ROIs.
**Results:** HC modulated beta power preceding/coincident with auditory stimulus onset bilaterally in A1, Putamen, Pallidum, Dorsomedial Thalamus, Ventrolateral Thalamus, Inferior Posterior Lobe of the Cerebellum, and Midcingulate Cortex. FEP showed reduced beta power preceding stimulus onset within Midcingulate (bilateral; $p < 0.05$) and left auditory cortex (A1, $p < 0.05$), while beta power during this period was increased in FEP within left Cerebellum ($p=0.05$).
**Discussion:** These results provide evidence for CSTC dysfunction in FEP and indicate a potential compensatory involvement of cerebellar systems.

## S170. Auditory and Motor Timing Dysfunction in First Episode Psychosis Indexed by Rhythmic Finger Tapping

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**Background:** Schizophrenia (SZ) is associated with impairments in neural timing, which is linked to dysfunction in the cerebello-thalamo-cortical (CTC) and cortio-striatal-thalamo-cortical (CTSC) brain circuits, impacting perceptual and motor-based timing processes. Individuals diagnosed with schizophrenia show an increase in the speed of their "internal clock" with evidence of decreased excitability of the CTSC and increased excitability of the CTC. Similarly, individuals diagnosed with schizophrenia also show abnormal patterns in temporal learning and an increase in motor-timing variability. Here, we examined if first-episode psychosis (FEP) individuals show similar impairments in neural timing and motor-timing variability to identify if the system-level dysfunction is apparent early in the course of the disorder.
**Methods:** We measured motor timing performance during EEG/MEG in seven FEPs and 12 healthy comparison individuals via a 2Hz rhythmic finger tapping (RFT) task, where participants first listened to, then tapped along with an auditory tone (1000 Hz, 50ms duration). After ten repetitions, the tone was discontinued, and participants continued tapping at the same rate for 30 repetitions. Performance was measured by the interval timing of button-presses relative to the 500 ms target rate. Self-paced tapping variability was defined by the standard deviation of the mean inter-tap intervals (ITI) across ten trials (300 repetitions). Additionally, the Wing-Kristofferson model was applied to divide response timing variance into clock and motor implementation variance subcomponents.
**Results:** Tap rate variability was greater for FEP than healthy controls; however, this effect only achieved trend-level significance ($p = 0.07$). Dividing this variability into clock and motor variance components revealed that group differences were driven by significantly greater clock variance in FEP ($p = 0.05$), with no difference in motor implementation variance ($p > 0.5$).
**Discussion:** Preliminary results indicate that FEPs display greater self-paced finger-tapping rate variability due to dysfunction in internal clock timing. These initial findings replicate prior research in long-term schizophrenia and provide further evidence of neural timing impairments in FEPs at the level of internal clock timing. and suggest dysfunction. Greater tapping variability suggests reduced temporal precision of CTC/CTSC in FEPs.

## S171. RNA Editing Signatures Powered by Artificial Intelligence: A New Frontier In Differentiating Schizophrenia, Bipolar and Schizoaffective Disorders

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**Background:** Psychiatric disorders like Bipolar Disorder (BD) and Schizophrenia (SZ), share many common features. Patients with Schizoaffective Disorder (SA) could present a very similar cross-sectional clinical pattern to those with SZ, but their longitudinal evolution resembles that of bipolar I patients. Adenosine-to-Inosine (A-to-I) RNA editing is a post-transcriptional modification that consists of the deamination of an Adenosine (A) nucleotide into an Inosine (I) nucleotide at precise locations along the RNA molecule. Depending on the location where RNA editing occurs along the RNA molecule, this mechanism can impact splicing, affect RNA stability, modulate gene expression, or directly modify protein structure and function. This highly dynamic process enhances gene diversity and is linked to regulatory systems in psychiatry. Recent studies identified a panel of A-to-I RNA editing biomarkers capable of differentiating healthy controls from depressed patients and, among depressed patients, those with major depressive disorder and those with bipolar disorder.
This study demonstrates that RNA editing biomarkers can accurately differentiate individuals with SZ, SA, BD, and healthy controls, highlighting the potential of artificial intelligence (AI)-based predictions for diagnosis.

**Methods:** A comparative analysis was performed with 85 healthy controls subjects (CTRL), 39 BD, 31 SZ, and 14 SA patients. Patient samples were collected from two independent cohorts (CEP No.1427/16; NCT02855918). Diagnostic assessments were conducted using SCID-1, HDRS, YMRS, and M.I.N.I., while healthy controls had no history of mental disorders or psychotropic medication use. After RNA extraction from the blood samples of recruited individuals, the data undergoes quality filtering based on read length and quality scores. Sequencing reads are then aligned to the reference human genome, followed by the identification of A-to-I RNA editing events.
**Results:** Significant differences in editing between groups (CTRL, BD, SZ, and SA) are analyzed, and the identified biomarkers are combined using machine learning approaches, such as the Random Forest algorithm, incorporating patients' clinical characteristics. The algorithm was trained on 70% of the population. Then, the test was performed on the 30% of the population who never saw the algorithm. The test analysis shows clear separation of CTRL, BD, SZ, and SA groups with high diagnostic performance.
**Discussion:** Personalized medicine has become increasingly relevant to many medical fields, including psychiatry, promising earlier intervention, more efficient drug therapies, and individualized care management. BD, SZ, and SA share similar depressive symptoms and episodes of mood fluctuations, and differential diagnosis may be difficult. The development of objective and reliable tools for the differential diagnosis of BD and SZ spectrum disorders is therefore essential, and several recent studies have highlighted promising research into biomarkers. RNA editing coupled with AI paves the way for improved classification of patients into specific disease subcategories and aligns with the principles of precision psychiatry. This approach aims to deepen our understanding of the pathophysiological mechanisms of depression and improve therapeutic care. This study serves as a pioneering proof-of-concept and provides compelling evidence for the establishment of an RNA editing signature for the diagnosis of these psychiatric conditions.

## S172. Mortality in First Episode Psychosis: A Cohort Study in Brazil

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**Background:** In rich countries, patients with first episode psychosis (FEP) show higher risk of death than the general population, mostly due to non-psychiatric causes. This study aimed to analyze the medium-term mortality of FEP in a Southeastern region of Brazil.
**Methods:** A population-based sample of FEP database was linked to the death certificates database, covering a period from April 2012 to December 2018. Crude mortality rates, standardized mortality ratios (SMR), years of life lost (YLL) and life expectancy were estimated.
**Results:** The sample comprised 584 FEP patients, yielding a total of 3,233 persons-years, with a median follow-up time of 5.5 years. Eleven deaths were observed, of which 7 from natural causes. The median age at death was 36.7 years. The estimated crude mortality ratio was 340/100,000 (95%CI: 333 to 346), the SMR was 2.9 (95%CI: 1.5 to 5.1), mean YLL estimate was 41.2 (95%CI: 33.4 to 48.9), with life expectancy of 41.4 years.
**Discussion:** In this cohort of FEP patients from a middle-income country risk of death was almost three times that of the general population, with a mean reduction of 40 years in their life expectancy. Women were relatively more impacted than men. Public policies and mental health care programs must target reducing such disparity.

## S173. The Impact of Source Country Gender Inequality on the Risk of Psychotic Disorders Among First-Generation Migrant Groups in Ontario

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**Background:** Although the risk of psychosis is more than two-times higher among first-generation migrant groups, the underlying etiology remains unclear. Certain sociodemographic and migration-related factors affect the risk of psychosis differently between men and women, suggesting that gender may play a role. Prior research has highlighted an association between country-level gender inequality and excess rates of depression among women. Migrants may uphold attitudes associated with gender inequality from their country of origin or adapt to the gendered norms of the host country. This study aims to assess the effects of source country gender inequality on the risk of psychotic disorders among first-generation migrant men and women in Ontario.
**Methods:** We constructed a retrospective cohort of 2 million migrants who arrived in Ontario between 1992-2011. Cohort members were followed in health administrative data to identify first-onset cases of non-affective psychotic disorder (NAPD). Poisson regression models were used to estimate the effects of source country gender inequality, as measured by the Gender Inequality Index, on the risk of NAPD among migrant men and women, adjusting for sociodemographic and migration-related factors.
**Results:** We previously demonstrated that migrant men have a higher incidence of NAPD than migrant women (IRR=1.20, 95% CI: 1.16, 1.23). The results of this project will be presented at the conference.
**Discussion:** This study will be the first to explore the impact of source country gender inequality on the risk of psychosis among migrants. This gendered metric can provide etiological insights into the migration-psychosis association and help identify high-risk groups for prevention and intervention efforts.

## S174. OPEN BOARD

## S175. Utilization of a Psychosis Consultation Service: Early Lessons From a Statewide Initiative

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**Background:** In February 2024, Specialized Treatment Early in Psychosis (STEP) clinic, based in Connecticut, launched a free consultation service as part of STEP Learning Collaborative to support clinicians, administrators, and healthcare leaders in the continuing care of young people with recent-onset psychosis (ages 16–35). As the only coordinated specialty care (CSC) clinic in the state offering this provider-to-provider service, STEP aims to address clinical and systemic challenges by providing expert guidance on medication management, psychotherapy, family engagement, and program development.
**Methods:** Consultations are requested through a brief online form publicly available on the STEP Learning Collaborative website (https://www.ctearlypsychosisnetwork.org/consultation-service1.html). Experts at STEP aim to respond within one business day to initiate discussions regarding the identified case. The service is designed to be flexible, offering one-on-one meetings, integrating consultations into existing team meetings at the requesters' agencies, and allowing outside organizations to observe STEP operations.
**Results:** To date, 26 consultations have been completed: 24 within the state and 2 from out-of-state. Within-state requests primarily involved direct clinical issues, such as treatment planning, transitions of care, and family support strategies. Out-of-state consultations focused on broader systemic needs, including the development of new early psychosis programs and collaborative networks.
**Discussion:** Feedback from consultees highlights the value of the service in enhancing the quality and accessibility of psychosis care. This initiative underscores the importance of leveraging specialized expertise to support both individual and systemic efforts in early psychosis intervention.

## S176. Patterns and Types of Cannabis use in Schizophrenia With Comorbid Cannabis use Disorder

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**Background:** Schizophrenia (SCZ) is a chronic psychiatric illness affecting around 1% of the U.S. population. Patients with SCZ not only have worse overall health outcomes but are additionally at higher risk for a concurrent substance use disorder, the most common of these being cannabis use disorder (CUD) (1). Tetrahydrocannabinol (THC) in cannabis has been shown to worsen psychotic symptoms and CUD has been associated with worse long-term outcomes in SCZ; as such, understanding the effects and use patterns of cannabis is crucial to effectively treat patients with SCZ (2). The current study sought to detail and explore cannabis products and patterns in a sample of people with SCZ and CUD compared to those with CUD only.

**Methods:** Data for this study were taken from the baseline assessments of a previous RCT (2) examining the effects of single-dose THC vs placebo in patients with and without both SCZ and CUD. 88 participants in New Hampshire and Vermont with either a dual diagnosis (DD) of comorbid SCZ and CUD (n=34) or single diagnosis of CUD alone (n=54) were enrolled between 2013 and 2019; diagnoses were assessed using the SCID for DSM-IV. Cannabis and alcohol use rates, type, and methods were assessed using the Timeline Follow-Back Calendar, and SCZ symptoms were measured via the Positive and Negative Syndrome Scale (PANSS). Participants were aged 18-55 and were psychiatrically stable in treatment with PANSS hallucinations subscale scores < 6 and all other positive symptom subscales < 5; current alcohol use disorder was allowed but all other substance use disorders were excluded (2). The study was approved by Dartmouth and the New Hampshire Department of Health and Human Services Committees for the Protection of Human Subjects.
**Results:** Over the previous 35 days, DD patients reported less frequent cannabis use compared to CUD patients (mean days 14.82, SD 10.24 vs 27.73, SD 10.28, $p < 0.01$). They also used smaller quantities of cannabis over the same period (mean joint equivalents 20.16, SD 20.47 vs. 51.53, SD 58.35, $p < 0.01$) and had a lower proportion of 'heavy use', i.e. ≥2 equivalents per day on average (2.9% vs. 22.2%, $p < 0.01$). Most people used leaf cannabis only. A quarter (25.0%) also used other products: there were no significant differences in the rate of alternative type or methods of cannabis use between groups (mean use across groups: edibles 5.7%, dabs 8.0%, vaporizer 12.5%) and 3.4% overall used a cannabidiol (CBD) product. In DD patients, quantity of joint use correlated weakly with positive symptoms ($r=0.21$, $p < 0.23$). DD patients also used less alcohol than the CUD only patients (mean days 6.12 SD 6.13 vs 15.98 SD 11.66 $p < 0.01$; mean drinks: 24.7 SD 31.52 vs 48.74 SD 46.51 $p < 0.01$). Regression analysis adjusting for alcohol use, age, sex, and level of education found that DD group predicted lower levels of cannabis use across outcomes of frequency ($\beta=-33.98$, $p < 0.01$), quantity ($\beta=-12.17$, $p < 0.01$), and rate of heavy use ($\beta=-0.21$, $p < 0.01$).
**Discussion:** First, stable patients with a dual diagnosis of SCZ and CUD used cannabis and alcohol at both lower frequency and overall quantity compared to their CUD-only counterparts; this cannabis effect was durable even when controlling for demographics and alcohol use. These data support the idea that DD patients may be unable to tolerate higher levels of use without symptom exacerbation. Second, DD and CUD participants did not differ in their use of alternative cannabis products, indicating that people with SCZ may be just a likely to access and use very high potency products with greater potential for harm. The lack of correlation between PANSS scores and amount of cannabis use in this small study sample is notable, but cannot inform whether cannabis use in SCZ could additionally be driven by possible impacts on cognitive reward functions or the differential effects of THC and CBD on symptoms in SCZ (4,5) . Future work should continue to characterize patterns of use and their potential clinical relevance for comorbid patients, as well as the neurological and environmental drivers of cannabis use in SCZ.

References

1. Hunt, G. E., et al (2018). Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. Drug and Alcohol Dependence, 191, 234–258. https://doi.org/10.1016/J.DRUGALCDEP.2018.07.011

2. Brunette, M. F., et al (2024). Randomized laboratory study of single-dose cannabis, dronabinol, and placebo in patients with schizophrenia and cannabis use disorder. Schizophrenia Bulletin. https://doi.org/10.1093/SCHBUL/SBAE097

3. Lawn, W., et al (2016). Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. Psychopharmacology, 233(19–20), 3537–3552. https://doi.org/10.1007/s00213-016-4383-x

4. Ahmed, S., et al (2021). The impact of THC and CBD in schizophrenia: a systematic review. Frontiers in Psychiatry, 12, 694394. https://doi.org/10.3389/FPSYT.2021.694394/BIBTEX

5. Boggs, D. L., et al (2018). The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo-controlled trial. https://doi.org/10.1007/s00213-018-4885-9

## S177. Temporal Complexity of the Triple-Network System in First-Episode Schizophrenia: A Multiscale Entropy at Rest

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**Background:** Disconnect in space of triple-network system (TPN) comprising the salience (SN), default mode (DMN), and frontoparietal (FPN), is a well-established pathophysiological substrate of schizophrenia. Nevertheless, several patients show intact TPN connectivity despite severe symptom burden. This study aims to investigate if the disconnect across time (temporal complexity) of TPN determine the burden of clinical symptoms in first-episode schizophrenia (FES).
**Methods:** Resting-state functional MRI data were acquired from 53 FES patients and 59 healthy controls (HC). Using multivariate group independent component analysis, we identified the SN, DMN (anterior and posterior), and FPN (bilateral) and assessed their temporal complexity(i.e., the dynamics of thoughts across time) via multiscale entropy (MSE), calculating Sample Entropy (SampEn) across multiple scales and deriving overall Complexity Index (CI). Partial correlation analyses were performed to investigate relationships between MSE metrics and clinical symptoms.
**Results:** The SN CI was significantly reduced in FES compared to HC ($p < 0.05$, FDR-corrected) and showed a negatively correlated with positive symptom scores ($r = -0.360$, $p=0.036$); conversely, anterior DMN CI was positively correlated with negative symptom scores ($r = 0.320$, $p = 0.027$). Furthermore, at scale 1 (original time resolution), compared to HC, the SampEn of the bilateral FPN was significantly elevated in FES ($p < 0.05$, FDR-corrected), potentially reflecting compensatory mechanisms specific to basic single-scale.
**Discussion:** These findings demonstrate disruptions in temporal complexity of TPN in FES, particularly SN. Understanding network- and symptom-specific temporal complexities could pave the way investigating potential mean to restore interruptions in thought dynamics (across time) that characterize several mental illnesses.

## S178. Neurocognition in Non-Affective Psychosis in the Second Half of Life: The Nap-2 Study

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**Background:** Neurocognitive deficits are at the core of non-affective psychoses (NAP) such as schizophrenia, occurring early in life and severely compromising the functioning of affected individuals. To date, due to a lack of data from older individuals with NAP, we do not know whether these cognitive deficits are aggravated in old age, beyond the cognitive decline observed in normal aging. It is likely however, that many affected individuals will experience increasing neurocognitive deficits in older age, due to risk factors associated with NAP (e.g. severe negative symptoms and psychosocial dysfunction) and its treatment (e.g. many years of antipsychotic medication). The prevailing view of stable neurocognitive deficits in older individuals with NAP hinders the development of targeted prevention and treatment for this vulnerable group. Thus, our study charts the difference in neurocognitive performance between individuals with NAP and healthy control individuals in their second half of life, especially in old age (70+). Plus, we aim to identify specific risk factors for further cognitive decline in NAP, examining psychopathology and other indicators of severity of illness, treatment history, psychosocial factors, and physical (especially cardiovascular) health.

**Methods:** By March 2025, we aim to recruit a sample of n = 80 individuals with NAP and n = 80 healthy controls (n = 20 in four age groups: 40-49; 50-59; 60-69; 70+). A subsample of n = 22 patients and n = 22 healthy controls matched for age and sex was selected for pilot analyses. Neurocognitive performance was assessed through a comprehensive selection of validated neuropsychological tests, measuring general cognition, memory, working memory, executive functions, verbal fluency, and social cognition. Psychopathology was assessed with the PANSS, SANS, SAPS and CDSS; functioning with the MINI-ICF. In an interview, we recorded sociodemographic information, further psychosocial variables, and treatment history. Blood samples and information on physical health were collected to determine the cardiovascular risk profile, and in the future, conduct biomarker and genetic analysis, and calculate a polygenic risk score for schizophrenia.

**Results:** Preliminary findings from our pilot analysis indicate that patients show a significantly lower performance in all neurocognitive tests compared to healthy controls. Age-related decline was enhanced in patients with NAP, as indicated by a stronger negative correlation between age and general cognition in patients ($r = -.524$, $p = .015$) as compared to healthy controls ($r = -.217$, $p = .332$). We refrained from more complex statistical analyses of pilot data due to the small sample size. We will provide extended analyses of the full study sample at the congress, comparing neurocognitive performance between individuals with NAP and healthy controls as well as between age groups, and analyzing which risk factors best explain the variance in cognitive function in the NAP sample.

**Discussion:** We interpret our preliminary findings as pointing to an increasing gap in neurocognitive function between NAP patients and healthy controls with age. We will further test this assumption through analysis of the final sample. More research, including longitudinal studies with elderly affected individuals, is essential to understand causal mechanisms underlying a potentially aggravated neurocognitive decline in aging individuals with NAP. Considering the negative consequences of severe cognitive dysfunction, the

associated stigma, vulnerability and personal suffering as well as societal and economic burden, it is crucial to facilitate more scientific and clinical innovation for aging individuals with NAP.

**S179. EEG Coherence Predicts Clinical Response to Antipsychotic Therapy**

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**Background:** Psychotic disorders affect 1–3% of the global population and are a leading cause of years lived with disability and premature mortality. Antipsychotic treatment response varies significantly: approximately 60% of patients remit with the first trial, while others require two failed trials before initiating clozapine, the only approved treatment for treatment resistance. Predicting non-response to first-line treatments could expedite clozapine use, thereby reducing the duration of acute psychosis, risks to self or others, and treatment disengagement. While functional MRI studies have shown promise for predicting treatment response, our study extends this exploration to EEG. Using pre-treatment EEG data from leads near the ears, we developed an individual prediction model for treatment response at 12 weeks in first-episode psychosis (FEP). These leads were chosen for their potential to inform predictions, and if validated, could support the use of auricular EEG as an alternative to traditional EEG. Auricular EEG, which requires fewer electrodes and no conductive gel, offers a more scalable and user-friendly approach for broader clinical implementation.
**Methods:** We recruited 42 patients initiating treatment for acute psychosis (<2 weeks of lifetime antipsychotic use). Participants followed a 12-week protocol of risperidone or aripiprazole with assessments conducted at baseline and weeks 2, 4, 6, 8, and 12. Treatment response was defined as two consecutive CGI ratings of "much" or "very much" improved and BPRS psychosis-item scores ≤3.
Baseline resting-state EEG (64 Ag–AgCl electrodes, 1024 Hz) was recorded, processed (0.5–40 Hz bandpass filtering, artifact removal, and downsampling to 128 Hz), and analyzed for specific channels (T8, TP8, TP7). Connectivity features included coherence, imaginary coherence, weighted phase lag index (wPLI), and weighted pairwise phase consistency (wPPC) across standard EEG bands. A cross-validated pipeline with recursive feature elimination (RFE) was used to select the 10 most predictive features per fold. A logistic regression model with L1 penalty was applied to mitigate overfitting. Prediction accuracy was evaluated using the area under the curve (AUC) of receiver operating characteristic (ROC) curves, with the process repeated five times for consistency.
**Results:** Response data were available for 27 participants. The most consistently selected features included wPLI_TP7_TP8_Alpha (selected in 30/30 iterations), Imaginary_Coherence_T7_TP7_Alpha (28/30), and wPLI_T8_TP8_Delta (26/30). The mean AUC of the model was 0.72 (SD = 0.045) across five repetitions, demonstrating stable predictive performance.
**Discussion:** This study demonstrates promising classification performance using EEG features from leads near the ears to predict treatment response in FEP. The inclusion of these leads is particularly significant, as successful predictions would justify transitioning to auricular EEG—a dry and highly scalable alternative to wet EEG. Such a shift could make personalized treatment approaches in schizophrenia more accessible. Validation in larger samples is necessary to confirm its potential. Additionally, while our analysis focused on functional connectivity measures across specific frequency bands, other electrophysiological parameters—such as spectral power, phase measures, and the 1/f slope (a measure of the

background EEG signal)—were not included in the current model. These parameters could provide complementary insights into underlying neural mechanisms and further enhance the predictive accuracy of the model.

**Lunch and Poster Session II**

## M1. Psychopathology, Cognitive and Social Function, and Erp Indices at the Lower State of Psychosis Continuum: Multidimensional Performance of Psychotic-Like Experiences

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**BACKGROUND:** Psychotic-like experiences (PLEs) have been widely used for high-risk population screening in community. However, current knowledge on PLEs is still limited. This study aimed to examine multidimensional psychopathology and function in this population, and to explore the potential biomarkers of PLEs among event-related potential (ERP) indices as well as the associations of ERP indices with multidimensional performances.
**METHODS:** Clinical symptoms, cognitive and social function, as well as auditory P300 (including P3b and P3a) and mismatch negativity (MMN) ERP were assessed in 46 participants with PLEs and 40 participants without PLEs.
**RESULTS:** Compared to the control group, PLEs participants scored significantly higher on depressive, anxiety and manic symptoms, and lower on social cognition (Cohen's d = 0.85, 0.63, 0.51 and 0.68, respectively) , but no significant differences in neurocognitive and social function. Among all included ERP indices, generalized estimating equations only suggested group effect at P3a, with shorter latency in the PLEs group compared to the control group (Cohen's d = 0.63). Further hierarchical logistic regression models also revealed that shortened P3a latency was the solely significant ERP index of PLEs state (OR = 0.989, p = .020). Finally, general linear models suggested significant associations between P300 and MMN indices with anxiety, mania, social cognition, and neurocognition in the PLEs group.
**DISCUSSION:** PLEs seem to be an undifferentiated state on the continuum of psychosis, characterized by muliti-dimensional suclinical symptoms, intact social function and neurocognition, slightly impaired social cognition, and shortened latency of auditory P3a.

## M2. Investigating the Protective Potential of Resilience Traits Within Individuals High in Schizotypy

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**BACKGROUND:** Schizotypy (SZY), a cluster of odd thoughts and behaviors (e.g., magical thinking, paranoia), exists on a continuum in the general population and is linked to negative psychological outcomes, including greater risk of schizophrenia, psychological distress and poor well-being. As such, most research has focused on identifying the factors linking high levels of SZY with these adverse outcomes. One such factor may be environmental stressors. According to the diathesis-stress model, environmental stressors interact with genetic vulnerabilities (SZY level), serving as the proverbial "lighter" that ignites these vulnerabilities and triggers schizophrenia, psychological distress, and poor well-being. However, the relationship between

environmental stressors and poor outcomes in individuals with high SZY is not deterministic: not everyone high on SZY experiences poor psychological outcomes.

Recent research suggests that variability in outcomes may be explained, in part, by psychological traits that confer resilience in the face of environmental stressors such as self-esteem, internal locus of control, and adaptive coping strategies. Collectively these traits form a network of psychological protective and promotive factors and processes (PPFPs) which confer positive outcomes in the face of substantial risk.

Despite this promise, no study has examined whether trait PPFPs can disrupt the cascading process linking environmental stressors to poor outcomes in individuals with high SZY. We predict that trait PPFPs will moderate and weaken the relationship between environmental stressors and negative psychological outcomes. Findings stand to reveal novel targets for interventions aimed at preventing transitions from high risk (i.e., high SZY) to poor outcomes.

**METHODS:** We recruited a sample of N = 147 college students scoring high on SZY, as measured by the Schizotypal Personality Questionnaire. Participants completed online surveys assessing environmental stressors, trait PPFPs (State Self-Esteem Scale; Internal-External Control Scale; Coping Orientation to Problems Experienced Inventory; Big 5 Personality Inventory), psychological distress (Depression and Anxiety Stress Scale), and psychological well-being (Psychological Well-Being Scale). Environmental stressors included stressful life events (Life Events Checklist), childhood trauma (Child Trauma Questionnaire), and perceived discrimination (Perceived Discrimination Scale). All analyses were conducted using structural equation modeling in Mplus 8.11.

**RESULTS:** In line with predictions, greater trait PPFPs predicted lower levels of psychological distress (b = -.39, p = .05; 95% CI [-1.19, -.05]). Trait PPFPs significantly moderated the relationship between childhood trauma (b = .01, p = .03; 95% CI [.01, .02]) and well-being. Childhood trauma negatively affected well-being in individuals high on SZY, but only in the context of low trait PPFPs. Trait PPFPs did not moderate the association between stressful life events (b = .02, p = .50; 95% CI [-.03, .07]), childhood trauma (b = -.01, p = .12; 95% CI [-.02, .01]), nor perceived discrimination (b = .01, p = .78; 95% CI [-.09, .16]) with psychological distress, nor did they moderate the association between stressful life events (b = -.00, p = .94; 95% CI [-.03, .03]), or perceived discrimination (b = -.05, p = .13; 95% CI [-.12, .02]) with psychological well-being.

**DISCUSSION:** Childhood trauma is associated with negative psychological outcomes in SZY. Importantly, trait PPFPs blunt the relationship between childhood trauma and well-being. These findings highlight the potential benefits of shoring up psychological resources in individuals high on SZY with a childhood trauma history.

### M3. Consistency of the Trajectories of Suicidal Ideation and Psychotic Experiences

Caihong Han*[1], Richard J Linscott[1]

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**BACKGROUND:** Psychotic experiences (PEs) are associated with subsequent suicidal ideation (SI). However, no studies, till now, have simultaneously considered changes of both over time. It

is unknown whether changes in the occurrences of PE and SI coincide over time. Our aim was to explore the trajectories of PEs and SI and whether their trajectories were consistent over time.
**METHODS:** Undergraduates (n = 502; 85.1% females; aged 17- to 45-years) completed self-report assessments of PEs and SI once every three days for a month. Linear, quadratic, and cubic growth models were estimated separately for PE and SI. Once the best fit model was chosen for both, bivariate growth modelling was used to test consistency of the trajectories of PE and SI over time. All models were tested in Mplus 8.6 version. Missing data were handled by full information maximum likelihood method robust estimation, which assumes missing data were missing at random and uses all available data to calculate parameter estimates. Indices used to evaluate model fit included the Akaike information criterion (AIC), Bayesian information criterion (BIC), and sample-size adjusted BIC (ssBIC).
**RESULTS:** The prevalence of SI at each assessment wave ranged from 12.5% to 17.9%, and for PEs, from 5.2% to 12.7%. For each, the rates were highest at the first assessment. Regarding the growth models, the linear model was selected to be the best model for SI based on parsimony, although AIC and BIC were inconsistent on the quadratic model (linear, AIC = 2679.068, BIC = 2700.161, ssBIC = 2684.290; quadratic, AIC = 2676.559, BIC = 2714.527, ssBIC = 2685.960; cubic, AIC = 2684.396, BIC = 2743.457; ssBIC = 2699.020). All information criteria were the lowest for the linear growth model for PEs (linear, AIC = 1610.384, BIC = 1631.477, ssBIC = 1615.607; quadratic, AIC = 1614.105, BIC = 1652.072, ssBIC = 1623.505; cubic, AIC = 1616.648, BIC = 1675.709; ssBIC = 1631.272). SI and PE trajectories declined over time with PEs declining more significantly (slope -1.153, $p < 0.001$) compared to SI (slope -0.027, $p = 0.017$). Variances analysis showed that the intercept and slope varied significantly among individuals for both SI (intercept, $p < 0.001$; slope, $p = 0.006$) and PEs (intercept, $p < 0.001$; slope, $p = 0.016$). The intercept was significantly related to the slope for PEs ($r = 0.765$, $p < 0.001$) but not for SI ($r = 0.275$, $p = 0.25$). Bivariate growths models suggested that baseline SI was not related to its growth over time ($r = 0.269$, $p = 0.221$), however, baseline PEs were ($r = 0.701$, $p < 0.001$). Baseline SI was significantly related to baseline PEs ($r = 0.438$, $p < 0.001$). Neither baseline SI nor PEs were related to each other's growth (SI: $r = 0.222$, $p = 0.104$; PEs: $r = 0.227$, $p = 0.111$). The change of SI was related to the change of PEs over time ($r = 0.815$, $p < 0.001$).
**DISCUSSION:** There was strong relatedness in the trajectories of PEs and SI over a month. These findings raise the possibility that PE may affect SI, or vice versa, and are important in reducing one another or that there may be a common underlying cause. This is the first study investigating the consistency of trajectories of SI and PEs over time. Multiple time points enhanced the credibility of the results. However, the type of sample employed may limit generalization. We did not make adjustment for histories of SI and PEs.

## M4. The Role of Global DNA Methylation and Epigenetic Aging in the Suicidality of Patients With Schizophrenia

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**BACKGROUND:** Patients with Schizophrenia Spectrum Disorders (SSDs) have significantly reduced lifespan compared to the general population, with suicide as a leading cause of death. Studies suggest that suicide attempters show increased DNA methylation and shorter telomere lengths, both linked to accelerated biological aging. Recent advances in epigenetics developed novel techniques that can estimate biological age and telomere length based on differential methylation at CpG sites. This provides a convenient and feasible way of estimating biological aging with high accuracy. However, the relationship between suicide and biological aging in schizophrenia has not been explored before. In this study, we investigated whether patients with SSD and a history of suicide attempts show greater biological aging than non-attempters.
**METHODS:** 60 SSD participants were recruited from the Centre for Addiction and Mental Health, Toronto, Canada, and were divided to suicide attempters (n=40) or non-attempters (n=20). Genomic DNA was isolated from venous blood and DNA methylation was analyzed using bisulfate conversion and the Illumina Infinium 900K array. Epigenetic age was calculated using the DNA Methylation Age Calculator for 6 clocks: Horvath DNAm, Hannum DNAm, Horvath Skin and Blood, PhenoAge, GrimAge, and DNAm Telomere Length. Lastly, epigenetic age acceleration (EAA) was calculated by regressing the epigenetic age over chronological age and calculating the residuals.
**RESULTS:** The regression model was significant for all six clocks used, indicating the validity of epigenetic age acceleration (EAA) calculation. Our results demonstrated that suicide attempters showed significantly higher EAA according to the Hannum clock ($p = 0.022$) compared to non-attempters, although other clocks displayed similar trends. Global methylation was not significantly different between the two groups.
**DISCUSSION:** These findings suggest that accelerated epigenetic aging could be associated with suicidality in schizophrenia and may serve as a biological marker for suicide risk paving the way for improved suicide prevention strategies.

## M5. Effort Expenditure for Rewards in Individuals at Clinical High Risk for Psychosis: Validating an Online and Remotely Administered EEfRT

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**BACKGROUND:** Negative symptoms are among the first symptoms reported in individuals who develop schizophrenia and are important prognostic factors. They are found in most individuals at clinical high risk for psychosis (CHR-P), correlating with illness severity and functional impairment. After decades of research, a consensus suggested that negative symptoms should be grouped into two areas of deficits: those related to expression (blunted affect, alogia) and experience (avolition, anhedonia, asociality). The latter grouping of “experiential” symptoms are unified in their neurobiological underpinnings and manifestation as reduced motivation to pursue meaningful occupations and relationships. To address functional impairment across the psychotic spectrum, there is a need to optimize the assessment of motivation, as experiential negative symptoms are more closely linked to daily functioning. Translational models suggest

that performance-based measures of effort-based decision making could be sensitive to deficits in motivation. Although overactivity of striatal dopamine does not affect the response to reward, it has been shown to impair the ability to represent the value of future positive outcomes, resulting in decreased willingness to work. There is consistent laboratory evidence of impairment in physical effort button-pressing tasks as well as correlations with indicators of social functioning in schizophrenia. The Effort Expenditure for Rewards Task (EEfRT) is a computerized task that assesses a subject's motivation to expend energy to earn a reward. EEfRT has been shown to be a promising paradigm in terms of detecting group differences, reliability, and utility as a repeated measure in schizophrenia. In the current study, we assessed, for the first time, the feasibility and tolerability of an online and remotely administered version of the task and examined initial associations with negative symptoms.

**METHODS:** All participants were assessed by Structured Interview for Psychosis-Risk Syndromes (SIPS) and met criteria for a CHR-P syndrome. Negative symptom burden was established by adding SIPS N1-N5 ratings. The Effort Expenditure for Rewards Task (EEfRT) requires participants to push a button repeatedly and quickly, to potentially earn a monetary reward. The task can be modified on three levels – difficulty of the task, reward levels, and probability of reward. In terms of difficulty, the participant can choose whether to complete a "low effort" task (30 button presses in 7 second with the dominant hand index finger) or a "high effort" task (100 button presses in 21 seconds with the little finger of the non-dominant hand). Participant choice of effort expenditure is based on the level of the reward ($1.00-$4.30) and on the probability of the reward (high 88%, medium 50%, or low 12%) for each trial. The task duration is 20 minutes, and all participants received $10.00 for task completion. The dependent variable is the rate of selecting the high effort choice across probability and reward levels. Correlation coefficients were calculated for the dependent variables and SIPS items. Feasibility was calculated via averaging total time spent on the task after installation. Tolerability was calculated via 7-point Likert scale of subjective pleasantness (1 = extremely unpleasant, 7 = extremely pleasant). The task was administered online and performed at the participants' home. Task performance was monitored by a staff member through video-conferencing software.

**RESULTS:** 17 individuals at CHR-P were enrolled. Feasibility was measured as average time from EEfRT installation to completion (including 20 min run-time) as 26 minutes. Tolerability average was 4.24 out of 7. Correlation coefficients with total negative symptom burden were -0.43 ($p = 0.09$) and -0.19 ($p = 0.47$) with EEfRT Magnitude and Probability, respectively. In both cases, the largest contribution came from N4 (Experience of Emotions and Self) which correlated significantly with EEfRT Magnitude at -0.63 ($p = 0.007$) but not EEfRT Probability at -0.21 ($p = 0.409$). As an exploratory outcome, correlations were calculated between SIPS items and total earnings within EEfRT, as a proxy for success (range $37.94 to $104.98, average $63.57). Correlation coefficients with total negative symptom burden was -0.23 ($p = 0.38$) and again the largest contribution came from N4 which showed a trend toward significance at -0.38 ($p = 0.13$).

**DISCUSSION:** In youth at CHR-P, EEfRT demonstrated utility, feasibility, and tolerability when taken online and at the convenience of the participants' home. Likelihood of selecting the hard task across reward magnitudes moderately correlated with lower total negative symptom burden and approached significance despite the small sample size. Among all negative symptoms measured by the SIPS, "Experience of Emotions and Self" correlated strongly and significantly. As a novel measure of performance related to effort-based decision-making, total monetary earnings in the program were weakly correlated with total negative symptom burden

and showed the same trend regarding individual symptoms. Altogether, our findings suggest that EEfRT may be a promising biomarker for negative symptoms in CHR-P, consistent with its utility in schizophrenia.

### M6. Social Rejection and Interpersonal Fear Conditioning as a Potential Causal Mechanism Underlying Paranoia-Like Thoughts in a Non-Clinical Sample

Paulina Bagrowska*[1], Łukasz Gawęda[1]

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**BACKGROUND:** Paranoid thoughts, characterized by extreme distrust and unfounded beliefs that other people are "out to get you," prevalent even in non-clinical populations, may result from complex interactions of genetic, psychological, and environmental factors. Recent research has linked paranoid thoughts to heightened social rejection sensitivity and interpersonal threat anticipation, i.e., actively seeking out and selectively responding to perceived threats, expecting harm or rejection from others. Despite the fact that social processes play a central role in paranoia, the underlying interpersonal mechanisms remain underexplored and inconsistent across existing studies. This study aims to provide empirical verification of the causal relationships between social rejection and social fear-conditioning as a potential mechanism explaining paranoia in non-clinical individuals, employing a novel, ecologically valid paradigm in immersive Virtual Reality (VR) settings.
**METHODS:** A total of 175 individuals (58.3% of females) recruited from a non-clinical community sample, including 103 participants with low levels of paranoia-like thoughts (LP) and 72 participants with high levels of paranoia-like (HP), took part in a VR study involving a social rejection / social inclusion task (Cyberball game) followed by a social fear conditioning paradigm. Paranoia levels were assessed at baseline and after each phase of the study.
**RESULTS:** HP individuals exhibited a significant increase in the level of paranoia-like thoughts in response to social rejection, whereas social inclusion resulted in a significant reduction in the level of such thoughts. The relationship between social rejection and increased paranoia-like thoughts was fully mediated by an increase in negative emotions. In the context of fear conditioning, HP participants showed a significant increase in paranoia-like thoughts following fear acquisition, followed by a significant decrease after fear extinction. These effects were observed independently of prior experience of social inclusion or rejection. Furthermore, the behavioral analysis of physical distance revealed that HP participants did not alter their distance from virtual agents after fear acquisition but significantly increased the distance following fear extinction. In contrast, LP individuals remained unaffected by both social rejection and fear conditioning paradigms.
**DISCUSSION:** The findings demonstrate that both social rejection and social fear conditioning independently contribute to the intensification of paranoia-like thoughts. This suggests that these factors may influence paranoia-like thoughts through both distinct processes and interactive mechanisms. Notably, physical distancing from virtual agents remained unchanged following fear acquisition but increased significantly after fear extinction in HP individuals. This may suggest a delayed behavioral response, which contrasts with self-reported anxiety and paranoia-like thoughts levels, indicating a potential discrepancy between subjective experiences and observable outcomes. Further exploration using physiological measures, such as electrodermal

activity (skin conductance response), is recommended to better understand this inconsistency between cognitive and behavioral reactions. Importantly, LP individuals exhibited no significant effects from either social rejection or fear conditioning, suggesting that these processes may specifically underlie paranoid thinking only in susceptible individuals.

## M7. Predicted and Observed 10-Year Cardiovascular Events and Mortality Among Adults Treated With Antipsychotic Drugs

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**BACKGROUND:** Cardiovascular disease (CVD) is the leading cause of death among individuals with serious mental illness (SMI), partly due to antipsychotic drugs (APDs). APDs affect blood pressure, lipid levels, and glycemic control, contributing to cardiometabolic complications that may reduce life expectancy in this population. This study aims to examine the impact of APDs on the predicted and observed cardiovascular (CVD) events and mortality over a 10-year follow-up period using data from the Veterans Health Administration (VA)'s electronic health records and VA Corporate Data Warehouse at the national level.
**METHODS:** This retrospective cohort study identified individuals with schizophrenia, schizoaffective disorder, or bipolar disorder who initiated APD treatment between January 1, 2004, and December 31, 2007, as the APD group. The control group included individuals without these diagnoses and without APD treatment. Both groups were free of CVD at baseline. Since the VA sample consists predominantly of males, this analysis is limited to males. The Framingham Risk Score (FRS) was used to estimate CVD risk. The observed CVD incidence during the 10-year follow-up was extracted. The study compared the APD group with the control group, matched for CVD risk factors.
**RESULTS:** A total of 5,092 individuals who had been on antipsychotic drugs (APDs) and 5,092 controls who had not been on APDs were included. The average age was 51.06 years (SD = 8.58) for the APD group and 51.92 years (SD = 8.69) for the control group. Individuals in the APD group were exposed to the drugs for an average of 6.04 years (SD=3.17). At baseline, 75% of veterans in the APD group met criteria for moderate or high risk (vs. 77.5% of the control group), and one year later, 76.38% of the APD group met criteria for moderate or high risk (vs. 76.89% of the control group). Observed CVD events 10 years later totaled 1,293 cases (25.39%) in the control group, compared to 1,372 cases (26.92%) in the APD group (p=0.08). However, 344 (6.75%) individuals in the APD group died within 10 years, compared to 235 (4.62%) in the control group, with most deaths attributed to CVDs. The hazard ratio (HR) for mortality among individuals in the APD is 58% higher risk of mortality compared to the control group (HR=1.58, 95% CI 1.34-1.87).
**DISCUSSION:** Our findings show a trend for the Framingham algorithm to identify a higher rate of CVD events at 10 years among individuals in the moderate to high-risk APD as contrasted with the matched control group at moderate to higher risk for CVD events (p=0.08).

Improved preventive management of hypertension, diabetes, and dyslipidemia may explain the lack of a significant increase in CVD events at 10 years. Notably, despite similar baseline and one-year CVD risk scores, 10-year mortality was higher in individuals treated with APDs. Future research should understand the factors contributing to the increased mortality rate among individuals with SMI. Developing and validating CVD risk with all-cause mortality for individuals with SMI could lead to better-targeted intervention in this high-risk population.

## M8. Mild Reinforcement Learning Impairment in People With Psychotic Experiences

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**BACKGROUND:** Numerous studies have examined reinforcement learning (RL) impairment in psychosis patients, with a few studies in people with psychotic experiences (PEs). Prior studies examining RL in PEs had modest sample size. To date, no study has distinguished between rapid and overall learning, and examined the association between RL measures and the severity of negative symptoms. This study aimed to examine RL in PEs and its relationship with negative symptoms.

**METHODS:** One hundred Chinese youths with PEs and 100 demographically-matched non-PE individuals were recruited from the Hong Kong Youth Epidemiology Study of Mental Health cohort (HK-YES) to examine probabilistic RL including rapid/explicit RL, overall RL, and value-guided choice with the use of well-validated Loss-Avoidance (GLA) tasks. PEs status was assessed using WHO Composite International Diagnostic Interview (CIDI 3.0) Psychosis Module. Additionally, participants were also assessed with clinical and cognitive assessments. For the hypothesized between-group comparisons, t-test was used. We used repeated-measures ANOVA to examine overall RL. Correlational analyses between RL measures and symptom severity were also conducted.

**RESULTS:** Individuals with PEs showed significantly lower lose-shift rate in block 1 than individuals without PEs ($t_{198}=2.03$, $p=0.044$). Mixed ANOVA indicated significant main effects of probability ($F_{1,198}=21.65$, $p < 0.001$; better performance with 90% than 80% pairs), valence ($F_{1,198}=7.71$, $p=0.006$; better performance with loss-avoidance learning), block ($F_{2.60,514.02}=121.19$, $p < 0.001$; better performance over time) and interaction effect of probability and group ($F_{1,198}=10.91$, $p=0.001$). Interaction effects of probability, valence and group ($p=0.068$) approached significance. Post-hoc contrast on marginal probability, valence and group interaction showed individuals with PEs performed significantly poorer in 80% probability with reward learning condition than individuals without PEs ($p=0.003$). The preference for choosing FW over FLA was not significant ($p=0.168$), with people with PEs displaying comparable difference scores with non-PE counterparts. Negative symptoms (BNSS total score) were negatively correlated with win-stay rate ($r_s=-0.35$, $p < 0.001$), overall accuracy ($r_s=-0.28$, $p=0.005$) and loss-avoidance learning accuracy ($r_s=-0.29$, $p=0.003$). Amotivation (BNSS amotivation domain score) were negatively correlated with win-stay rate ($r_s=-0.37$, $p < 0.001$),

overall accuracy (rs=-0.31, p=0.002), reward learning accuracy (rs=-0.26, p=0.009) and loss-avoidance learning accuracy (rs=-0.28, p=0.006).
**DISCUSSION:** This is the first study examining RL and its relationship with negative symptoms in PE individuals. In general, our findings indicated mild and circumscribed RL deficits in people with PEs. We found mild deficits in punishment-driven rapid RL and reward-driven overall RL. In addition, PE individuals exhibited preserved value-guided decision making. We also found some negative correlations between RL and negative symptoms. Owing to the scarcity of research, more studies in PEs are needed to verify our current findings.

## M9. Life Stress as a Mediator Between Childhood Trauma and Sleep Disturbances in a Clinical High-Risk Psychosis Population

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**BACKGROUND:** Clinical high-risk (CHR) populations represent individuals experiencing prodromal symptoms or exhibiting significant risk factors for developing psychosis, a group characterized by heightened neurobiological vulnerability and increased psychological distress. Childhood trauma emerges as a critical risk factor in this population, with extensive research demonstrating its profound impact on neurodevelopmental trajectories and increased likelihood of psychotic disorder onset. Sleep disturbances are particularly prevalent among CHR individuals, representing both a potential early marker of emerging psychopathology and a potential mechanism through which traumatic experiences may disrupt neurocognitive functioning and emotional regulation.
**METHODS:** This study aims to investigate the mediating role of life stress events in the relationship between childhood trauma and sleep disturbances, using data from the North American Prodrome Longitudinal Study (NAPLS3) with a sample of 664 participants. We employed a causal mediation analysis using nonparametric bootstrap confidence intervals with the percentile method to examine the complex pathways between childhood trauma, life stress events, and sleep disturbances.
**RESULTS:** The results reveal a significant mediating effect of life stress events on the relationship between childhood trauma and sleep disturbances. The average causal mediation effect (ACME) was 0.0401 (95% CI: 0.0117, 0.07; p = 0.010), suggesting that a considerable portion of childhood trauma's impact on sleep disturbances occurs through life stress events. Interestingly, the direct effect of childhood trauma on sleep disturbances was not statistically significant (estimate = 0.0189, p = 0.642), and the total effect was marginally significant (estimate = 0.0590, p = 0.094).
The proportion of the total effect mediated by life stress events was 0.6789, though this did not reach statistical significance (p = 0.104).
**DISCUSSION:** Our findings provide crucial insights into the complex pathways through which childhood trauma may influence sleep disturbances. The significant mediating role of life stress events suggests that interventions targeting stress management and resilience-building might be particularly effective in mitigating sleep-related challenges among individuals with a history of childhood trauma. The study highlights the importance of a holistic approach to understanding

trauma's long-term effects, moving beyond direct linear relationships to explore more nuanced mechanisms of psychological adaptation.
Limitations include the marginally significant total effect and the need for further validation of the mediation model. Future research should focus on longitudinal studies with more diverse populations, exploring additional potential mediators and moderators in the trauma-sleep relationship.

## M10. Altered Startle Reactivity, But Intact Downregulation, in Clinical High Risk

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**BACKGROUND:** The autonomic nervous system has been theoretically centered in schizophrenia since early models. More recent paradigms investigating the startle reflex demonstrate increased baseline arousal, increased or decreased baseline startle reactivity, reduced pre-pulse inhibition (reflexive inhibition of the startle response), and reduced habituation in schizophrenia. Similar patterns have been observed in individuals at a clinical high risk for psychosis (CHR), to the extent that reduced pre-pulse inhibition has been proposed as an endophenotypic marker of psychosis risk. As such, modulation of the startle response may provide meaningful insight into the development and mechanisms of psychosis. Our study expands on the literature by examining intentional downregulation of the startle response in CHR, to determine whether deficits in startle reflex modulation are related to altered reflexive responses or a broader deficit in autonomic nervous system regulation. The current study leveraged a clinically enriched control group (EC; with other non-psychotic psychopathology and/or subthreshold psychosis risk symptoms), which allowed unique insight into studying features unique to the clinical high risk state rather than more diffuse psychopathology.
**METHODS:** We investigated skin conductance responsivity to an acoustic startle stimulus (115 db burst of white noise, 100 milliseconds in duration) in 28 CHR and 42 EC during unwarned, warned (with a 20 second countdown), and downregulated (with an instruction to relax and downregulate the startle response, then a 20 second countdown) startle stimuli. Baseline arousal was measured using skin conductance level and frequency of non-specific skin conductance responses prior to each stimulus, and startle response was indexed using skin conductance response (SCR) size, latency, and rise time. We also investigated the relationship between electrodermal parameters during the startle response and clinical symptom severity.
**RESULTS:** CHR showed a significant decrease in frequency of non-specific SCRs from unwarned (u) to warned (w) to downregulated (d) trials ($W(u/w)= 546$; $W(u/d)=604$, $W(w/d)=519$), and a significant decrease in SCR size from unwarned to downregulated and warned to downregulated trials ($W(u/d)=605.5$; $W(w/d)=573.5$). HC also showed a significant decrease in frequency of non-specific SCRs from unwarned to warned to downregulated trials ($W(u/w)=1239.5$, $W(u/d)=1289.5$, $W(w/d)=1070$), and a significant decrease in SCR size only from unwarned to downregulated trials ($W=1231$). On warned trials, CHR showed a significantly higher SCR size than EC ($W=783.5$). CHR showed higher SCR responsivity on unwarned trials, but this effect did not survive correction for multiple comparisons. CHR and EC did not

significantly differ on any parameters on downregulated trials. SCR size during unwarned stimulus delivery was significantly and positively related to psychosis risk symptoms (rs=0.33).
**DISCUSSION:** These results suggest that CHR demonstrate increased electrodermal reactivity to an expected startle stimulus, such that it does not significantly differ from a completely unwarned startling stimulus. This increased responsivity relates to severity of psychosis risk symptoms. This is consistent with findings of reduced automatic inhibition of the startle reflex in CHR. However, we also demonstrate that CHR may be able to effectively downregulate their startle response with directed attention. This finding has important implications for the way we consider modulation of autonomic signaling in psychosis, as well as the potential for interventions targeting mindful awareness.

## M11. Altered Adaptive Coding Activation in Posterior Mid-Cingulate Cortex in People With Schizotypal Traits, Subthreshold Depression and Autistic Traits

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**BACKGROUND:** Anhedonia is a transdiagnostic symptom of schizophrenia, major depressive disorder and autism spectrum disorders. Adaptive coding has been implicated in the pathophysiology of anhedonia given its role in enhancing value discriminability and sensitivity. However, no study has compared the neural responses to adaptive coding of expected value (EV) and outcome value (OV) in people with schizotypal trait (ST), subthreshold depression (SD), and autistic trait (AT).
**METHODS:** We recruited 35 ST, 35 SD, 23 AT and 34 HC to undertake the functional magnetic resonance imaging while performing a Monetary Incentive Delay Task-adaptive version to measure adaptive coding. All participants also completed a set of self-reported anhedonia checklists after the scanning.
**RESULTS:** Our results showed that posterior mid-cingulate cortex(pMCC) responses exhibited adaptive coding during the EV representation. Participants with ST, SD and AT exhibited hyperactivation of the pMCC than HC. Participants with SD exhibited increased activation in the supplementary motor area than HC during the time of OV representation. We also found significant associations between neural and behavioural performance of adaptive coding with self-reported pleasure experience in participants with ST, SD and AT.
**DISCUSSION:** These findings suggested that people with ST, SD and AT exhibited both common and distinct neural responses to adaptive coding. Adaptive coding performance showed consistent association with anhedonia in these three subclinical samples. These findings highlighted the important role of adaptive coding in anhedonia formation or maintenance.

## M12. Hypervigilance, Suspiciousness, and the Paranoia Spectrum: A Latent Factor Structure and Measurement Invariance Investigation Across Ethnoracial Groups

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**BACKGROUND:** Hypervigilance and suspiciousness are conceptually overlapping constructs included in measures of paranoid ideation. Critically, presence of symptoms of hypervigilance versus suspiciousness may determine whether an individual meets criteria for a psychosis-risk syndrome as assessed by a gold-standard diagnostic instrument, making it important for researchers and practitioners to understand potential construct overlap. Additionally, differences exist in the endorsement of hypervigilance and suspiciousness among Asian, Black, Hispanic, and non-Hispanic White individuals in the United States; however, no studies have examined potential racial/ethnic differences across the paranoia spectrum. As a primary aim, we hypothesized that hypervigilance and suspiciousness are related constructs on a general paranoia spectrum, thus a bifactor hierarchical model would best fit the data across ethnoracial groups. As a secondary aim, we tested measurement differences across ethnoracial groups.

**METHODS:** Asian, Black, Hispanic, and non-Hispanic White adolescents and young adults aged 16-30 were ascertained from the community-based Multi-site Assessment of Psychosis-risk (MAP) study, which recruited participants across four ethnoracially/economically diverse, urban catchment areas in the United States. Participants self-reported hypervigilance symptoms on the PTSD Checklist-Civilian Version (PCL-C; nAsian=593, nBlack=191, nHispanic=490, nWhite=921) and suspiciousness symptoms on the Prodromal Questionnaire (PQ; nAsian=1,778, nBlack=858, nHispanic=1,172, nWhite=3,566). Analyses were conducted in each ethnoracial group and across the full sample. Confirmatory factor analyses tested a bifactor hierarchical model, and a comparison 2-factor model. Measurement invariance analyses were conducted on the optimal latent factor structure.

**RESULTS:** Model fit for the bifactor hierarchical model was good in each ethnoracial group and the full sample (all CFI values > 0.99, RMSEA values < 0.03). However, not all factor loading magnitudes were considered adequate (< 0.30) and some items did not have significant loadings ($p > 0.05$) onto their respective factors. The 2-factor first-order model demonstrated similarly good model fit, adequate factor loadings for all items (all loading magnitudes > 0.50), and all items significantly loaded onto their respective factors (all $p < 0.001$). Factors were moderately correlated among all ethnoracial groups (all r > 0.58-0.65). Measurement invariance analyses demonstrated good model fit across the configural, metric, and scalar models (all CFI values > 0.99, RMSEA values < 0.03) and changes between levels of invariance of CFI/RMSEA values < 0.01.

**DISCUSSION:** Rather than a bifactor structure, hypervigilance and suspiciousness are moderately correlated constructs, reflecting the highly co-morbid nature of these symptoms within psychosis-spectrum individuals. Tests of measurement invariance showed that the PCL-C and PQ assess self-reported symptoms of hypervigilance and suspiciousness, respectively, similarly across Asian, Black, Hispanic, and non-Hispanic White individuals. Findings suggest that hypervigilance and suspiciousness are distinct and may have multifinality, which researchers and clinicians should further study in terms of diagnosing psychosis-risk syndromes in individuals with diverse ethnoracial identities.

## M13. Two-Staged Identification of Clinical High Risk for Psychosis Among Youth in Community: Results From a Pilot Study From India

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**BACKGROUND:** Early Intervention services in India are sparse. In India, there is a large treatment gap and low help-seeking for psychiatric conditions, more so for subsyndromal symptoms. Therefore, community-based identification of clinical high risk for psychosis becomes crucial. Such a study has not been attempted earlier in India.
**METHODS:** This pilot study was conducted in Telangana, a Telugu-speaking state in India; one rural and one urban area were selected. We employed a two-stage process, wherein self-report screening using the Telugu version of the PRIME Screen-Revised (PS-R) preceded a structured interview using the structured interview for psychosis-risk syndromes (SIPS). 2025 youth aged 15-24 years were recruited by probability sampling. Selected cohorts- CHR-P positive and negative ones were assessed for psychosis transition every 3 months.
**RESULTS:** In the first stage screening on PS-R, 110 individuals were deemed positive. The second stage interview using the SIPS could be conducted only on 67 out of 110 individuals. Here, 62 (92.54%) individuals were confirmed to be CHR-P positive. The sensitivity and specificity of PS-R were 98.41% and 90.74%, respectively. During the 15-month follow-up period, three CHR-P participants transitioned to psychosis.
**DISCUSSION:** We established that the two-staged screening is effective for identification of CHR-P in the community youth sample in Telangana. There is a need to up-scale the study methods using a multicentre study design across various states of India.

## M14. Cinematic Virtual Reality Psychosocial Treatment Program in Schizophrenia: A Randomized Controlled Study

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**BACKGROUND:** Patients with schizophrenia exhibit significant impairments in psychosocial functioning. Virtual Reality (VR) presents a promising intervention method for psychosocial impairments in schizophrenia. In this study, we aimed to study the effects of a cinematic VR psychosocial treatment program (cVR-PTP) to improve psychosocial functioning in patients with schizophrenia.
**METHODS:** The study included 36 patients with schizophrenia, diagnosed according to DSM-V criteria. Eleven participants dropped out during study progress. Participants were randomly assigned to one of two groups: an experimental group that received weekly cVR-PTP sessions

(n=14) and a control group (CG, n=12) that had non-interventional face-to-face sessions once a week for 12 weeks. Severity of schizophrenia symptoms of the patients was evaluated by using Positive and Negative Syndrome Scale (PANSS). Psychosocial functioning was assessed via Personal and Social Performance Scale (PSP) and Social Functioning Scale (SFS). Dokuz Eylul Theory of Mind Index (DEZIKO), Facial Emotion Identification (FEIT), and Facial Emotion Discrimination (FEDT) tests, and Reading the Mind in the Eyes (RMET) were used to measure social cognition. Neurocognitive functions were measured using the Turkish version of Screen for Cognitive Impairment in Psychiatry (SCIP). Clinical, psychosocial and cognitive tests were conducted at baseline, post-treatment, and 3-month follow-up. Only PSP was measured by an independent blind rater. Data were analyzed using mixed-model ANOVA.
**RESULTS:** There was no significant difference between the intervention and non-intervention groups regarding psychosocial improvement. Also, there was no time x intervention between groups. We found that cVR-PTP was not superior to standard non-interventional interview. Both groups demonstrated significant improvements in psychosocial functioning, theory of mind (ToM), neurocognition, and clinical symptoms. For both groups a main effect of time was observed in PSP [$F(1,24)=51.15$, $p < .001$, $\eta p2=.68$], and SFS [$F(1,24)=6.1$, $p=.021$, $\eta p2=.20$] scores. In addition to that for social cognition, a main effect of time was observed in DEZIKO scores for both groups, [$F(1,24)=10.8$, $p=.003$, $\eta p2=.31$]. A main effect of time was observed in global cognition scores, [$F(1,24)=11.27$, $p=0.003$, $\eta p2=0.32$] for both groups. A main effect of time was observed for clinical symptom severity in PANSS total scores, [$F(1,24)=54.28$, $p < .001$, $\eta p^2=0.69$] as well as positive symptoms [$(F(1,24)=19.73$, $p < .001$, $\eta p^2=0.45$], negative symptoms [$F(1,24)=25.52$, $p < .001$, $\eta p^2=0.52$], and general symptom severity [$F(1,24)=30.14$, $p < .001$, $\eta p^2=0.56$]. These improvements were preserved in 3-month follow-up evaluations.
**DISCUSSION:** While virtual reality (VR) holds promise as a tool for psychosocial interventions in schizophrenia, the VR-based psychosocial therapy program (cVR-PTP) was not found to be superior to standard face-to-face sessions. The supportive research environment and regular interactions with the research team may have positively influenced both groups, thereby minimizing differences between the interventions. Future research should account for these external factors to more accurately evaluate the unique effects of cVR interventions.

## M15. Defining Cognitive Impairment Associated With Schizophrenia: An Administrative Claims and Electronic Health Record Study

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**BACKGROUND:** Cognitive impairment associated with schizophrenia (CIAS) impacts quality of life. Though CIAS impact on patients is recognized, there is no standard diagnostic code or approved pharmacotherapies for CIAS. We aimed to develop a definition for identifying patients with CIAS and determine whether CIAS can be distinguished using this definition.
**METHODS:** This was a non-interventional retrospective study using de-identified real-world data (RWD) from US-based administrative claims and electronic health records (EHR) in the Optum Market Clarity database. Patients were included if they had ≥2 schizophrenia diagnosis

claims (Oct 1, 2016, to Mar 31, 2022) and ≥1 year of continuous enrollment pre-index date (first schizophrenia diagnosis).

Diagnosis/procedure codes from claims and natural language processing (NLP)-based indicators (keywords, sentiments, attributes) or NLP psychiatric measurement scores from clinical notes in EHRs were extracted to identify patients with CIAS. A data source of 20 ICD-9/-10 diagnosis codes, 11 procedure codes, 91 NLP key terms with sentiment or attribute data, and 6 NLP measure scores was developed. The weight for code-defined CIAS events was 1. The weight for NLP-based indicators was 1 (CIAS positive) or −1 (CIAS negative).

After extracting core CIAS indicators during 90 days around any schizophrenia diagnosis date, a CIAS sum score was calculated based on the sum of each CIAS indicator score with weight and absolute distance between CIAS indicator and diagnosis date. If patients had ≥1 score > 0 they were defined as CIAS patients at that diagnosis date. If patients had a score ≤0 they were identified as no CIAS at the diagnosis date. During disease prognostic process, based on the CIAS indicators' collection, the sum score could fluctuate in magnitude or positive/negative attribute. If patients had any score > 0 pre-index date they were included in the history of CIAS cohort, whereas anyone with a score > 0 on or after index date was included in the follow-up CIAS cohort.

Alignment analysis identified associations between claims code-based and positive NLP measure-based CIAS indicators within CIAS positive events. Pairwise Pearson Correlation coefficient and eLasso association weight were used to rank pairs.

**RESULTS:** 183,483 patients were included in the study. Of these, 51,234 (27.9%) patients had core CIAS indicators during the study period, and 44,236 (24.1%) had any CIAS sum score > 0 with 1,036,861 positive CIAS events. Of these, most patients had diagnosis code defined events (32,024 patients had 719,229 [69.4%] events), followed by NLP score defined events (7460 patients had 133,493 [12.9%]) and NLP term defined events (6558 patients had 92,591 [8.9%]).

3538 patients had a recorded CIAS event defined through both diagnosis/procedure codes and NLP terms/scores. Among these, there were 59,501 CIAS positive events. The top paired claims and NLP terms ranked by eLasso weights were: NLPterm_cognitive_impaired and PROC_97532 (eLasso value: 3.53), NLPterm_cognitive_impaired and PROC_G0515 (2.79), NLPterm_mild_cognitive_impairment and ICD_G3184 (2.51), and NLPterm_cognitive_impaired and ICD_R41841 (2.01).

**DISCUSSION:** Patients with CIAS were categorized using a definition developed based on RWD. CIAS sum score allows for dynamic ascertainment of CIAS over time. Pearson and eLasso analysis indicated correlation between NLP-based data and claims codes, which could serve as validation between NLP data and medical code data. This definition could facilitate characterizing patients with CIAS, which may help improve recognition and treatment of CIAS, reducing burden and improving the lives of those with schizophrenia.

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## M16. Remote Cognitive Bias Modification Training (CBMT) With Dynamic Avatars for Social Anxiety in People With Psychosis

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**BACKGROUND:** Nearly 30% of individuals with early psychosis have social anxiety. Cognitive Bias Modification Training (CBMT) uses repetitive training to force people to spend more time on stimuli contradicting an attentional bias. In social anxiety, people tend to quickly attribute negative intentions to neutral faces (an attentional bias). Our objective was to evaluate the efficacy of CBMT on improving social anxiety in people with early psychosis.
**METHODS:** Participants with social anxiety disorder and early psychosis, as well as young people with social anxiety without psychosis, were recruited to take part in the online training condition (n = 55), or the control group (n = 25). The training involved an online emotion recognition task for 20 minutes, 3 times a week, over the course of 8 weeks. The remote CBMT uses realistic dynamic facial avatars, with training whereby participants need to identify the correct facial emotion, among four basic emotions (joy, anger, fear and neutral), with feedback (for the right or wrong answer) and visual noise that increases or decreases according to the participant's performance.
**RESULTS:** The intervention was effective in decreasing social anxiety with medium and large effect sizes (across two measures: LSAS-SR and BFNE), regardless of having psychosis or not. Significant improvements on other clinical variables (with small effect sizes), such as general anxiety and cognitive distortions, were found.
**DISCUSSION:** Remote CBMT appears like a promising avenue for treating social anxiety in early psychosis, particularly for people who have transportation issues, or who are currently too fearful to leave their domicile.

## M17. The Application of Social Cognitive Skills in Intimate Interactions: Predictors of Sexual and Romantic Functioning in Early Psychosis

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**BACKGROUND:** Intimate relationships are integral to well-being and recovery for many people experiencing psychosis. However, psychiatric symptoms, cognitive deficits, and social cognitive impairment can disrupt the formation and maintenance of these relationships. Traditional social cognition assessments may not fully capture the complexities and barriers encountered in intimate, romantic, and sexual contexts. This study examined if individuals with psychosis faced specific social cognitive challenges in a novel task assessing one's ability to identify and make judgements about romantic and sexual cues (referred to as "romantic/sexual social cognition"), how this performance is related to psychiatric symptoms, cognition, and

social cognition, and whether these abilities uniquely predict real-world romantic relationship and sexual functioning.
**METHODS:** Participants (35 early psychosis outpatients, 38 matched controls) completed measures assessing psychiatric symptoms, cognition, social cognition, romantic relationship functioning, and sexual functioning. Participants also completed a novel task measuring social cognition in romantic/sexual interactions, in which they were required to view short animations of two characters interacting and answer questions about the characters' relationship statuses and whether sexual or romantic interest is being expressed.
**RESULTS:** Participants with psychosis performed significantly worse than controls on cognitive and social cognitive tasks. On the novel romantic/sexual social cognition task, participants with psychosis were significantly less accurate than controls when identifying others' relationship statuses and depictions of romantic and/or sexual interest. Males with psychosis performed significantly worse on this task compared to females with psychosis and male controls. Romantic/sexual social cognition predicted real-world romantic relationship functioning and sexual functioning, respectively, above and beyond the effects of psychiatric symptoms, cognition, and general social cognition.
**DISCUSSION:** The social cognitive abilities required to navigate intimate, romantic, and sexual contexts may not be fully captured by traditional measures, highlighting the need to better assess for and understand specific barriers to the application of social cognitive skills in intimate contexts. These findings may be used to inform interventions targeting intimate relationship functioning, as these areas may not improve with traditional social skills training alone. Given the sex differences observed in the present study, such interventions may benefit from being tailored across genders. To better support individuals with psychosis who have recovery goals centered around close relationships, future work should continue to examine specific social cognitive challenges in navigating romantic and sexual interactions, and how these challenges may affect the initiation and maintenance of close relationships.

## M18. Prompted Speech Elicitation With a Story Re-Telling Task Captures Variations in Processing Speed Among Patients With Psychosis: A Discourse Protocol Study

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**BACKGROUND:** The ability to read, integrate, and recall information is essential to one's capacity to function in modern educational, occupational, and even recreational environments. Effective reading performance requires the integration of several complex cognitive components, ranging from decoding and sensory processing, up to higher order memory and executive functions, such as managing attentional resources. For patients with schizophrenia and related psychotic disorders, disruptions in several cognitive domains related to reading performance - including processing, and fluency - are well established. However, the degree to which naturalistic story reading and re-telling can track validated clinical (positive and negative

symptoms) and cognitive measures (processing speed, verbal fluency) is unclear. We investigate this issue using a speech elicitation protocol in patients with psychosis and healthy controls.
**METHODS:** 39 patients with a diagnosed primary psychotic disorder enrolled at the Prevention and Early Intervention Program for Psychoses (PEPP) in London Ontario, Canada and 19 healthy controls were assessed using clinical, cognitive, and linguistic data derived from the Discourse in Psychosis (v2.0, English) protocol. Subjects completed a demographic and clinical battery including the Positive and Negative Syndrome Scale 10-item version (PANSS-10), as well as a brief cognitive battery including the Category Fluency test and modified Digit Symbol Substitution Test (DSST), a measure of processing speed. Finally, subjects engaged in a guided discourse with the interviewer based on the prompts from the speech elicitation protocol. The "Reading and Recall" part of speech involved reading a modified Aesop fable (11 sentences, 116 total words, 2nd – 3rd grade reading level) out loud. Upon completion, subjects were asked to retell the story to the researcher with responses audio-recorded. Recall scores were based on the number of correct details recorded during the recall portion of the task.
**RESULTS:** As predicted, our analyses revealed that patients scored significantly lower than healthy controls on measures of recall performance [patient= 7.29 (2.38), HC= 9.0 (2.31), t=2.53, p=0.015], which persisted after controlling for gender and parental socioeconomic status (Z=-2.43, p= 0.015). When our analyses were limited to patients, recall performance was correlated with DSST scores (r=0.46, p=0.007), but not to the severity of positive or negative symptoms, or category fluency scores. When parental SES, patient education, gender, and category fluency, were added to the model, the model remained significant with DSST as the only independently significant factor.
**DISCUSSION:** Processing speed deficits affect the performance in a simple reading and recall paradigm in patients with psychotic illness. Assessing the recall performance from a short story sufficiently captures cognitive variance among patients with psychosis. These findings support the emerging call for using ecologically valid assessment procedures that obviate motivational confounds when assessing neurocognitive processes in psychosis.

## M19. Rewarding Versus Reinforcing: Predictors of Real-World Social Engagement in Veterans With Psychotic-Spectrum Disorder

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**BACKGROUND:** Background: Social withdrawal and anhedonia are pervasive, disabling features of schizophrenia. Yet, studies show people with schizophrenia report desire for social affiliation and experience commensurate positive emotion during daily social activities as controls. To help explain this phenomenon, laboratory research has examined differences in reinforcement learning, finding those with schizophrenia exhibit deficits in reward learning yet intact ability to avoid punishments. Although reinforcement learning has been studied in laboratory paradigms, researchers have yet to translate these findings to the real world.
**METHODS:** Methods: This study examined predictors of real-world social motivation and engagement using ecological momentary assessment (EMA). Veterans with psychotic-spectrum disorder completed 4 electronic surveys per day over 1 week and reported their subjective

appraisals and enjoyment during social interactions as well as desire for future socialization and participation in later social interactions. This design allowed us to determine if social rewards (i.e., feelings of enjoyment, connection, and comfort during interactions) and/or negative social appraisals (i.e., feelings of suspiciousness, rejection, and difficulty during interactions) predicted social motivation (i.e., desire for future socialization) and behavior (i.e., number of subsequent social interactions).
**RESULTS:** Results: Ninety-one veterans with a psychotic disorder participated in the study. The sample was 85% male, 61% white, and 89% non-Hispanic with a mean age of 56 (SD=15). Multilevel modeling suggested momentary social rewards significantly predicted greater desire for future socialization (b=0.05, SE=0.01, $p < 0.001$), but not number of subsequent interactions (b=-0.01, SE=0.03, p=0.66). Negative social appraisals did not predict either social outcome (desire: b=-0.02, SE=0.03, p=0.41; number of subsequent interactions: b=-0.02, SE=0.04, p=0.57). The effect of social rewards on desire for future socialization was maintained even after controlling for positive and negative symptom severity. Exploratory analyses examining the effects of the individual EMA items found that enjoyment during current interactions was the greatest predictor of desire for future socialization. Moreover, self-reported difficulty during interactions significantly predicted less desire for future socialization, even after controlling for enjoyment and symptom severity (b=-0.10, SE=0.05, p=0.03).
**DISCUSSION:** Discussion: Unlike laboratory studies that find those with schizophrenia exhibit deficits in reward learning, our results suggest real-world social rewards do impact desire for socialization, at least in the short-term. Moreover, state-level social rewards were predictive above and beyond trait-levels of negative symptoms like social anhedonia, highlighting the value of EMA to measure momentary reports of these constructs. However, momentary social rewards do not predict an increase in later social activity, suggesting a discrepancy between "wanting" and "doing" in schizophrenia. Moreover, self-reported difficulty during social interactions contributed to less desire for later socialization, while feelings of suspiciousness and rejection did not. This implicates feelings of self-efficacy as an important determinant of social motivation, over paranoia or persecutory beliefs. Clinical implications, including potential targets for social functioning interventions in schizophrenia, will be discussed.

## M20. Predicting Social Participation Using Brain MRI, Environmental and Genetic Measures in the UK Biobank Using Extreme Gradient Boosting (XGBOOST)

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**BACKGROUND:** Experience of psychosis is often associated with poor social outcomes, even with successful antipsychotic treatment. Understanding which factors influence an individual's social behaviour is an important step in understanding this problem. Here, we aim to identify to what degree social participation (SP) can be predicted in healthy individuals and by which specific brain MRI metrics, and environmental and genetic factors.
**METHODS:** SP (range: 0 – 10) was defined based on a metric comprised of frequency of friend/family visits (UKB:p1031) and leisure/social activities (UKB:p6160). Individuals were classed as having low SP (n=8,288) or high SP (n=5,681) using cutoffs related to the top and

bottom quartile of the SP distribution. Measures of brain MRI volume (n=451), environmental exposures (n = 32) and genetic polygenic risk scores (PRS) (n=36) with < 10% missingness, as well as age, sex and educational attainment (EA) were used to predict SP in healthy individuals in the UK Biobank. Data were split into 75:25 training: test cohorts.
**RESULTS:** Balanced prediction accuracy for classifying high/low SP in the test set was 61.4%. ROC analysis indicated a total AUC of 69.4%. Precision and recall were 66.7% and 84.5% respectively. Age was the most significant predictor by variable importance, followed by friendships satisfaction, length of time at current address, sex and household income. Among the top 20 predictors, 8 (40%) were environmental, 8 (40%) were brain measures, and 1 (5%) was genetic.
**DISCUSSION:** This work suggests that SP is a predictable measure and that brain MRI features and environmental exposures are more important factors than genetic factors. Although literature details the link between brain MRI features behaviour, the role and causality of environmental factors appears less clear. Further work including robust feature selection of factors and validation in affected individuals is required to fully understand the environmental and biological factors that influence social behaviour in psychosis.

## M21. Pattern of Cognitive Dysfunction in Patients With Psychiatric Disorders With Lateral Ventricle Enlargement and Cognitive Impairment

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**BACKGROUND:** Psychiatric diagnoses traditionally rely on symptom-based operational criteria without considering biological pathology. However, recent efforts have aimed to refine psychiatric diagnoses using objective test findings. A previous study classified four brain biotypes based on subcortical volumes in a cohort of 5,602 individuals, including 2,525 patients with major psychiatric disorders and 3,077 healthy controls (HC). Further analyses of biological and clinical characteristics revealed that patients with severe symptoms could be stratified based on the presence of moderate-to-severe cognitive dysfunction and lateral ventricle volumes exceeding three standard deviations above the mean of healthy controls. This subgroup was further characterized by a high prevalence of abnormal electroencephalography findings, schizophrenia diagnoses, and rare copy number variations. In this study, we investigated the patterns of cognitive dysfunction in psychiatric patients with lateral ventricle enlargement and cognitive impairments. The study was conducted with the approval of the Ethics Committee of the National Center of Neurology and Psychiatry.
**METHODS:** We analyzed data from nine patients with psychiatric disorders presenting with both enlarged ventricles (≥3SD above HC) and moderate or greater cognitive impairment (EV-CI). These were compared to 292 patients with schizophrenia without EV-CI (SZ) and 1168 HC. Cognitive function was assessed across 18 tasks, including cognitive decline (current IQ - estimated premorbid IQ), estimated premorbid IQ, current IQ, WAIS index scores, WMS index scores, AVLT, VF, CPT, and WCST. Additional comparisons were made with 129 subjects

without enlarged ventricle and with cognitive impairment (nonEV-CI), 29 subjects with enlarged ventricle and without cognitive impairment (EV-nonCI), and 1422 subjects without enlarged ventricle and cognitive impairment (nonEV-nonCI).
**RESULTS:** The patterns of cognitive impairment in the EV-CI and SZ groups were generally similar. Both groups showed significant differences across all cognitive tasks compared to the HC group, with five tasks significantly differing between the EV-CI and SZ groups. Cognitive impairment patterns in the EV-CI, nonEV-CI, and EV-nonCI groups were broadly similar. Both the EV-CI and nonEV-CI groups differed significantly from the nonEV-nonCI group but not from each other. The nonEV-CI group exhibited more severe impairment than the EV-nonCI group across 12 tasks. The EV-CI group showed significant differences from the EV-nonCI group in 11 tasks. Average effect sizes for cognitive impairment were -0.16 in the nonEV-nonCI group, -0.77 in the EV-nonCI group, and -2.61 in the EV-CI group. The difference between the average effect size for cognitive impairment in the EV-nonCI group and the average effect size for cognitive impairment in the nonEV-nonCI group was -0.61, which is the difference between the nonCI groups with and without EV. In other words, the average effect size for cognitive impairment in the EV condition was considered to be -0.61. Furthermore, the difference between the average effect size for cognitive impairment in the EV-CI group and the average effect size for cognitive impairment in the EV-nonCI group was -1.84, which is the difference between the presence or absence of CI pathology in the EV group. In other words, the effect size for cognitive impairment in CI pathology was considered to be -1.84.
**DISCUSSION:** The average effect size of -2.61 for cognitive dysfunction in the EV-CI group was equal to the sum of the average effect size of -0.16 for cognitive dysfunction in the non-EV-non-CI group, the average effect size of -0.61 for cognitive dysfunction in the EV pathology, and the average effect size of -1.84 for cognitive dysfunction in the CI pathology. The cognitive dysfunction that occurs in the EV-CI group may be a condition that is a superposition of the process from the nonEV-nonCI group to the EV-nonCI group and the process from the EV-nonCI group to the EV-CI group.

## M22. Changes in Cognitive Functioning and Emotion Regulation in Schizophrenia Patients Starting Treatment with Cariprazine

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**BACKGROUND:** Cognitive impairments are considered to be core features of schizophrenia and have previously been shown to exert a greater influence on social and vocational functioning than the presence or severity of positive or negative symptoms. Patients with schizophrenia have a broad range of cognitive impairments, including deficits in attention, executive function, visual and verbal learning and memory, working memory, processing speed, and social cognition. Available antipsychotic treatments have not yet demonstrated substantial efficacy in treating cognitive symptoms, which is a major unmet need in these patients. Based on the encouraging research data derived from animal studies, it is hypothesized that cariprazine treatment is associated with improvements in cognitive functioning.
**METHODS:** This 28-week, open label signal detection study investigates patients with schizophrenia (ICD-10) who are in need of adjustment of oral antipsychotic treatment as judged

by their treating psychiatrists. Cognitive functioning is measured with the Brief Assessment of Cognition in Schizophrenia (BACS) and the Heidelberg Form for Emotion Regulation Strategies (HFERST). Changes in psychopathology are assessed with The Positive and Negative Syndrome Scale (PANSS).
**RESULTS:** So far, 10 individuals have been included into the study and has so far been completed by 6 people. Preliminary findings indicate significant improvements in clinical symptoms (PANSS) ($z = -2.214$, $p = .027$) and in attention/ speed of information processing on the Symbol Coding Task ($z = -2.201$, $p = .028$). No significant changes were found in neurocognitive functioning (BACS) ($z = 1.153$, $p = .249$) and in the use of functional emotion regulation strategies (HFERST: dysfunctional $z = -.524$, $p = .600$; functional $z = 1.156$, $p = .248$) over time.
**DISCUSSION:** Despite the low number of participants, this study provides initial indications of a positive effect of cariprazine on the cognitive symptoms of schizophrenia. However, further studies with larger numbers of cases are needed to confirm this finding.

## M23. Characterizing the Demographics and Disease Burden of People With Cognitive Impairment Associated With Schizophrenia: A Non-Interventional Cohort Study of Real-World Data

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**BACKGROUND:** Although cognitive impairment associated with schizophrenia (CIAS) significantly impacts daily activities and quality of life, there is no approved pharmacotherapy for CIAS and no standardized diagnostic code, making it difficult to identify in insurance claim data. This study aimed to identify adults with CIAS and characterize their associated demographics and disease burden using linked electronic health records (EHR) and claims data from a US de-identified database.
**METHODS:** A non-interventional, retrospective, cohort study was conducted using EHR and claims data from the Optum Market Clarity database. During the identification period (Oct 1, 2016–Mar 31, 2022), data were assessed for adults with ≥2 claims for schizophrenia and ≥1 year of continuous enrollment prior to index date (first schizophrenia diagnosis). Adults with Alzheimer's disease, dementia, epilepsy, attention-deficit hyperactivity disorder, bipolar disorder, or intellectual disability were excluded. Diagnostic and procedural claims codes and natural language processing-derived clinical data from free-text EHR were used to confirm CIAS in the dataset. Data were stratified into those with a history of CIAS or CIAS at follow-up (CIAS-Y) and those with no history of CIAS or CIAS at follow-up (CIAS-N). Demographic data are reported for the baseline period (1 year pre-index), and comorbidities and medication use are reported at 1-year follow-up. All outcomes are reported descriptively.
**RESULTS:** Data from 183,483 adults with schizophrenia were assessed, with 44,236 (24.1%) categorized as CIAS-Y and 139,247 (75.9%) as CIAS-N. In the CIAS-Y and CIAS-N groups, mean (SD) age was 52.2 (16.7) and 46.5 (15.9) years; proportion of males was 59.8% and 63.3%; and the most common insurance was Medicaid at 34.8% and 36.5%, respectively.

Common mental health comorbidities in the CIAS-Y and CIAS-N groups included major depressive disorder (44.9%, 36.7%), anxiety (38.8%, 32.2%), substance-related disorders (34.5%, 32.2%), neurodegenerative disorders (17.2%, 5.4%), adjustment disorders (13.8%, 12.7%), and other mood disorders (8.4%, 5.9%), respectively. Mean (SD) Elixhauser comorbidity score was 5.9 (3.7) for CIAS-Y and 4.3 (3.0) for CIAS-N. Elixhauser comorbidities in the CIAS-Y and CIAS-N groups included uncomplicated hypertension (56.8%, 42.0%), arrhythmias (30.2%, 17.5%), uncomplicated diabetes (29.5%, 20.6%), obesity (23.3%, 19.8%), complicated diabetes (21.0%, 13.6%), complicated hypertension (15.3%, 7.8%), peripheral vascular disease (13.6%, 7.2%), and congestive heart failure (13.5%, 6.9%), respectively. Medication use in the CIAS-Y and CIAS-N groups included lorazepam (25.1%, 12.8%), haloperidol (22.6%, 12.5%), and benztropine (21.8%, 14.7%), respectively. Medication classes used by the CIAS-Y and CIAS-N groups included second-generation antipsychotics (63.4%, 55.5%), anxiolytics (48.3%, 36.7%), antidepressants (46.7%, 39.4%), anticonvulsants (38.9%, 25.3%), first-generation antipsychotics (31.6%, 19.0%), mood stabilizers (29.3%, 21.7%), hypnotics and sedatives (28.6%, 18.9%), and substance-related disorder medications (18.6%, 11.8%), respectively.

**DISCUSSION:** In this study population, ~25% had CIAS and mean age was slightly higher in the CIAS-Y versus CIAS-N group. The proportions of adults with mental health and Elixhauser-index comorbidities tended to be higher in the CIAS-Y than CIAS-N group, and medication use also tended to be higher in the CIAS-Y group. The RESULTS: of this cohort study highlight the disease burden of CIAS and indicate the potential of characterizing CIAS for earlier identification in the patient journey.

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## M24. Emotional Face Processing Indexed by N170 Modulation in Chronic and First Hospitalized Schizophrenia

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**BACKGROUND:** Facial emotion recognition is impaired in schizophrenia and contributes to the symptoms and functional impairments of the disorder. Psychiatrically-well individuals exhibit larger N170 visual evoked potentials to faces compared to other complex objects, and to emotional faces compared to neutral faces. Patients during chronic stages of schizophrenia have a reduced N170 response to faces despite preserved N170 enhancement in early-stage psychosis. Preliminary evidence also suggests an inability to modulate N170 amplitude by emotional expression during chronic stages of the illness. The present investigation examined modulation of the N170 by emotional facial expression among patients with chronic (ChSz) and first hospitalized (FHSz) schizophrenia spectrum illness.

**METHODS:** Behavioral and neurophysiological responses of 26 FHSz and 28 ChSz participants were compared to 19 matched young controls (YC) and 21 matched older controls (OC), respectively. Participants were asked to detect neutral faces among happy, angry, disgusted, fearful, and sad faces. N170 amplitudes were measured from P9/P10 electrodes which showed

the most robust response. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Correlations between task performance, N170 amplitude, N170 modulation (mean N170 across emotional expression minus N170 to neutral faces), and symptoms were assessed among FHSz and ChSz.
**RESULTS:** While FHSz and YC did not differ in task performance (p=.33), ChSz made significantly fewer correct detections of neutral faces compared to OC (t47=-2.42, p=.01). Modulation of the N170 by emotion was observed across FHSz and YC (F5,215=5.53, p < .001) with no significant difference in this effect between groups (p=.26), though the typical right-hemisphere lateralization of this response observed in YC (t18=3.77, p=.001) was absent in FHSz (p=.56). In contrast to OC (F5,100=3.24, p=.009), ChSz did not exhibit N170 modulation by emotion (p=.32). Among ChSz, both task correct detections (r= -.53) and N170 emotional modulation at P9 (r= -.53) were inversely correlated with PANSS negative scores following correction for multiple comparisons.
**DISCUSSION:** Evidence from this cross-sectional dataset suggests a progressive impairment of emotional facial expression processing as indexed by N170 modulation across illness stage. While preserved in FHSz, modulation of the N170 amplitude to emotional versus neutral expressions was diminished in ChSz. This deficit was also associated with negative symptoms among ChSz, implicating progressive pathology of N170 generators in the most persistent and impairing symptoms of the disorder. Interestingly, absent N170 lateralization observed in FHSz and the inverse relationship between left-hemisphere N170 modulation and symptoms in ChSz may reflect a compensation for disruptions in traditional face-processing circuitry.

## M25. Bidirectional Relationships Between Inflammation and Executive Functioning in Schizophrenia: A Longitudinal Analysis

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**BACKGROUND:** Executive functioning deficits are one of the hallmark symptoms of schizophrenia. People with schizophrenia (PwS) also exhibit higher inflammation, which has been shown to influence the onset and progression of the disease. Inflammation may influence cognition and executive functioning through its effects on the blood-brain barrier and neurotransmitter production. At the same time, executive functioning deficits may also affect inflammation via poor health-related decision-making. Longitudinal studies may elucidate bidirectional relationships between inflammation and executive function.
**METHODS:** This longitudinal study investigated the bidirectional relationships between cytokines (high sensitivity C-Reactive Protein (hs-CRP), Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α, and Interleukin (IL)-6, −8, and − 10) and executive functioning among 186 PwS and 164 non-psychiatric control (NC) participants (350 total participants). The participants were followed for up to 10 years between 2012 and 2022 with 0 to 5 follow-ups since baseline. A composite score (ExComp) of Trail Making, Color-Word Inhibition, and Letter Fluency subtests of the Delis-Kaplan Executive Function System was created to account for the multidimensionality of executive functioning. Linear mixed-effects models (LMMs) were used to investigate the longitudinal variable trajectories. Continuous time structural equational modeling (CTSEM) was used to examine the cross-lagged relationships between each cytokine

and executive functioning. For all analyses, covariates included diagnostic group, baseline age, sex, race/ethnicity, and education.
**RESULTS:** The results of LMMs showed that PwS had significantly lower performance on tests of executive functioning and higher levels of hs-CRP, IL-6, IL-10, TNF-α, but not IL-8 and IFN-γ. In both groups, ExComp, IL-8, and IFN-γ increased with each additional year of follow-up. The cross-lagged results revealed a significant effect of IL-6 (Est. = -6.91, SD = 1.51, 95% CI [-9.70; -3.90]), IL-10 (Est. = -7.56, SD = 0.52, 95% CI [-8.54; -6.59]), and TNF-α (Est. = -27.38, SD = 0.62, 95% CI [-28.62; -26.16]) on ExComp with a one-year lag, with higher levels of these cytokines associated with poorer ExComp performance. The relationship of earlier IL-10 to later ExComp was stronger among PwS. The opposite directionality was observed between hs-CRP (Est. = 1.56, SD = 0.60, 95% CI [0.38; 2.72]) and IFN-γ (Est. = 3.16, SD = 0.96, 95% CI [1.21; 5.07]) and ExComp, with higher levels of these two cytokines associated with better EXCOMP performance with a one-year lag. These relationships were more robust in PwS than in NCs. The relationship EXCOMP à cytokines was observed with IL-8 (Est. = -0.75, SD = 0.29, 95% CI [-1.35; -0.18]), IL-10 (Est. = -3.37, SD = 0.45, 95% CI [-4.24; -2.50]), and TNF-α (Est. = -6.68, SD = 1.28, 95% CI [-9.22; -4.07]), with no differences between diagnostic groups, such that higher earlier executive functioning was associated with later lower levels of IL-8, IL-10, and TNF-α.
**DISCUSSION:** Our results suggest a nuanced relationship between inflammation and executive functioning in PwS. IL-10 was more strongly associated with later executive function performance among PwS than NCs, suggesting it as a potential target for intervention. The positive influence of hs-CRP and IFN-γ on later performance may be explained by the imbalance in immune response in PwS, wherein a lower production of some cytokines but not others has been noted. Therefore, an increase in the production of cytokines such as IFN-γ or hs-CRP may, in some contexts, contribute to a more balanced immune response, exerting protective effects on cognition. These findings highlight a potential for tailored anti-inflammatory interventions for PwS.

## M26. Validity of a Modified Version of the Ambiguous Intentions Hostility Questionnaire: Assessing Attributional Style Using Social Media Posts

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**BACKGROUND:** People with schizophrenia-spectrum disorders and subclinical psychotic-like experiences (PLEs) demonstrate impairments in social cognition. Relatedly, research suggests that people with PLEs often overinterpret ambiguous and accidental social situations as aggressive or hostile and tend to place increased blame on others. Attributional style in these populations is often measured with the Ambiguous Intentions Hostility Questionnaire (AIHQ). Limited work has investigated attributional style in the context of social media. Social interactions online are highly prevalent, and research indicates that there may be greater ambiguity within online interactions. Given this, better understanding of relationships between PLEs and attributional style in interactions online is needed. The current study aimed to assess

the psychometric properties of a modified version of the AIHQ and to explore relationships between this modified measure, PLEs, and social functioning.
**METHODS:** In the original AIHQ, participants are presented with 10 second-person vignettes of negative social situations that are either accidental or ambiguous. They are then asked to rate how angry the situation would make them feel, how much they would blame the person in the scenario, and if they feel the person acted that way towards them intentionally. Scores on each of these items are then averaged together for a total AIHQ score.

We modified the AIHQ to mimic Facebook posts from a "friend." Accidental and ambiguous vignettes were reworded using first-person language from the friend's perspective (e.g., "I've been at a new job for three weeks…"). Questions about anger, blame, and perceived intentionality were reworded to ask participants to indicate how they thought their friend would feel in the situation described.

Participants with high quality data (n = 132) were recruited via Prolific and completed self-report measures of paranoia, schizotypy, interpersonal functioning, and the modified version of the AIHQ online. A subset of participants (n = 68) also completed the original version of the AIHQ.
**RESULTS:** The modified AIHQ and original AIHQ were significantly correlated on each subscale (anger: $r = .69$, $p < .001$; blame: $r = .60$, $p < .001$; intention: $r = .86$, $p < .001$) and on the total score ($r = .75$, $p < .001$). Additionally, internal consistency across the subscales (anger = .79; blame = .76; intention = .70) and across all items (.86) on the modified AIHQ was adequate. Higher total score on the modified AIHQ was associated with greater paranoia ($r = .46$, $p < .001$), greater schizotypy ($r = .25$, $p = .005$), lower emotional support ($r = -.20$, $p = .02$), as well as higher perceived hostility ($r = .26$, $p = .002$) and higher perceived rejection from others ($r = .31$, $p < .001$). Relationships between modified AIHQ total score and levels of reported friendship were non-significant ($r = -.11$, $p = .22$).
**DISCUSSION:** Overall, our findings provide preliminary support for the validity of the modified AIHQ to assess attributional style from social media posts. Specifically, results suggest strong relationships between the modified and original AIHQ, and the modified AIHQ demonstrated adequate internal consistency on the subscales and across all items of the measure. Further, the modified AIHQ demonstrated convergent validity with related constructs (i.e., perceived hostility and rejection) and with constructs known to be related to the original AIHQ, including paranoia and schizotypy. Future work should continue to explore the psychometric properties of this modified measure, including in larger and diverse samples. Investigations of the use of this measure in schizophrenia-spectrum populations may also be informative.

## M27. Semantic Network Linked to Social Functioning in Patients With Schizophrenia

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**BACKGROUND:** Schizophrenia is characterized by language-related symptoms stemming from disorganized semantic memory, which often lead to poor social functioning. Although numerous studies have attempted to elucidate the association between these symptoms and social functioning, it remains unclear whether semantic memory disorganization leads to poor social functioning.
**METHODS:** We investigated this association by utilizing advanced automated scoring techniques to quantify individual-specific semantic memory parameters from the Category Fluency Test (CFT). Specifically, the similarity between consecutive responses from the CFT was calculated using distributional representations, forming the basis for the semantic parameters.
**RESULTS:** Schizophrenia patients (n = 139) exhibited semantic memory disorganization compared to healthy controls (n = 98). Generalized linear models predicting social functioning within the schizophrenia group, as measured by the Specific Levels of Functioning Scale, revealed that higher semantic parameters were associated with better social functioning scores ($\beta$= 0.07, z = 48 4.90, $p < 0.01$), with a pseudo-R2 of 0.29.
**DISCUSSION:** These findings suggest that social functioning is related to semantic memory organization, thus providing a framework for the exploration of social functioning by assessing semantic memory organization in schizophrenia patients.

## M28. Speaking of Yourself: A Meta-Analysis of 80 Years of Research on Pronoun use in Schizophrenia

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**BACKGROUND:** Schizophrenia involves significant language disturbances, notably in pronoun usage, which is essential for social and contextual discourse. The variability of these disturbances among patients is unclear. This systematic review and meta-analysis, adhering to PRISMA guidelines, aims to address this gap by examining pronoun use and grammatical aberrations in schizophrenia.
**METHODS:** Databases searched included PubMed, PsycINFO, Scopus, Google Scholar, and Web of Science up to May 1, 2024. Studies analyzing pronoun frequency, accuracy, and context in schizophrenia were included. Bias was assessed using a modified Newcastle–Ottawa Scale, and a Bayesian meta-analysis with model averaging estimated effect sizes and moderating factors.
**RESULTS:** 13 studies with n=917 unique participants and 13 case-control contrasts were included. 37.9% of patient samples were women, with a weighted mean (SD) age of 34.45 (9.72) years. 53.85% of the studies were in languages other than English. Bayesian meta-analysis revealed a medium-sized effect for first-person pronoun impairment in schizophrenia (model-averaged d=0.89, 95% CrI (0.44,1.33). There was significant heterogeneity moderated by age. Evidence for publication bias was weak, with strong support for first-person pronoun impairment after accounting for bias and heterogeneity. There was weak evidence for a small reduction of

inter-individual variability in first-person pronoun use compared to healthy controls (lnCVR=-0.12, 95% CrI [-0.35, -0.13]). While all pronoun use was also high in patients, this was not robust due to heterogeneity and publication bias.
**DISCUSSION:** Individuals with schizophrenia excessively use first-person pronouns which may serve as an illness marker related to self-referential processes.

### M29. From Pixels to Perceptions: Sensory Experiences in Gamers

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**BACKGROUND:** Game Transfer Phenomena (GTP) is a sensory experience characterised by spontaneous sensory perceptions, mental processes, and automatic behaviours related to video game content (Ortiz de Gortari and Griffiths, 2012), and is related to increased gameplay. GTP has been described as hallucinatory; examples include seeing player icons or hearing game-related music in real-life. Research highlights positive appraisals of GTP, with links to creativity, and feelings of intelligence and fun. Research has not specifically investigated negative appraisals of GTP.
This study developed the revised Game Transfer Phenomena Scale – Consequences, Distress, Intrusiveness, and Intensity (GTPS-CDII). We hypothesised 1) more frequent gameplay would correlate with higher GTP-CDII scores, 2) experiencing GTP and mental health problems would be related to greater hallucination-proneness vs controls, and 3) GTP-CDII scores would correlate with hallucination-proneness.

**METHODS:** 276 participants completed an online questionnaire (GTP=70, mean age= 21.14, SD = 3.84; 67.1% female; Controls=206, mean age= 19.75, SD = 2.83; 81.6% female). Participants completed the GTPS-CDII, measuring GTP experience, frequency, and context. Sub-scales rate associated distress, intrusiveness and intensity on a 6-point Likert scale, ranging from not at all (0) to extremely (5). Consequences measure behavioural responses to GTP (urge to act, acting on experience, attempts to prevent/avoid, control, related impairment, disruption to daily life, camouflaging and perceived reality of GTP) on a 6-point Likert scale, ranging from not had this experience (0) to has had an extreme case of this experience (5). We also measured hallucination-proneness using Multimodal Unusual Sensory Experiences Questionnaire (MUSEQ) (Mitchell et al., 2017).
Participants were grouped: Controls (n=109, no GTP or mental health history), Mental Health-only (n=96, no GTP but with mental health history), GTP (n=23, GTP experience without mental health history), and GTP+Mental Health (n=47, GTP experience with mental health history).

**RESULTS:** Experiences: GTP was frequently reported while falling asleep, in darkness, and during everyday activities including walking, dancing, watching TV, listening to music, and doing chores. Mean scores of GTPS-CDII sub-scales were < 1, except for GTP Intensity (M=1.20).
Correlations: There was no significant association between gaming frequency and GTP-CDII sub-scale scores. There was a small association between MUSEQ total and gaming frequency (total hours r=.124, p=.04; , hours per day r=.136, p=.02).

MUSEQ total was significantly associated with GTPS-CDII distress (r= .364, p=.002), intrusiveness (r=.382, p=.001), intensity (r=.421, p < .001), and consequences: urge to act

(r=.323,p=.006), acting on experience (r=.349, p=.003), impairment (r=.320, p=.007), disruption to daily life (r=.332, p=.005), camouflaging (r=.4, p < .001) and perceived reality (r=.298, p=.012).

Group comparisons: Age-adjusted ANCOVA revealed greater hallucination-proneness in individuals with GTP, regardless of mental health status, $F(3, 271)= 4.41$, $p < .001$.

**DISCUSSION:** GTP was reported during everyday activities, was not intense or intrusive, and did not cause distress or disruption. While GTP was linked to higher hallucination-proneness compared to controls, this was unaffected by mental health status. Hallucination-proneness was associated with GTP distress, intrusiveness, intensity, and more frequent gameplay. These findings add to the discussion about the impact of video games on wellbeing, and highlight how hallucination-proneness manifests in non-clinical contexts.

## M30. Proteomic Biomarkers of Cognitive Improvement in First-Episode Psychosis: Exploring the Impact of a Cognitive Rehabilitation Program on Working Memory

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**BACKGROUND:** Cognitive impairments, particularly in working memory, are a core feature of first-episode psychosis (FEP) and are associated with functional difficulties. Biomarkers, including proteomics, may serve as valuable predictors of cognitive outcomes and responses to cognitive rehabilitation programs. This study investigates the effects of a cognitive rehabilitation program on working memory in FEP patients, with a focus on identifying proteomic biomarkers that could predict cognitive improvements.

**METHODS:** A randomized clinical trial was conducted with 28 clinically stable FEP patients (ages 18-35 years) recruited from Early Intervention Services for Psychosis (Sabadell, Parc Taulí Hospital Universitari). Participants were randomized into a cognitive rehabilitation group (n = 14) or a treatment as usual (TAU) group (n = 14). The intervention consisted of a 12-week cognitive rehabilitation program (Neuropersonal Trainer), which targeted cognitive domains such as memory, executive function, and social cognition. Working memory performance was assessed using the One Touch Stockings of Cambridge (OTS) and Spatial Working Memory (SWM) tasks. Fasting blood samples were collected and processed for proteomic analysis to test protein concentrations using the Olink Target 96 Neurology panel, a high-multiplex immunoassay technology. Lasso regression was used to identify proteins associated with cognitive changes, and mixed linear regression tested the time-by-group-by-biomarker interactions.

**RESULTS:** Several biomarkers were associated with cognitive changes in the OTS and SWM tasks. In the OTS task, significant associations were found with RSPO1 (R-spondin 1) ($\beta$ = -0.492), CLEC1B (C-type lectin domain family 1 member B) ($\beta$ = -0.190), and GDF8 (Growth differentiation factor 8) ($\beta$ = 0.153) for the Median Latency to First Choice (OTSMDLFC). In the SWM task, sFRP3 (Secreted Frizzled-Related Protein 3) ($\beta$ = -0.618) was associated with better spatial working memory performance on the SWM Strategy (6-8 Boxes) measure. No

significant time-by-group-by-biomarker interactions were observed in the mixed linear regression models.
**DISCUSSION:** The cognitive rehabilitation program appears to enhance working memory performance in FEP patients, with biomarkers such as RSPO1, CLEC1B, GDF8, and sFRP3 potentially influencing cognitive improvements. Although no significant interactions were found, these biomarkers might help predict cognitive outcomes and responses to cognitive rehabilitation in FEP. Further studies are needed to validate these findings and explore their therapeutic potential for targeting cognitive impairments in psychosis.

## M31. Novel Peripheral Biomarker for Muscarinic Acetylcholine Receptor Related to Psychosis

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**BACKGROUND:** Up to 3% of the population meet diagnostic criteria for a psychotic disorder, with an even larger portion experiencing psychosis. The underpinnings of psychosis remain enigmatic, although a wide array of comorbid metabolic, inflammatory and cardiovascular conditions suggest systemic pathology, including autonomic nervous system dysfunction. Abnormal vagal and adrenergic activity, reflecting parasympathetic and sympathetic tone, are well described and studied, but far less understood is the origin of dysfunction, occurring supratentorially or peripherally. Sudomotor function, an autonomic reflex to regulate body temperature through sweat is entirely mediated through peripheral functioning, which was analyzed using the Quantitative sudomotor axon reflex test (QSART).
**METHODS:** 75 subjects (23 with psychosis, 19 with affective disorders, 33 healthy controls) underwent QSART tests to assess autonomic function. These groups were further compared with regards to anti-cholinergic burden (ACB), stratified with a high or low ACB score. The output of the sweat production, measured by the change in humidity, was analyzed by area under the curve to determine the maximal sweat production and sweat onset latency yielding a sudomotor score. This was calculated via a CASS score and validated with the internal battery, mCASS. Differences in sudomotor scores between groups and for different comorbidities were analyzed with ANOVA. Pearson correlations were computed to examine associations between ACB and sudomotor function. Mann-Whitney U-tests were used to examine differences in sudomotor function between those with high and low ACB.
**RESULTS:** Sudomotor scores differed between the groups ($F=5.30$, $p=.017$, Partial $\eta 2=.132$, with more dysfunction in the psychosis group compared to healthy controls ($p=.002$) and in affective disorders group compared to the controls ($p=.028$). The psychosis and affective disorders groups did not differ. When controlling for anti-cholinergic burden (ACB), only the psychosis group had more dysfunction compared to healthy controls ($p=.011$). In the affective disorders group, there was a significant association between ACB and sudomotor score ($r=.494$, $p=.044$) but these were not correlated in the psychosis group ($r=.161$, $p=.349$). Within the psychosis group sudomotor scores did not differ between those with high ACB (N=14) and those with low ACB N=17) scores (Mann Whitney $U=117.50$, $P=.750$). This difference was independent of age and sex.

**DISCUSSION:** Using a specific measure of peripheral autonomic functioning with the QSART, this study was able to show statistically significant differences between those with and without a psychotic illness. This change was independent of use of anti-cholinergic medications. Further, individuals diagnosed with an affective disorder and who had sudomotor dysfunction could only be explained through the use of anti-cholinergic medications. This finding proposes the possibility of a novel peripheral biomarker for identifying psychosis and helps indicate a mechanism by which nervous system pathology exists. Further it demonstrates a rather isolated dysfunction in the peripheral nervous system and the parasympathetic nervous system. Limitations include the small sample size of the study, further stratification by diagnosis, lack of control for confirmed peripheral neuropathy, and lacks to demonstrate causality.

## M32. Toward a New Biomarker of Social Dysfunction in Schizophrenia

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**BACKGROUND:** Schizophrenia (SZ) is often characterized by impairments in social functioning, including increased levels of social isolation (fewer and weaker ties to friends and family) and loneliness (subjective feelings of social disconnection). Both social isolation and loneliness are associated with substantial harms, including reduced quality of life, physical health problems, and early mortality. Yet, few treatments have been shown to improve social functioning in SZ, in part because changes in social isolation and loneliness are inherently slow to develop and therefore difficult to assess in a typical clinical trial. Recent research in healthy samples has identified relationships between measures of social isolation/loneliness and the typicality of individuals' brain activity measured with fMRI while viewing naturalistic video stimuli. In an ongoing study, we are investigating whether such effects might provide the basis for a novel biomarker of social functioning in SZ.

**METHODS:** An interim sample of 62 SZ and 60 healthy control (HC) participants completed an MRI scan. Across three fMRI runs totaling about 40 minutes, participants freely viewed a set of naturalistic audiovisual clips in the same order. Data were preprocessed and quality issues were identified using a standardized pipeline (fMRIprep). Cortical regions were delineated using a standard parcellation. We then used an inter-subject correlation (ISC) approach to assess how typical each individual's brain activity was while watching the videos. Specifically, we computed within-group ISCs to quantify the degree of typicality of brain activity in each region for each individual, relative to all other members of the same group. Participants also provided ratings of social isolation (Lubben Social Network Scale) and loneliness (UNIVERSITY OF CALIFORNIA, LOS ANGELES Loneliness Scale).

**RESULTS:** Interim analyses show a clear relationship between brain responses to the naturalistic video stimuli and social functioning in HCs. Broadly across much of the brain, but especially in lateral occipitotemporal and posterior cingulate cortex, individuals with more typical responses to the videos are less socially isolated and less lonely. In the SZ group, relationships between brain activity and social functioning are somewhat less clear-cut, and associations between brain activity and social functioning appear weaker throughout the cortex. However, some regions that do not show prominent relationships between response typicality

and social functioning in HCs do show such relationships in the SZ group (e.g., superior parietal areas).
**DISCUSSION:** The present data clearly replicate and extend previous findings in healthy samples, which have shown that individuals with more typical brain responses to naturalistic stimuli tend to be less socially isolated and less lonely. At the same time, our results suggest that although similar relationships may exist in SZ, the spatial distribution of these associations might be markedly different and more localized. Nevertheless, the presence of associations between brain responses to naturalistic stimuli and measures of isolation and loneliness in SZ opens the door to the development of new biomarkers of social functioning in the condition. Such biomarkers could allow investigators to measure potential changes in social functioning (e.g., in response to a new treatment) on a rapid timescale, long before changes would appear in traditional assessments. In future analyses, we will evaluate possible multivariate predictors of social isolation and loneliness in SZ and HCs and examine potential influences of particular stimulus features on the strength of these relationships.

## M33. Protein Correlations Predict Schizophrenia Risk and Enable Biomarkers

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**BACKGROUND:** Levels of certain circulating coagulation-system molecules are consistently altered in persons with schizophrenia and predict conversion to psychosis in clinical high-risk (CHR) cohorts. In addition to absolute analyte levels, we sought analytes in correlation networks that could be prognostic. In a study using the North American Longitudinal Study 2 (NAPLS2) cohort we reported correlation of two proteins, SERPINE1 and TIMP1, was higher in peripheral blood plasma in CHR participants who later converted to psychosis compared to nonconverters. Here we confirmed their elevated correlation and examined their correlation with other coagulation proteins including PLAT. In addition, we developed a metric that reflects correlation and so may be applied to individual risk prediction.
**METHODS:** We employed similar methods in NAPLS2 and NAPLS3 related to ascertainment, syndrome determination, inclusion and exclusion criteria, demographics, cross-site reliability, and clinical and biological measures. CHR status was determined by the Structured Interview for Prodromal Syndromes. Here report findings from the NAPLS3 cohort, including 55 psychosis converters, 57 nonconverter, and 32 unaffected subjects. Subjects were followed until psychosis conversion, loss to follow-up, or end of study at two-years. Assays were performed by Myriad RBM (Austin, Texas) using the Luminex platform that included additional coagulation system analytes. Assay values were converted to z-scores relative to average and SD values for unaffected subjects. We regressed pairs of proteins, such as TIMP1 and SERPINE1. We plotted the values for the protein pairs and then calculated the orthogonal distance from the subjects' values to the regression line. For perfectly correlated proteins, this measure is constantly zero. We used a greedy algorithm (CALF) to select the pairs of proteins that best distinguished psychosis converters from non-converters in NAPLS3 and NAPLS2.

**RESULTS:** Indeed, as with NAPLS2, in NAPLS3 SERPINE1 vs. TIMP1 was significantly more correlated in CHR converters vs. CHR nonconverters. Given that cardiovascular disease is elevated in schizophrenia patients and that SERPINE1 is considered the master regulator of "clot-buster" PLAT, we found, as anticipated, reduced correlation (homeostasis) in SERPINE1 vs. PLAT. Using the orthogonal distance from the regression line as our measure we determined that a combination of three protein pair distances distinguished CHR converters from nonconverters with permutation test p-value < 0.010. Using an optimized cut-off the predictor yielded right Fisher exact test = 5.09E-4 (e.g., sensitivity = 0.55, specificity = 0.77. If developed with a larger cohort and used in conjunction with other classifiers, we would expect SERPINE1, TIMP1, and PLAT to contribute to enhanced diagnostic performance.
**DISCUSSION:** NAPLS3 results confirmed our hypothesis of increased correlation for CHR study participants who eventually converted to psychosis. We also hypothesized reduced correlation of SERPINE1 with PLAT, hence degradation of coagulation homeostasis. The literature describes other proteins including TGFB1 and CCN2 (aka CTGF) as modulators of SERPINE1 and TIMP1, suggesting platforms for pharmaceutical intervention. Thus, additional high-quality data are needed to refine the biomarker. Additional replication could lead to its use together with other classifiers toward the goal of accurate diagnoses of schizophrenia risk and perhaps clinical trials of modulators of shared triggers of SERPINE1 and TIMP1.

### M34. Associations Between Sleep Maintenance Disturbances and Psychotic-Like Experiences in Healthy Individuals in the C.a.t.c.h. In. He.ad. Study

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**Background:** Self-reported sleep disturbances have been associated with the onset of psychotic-like experiences (PLEs) in non-clinical samples. However, the association between objectively assessed sleep maintenance disturbances (i.e., prolonged night-time awakenings) and PLEs remains debated. Also, it is yet to be determined whether objective sleep maintenance disturbances can contribute to PLEs after controlling for well-known predictors of PLEs including anxiety symptoms and personality. Given the role of PLEs in increasing the risk of psychotic disorders, it is important to understand the precursors of PLEs. Within the C.A.T.C.H. IN. HE.AD. study, the present examination investigates the cross-sectional associations between objective sleep maintenance disturbances and PLEs.

**Methods:** Forty non-clinical individuals (29.9±12.7 years old, 56.4% females) completed a psychometric battery including the Community Assessment of Psychic Experiences (CAPE-15) assessing persecutory ideation, bizarre experiences, and perceptual abnormalities. Sleep was ecologically monitored for one week using standard actigraphy (Mini-Motionlogger Monitoring, Ardsley, NY) for the assessment of wake after sleep onset (WASO) as reflecting objective sleep maintenance disturbances. Control measures were self-reported anxiety symptoms and schizotypal personality traits. Bivariate correlations and hierarchical multiple regression analysis were conducted. In the latter, anxiety symptoms and schizotypal personality traits were included in the first step, and actigraphy-derived WASO was included in the second step to examine the hypothesized impact of objective sleep maintenance disturbances on PLEs after controlling for covariates.

**Results:** WASO significantly correlated with persecutory ideation (r=.33, p=.04) but not with bizarre experiences (r=.21, p=.20) and perceptual abnormalities (r=.23, p=.16). The second step of the hierarchical multiple regression model showed that WASO was significantly associated with persecutory ideation (β= .327, p=.03) after controlling for covariates (F(1,35) =4.86, p=.03, ΔR2=.09); among the control variables, only schizotypal personality traits (β= .457, p<0.01) significantly contributed to persecutory ideation. WASO did not significantly predict bizarre experiences nor perceptual abnormalities. Neither age nor gender correlated with PLEs (p>0.05).

**Discussion:** The results show that objective sleep maintenance disturbances (WASO) were associated with persecutory ideation above and beyond the role played by well-known predictors of PLEs such as schizotypal personality. Possible mediatory processes between WASO and persecutory ideation may include negative affect and perseverative cognition. The cross-sectional nature of the data precludes robust directionality inference. Moreover, results should be interpreted considering the small sample. Future larger longitudinal studies are therefore needed to examine the influence of objective sleep maintenance disturbances on persecutory ideation and other PLEs overtime, as well as the impact on psychosis risk.

## M35. Heartbeat Evoked Potentials in Schizophrenia: An Electroencephalography Index of Cardiac Interoception

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**BACKGROUND:** Disrupted interoceptive processing (i.e., perception of internal bodily states and signals) may impact emotion processing and one's sense of self and bodily agency, and may contribute to core features of schizophrenia (Sz), including positive, negative, disorganized, and affective symptoms (Yao and Thakkar, 2022). Here, we investigate the heartbeat evoked potential (HEP), an electroencephalography (EEG) event-related potential (ERP) waveform that is time-locked to the electrocardiography (ECG) R-wave peak and is thought to reflect cortical processing of the cardiac signal, or cardiac interoception (Coll et al., 2021). To date, only one prior study of HEP in Sz has been published (Koreki et al., 2024), which reported a blunted HEP response. The aim of this study is to replicate and extend the previous findings by testing the clinical, cognitive, and functional correlates of HEP. We predicted that HEP would be blunted in Sz compared to non-psychiatric comparison (NPC) participants, and that blunted HEP would be associated with worse cognitive, clinical, and functional outcomes in Sz.

**METHODS:** Data for this project are part of an ongoing study at the University of Iowa, with a recruitment target of approximately 25 Sz and 20 NPC participants by March 2025. All study participants are characterized with diagnostic interviews (SCID-5), assessments of cognitive performance (MCCB), and self-reported assessments of depressive symptoms (PHQ-9) and alexithymia (TAS-20). Sz participants also complete a clinical interview for the assessment of positive, negative, disorganized, and affective symptoms (BPRS) and daily functioning (RFS). Simultaneous resting state EEG and ECG are collected from each participant, and the EEG data are epoched into trials that are time-locked to ECG R-wave peaks. HEP was characterized as the mean ERP amplitude of the negative-going waveform occurring in the 250ms to 450ms post R-wave time window and averaged across the right frontal electrodes (FP2, AF8, AF4, F2, F4, F6,

F8). Group comparisons are tested with independent samples t-tests and bivariate associations with Pearson's r.
**RESULTS:** Preliminary data gleaned from the first 13 participants with Sz and 4 NPC participants in the study indicates that HEP can be reliably extracted from resting state EEG data. Consistent with the prior study of HEP in Sz (Koreki et al., 2024), early results suggest that HEP amplitude may be attenuated in Sz ($p = .14$, $d = .655$). Regarding preliminary associations in Sz, HEP amplitude was significantly associated with severity of clinician-rated depressive symptoms (BPRS Depression factor, $r = -.621$, $p = .04$). However, the direction of effect was opposite of our predictions; greater negativity of HEP amplitude was associated with greater depressive symptom burden. A trend-level association between HEP negativity with self-reported depression was also observed in Sz (PHQ-9 total score, $r = -.526$, $p = .07$). Greater HEP negativity was also associated with better cognitive performance in Sz (MCCB Composite Score, $r = -.629$, $p = .04$). No other correlations approached statistical significance in the preliminary data.
**DISCUSSION:** These preliminary results suggest that HEP, a putative ERP index of cardiac interoceptive processing, may be abnormal in Sz. In this initial small sample of Sz participants, a more robust HEP was associated with greater severity of depressive symptoms and better cognitive performance. Data collection and analyses are ongoing. Results from the complete dataset will be presented at the meeting, including group differences in HEP amplitude, and associations between HEP amplitude and cognitive performance, clinical symptom clusters, and daily functioning in Sz.

## M36. Increased Microsacades and Reduced Fixational Stability in High-Functioning Adults With Schizophrenia

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**BACKGROUND:** In non-clinical populations, visual acuity and oculomotor behavior at fixation are tightly linked. For the first time, we leveraged high-precision eye tracking to determine whether fixational eye movements are abnormal in schizophrenia and whether such abnormalities may contribute to reduced visual acuity.
**METHODS:** Visual acuity was first assessed with habitual correction in 14 patients and 13 age-matched healthy controls, none with ocular pathologies or worse than 20/20 Snellen acuity. Patients in our sample were asymptomatic (average PANSS 5-factor item score: positive = 2.1, negative = 1.6, disorganized = 1.6). To record eye movements with high precision, participants were asked to view stimuli without their habitual visual correction and were best corrected using a Badal Optometer. Subjects performed a 4AFC acuity task. Stimuli consisted of digits in Pelli's font, whose size changed based on an adaptive staircase. Each trial began with a 400-ms blank screen followed by a 500-ms stimulus presentation.
**RESULTS:** Although both groups averaged near 20/20, patients exhibited poorer Snellen acuity (20/20 vs. 20/16; Wilcoxon rank sum test: $p = 0.01$, Cohen's $d = 1.06$). Visual acuity thresholds measured with the adaptive procedure were slightly elevated but not significantly different in patients compared to controls (Wilcoxon rank sum test: $p = 0.3$, Cohen's $d = 0.52$). However,

patients exhibited significantly greater between-subject variability in these thresholds (p = 0.03, Levene's test). Our findings also revealed that fixation stability, quantified using the bivariate contour ellipse area, was reduced in patients (0.12± 0.03 deg^2 (patients) vs. 0.08±0.04 deg^2 (controls); Wilcoxon rank sum test: p = 0.005, Cohen's d = 0.98). Further, whereas healthy controls effectively suppressed microsaccades during stimulus presentation, patients did not and were characterized by a higher microsaccade rate (0.3±0.25 ms/s (controls) vs. 0.88±0.46 ms/s (patients), Wilcoxon rank sum test: p = 0.003, Cohen's d = 1.3).
**DISCUSSION:** These findings show that patients with schizophrenia exhibit worse Snellen acuity, less stable fixation, and a higher rate of microsaccades, highlighting the possibility that these ocular abnormalities may contribute to an overall worse acuity, and eye movement differences may emerge even in stable asymptomatic patients.

**M37. OPEN BOARD**

## M38. Retinal Functional Anomalies and Visual Episodic Memory Deficits in Children at Familial Risk of Schizophrenia and Mood Disorder

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**BACKGROUND:** tudies have reported retinal abnormalities in electroretinography (ERG) in patients with schizophrenia (SZ), bipolar disorder (BP) and major depressive disorder (MDD) (Hébert et al, Biol. Psychiatry, 2020). Importantly, healthy children and adolescents at familial high risk (FHR) for these disorders show the same ERG abnormalities in childhood as observed in adult patients, such as reduced amplitudes and prolonged latencies, suggesting a developmental origin for these abnormalities in adult patients (Maziade et al, Prog Neuro-Psych Biol Psychiatry, 2022). ERG abnormalities, as a surrogate for brain dysfunction, may be powerful markers in childhood to monitor the risk trajectories of FHRs. However, little is known about the correspondence between retinal ERG abnormalities and central dysfunction (Constable et al., Front Neurosci, 2023).
**METHODS:** Given that visual episodic memory deficits have been consistently reported in both FHRs and adult patients (Maziade et al., Schizophr Bull, 2011), our aim was to investigate the early relationship between cone or rod ERG response and visual episodic memory deficits observed in FHRs.
**RESULTS:** When FHRs and CTRLs were compared by sex using interaction terms with the four ERG variables, there were no significant sex-specific associations with copy test scores in either group. Focusing on FHRs, we then entered the effect of childhood trauma into the model. The interaction terms were not significant, suggesting no trauma-specific effect. However, including trauma as a covariate revealed an association between poor performance on the copy and reduced photopic b-wave amplitudes in girls (β=-0.15, p=0.008) and reduced scotopic b-wave amplitudes in both sexes (girls β=-0.05, p=0.03; boys β=-0.05, p=0.03).

Results were different regarding the delayed recall: the interactions terms implicating trauma in FHRs was significant suggesting a by sex trauma-specific effect: b-wave scotopic amplitude was associated with delayed recall among girls without trauma exposure (β=0.11, p=0.0006).

**DISCUSSION:** To our knowledge, this study is the first to investigate the relationship between ERG abnormalities and visual episodic memory performance in FHRs. Our data suggest an association between reduced rod response amplitude and visual episodic memory deficits, but only when childhood trauma and gender are included in the model. Our study may suggest a link between deficits in visual episodic memory and either a peripheral deficit in vision per se or an underlying brain dysfunction expressed by the ERG. We will discuss i) how this finding may contribute to the understanding of childhood risk trajectories and FHR risk status and ii) how these results may guide future research into the developmental brain dysfunctions that may underlie the cone and rod response abnormalities in the causes of SZ, BP and MDD.

## M39. Cumulative Exposure to Childhood Trauma Would Affect the Thickness of Retinal Layers in Children at Familial Risk of Schizophrenia, Bipolar Disorder and Major Depressive Disorder

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**BACKGROUND:** Background. The neurodevelopmental origins of schizophrenia (SZ), bipolar disorder (BPD), and major depressive disorder (MDD) imply the influence of environment, particularly childhood trauma (Teicher et al., 2022, Mol Psychiatry). Familial high-risk (FHR) children born to an affected parent provide a unique perspective for inspecting the effect of trauma (Maziade, New Eng J Medicine 2017). The retina, having similarities with the brain, is a promising site for non-invasive investigation of neurodevelopment (Gagne et al.,2020, Prog N.; Maziade and Silverstein, 2020, Schiz Res). Studies on the structure of the retina as measured by Optical Coherence Tomography (OCT) have consistently reported a thinning of the retinal nerve fiber (RNFL) and ganglion cell layers (GCL) in SZ and BP adult patients (Lizano et al., 2020, Schiz Bull). However, no study has approached the effect of trauma on retinal structures in FHRs during childhood.
Objective. To test our hypothesis that cumulative exposure to trauma would be associated in FHRs with a thinning of the retinal GCL and RNFL.

**METHODS:** Method. Retinal morphology was assessed using spectral domain OCT scans performed on both eyes. A Revo 60 device and the SOCT software 11.0.5 were used to measure the thickness of retinal layers. OCT was performed on a subsample of 63 control children and adolescents and 38 FHRs (Mage = 13.86, 50% male), including 12 FHRs (31.7%) exposed to childhood trauma. Five types of childhood trauma were assessed in FHRs using the Traumatic Event Screening Inventory: physical, sexual, and emotional abuse, neglect, and domestic violence. First, an ANOVA corrected for sex and age was used with a robust variance estimator accounting for the small sample size to evaluate differences in retinal structures between FHRs (n=38) and controls (n=63). Second, we performed linear regressions controlling for sex and age to evaluate the association between cumulative exposure to trauma and thinning of GCL and RNFL in FHRs.

**RESULTS:** Results. Using the mean of both eyes, total sample of FHRs displayed thinner GCL (ES=0.25, p=.007) than controls, but similar RNFL (p > .05). Cumulative exposure to childhood trauma was associated with RNFL thickness in several regions but, unexpectedly, the higher the number of trauma types in a FHR, the thicker the layer: superior (ES =.448, p=0.001), superonasal (β=.306, p=0.025), temporoinferior (β=.237, p=0.054), and inferotemporal (β=.257, p=0.069). No association was found with GCL.
**DISCUSSION:** Discussion. Young FHRs overall displayed a thinner GCL than controls, as shown in adult patients (Lizano et al., 2020). However, contrary to the expectation that trauma would induce inflammation and neurogenerative processes entailing a thinning of retinal structures (Blose, 2024), our data suggest that trauma would rather provoke, in young FHRs, a thickening of the RNFL only, explaining perhaps the absence of difference on RFNL between controls and FHR in the whole sample. An interpretation could be that inflammation would indeed be involved, by inducing axonal edema, a phenomenon documented as preceding axonal death and thinning of retinal structures following retinal injury in animal models (Ma et al., 2024) and humans (Kupersmith et al., 2011; Ziemssen et al., 2013;). Since trauma has been shown in FHRs to be a powerful enhancer of the accumulation of risk indicators predictive of a later transition to a major psychiatric disorder (Berthelot et al., 2022, Schiz Bull Open), these preliminary findings may suggest that OCT would detect a first inflammatory hit to the brain CNS. If replicated, this may inform early detection, surveillance, and prevention in FHRs, possibly by attempting to reduce subtle inflammatory processes (Palmer et al., 2024, JAMA Psychiatry).

## M40. Clinically Meaningful Response Achieved After 4-Week of Double-Blind Treatment With Evenamide Added to a Second-Generation Antipsychotic: Additional Results From an International Placebo-Controlled Trial in Poor-Responders

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**BACKGROUND:** Around 30% of patients suffering from schizophrenia fail to adequately benefit from treatment with marketed antipsychotics (APs). Evidence from neuroimaging and neurochemistry studies, indicating excessive glutamatergic rather than decreased dopaminergic transmission in patients with poor response to APs, support the idea that treating these patients with a glutamate modulator would provide additional benefit (Mouchlianitis et al., 2023). Several new therapeutic agents targeting the glutamatergic system have been developed and have demonstrated promising evidence of efficacy as augmentation therapy (Goh et al., 2021). Evenamide is a voltage-gated sodium channel blocker devoid of activity at > 150 CNS targets that normalizes excessive glutamate release without affecting its basal levels. Numerous pre-clinical studies have shown the efficacy of evenamide in attenuating abnormal behaviors in animal models of psychosis, both as monotherapy and as add-on to APs. In addition, treatment with evenamide as add-on to an AP showed clinically important benefits in patients with treatment-resistant schizophrenia (Anand et al, 2023).

**METHODS:** Study 008A is a phase 2/3 international, randomized, double-blind, placebo-controlled, 4-week trial that assessed the efficacy and safety of evenamide 30 mg bid as add-on in patients poorly responding to an SGA. Outpatients with a diagnosis of schizophrenia, still

symptomatic (PANSS 70-85; PANSS positive > 20; CGI-S 4-6) despite treatment with an atypical AP at a therapeutic dose (confirmed through plasma levels) for an adequate period, were enrolled. The proportion of patients reaching a clinically important improvement on the PANSS (≥20% reduction from baseline, as described by Rosenheck et al., 1997 and Meltzer et al., 2008) and CGI-C (rating of at least "much improved") were compared between groups using a logistic regression model (chi-square test). Safety measures comprised: TEAEs, vital signs, lab exams, ECG, seizure checklist, EEG, physical/neurological/eye examinations, C-SSRS, ESRS-A, CDSS.
**RESULTS:** Add-on treatment with evenamide 30 mg bid was well tolerated and associated with a statistically significant greater improvement compared to placebo on the primary (PANNS total) and key secondary (CGI-S) efficacy measures. Furthermore, a significantly higher proportion of patients treated with evenamide, compared to those receiving placebo, achieved a clinically meaningful level of response measured on the PANSS and CGI-C. Additional post-hoc analyses exploring the demographic and baseline characteristics, including the background AP treatment (e.g. clozapine), that predict response will be presented at the Congress.
**DISCUSSION:** Study 008A is the first international, randomized, double-blind, placebo-controlled trial demonstrating the clinically meaningful benefits associated with evenamide, a glutamate modulator, when added to an SGA (including clozapine) in patients with chronic schizophrenia not adequately responding to their antipsychotic treatment. If confirmed in a phase 3 trial, these data would advocate for the need of glutamatergic modulation for the optimal treatment of poor/non-response in schizophrenia.

## M41. Lumateperone for the Prevention of Relapse in Patients With Schizophrenia: Results From a Double-Blind, Placebo-Controlled, Randomized Withdrawal, Phase 3 Trial

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**BACKGROUND:** Relapse is common in patients with schizophrenia and is associated with worsening symptoms, cognitive deterioration, poorer quality of life, and functional impairment. Psychosocial outcomes further decline with increasing frequency of relapse. As such, maintenance pharmacological treatment that helps prevent relapse may lead to long-term benefits for patients with schizophrenia. Lumateperone is an FDA-approved antipsychotic to treat schizophrenia in adults and depressive episodes associated with bipolar I or bipolar II disorder. This Phase 3, multicenter, multinational, double-blind, placebo-controlled, randomized withdrawal trial (Study 304, NCT04959032) investigated the efficacy and safety of lumateperone 42 mg for the prevention of relapse in adult patients with schizophrenia.
**METHODS:** Eligible adults (18-60 years, inclusive) had DSM-5 diagnosed schizophrenia for ≥1 year and a Positive and Negative Syndrome Scale Total score 70-120 (inclusive). Patients received open-label lumateperone 42 mg treatment for 18 weeks (6-week run-in phase and 12-week stabilization phase). Stable patients were then randomized 1:1 to double-blind treatment with lumateperone 42 mg or placebo for 26 weeks or until relapse. Primary and key secondary endpoints were time to first symptom relapse and time to all-cause discontinuation during the double-blind treatment phase, respectively. Safety was also assessed.

**RESULTS:** Of 592 patients treated with lumateperone 42 mg in the open-label run-in phase, 228 patients meeting stabilization criteria were randomized to double-blind treatment (lumateperone, n=114; placebo, n=114). Lumateperone met the primary endpoint, significantly delaying the time to relapse vs placebo during double-blind treatment (hazard ratio, 0.37; 95% CI, 0.22-0.65; P=.0002). Fewer relapses occurred with lumateperone (n=18 [16.4%]) than placebo (n=44 [38.6%]) corresponding to a number needed to treat of 5. Lumateperone also met the key secondary endpoint demonstrating significantly delayed time to all-cause discontinuation compared with placebo (P=.0007). Lumateperone was generally safe and well tolerated. The most common treatment-emergent adverse event (≥5%; or ≥5% with lumateperone and > 2x the rate of placebo) was only headache during the open-label phase (lumateperone, n=78 [13.2%]) and double-blind treatment phase (lumateperone, n=9 [8.2%]; placebo, n=4 [3.5%]).
**DISCUSSION:** Lumateperone 42 mg demonstrated significant efficacy as a maintenance treatment compared with placebo in patients with schizophrenia and was generally safe and well tolerated. These results support the benefit of continued long-term treatment with lumateperone 42 mg in adults with schizophrenia.

## M42. Long-Term Efficacy of Xanomeline and Trospium Chloride in Schizophrenia: Further Analyses From the 52-Week, Open-Label Emergent-4 Trial

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**BACKGROUND:** Xanomeline and trospium chloride (formerly known as KarXT), an agent comprising the M1/M4 preferring muscarinic receptor agonist xanomeline and peripherally restricted muscarinic receptor antagonist trospium chloride, has recently been approved for the treatment of schizophrenia in adults. In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium improved symptoms and was generally well tolerated in people with schizophrenia experiencing acute psychosis. Xanomeline/trospium was associated with continued symptom improvement over 52 weeks in the open-label, long-term EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials. We further characterize the efficacy seen in EMERGENT-4 by performing a responder analysis of the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression–Severity (CGI-S) scores.
**METHODS:** EMERGENT-4 was a 52-week, open-label extension trial enrolling people who completed the EMERGENT-2 or EMERGENT-3 acute trials. Participants received twice-daily oral doses of xanomeline 50 mg/trospium chloride 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium chloride 30 mg for 52 weeks. Efficacy analyses were performed in the modified intent-to-treat (mITT) population (participants receiving ³1 dose of xanomeline/trospium and with ³1 postbaseline PANSS assessment). Efficacy measures included change from baseline to week 52 in PANSS total, PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and CGI-S scores; responder analyses were performed by assessing PANSS responders (the proportion of participants with ≥30% reduction in floor-

adjusted PANSS total score), CGI-S responders (≥1-point improvement in CGI-S score), and CGI-S score ≤3

**RESULTS:** A total of 111 participants were included in the mITT population, of which 49 and 62 had received xanomeline/trospium and placebo, respectively, in the acute trials. After initiating treatment with xanomeline/trospium, improvements in all efficacy measures were seen as early as 2 weeks and were maintained through week 52. The proportion of participants who were PANSS responders increased over the course of the trial. By week 52, 68.6% of completers achieved ³30% improvement in PANSS total score from the acute trial baseline; ³30% improvement was seen in 73.7% and 62.5% of those who received xanomeline/trospium and placebo, respectively, in the acute trials. Other PANSS responder thresholds will be analyzed and presented. At acute trial baseline, CGI-S scores for all participants were ≥4, representing ratings of "moderately ill" or greater illness severity. By week 52, 42.8% of completers had CGI-S scores of ≤3 ("mildly ill," "borderline ill," or "not at all ill"); 47.4% and 37.5% of those who received xanomeline/trospium or placebo in the acute trials, respectively, had CGI-S scores of ≤3. CGI-S responders data will be presented.

**DISCUSSION:** Treatment with xanomeline/trospium led to continued, durable improvements in PANSS total, PANSS positive subscale, PANSS negative subscale, and CGI–S scores, over 52 weeks. These results were paralleled in responder analyses showing nearly 70% of participants achieved ³30% improvement in PANSS total score from the acute trial baseline and ≈50% had disease regarded as "mild" or better using the CGI-S after 52 weeks of treatment.

## M43. Onset, Duration, and Intensity of Adverse Events With Xanomeline and Trospium Chloride in the Phase 3 Open-Label Extension Emergent-4 Trial

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**BACKGROUND:** Xanomeline/trospium combines the M1/M4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride and was recently approved in the U.S. for the treatment of adults with schizophrenia. In the 5-week EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium improved symptoms and was generally well tolerated in adults with schizophrenia experiencing acute psychosis. Participants who completed EMERGENT-2 or EMERGENT-3 were eligible to enroll in the 52-week, open-label extension EMERGENT-4 (NCT04659174) trial. Primary analysis of EMERGENT-4 found xanomeline/trospium was generally well tolerated and associated with continued symptom improvement over 52 weeks. Here, we report findings from post hoc analyses characterizing the onset, duration, and intensity of the most common treatment-emergent adverse events (TEAEs) with xanomeline/trospium.

**METHODS:** Adults (aged 18-65 years) with schizophrenia who completed the treatment period of EMERGENT-2 or EMERGENT-3 were eligible for EMERGENT-4. All participants initiated BID oral doses of xanomeline 50 mg/trospium 20 mg, titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for 52 weeks. Analyses were conducted in the safety population, defined as all participants who received ≥1 dose of xanomeline/trospium during the extension trial.

TEAE intensity was graded using a mild, moderate, and severe classification. TEAE duration was calculated as TEAE end date − TEAE start date + 1, except TEAEs ongoing at the end of the trial, for which duration was imputed using each participant's end of trial date instead of TEAE end date.
**RESULTS:** The safety population included 152 participants, 68 who received xanomeline/trospium during the acute trials and 84 who received placebo. Among 81 participants with TEAEs, 40 (49.4%) had the highest intensity as mild, 34 (42.0%) had the highest intensity as moderate, and 7 (8.6%) had the highest intensity as severe. Treatment-related TEAEs occurring in ≥5% of participants were nausea (9.2%), vomiting (7.9%), dyspepsia (5.9%), dry mouth (5.3%), and hypertension (5.3%). Overall, 17.8% of participants experienced ≥1 procholinergic symptom TEAE with a difference in incidence of approximately 11% between participants who had received xanomeline/trospium vs placebo in the acute studies (11.8% vs 22.6%). Anticholinergic symptom TEAEs were reported in 14.5% of participants with similar rates between acute trial treatment groups. Procholinergic and anticholinergic TEAEs were generally transient and most likely to first occur within 2 weeks of initiating treatment. TEAEs leading to trial medication discontinuation that were possibly, probably, or definitely related to xanomeline/trospium were reported by 4, 3, and 3 participants, respectively.
**DISCUSSION:** Results from EMERGENT-4 showed that long-term treatment with xanomeline/trospium was safe and generally well tolerated; no new safety or tolerability issues emerged.

## M44. Study Retention Rates in the OLZ/SAM Phase III Clinical Program

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**BACKGROUND:** Efficacy and safety of the combination of olanzapine and samidorphan (OLZ/SAM) were assessed in 6 phase 3 studies of adults with schizophrenia or bipolar I disorder. We reviewed retention rates across these studies.
**METHODS:** Patients in 3 randomized controlled trials (RCTs) of 1, 3, or 6 months' duration had the option to continue into two 1-year open-label extensions and one 4-year open-label study. Demographics and clinical characteristics were summarized. Proportions of patients completing the treatment period and reasons for study discontinuation were assessed descriptively for each study.
**RESULTS:** In the RCTs, 134, 211, and 274 patients received ≥1 dose of OLZ/SAM, whereas 277 and 265 in the 1-year extensions and 523 in the 3-month study or the 1-year extensions who continued into the 4-year open-label study did so. Proportions of patients who completed the OLZ/SAM treatment period were 91.0% (122/134, 1-month trial), 78.2% (165/211, 3-month trial), 64.2% (176/274, 6-month trial), 66.1% (183/277, 1-year extension), and 63.0% (167/265, 1-year extension). In the 4-year open-label study, retention rates were 53.7% (242/451) at 2 years and 32.5% (109/335) at 4 years. Withdrawal by subject was the most common reason for discontinuation from each study (6.0% [8/134, 1-month trial]; 9.5% [20/211, 3-month trial]; 15.5% [43/277, 1-year extension]; 13.6% [36/265, 1-year extension]; 25.4% [133/523, 4-year open-label study]) except the 6-month trial (adverse event, 12.0% [33/274]).

**DISCUSSION:** Across the OLZ/SAM phase 3 clinical program, retention rates were high. Overall, 70% of dosed patients completed studies ≤1 year in duration, whereas retention rates were 54% at 2 years and 33% at 4 years in the 4-year open-label study.

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## M45. Baseline Severity of Illness and Response to Treatment With Aripiprazole Lauroxil Every 2 Months: A Post Hoc Analysis of Phase 3 Alpine Clinical Trial Data

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**BACKGROUND:** This post hoc analysis examined the efficacy and safety of aripiprazole lauroxil (AL) by baseline severity of illness in the double-blind ALPINE study (NCT03345979) in patients with schizophrenia treated with AL every 2 months.
**METHODS:** Adults with acute schizophrenia were randomized to AL 1064 mg every 2 months initiated with a NanoCrystal Dispersion formulation of AL (ALNCD) 675 mg or active control (paliperidone palmitate [PP] 156 mg monthly). Based on Clinical Global Impression–Severity scores, baseline severity of illness was categorized as moderate, marked, or severe. Changes from baseline in Positive and Negative Syndrome Scale (PANSS) Total score were assessed at week 25, along with PANSS items related to hostility/excitement. Numbers of patients with activation adverse events (AEs; anxiety, agitation, and insomnia) were also evaluated.
**RESULTS:** Of 96 AL patients assessed, 31 (32%) were moderately ill at baseline, 52 (54%) were markedly ill, and 13 (14%) were severely ill (PP: moderate, 26/99 [26%]; marked, 57 [58%]; severe, 16 [16%]). With AL treatment, mean ± SE changes from baseline in PANSS Total score at week 25 for each subgroup were −21.1 ± 2.5 (moderately ill; baseline mean, 87.1), −24.1 ± 1.8 (markedly ill; baseline mean, 95.3), and −25.6 ± 6.4 (severely ill, baseline mean, 106.1). With AL treatment, improvements from baseline in PANSS scores related to hostility/excitement items were similar among severity subgroups; a similar pattern was found for PANSS Total scores and those related to hostility/excitement in the PP subgroups. Activation AEs occurred in 7 AL-treated patients (moderate, 3/31 [10%]; marked, 3/52 [6%]; severe 1/13 [8%]) and 10 PP-treated patients (moderate, 5/26 [19%]; marked, 2/57 [4%]; severe, 3/16 [19%]).
**DISCUSSION:** In this post hoc analysis, AL efficacy and safety were comparable across baseline severity-of-illness subgroups of patients with schizophrenia.

This study was sponsored by Alkermes, Inc. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

## M46. Effect of Xanomeline and Trospium Chloride on Social Functioning and Life Engagement in Schizophrenia: Post Hoc Pooled Analysis From the Emergent Trials

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**BACKGROUND:** Schizophrenia significantly hinders a person's ability to function in daily life. Although managing core symptoms of schizophrenia is crucial, social difficulties and a lack of engagement further reduce quality of life. Life engagement refers to positive health aspects, like motivation and social interaction, which contribute to a sense of agency and fulfilment. There is growing focus on patient-centred goals for people with serious mental illnesses, particularly improving social functioning and engagement. However, addressing these areas can be challenging, and there is limited evidence for improvement in these domains in people with schizophrenia, even among people who are adherent with their medications. In the 3 EMERGENT trials, the dual M1/M4 preferring muscarinic receptor agonist xanomeline and trospium chloride significantly improved positive and negative symptoms and was generally well tolerated in people with schizophrenia [1-3]. We conducted post hoc analyses of pooled data from the EMERGENT trials to evaluate the effects of xanomeline/trospium on Positive and Negative Syndrome Scale (PANSS)-derived measures of social functioning and life engagement.
**METHODS:** The 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials enrolled inpatient participants with schizophrenia experiencing a recent worsening of psychosis warranting hospitalisation. Xanomeline/trospium dosing (mg xanomeline/mg trospium) started with 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID by the end of week 1. Social functioning was assessed using a PANSS-derived prosocial factor consisting of 6 PANSS items: active social avoidance (G16), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), stereotyped thinking (N7), hallucinatory behaviour (P3), and suspiciousness/persecution (P6) [4]. Life engagement was assessed using 11 PANSS items reflecting improvement and well-being beyond improvement in core symptoms: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), difficulty in abstract thinking (N5), lack of spontaneity/flow of conversation (N6), depression (G6), motor retardation (G7), disturbance of volition (G13), preoccupation (G15), and active social avoidance (G16) [5]. Least squares mean (LSM) change from baseline to week 5 in the PANSS-derived prosocial and life engagement factors was calculated in the modified intent-to-treat population, defined as all participants who received at least 1 dose of trial medication and had a baseline and at least 1 postbaseline PANSS rating.
**RESULTS:** A total of 640 people were included in the post hoc analyses (xanomeline/trospium, n=314; placebo, n=326). At week 5, xanomeline/trospium was associated with greater reductions than placebo in PANSS-derived prosocial and life engagement factors. LSM change from baseline to week 5 in PANSS-derived prosocial factor was -5.8 in the xanomeline/trospium group vs -2.7 in the placebo group. LSM change from baseline to week 5 in PANSS-derived life engagement factor was -6.9 in the xanomeline/trospium group vs -3.3 in the placebo group.
**DISCUSSION:** In the 3 EMERGENT trials, xanomeline/trospium was associated with significant improvements in PANSS-derived measures of social functioning and life engagement, both of which are important determinants of functional outcomes in people with schizophrenia.

## M47. Association of Clozapine use With Risk Of Hospitalization Among People With Schizophrenia: A Self-Controlled Case Series Study

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**BACKGROUND:** Previous studies have indicated that clozapine is significantly associated with a reduced risk of hospitalization, particularly regarding psychiatric admissions. Concurrently, emerging evidence suggests that long-acting injectable antipsychotics (LAIAs) may also contribute to decreased rates of psychiatric hospitalization. However, the effectiveness difference of clozapine versus LAIAs in preventing hospitalizations remains controversial, and their impact on non-psychiatric hospitalizations has not been thoroughly examined. Therefore, this study aims to systematically investigate the association between clozapine use and the risks of all-cause, psychiatric, and non-psychiatric hospitalizations, while also evaluating the comparative effectiveness of clozapine and LAIAs on these outcomes.

**METHODS:** Individuals diagnosed with schizophrenia (ICD-9-CM 295) between January 1993 and March 2023 were extracted from the Hong Kong Clinical Data Analysis and Reporting System (CDARS). We identified patients who initiated clozapine treatment between 2003 and 2012 and had at least 1 hospitalization record during the observation period. The period commenced on January 1, 2003, or two years prior to clozapine initiation (whichever was later), and ended on March 31, 2023, or at death (whichever was earlier). Based on outpatient prescription data, exposure periods were categorized into four groups: clozapine alone, LAIAs alone, combination use of clozapine and LAIAs, and other antipsychotics (baseline period). Each clozapine treatment period was further divided into first and subsequent exposures, along with pre-exposure (90 days prior) and washout periods (42 days following the first clozapine exposure). We utilized a self-controlled case series (SCCS) design to address potential indication bias. SCCS analyses compared hospitalization incidence rates during the first and subsequent clozapine exposure periods, and the pre-exposure and washout periods against the baseline period. Incident rate ratios (IRR) were estimated using conditional Poisson regression, adjusted for age and seasonality. Additionally, we evaluated the hospitalization risk during periods of LAIA use alone and in combination with clozapine, comparing these risks to those associated with clozapine use alone.

**RESULTS:** Of the 4,794 individuals who initiated clozapine treatment (2,515 women [52.5%]; mean [SD] age, 39.3 [13.2] years), 1,910 (39.8%) received LAIAs alone, and 558 (11.6%) used a combination of clozapine and LAIAs. Compared to other antipsychotics, clozapine was associated with a lower risk of hospitalization for all-cause (first exposure: n=2,967; incidence rate ratio [IRR], 0.40 [95% CI, 0.38–0.42]; subsequent exposure: n=13,046; IRR, 0.54 [0.52–0.55]), psychiatric (first exposure: 843; IRR, 0.21 [0.19–0.23]; subsequent exposure: n=3,270; IRR, 0.28 [0.27–0.30]), and non-psychiatric hospitalization (first exposure: 2,133; IRR, 0.69 [0.65–0.73]; subsequent exposure: n=9,776; IRR, 0.83 [0.80–0.87]). In contrast, both the pre-exposure (all-cause: IRR, 1.71 [1.63–1.80]; psychiatric: IRR, 2.00 [1.88–2.13]; non-psychiatric: IRR, 1.30 [1.19–1.42]) and washout periods (all-cause: IRR, 2.32 [2.14–2.51]; psychiatric: IRR, 2.49 [2.24–2.76]; non-psychiatric: IRR, 2.12 [1.86–2.41]) of clozapine treatment were linked to increased hospitalization risks. Additionally, LAIAs alone (all-cause: IRR, 1.93 [1.85–2.02]; psychiatric: IRR, 3.81 [3.57–4.05]; non-psychiatric: IRR, 1.21 [1.13–1.29]) and combination use (all-cause: IRR, 1.13 [1.03–1.24]; psychiatric: IRR, 1.40 [1.21–1.61]; non-psychiatric: IRR, 1.21

[1.07–1.37]) were associated with higher hospitalization risks compared to clozapine treatment alone.
**DISCUSSION:** Our findings indicate that clozapine is linked to significantly lower rates of all-cause, psychiatric, and non-psychiatric hospitalizations during both initial and subsequent exposure periods compared to other antipsychotics. Notably, the pre-exposure and washout periods of clozapine treatment were associated with higher hospitalization risks, highlighting the need for enhanced monitoring during clozapine discontinuation. Furthermore, while prior evidence suggested that long-acting injectable antipsychotics (LAIAs) may reduce hospitalization risks, our results indicate that they may not be as effective as clozapine in preventing hospitalizations. These findings highlight the critical need for personalized treatment strategies when managing schizophrenia with clozapine.

## M48. Selective NMDA Receptor Dysfunction in First-Episode Psychosis Revealed by Computational Synaptic Modeling of Mismatch Negativity

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**BACKGROUND:** Mismatch Negativity (MMN) responses to pitch (pMMN) and duration (dMMN) deviant stimuli are notably more attenuated in individuals with chronic psychotic illness compared to those experiencing their first episode of psychosis (FEP). Recent studies have demonstrated that employing source modeling techniques on magnetically-recorded MMN can enhance the detection of deficits specifically in the left auditory cortex among individuals with FEP. Similarly, computational circuit modeling of electrically-recorded MMN has revealed abnormalities in the left hemisphere auditory cortex. Dynamic Causal Modeling (DCM) offers a framework to infer synaptic activity from EEG scalp recordings.
**METHODS:** We used Electroencephalography (EEG) to measure pMMN and dMMN in 26 individuals with FEP and 26 matched healthy controls (HC), employing a DCM conductance-based neural mass model incorporating AMPA, NMDA, and GABA receptors to examine changes in effective connectivity and receptor rate constants in FEP. Our model included MMN sources in bilateral A1, superior temporal gyrus (STG), and inferior frontal gyrus (IFG), using a boundary element model in MNI space as a standardized brain template.
**RESULTS:** Our results indicated no significant differences in model parameters between groups for pMMN. However, for dMMN, we observed reduced NMDA receptor activity specifically in the right IFG among individuals with FEP.
**DISCUSSION:** This aligns with existing literature on prefrontal NMDA receptor hypofunction in chronic schizophrenia (SZ), suggesting that impaired NMDA-induced synaptic plasticity may be present at the onset of psychosis, where scalp dMMN responses are only moderately reduced. DCM presents a promising approach for investigating, non-invasively, cortical circuit activity and interactions, offering insights into subtle functional auditory processing deficits in early psychosis, even in cases where sensor MMN responses are generally within normal limits.

## M49. Parsing Clinical and Neurobiological Heterogeneity in First-Episode Psychosis Patients: A Normative Modeling Approach With a Focus on the Deficit Syndrome of Schizophrenia

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**BACKGROUND:** Schizophrenia is highly heterogeneous in its neurobiological and clinical presentations, which hinders attempts to understand its etiology and pathophysiology, limits efforts to identify biomarkers, and deters optimal patient care. Understanding this heterogeneity is essential, and identifying biologically distinct, less heterogeneous clinical subtypes represents a promising approach. A prominent strategy for addressing clinical heterogeneity is to stratify patients based on the presence of the deficit syndrome, which is characterized by primary and persistent negative symptoms and is believed to exhibit lower heterogeneity than the non-deficit form of the schizophrenia. An effective strategy for parsing neurobiological heterogeneity is normative modeling, which can capture inter-individual variability. Here, we utilized a multimodal normative modeling approach to investigate abnormalities in cortical thickness and resting-state functional connectivity in antipsychotic-naïve first-episode psychosis patients with and without features of the deficit syndrome. We hypothesized that, at the individual level, patients with features of the deficit syndrome would exhibit lower structural and functional heterogeneity compared to those without.

**METHODS:** We analyzed T1-, T2-weighted MRI and resting-state fMRI data from 101 antipsychotic medication-naïve first-episode psychosis (FEP) patients—24 with features of deficit syndrome (FEP-DS) and 77 without (FEP-NDS). We compared the two groups based on the mean, variance, and distribution of raw cortical thickness and resting-state functional connectivity values. Normative modeling was employed to quantify deviations in cortical regions and functional networks relative to a reference cohort, focusing on mean, variance, and distribution of these deviations.

**RESULTS:** Group-level comparisons of raw cortical thickness revealed five cortical regions across the frontal, temporal, and occipital areas, which were, on average, thinner in FEP-DS compared to FEP-NDS. However, individual-level analyses showed that FEP-DS patients exhibited similar mean, variance, and distribution of positive and negative cortical thickness deviations compared to FEP-NDS patients. Furthermore, there were no significant differences between FEP-DS and FEP-NDS in terms of the mean, variance, or distribution of raw functional connectivity values, or in positive and negative functional deviations.

**DISCUSSION:** To our knowledge, this is the first study to apply normative modeling to parse clinical and neurobiological heterogeneity in antipsychotic-naïve FEP patients with and without features of the deficit syndrome. We found that, at the individual level, FEP-DS exhibited similar neurobiological heterogeneity compared to FEP-NDS. This challenges the idea that the deficit syndrome is a more homogeneous subtype of schizophrenia which, so far, has only been tested in group-level comparisons, not taking heterogeneity into account. Normative modeling

successfully captured inter-individual variability, allowing for a more nuanced understanding of heterogeneity in FEP patients, thereby addressing the limitations inherent in group-level analyses. This underscores the potential of normative modeling to facilitate a deeper comprehension of schizophrenia, particularly in the context of identifying biologically distinct, less heterogeneous clinical subgroups. Defining neurobiologically more homogeneous subgroups may lead to clinically useful applications, such as tailored treatments with better, less heterogeneous, treatment responses.

## M50. Categorization of Catatonia Following ICD-11: Multimodal Identification of Specific Brain Signatures

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**BACKGROUND:** Catatonia is a psychomotor syndrome observed in various psychiatric disorders, including schizophrenia spectrum (SSD) and mood disorders (MOD). Understanding its biological underpinnings could greatly enhance the development of targeted therapies and refine diagnostic criteria. Therefore, this study investigated whether region-of-interest (ROI)-based resting-state functional connectivity (FC), and structural brain measures such as cortical thickness can differentiate catatonia from other mental disorders using for the first time the ICD-11 classification system. We additionally compare the ICD-11 criteria to previously used definitions of catatonia such as DSM-5, Bush-Francis Catatonia Rating Scale and Northoff Catatonia Rating Scale.

**METHODS:** In our initial findings, we collected structural MRI and resting-state fMRI data from 57 patients with catatonia, along with 102 age-, sex-, and medication-matched patients diagnosed with schizophrenia spectrum disorder (SSD) or mood disorders (MOD) according to ICD-11 criteria. Our analysis pipeline comprises three key components: (I) Bayesian hyperparameter optimization, (II) a feature selection algorithm known as minimum redundancy maximum relevance (mRMR), and (III) model fitting using logistic regression and support vector machines within a 10-fold nested cross-validation framework.

**RESULTS:** Our initial results show, using the ICD-11 criteria, of rs-fMRI data, catatonia patients could be differentiated from SSD and MOD patients with a balanced accuracy of 64%, which increased to 69% with stricter motion correction. Segregating the cohort to include only catatonia associated with MOD led to a classification accuracy of up to 88%. Feature analysis revealed consistent importance of FC between the superior temporal gyrus and occipital pole, and between the lateral occipital and intracalcarine cortices. Especially, connections between and within temporal and limbic regions. Models using catatonia categorization based on different cut-off criteria of rating scales did not achieve comparable accuracy and remained at chance levels

**DISCUSSION:** In conclusion, this study offers preliminary evidence that catatonia associated with another mental disorder can be identified based on inter-ROI FC, particularly in MOD-

patients, and the ICD-11 categorization could play a crucial role in identifying novel neural signatures. Although the observed predictive accuracy suggests limitations for immediate clinical application, the findings could enhance understanding of catatonia's pathophysiology, potentially guiding future therapeutic strategies. Our next step is a multimodal data integration with structural MRI data and acquiring a validation cohort for our findings.

## M51. A Demographic-Based Graph Neural Network Enhances Performance of a Functional Connectivity-Based Prognostic Deep Learning Classifier in Recent Onset Psychosis

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**BACKGROUND:** The ability to predict response to treatment in recent onset psychosis is of great interest to clinicians. Unfortunately, no effective tools yet exist that can accomplish this task. Prior work from our laboratory and others suggests that brain functional connectivity may be associated with treatment response, albeit often in smaller samples and to a degree that is insufficient to meet clinical standards. It has been argued that sample demographic heterogeneity may limit generalizability of machine learning (ML) models to predict outcomes, hindering their performance. Here we evaluated the ability of a demographic information-based graph neural network (GNN) to affect performance of a deep learner that uses functional connectivity data from a cognitive control task to predict treatment response in an early psychosis (EP) sample.
**METHODS:** fMRI connectivity data were extracted during a cognitive control task from a whole-brain atlas in 82 individuals with early psychosis (≤ 2 years from onset) and used to predict “Improver” (n = 47) vs. “Non-Improver” (n = 35) status, with Improver defined as showing a 20% reduction in total Brief Psychiatric Rating Scale score after 1 year of treatment. Models were trained using only fMRI data, using fMRI data + demographic information (age, sex, race, education, parental education), and using fMRI data that has been clustered prior to training according to demographic similarity in a GNN-based framework. Models were trained using 10-fold cross-validation. This process was repeated 25 times to calculate mean performance metrics (e.g., accuracy) across the 25 runs.
**RESULTS:** The GNN-based model showed significantly higher mean accuracy (72% (95% CI = 71 – 73%)) and receiver operating characteristic area under the curve (ROC AUC) (73% (95% CI = 72 – 73%)) compared to 2-deep neural network learner that incorporated fMRI and demographic features without a GNN (accuracy = 60% (95% CI = 59 – 61%), ROC AUC = 56% (95% CI = 55 – 57%)). Enhancement of ROC AUC using the GNN-based model was driven by significantly higher accuracy in Non-Improvers (Non-Improver accuracy for the GNN-based model = 76% (95% CI = 74 – 78%), Non-Improver accuracy for the model with no GNN = 23% (95% CI = 22 – 25%)).
**DISCUSSION:** These results suggest that using a GNN to cluster individual fMRI data according to demographics may enhance ML performance while developing tools for personalized medicine. Future studies will examine the ability of GNNs to improve performance in larger datasets.

## M52. The Cognitive Metabolomic Signatures in Schizophrenia Spectrum Disorders: A Systematic Review

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**BACKGROUND:** Understanding the metabolome, the metabolite profile within bio-samples, can provide insight into the mechanisms and processes involved in schizophrenia spectrum disorders (SSDs). As such, investigating changes in and associations between the metabolome and cognitive impairments inherent to SSDs may be able to provide a biomarker that can identify this symptom domain. Currently, there are no systematic reviews exploring the associations between cognition and metabolomic signatures, therefore, the objective of this systematic review is to identify these associations.
**METHODS:** A systematic database search was conducted in Ovid MEDLINE, EMBASE and Scopus for studies related to the following three conceptual domains: "schizophrenia spectrum disorders", "metabolomics", and "cognition." Studies with a case–control component and/or association analyses were included in the review. Risk of bias assessment was conducted using the appropriate Johanna Briggs Critical Appraisal tool.
**RESULTS:** Nine studies were included for the analysis, and it was found that 44 metabolites were dysregulated in cognitively impaired patients with SSDs when compared to cognitively normal patients, with 38 metabolites downregulated and 6 upregulated. For the association analyses, a mixture of positive and negative associations was found, and the top classes dysregulated were glycerophospholipids, glycerolipids, fatty acyls and indoles and indole derivatives.
**DISCUSSION:** Metabolomics is a tool that can be used to better our understanding of SSD phenomena and pathophysiology as the identified metabolites are involved in pathways that may impact cognition in SSDs.

## M53. Evaluating the use of the MMPI-3 to Assess Psychotic Phenomena: A Systematic Review and Meta-Analysis

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**BACKGROUND:** The Minnesota Multiphasic Personality Inventory (MMPI) is a widely used self-report measure to assess personality and psychopathology. The MMPI-3, the most recent version of the test, includes three broad psychosis scales (THD, RC8, PSYC). The MMPI technical manual is frequently cited as supporting the validity of the test. However, the technical manual includes 53,889 correlations between numerous criterion variables and all MMPI scales, without any indication which criterion variables should be related to specific scales. This makes it hard to draw conclusions about the validity of individual scales from the test manual. Furthermore, no meta-analysis has been conducted on the validity of the MMPI psychosis scales. Therefore, we conducted a systematic review and meta-analysis of the relationship between the three MMPI-3 psychosis scales and psychotic symptoms.

**METHODS:** The meta-analysis was based on data from the MMPI-2-RF Technical Manual and a systematic review of published MMPI-2-RF and MMPI-3 literature. The MMPI-2-RF Technical Manual was used rather than the MMPI-3 Technical Manual, as both versions include the same psychosis scales and no data from psychotic patients was included in the MMPI-3 Technical Manual. As psychotic symptoms must be assessed by a trained clinician, we focused on the associations between the MMPI psychosis scales (THD, RC8, PSYC) and clinician ratings of hallucinations, delusions, disorganized speech and disorganized behavior, which constitute the main positive symptoms of psychosis. We hypothesized that the psychosis scales would be associated with ratings of psychotic symptoms. Further, we expected stronger associations with clinician ratings of hallucinations, especially auditory hallucinations, than with clinician ratings of disorganized speech and behavior. We also examined the association of RC6 with clinician ratings of persecutory delusions and auditory hallucinations.
**RESULTS:** Overall, the MMPI-3 psychosis scales (THD, RC8, PSYC) showed small effect size associations with clinician ratings of hallucinations, delusions, disorganized speech and behavior in clinical and forensic settings. As hypothesized, THD, RC8, and PSYC were most strongly correlated with clinician ratings of auditory hallucinations with medium effect sizes. Further, the scales had the smallest effect sizes for their association with clinician ratings of disorganization. Although RC6 does not include hallucination items, RC6 had a slightly larger correlation with clinician ratings of auditory hallucinations than with persecutory delusions, which it is designed to measure.
**DISCUSSION:** The results indicate that the MMPI-3 psychosis scales are only weakly associated with clinician ratings of positive psychotic symptoms. The scales were most strongly correlated with clinician ratings of auditory hallucinations. As hallucinations are an internal experience, their assessment requires the clinician to ask the patient about their experience. Therefore, the method of assessment for hallucinations most closely resembles a self-report instrument. However, disorganized speech and behavior cannot be assessed via self-report. Thus, clinicians should be cautious when interpreting the MMPI-3 psychosis scales and need to follow up with clients on how they interpreted the items they indorsed.

## M54. Predicting Work Outcome Based on Daily-Living Acts: Transdiagnostic Comparison

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**BACKGROUND:** Functional outcomes in people with mental disorders cover a wide range of domains from everyday living behavior to residential independence including work. Previous studies reported that daily-living skills was closely associated with cognitive function (Harvey, 2,016) and also an important predictor for work outcome in patients with schizophrenia

(Sumiyoshi 2024) and bipolar disorder (Bowie 2010). In some diagnoses, however work outcome remain poor even when cognitive ability was reserved (Sumiyoshi, 2018). It suggests that the beneficial effect of cognitive improvement may not be uniform across disorders. Accordingly, it was assumed that daily-living skills, linked to cognition, also differently contribute to work outcome among diagnoses. The aim of this study was to investigate this issue using multi-level modeling (MLM) analyses.
**METHODS:** Participants: In total, 454 participants (schizophrenia=396, Mood disorders=32, autism spectrum disorder=26) entered the study. They were treated at the Department of Psychiatry, Osaka University Hospital or National Center Hospital, National Center of Neurology and Psychiatry. This study was approved by ethical committee of the facilities and the procedures were conducted according to the
Declaration of Helsinki.

Assessment: The score of daily-living skills was obtained from the Independence-performance domain in the Social Functioning Scale Japanese version. The measure of work outcome was work hours per week assessed by the Social Activity Assessment.

Analyses: Three models were built in MLM analyses to clarify the overall effect of daily-living skills on work outcome and its interaction effect with diagnoses. The former was tested at random intercept model and random slope model, while the latter was examined at coefficients model adding an interaction term (daily-living skills x diagnoses).

**RESULTS:** The fixed effects of daily-living skills were significant in both random slope and intercept models suggesting its effect on work outcome irrespective of diagnoses. However, the interaction effect was also significant at random coefficient model indicating that the degree of effects varied depending on diagnoses.
**DISCUSSION:** The MLM analyses showed that ability in everyday-living acts differently contributed to quantitative achievement at work. It may be difficult for some patients to translate their cognitive potential into real-world functioning. Possibly, multiple preventing factors may exist. It is needed to identify them and to consider the strategy to remove disturbing mediators to reduce the competence-performance gap in people with mental disorders.

[References]

Bowie, C et al., Am J Psychiatry. 2010:167, 1116-24.

Cardenas, V. et al., Schizophrenia Bull. 2012:39, 908-916.

Harvey et al., Neuropsychology. 2016:30, 28-39.

Harvey et al.,World Psychiatry. 2012: 11, 73-79

Sumiyoshi, C., et al. BJPsych Open. 2022:3;8(4):e98.

## M55. Transdiagnostic Relationships Between Memory Impairments, Negative Symptoms, and Social Functioning: Insights From the UK Biobank

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**BACKGROUND:** Memory impairments have long been considered a hallmark of schizophrenia spectrum disorders and are increasingly recognized as transdiagnostic features across psychiatric conditions. Our previous work proposed and validated a multiscale model linking memory performance, negative symptoms, and social dysfunction in the progression of psychosis, highlighting memory as a key predictor of symptoms and functional outcomes. Given the prevalence of negative symptoms and social dysfunction across disorders, the current study explores the relationships between memory performance, negative symptoms (Motivation and Pleasure factor), and social functioning in a transdiagnostic sample. We also examine how sex differences influence these relationships.
**METHODS:** We used open data from the UK Biobank, which includes cognitive and psychiatric data. Our sample consisted of 3,593 patients diagnosed with various psychiatric conditions (ICD-10) and 3,593 healthy controls with no neurological or psychiatric disorders. Participants were matched on sociodemographic variables (age, sex, index of multiple deprivation) using propensity score matching. The patient sample was stratified into broad diagnostic categories, including schizophrenia-spectrum (SZ), depression (DEP), anxiety (ANX), bipolar (BD), obsessive-compulsive (OCD), somatoform (SOM), other neurotic (NEU), eating (ED), substance use (SUD), personality (PD), non-organic sleep, stress/adjustment (stress-adj), puerperium-related (PR), and sexual dysfunction (SD) disorders.

We examined relationships between verbal memory (paired associates learning; Datafield 20197), negative symptoms (Datafield 2060: Frequency of unenthusiasm/disinterest in the last 2 weeks), and social functioning (Datafield 1031: Frequency of friend/family visits). Spearman correlations were calculated for these variables by group (patients vs. controls), and sex differences in correlations were assessed using Fisher's z-transformation. Within-diagnosis correlations were also examined. P-values were calculated to test statistical significance across all analyses.
**RESULTS:** We observed significant group differences between controls and patients in memory and negative symptoms. Patients had lower memory scores ($6.87 \pm 2.68$ vs. $7.04 \pm 2.63$, $p < 0.001$) and more negative symptoms ($1.32 \pm 0.62$ vs. $1.16 \pm 0.44$, $p < 0.001$). A significant sex difference in the relationship between memory and lower social functioning emerged in patients ($z=-2.37$, $p < 0.05$), with male patients showing a positive correlation ($r=0.065$, p). In contrast, female patients showed a negative correlation ($r=-0.015$, $p > 0.05$).

By diagnosis, negative symptoms and lower social functioning showed significant moderate to small positive correlations in BD ($r=0.290$, $p < 0.05$), DEP ($r=0.114$, $p < 0.05$), SUD ($r=0.113$, $p < 0.001$, ANX ($r=0.082$, $p < 0.05$), and stress-adj ($r=0.099$, $p < 0.05$). Small positive trends ($p > 0.1$) were also observed in PR, SOM, ED, and PD. Conversely, small negative trends were observed in OCD and sleep disorders. One significant weak negative correlation was found in SUD ($r=-0.062$, $p < 0.05$) for memory and negative symptoms. Although non-significant ($p > 0.1$), small negative trends were observed in SZ, PD, NEU, and SUD. Interestingly, OCD exhibited a small positive trend between memory and negative symptoms. Finally, the strongest trends ($p > 0.1$) were observed between memory and lower social functioning, where SZ ($r=-0.355$) and PD (-0.253) showed moderate negative trends, while OCD ($r=0.278$) showed a moderate positive trend. Smaller negative trends were also observed in NEU, ED, and sleep disorders, though also non-significant ($p > 0.1$).

**DISCUSSION:** Our results provide preliminary evidence suggesting that memory impairment may be a transdiagnostic feature and predictor of negative symptoms and social dysfunction across psychiatric disorders. Significant differences in memory (PAL) and negative symptoms (NS) between patients and controls support the relevance of these deficits across diagnoses. The sex differences in these relationships suggest sex may moderate the relationship between memory and social functioning. In line with our previous work in psychosis, poorer memory generally related to more negative symptoms and poorer social functioning, with some exceptions, such as in OCD. The strength of relationships varied by disorder.

A limitation of our study is the small sample sizes in certain diagnostic categories (e.g., SZ, PD, OCD), which may explain non-significant disorder-specific findings, while larger strata (e.g., DEP, SUD) showed stronger relationships. Additionally, some disorders exhibited opposite relationships between memory, negative symptoms, and social functioning, highlighting a limitation of transdiagnostic approaches that don't account for disorder-specific effects, which may mask nuanced relationships.

This work is crucial for informing future investigations into the mechanisms that link memory deficits, negative symptoms, and social dysfunction across diagnostic categories. More broadly, these findings suggest that while memory impairment may play a role in symptom expression and functional outcomes, its impact can vary between disorders.

## M56. Motor Impairment Over Time in the Early Course of Psychosis

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**BACKGROUND:** Previous work from our group has shown associations between motor functioning and negative symptoms at a cross-sectional timepoint, and similar motor impairments across people with schizophrenia spectrum disorders (SSD) and mood disorders with psychosis (MDP). In psychosis, motor abnormalities are shown to predict negative symptom change at follow-up, but motor functioning prediction of specific negative symptom domains hasn't been shown. We predicted that (1) motor impairments would be similar in SSD and MDP groups in the early course of psychosis and that (2) baseline motor functioning would predict negative symptoms at follow-up.
**METHODS:** Participants with SSD (N=31) or MDP (N=46), ages 17-35, within 6.5 years of onset were assessed at baseline and follow-up ($\bar{x}$ = 12 months) on negative symptoms and motor functioning. Chlorpromazine equivalents (CPZE) were calculated using the Defined Daily Dose method. Groups were compared using t-tests, and linear regression was used to predict negative symptoms at follow-up by baseline motor functioning.
**RESULTS:** SSD and MDP groups did not differ on motor measures (p's > .05). While models were significant predicting BNSS Anhedonia, Lack of Normal Distress, Avolition, CAINS MAP and EXP, as well as BNSS and CAINS total scores, no motor measures at baseline significantly predicted negative symptoms at follow-up (p's > .05). However, CPZE emerged as a significant

predictor for the BNSS Anhedonia, Lack of Normal Distress, Avolition, Blunted Affect, and Alogia, CAINS Expression subscales, as well as the BNSS and CAINS total scores (p's < .05). Parental SES emerged as a significant predictor for the BNSS Anhedonia, Avolition, and CAINS Expression subscales (p's < .05). Time in months emerged as a significant predictor for the CAINS MAP subscale (p < .05).
**DISCUSSION:** CPZE may be more predictive of specific negative symptom subdomains than motor functioning. One possibility is that people with a higher antipsychotic load have a more severe illness trajectory. We will examine these associations over multiple timepoints in a larger cohort as data are available.

## M57. The Relationship Between Semantic Coherence and Cognition in Childhood Onset Psychosis

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**BACKGROUND:** Childhood onset schizophrenia is associated with language delays, persistent subtle changes in language structure and cognitive deficits. Recent advances in natural language processing (NLP) have revealed consistent quantifiable changes in language structure associated with changes in cognition in adults with schizophrenia. The relationship between NLP based measures and cognition has not been examined in children and young adolescents with psychosis of any cause including affective and nonaffective psychoses. The goal of this preliminary study was to identify the relationship between NLP based measures and cognition in children and young adolescents with psychosis.
**METHODS:** All protocols were approved by the Institutional Review Board at Rutgers University. Cases were defined as psychosis of any cause including affective (50%), schizophrenia spectrum (40%) and other psychosis (10%). Controls were defined as having no personal history of psychosis. Cases (N=10) mean age 11.8 (+/- 1.7) and controls (N=4) mean age 11.8 (+/- 1.3) years old. Clinical assessment for psychosis included the Kiddie Schedule for Affective Disorders and Schizophrenia and the Structured Interview for Psychosis-Risk Syndromes. The Story Game was utilized to collect samples specifically for language analysis as it has been validated to elicit expression of thought disorder in children. Cognitive data were collected using an online remote platform (verbal memory, digit symbol, matrix reasoning, Wechsler Test of Adult Reading (WTAR). Interviews were conducted via remote video conferencing and recorded. All recordings were manually transcribed verbatim by a medical transcription service. Pseudo-perplexity was calculated using Bidirectional Encoder Representations from Transformers (BERT) as a measure of semantic coherence. A higher pseudo-perplexity score for a sentence represents words that are less likely to be predicted to be in the sentence based on the context thus representing lower semantic coherence. To test whether the interaction between pseudo-perplexity and the cognitive measures could differentially predict psychosis a binary logistic regression model was fitted. Case status (presence or absence of psychosis) is the dependent variable and pseudo-perplexity, verbal memory, digit symbol, matrix reasoning, WTAR and the interactions between pseudo-perplexity and each cognitive predictor

are the independent variables. Two additional models using only pseudo-perplexity and cognition were also generated for comparison.
**RESULTS:** The logistic regression model which included pseudo-perplexity, cognition and the interactions between these terms (prediction accuracy: 1, leave one out cross validation (LOOCV) accuracy: 0.79) outperformed the model with cognition alone (prediction accuracy: 0.79, LOOCV accuracy: 0.57) and pseudo-perplexity alone (prediction accuracy: 0.71, LOOCV accuracy: 0.57). A significant interaction term was revealed for pseudo-perplexity and digit symbol (LRT p=0.0022) and a trend level interaction term for pseudo-perplexity and WTAR (LRT p=0.0811).
**DISCUSSION:** We present novel evidence revealing the interaction between semantic coherence and cognition in a broad psychosis phenotype in children and adolescents. A binary logistic regression model based on pseudo-perplexity and cognition provided reasonably accurate predictions and revealed significant interactions between pseudo-perplexity and cognitive measures.

## M58. Behavioral Health Service Utilization in Early Psychosis: A Comparison of Individuals Served by Coordinated Specialty Care vs Usual Care in San Diego County

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**BACKGROUND:** Coordinated specialty care (CSC) is an effective early intervention for psychosis that has expanded rapidly across the U.S. over the past decade. Data suggest that it may be cost-effective, as well. As public and private behavioral health systems consider implementing CSC programs, they seek to predict the expected impact on service utilization across their systems. Specifically, more research is needed to understand how behavioral health service utilization shifts as individuals develop a first episode of psychosis and whether it differs for those receiving care in CSC versus usual care.
**METHODS:** We used administrative data from January 1, 2015, through June 30, 2022, from San Diego County Behavioral Health Services to identify clients who initiated services in Pathways
Kickstart, an early psychosis (EP) CSC program, and a comparison group (CG) of clients who utilized other outpatient services during the same period. Clients were included in the sample if they were ages 12 to 25 years old and received a first (index) diagnosis of psychosis from January 1, 2017, through June 30, 2021. Mental health service use was compared between the EP and CG groups across eight time periods: four (90 day) quarters both prior and post index diagnosis. We created client-level indicator variables for receipt of outpatient, inpatient and emergency system services during the quarter and calculated the number of outpatient services per quarter. We used logistic regression to estimate the probability of using each type of service in each quarter in the EP and CG groups. Age, gender, race/ethnicity, preferred language, clinical diagnosis, and comorbid substance use disorder were included as additional control covariates.
**RESULTS:** We identified 94 EP clients and 1531 CG clients with first episode psychosis. Among EP clients, the mean age was 18±3, 27% were female; 21%) were non-Latino white,

15% were non-Latino Black, 1% was non- Latino Asian, 54% were Latino, and 7% were of other or unknown race/ethnicity. Youth in the EP group were younger (the mean age of the CG group was 22±3) and were less likely to receive a substance use disorder diagnosis. The majority of youth in the EP group entered the CSC program in the first quarter after diagnosis.

There were small differences in outpatient service use in the year prior to the first diagnosis of psychosis. In the year following diagnosis, service use was significantly higher in the EP group than in the CG group. EP clients were more likely to use services than CG clients during the second through fourth quarters following diagnosis ($p < .001$, each). The mean number of outpatient visits made by EP clients was also greater in the first through fourth quarters following diagnosis compared to CG clients ($p < .001$, each).

For both groups, the probability of inpatient use increased in the quarter prior to diagnosis, was greatest during the quarter following diagnosis, and then declined in the following quarters. Clients in the EP group were more likely to use inpatient services than clients in the CG group during the quarter prior to diagnosis (24% vs 9%, $p < .001$), but were less likely in the quarter following diagnosis (21% vs 47%, $p=.039$).

The probability of emergency service use similarly increased in the quarter prior to diagnosis, was greatest during the quarter following diagnosis, and then declined in the following quarters. Also, following the pattern of inpatient use, clients in the EP group were more likely to use emergency services during the quarter prior to diagnosis (22% vs 13%, $p=.005$), but were less likely in the quarter following diagnosis (26% vs 53%, $p < .001$).

**DISCUSSION:** In this study, individuals with early psychosis received more outpatient care after entry into CSC than similar individuals in usual care, consistent with existing literature. Inpatient care and use of emergency services followed similar patterns. Use peaked during the period around first diagnosis for both groups. For the EP group, use was higher just before diagnosis, perhaps triggering referrals to CSC. Use of both inpatient care and emergency services was lower after diagnosis and CSC enrollment for the EP group, consistent with the goal of CSC to offer more intensive outpatient services and reduce reliance on higher levels of care. Future research will examine costs related to service utilization in this sample.

## M59. Social Engagement Moderates the Relationship Between CRP and Negative Symptoms in Individuals at Clinical High Risk of Psychosis

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**BACKGROUND:** Negative symptoms are common in individuals at clinical high risk of psychosis (CHR-P), are debilitating, and may predict conversion to psychosis. There are few treatment options for negative symptoms, and as such, discovering novel mechanisms in young CHR-P individuals is of great significance. One potential mechanism that may contribute to the development of negative symptoms is inflammation. Inflammatory markers have been shown to be elevated in CHR-P individuals and may be associated with negative symptoms. Deficits in social engagement are negative symptoms and play an important role in outcomes for CHR-P individuals. In fact, social engagement may buffer the effects of risk factors on psychosis. Social engagement in early developmental periods may decrease stress and interact with downstream processes, such as inflammation. Herein, we hypothesized that lifetime social engagement may moderate the association between C-Reactive Protein (CRP), a marker of inflammation, and negative symptoms in CHR-P young adults such that this association would be significant only among those with lower, but not greater, social engagement.
**METHODS:** 48 individuals (30 CHR-P and 18 health controls; HC), which comprised the entire subgroup with data on CRP, negative symptoms, and social engagement from the North American Prodromal Longitudinal Study (NAPLS)-2 cohort, were included in this analysis. Negative symptoms were assessed using the Scale of Prodromal Symptoms (SOPS), and social engagement was calculated using the sum of five items from the Life Events Stress scale: (1) involvement in church or synagogue, club, neighborhood, or other organization; (2) took a vacation; (3) took up a new hobby, sport, craft, or recreational activity; (4) acquired a pet; and (5) made new friends. A generalized linear model with robust estimation was used to test the association of CRP, diagnosis, and social engagement (and their interactions) with negative symptoms, adjusting for age, sex, ethnicity, poverty, and depressive symptoms. Simple slopes for the association between negative symptoms and CRP moderated by social engagement were calculated and stratified by CHR-P groups.
**RESULTS:** The mean age of the cohort was 22.6 and 21.9 for the CHR-P and HCs, respectively. Eight subjects in each group were female. CHR-P subjects had significantly greater negative symptoms than HC subjects ($p < 0.001$), though there was no significant difference in CRP or social engagement. In the generalized linear models, negative symptoms were significantly associated with CRP (beta=1.34, SE=1.35, 95%CI -1.31 to 4.00, p=0.035) as well as CHR-P (beta=8.16, SE=1.71, 95%CI 4.80 to 11.52, $p < 0.001$). There was a significant association between negative symptoms and the interaction of CRP-by-social engagement (beta=0.37, SE=0.56, 95%CI -0.74 to 1.47, p=0.008), but not the interaction of CRP-by-CHR-P or CHR-P-by-social engagement (both $p > 0.25$). There was a significant association between negative symptoms and the three-way interaction CRP-by-CHR-P-by-social engagement (beta=-5.27, SE=1.70, 95%CI -8.60 to -1.94, p=0.002). Based on the simple slopes analysis, we observed a significant positive association between negative symptoms and CRP amongst the CHR-P group at low (-1SD; p=0.02) and mean levels of social engagement (p=0.04) but not in the individuals with high social engagement (+1SD; p=0.34) or in any of the HC social engagement levels (p all $> 0.2$).
**DISCUSSION:** In this sample of CHR-P individuals, there was an association between negative symptoms and the interaction between diagnosis, inflammation, and social engagement, adjusting for relevant clinical and demographic covariates. Greater engagement in social activities appeared to buffer the relationship between inflammation, as measured by CRP, and negative symptoms. We have previously shown that inflammation is associated with negative symptoms related to motivation and pleasure, including asociality, in patients with

schizophrenia, which is consistent with the preclinical and clinical literature of exogenous administration of inflammatory stimuli leading to avolition and anhedonia as well as studies of endogenous concentrations of inflammatory markers in patients with depression being associated with similar phenotypes. The data herein suggests that these associations in young individuals at risk for psychosis may be buffered by social engagement, perhaps by limiting stress and its downstream impacts on the brain and behavior. Though this study is limited by a small sample size, future studies should seek to replicate these findings in a larger sample, and future studies with interventions that target social engagement may be important for limiting negative symptom burden in CHR-P individuals with increased inflammation.

## M60. Exploring Attendance, Engagement, and Outcomes in an Online Group Intervention for First-Episode Psychosis

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**BACKGROUND:** The COVID-19 pandemic prompted a rapid and drastic shift to online mental health services, accelerating the trend of remotely delivered mental health interventions driven by advancements in technology. This recent shift brought to light the paucity of remote treatment options for those experiencing psychosis. Despite the potential for this modality to improve access to specialized interventions, little is known about how individuals with psychosis engage with and benefit from online interventions. Even less is known about group interventions, although they play a key role in evidence-based treatments for psychosis. Some research examining online group interventions for those with psychosis was conducted during the pandemic, however much of the focus was on acceptance and feasibility, and little remains known about how individuals with psychosis attend, engage with, and benefit from online group interventions. As such, the current study explored attendance, engagement, and outcomes in an online group intervention for first-episode psychosis (FEP).

**METHODS:** 51 individuals with FEP took part in an online group intervention designed by our research team, Be Outspoken and Overcome Stigmatizing Thoughts (BOOST). BOOST is an eight-session group intervention that incorporates cognitive behavioural techniques, psychoeducation, and a peer support facilitator with the aim of reducing self-stigma in those with FEP. Participants completed self-reported measures of anxiety, mood, beliefs about recovery, and internalized stigma before and after the intervention. Attendance was tracked across all sessions and was coded using a binary system (0 = did not attend, 1 = attended). Engagement was coded from clinical notes based on individuals' verbal participation during in-session activities and was scored from 0-3 for each session (0 = no engagement, 1 = passive engagement, 2 = active engagement, 3 = consistent engagement).

**RESULTS:** On average, participants attended 76% of sessions and made some novel verbal contributions throughout the intervention (M = 2.19, SD = .907). Neither attendance nor engagement were significantly related to baseline anxiety or depressive severity or beliefs about recovery. Level of engagement was not significantly associated with change in self-stigma across the intervention, despite significant reductions in self-stigma ($p < .001$, $\eta p2 = .390$). A

significant interaction was observed between level of engagement and the degree of change in recovery beliefs ($p = .021$, $\eta p2 = .147$).
**DISCUSSION:** The findings further highlight the potential for online group interventions for individuals with psychosis. As individuals with psychosis often struggle to engage with existing healthcare models, it is essential to explore the factors that facilitate attendance and engagement in online modalities. Although engagement remains a challenging construct to measure, the results call attention to the potential role of verbal engagement in online interventions, warranting further research.

## M61. Mental Health Stigma Predicts Treatment Engagement in Youth With First-Episode Psychosis

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**BACKGROUND:** Youth with first-episode psychosis (FEP) continue to experience significant barriers to care, despite ongoing advances in early intervention. Studies have demonstrated that approximately 30% of individuals receiving FEP services eventually discontinue treatment prematurely, with stigma being cited as a key barrier to treatment engagement among this population. Youth with FEP frequently endorse high levels of perceived public stigma and discrimination associated with their illness, as well as high levels of internalized mental health stigma, including feelings of shame or disillusionment. They may also be particularly vulnerable to the negative effects of stigma, given the increased emphasis on social acceptance and identity development during adolescence and young adulthood. Exposure to stigma during early psychosis also has increased potential to shape long-term attitudes towards mental health treatment.

As both stigma and treatment engagement represent multidimensional constructs, the current study aimed to examine the effects of three distinct types of stigma on both objective (attendance) and subjective (self-reported motivation for treatment) aspects of engagement over a 6-month treatment period. We hypothesized that higher levels of public and internalized stigma would be associated with poorer treatment engagement (i.e., reduced attendance and motivation), whereas higher levels of stigma resistance would be associated with greater engagement among youth with FEP. We also hypothesized that higher initial levels of stigma would predict poorer treatment engagement over time.

**METHODS:** Individuals with FEP (n = 82) were recruited through the UNIVERSITY OF CALIFORNIA, LOS ANGELES Aftercare Research Program, where they received medication management, case management, and psychotherapy. As part of a 6-month RCT (NCT02823041), each participant was randomly assigned to either: a) a combined intervention of cognitive training (CT) and aerobic exercise, or b) CT and a didactic healthy living group.

Perceived public stigma was measured using the Perceived Devaluation and Discrimination Scale (PDD), internalized stigma was measured using the Internalized Stigma of Mental Illness

Inventory (ISMI), and stigma resistance was measured using the Stigma Resistance Scale (SRS). Stigma measures were completed at baseline and 6-month timepoints. Attendance was assessed via the proportion of exercise and/or CT sessions attended over the 6-month period, and motivation for treatment was measured using the Intrinsic Motivation Inventory for Schizophrenia Research.

**RESULTS:** Pearson correlations revealed significant associations between baseline PDD and ISMI scores and baseline motivation for CT, as well as exercise attendance over 6 months, with higher levels of stigma being associated with both reduced motivation and attendance. Baseline PDD, but not ISMI scores, predicted CT attendance over 6 months. Baseline PDD and ISMI scores did not appear to predict baseline motivation for exercise, nor motivation for CT or exercise at 6-month follow-up. These non-significant associations may be partly due to limited sample sizes in these analyses (ns ranging from 21 to 54). Baseline SRS scores were not found to be significantly correlated with any of the motivation or attendance measures at any time point.

**DISCUSSION:** Findings from the current study provide further evidence that different types of mental health stigma can negatively impact treatment engagement in youth with FEP, a population that has historically been difficult to engage in care. Our results suggest that efforts to reduce stigma early in treatment may help improve overall treatment engagement over time.

## M62. The Australian Early Psychosis Clinical Quality Registry (CQR) – Considerations For Implementing a National CQR in Early Psychosis

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**BACKGROUND:** For several decades the early intervention for psychosis intervention services (EIP) model of care has demonstrated high-quality care in early intervention and a shortened duration of untreated psychosis is associated with improved outcomes. Despite significant global evidence towards the effectiveness of the EIP model there continues to be a clear gap between clinical practice, and evidence-based practice, leading to a continuation of adverse experiences and poor outcomes for young people experiencing early psychosis. Additionally, mid and long-term outcomes are not well understood. Clinical quality registries (CQR) have been integrated into the Australian physical health sector for several decades, with clear evidence of the pivotal role in collecting quality clinical data and enabling benchmarking and research into healthcare effectiveness to inform quality improvements nationally. The Australian Early Psychosis Collaborative Consortium (AEPCC) has developed and implemented a CQR in the national early psychosis sector, the first in mental health. The AEPCC CQR commenced implementation with 5 foundation sites across Australia in 2021, and with further funding confirmed, this will be rolled out to an additional 20 sites by 2029, covering an estimated 75% of sites nationally.

**METHODS:** We will describe the process of designing and evaluating a rigorous implementation strategy that is adaptable to local needs while maintaining core functions for both the CQR and evidence-based practice, such as informed consent, clinical guidelines, and data integrity. The duality of these outcomes will reflect Australia's unique cultural and geographical characteristics, as well as variations in health system structures and models of care. 'Implementation by its very nature is a social process that is intertwined with the context in which it takes place'. (Damschroder et al., 2009).

**RESULTS:** Findings from the early implementation outcomes with foundation sites (5) and longer-term considerations to measure success and support sustainability will be discussed. Additionally, the systemic factors that support sustainability of the CQR and evidence-based practice will be addressed. Early indicators suggest factors may include but not limited to individuals' reduction in adverse events for young people experiencing early psychosis, and enhanced access to treatment, organisational capacity and capability improvements, and innovative large-scale research into new treatments, and refinement of clinical guidelines.
**DISCUSSION:** The implementation strategy acknowledges the challenges of systemic and individual change when integrating a novel digital strategy into the mental health sector. The AEPCC CQR has been adapted and codesigned with key stakeholders across the early psychosis and broader health economic sector, and with successful implementation there is clear potential for clinicians, services and policymakers to utilise the CQR and bridge the gap between research and practice. With the aim to strengthen care, the AEPCC CQR national dataset will provide access to clinical information on the appropriateness and effectiveness of healthcare in early psychosis. Young people experiencing early psychosis will receive timely, evidence-based and person-centred care, leading to better outcomes with recovery.
Government endorsement will be a critical factor for implementing and integrating a national clinical quality registry in early psychosis. The Australian Institute for Health and Welfare (AIHW) in partnership with Australian State/Territory governments leads a 10 year national strategy for maximising and establishing CQRs, prioritising the value of national clinical quality outcomes datasets (Care, 2023).

The CQR is a fundamental component of care in early psychosis, and with successful implementation, will drive long-term innovative research to enhance understandings of the disorders and improve treatment for better outcomes.

A comprehensive, meaningfully synthesized archive of measures can advance measurement-based care, services research, and data harmonization in early psychosis. (Ferrari et al., 2023)

## M63. Stressful Life Events and Symptom Relapse in Deficit and Non-Deficit Syndromes in First-Episode Psychosis

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**BACKGROUND:** Negative symptoms in schizophrenia are less responsive to medications and associated more functional impairment. Persistent negative symptoms are also present in earlier phases of psychotic illness including among first-episode patients, and are associated with worse outcomes. In an effort to understand the nature of negative symptoms, distinct subtypes have been studied including patients with and without a deficit syndrome (DS). DS is characterized by the presence of enduring primary negative symptoms that are direct expressions of the illness pathology. A better understanding of potential negative symptom subtypes as well as factors that contribute to and maintain negative symptoms during the illness course would likely lead to

more targeted interventions. Theoretical conceptualizations regarding the pathophysiology of schizophrenia generally postulate that stress exposure contributes to illness vulnerability and progression. Given its ability to alter brain structure and function, stress exposure could be one possible mechanism underlying persistent negative symptoms. The goal of the present study is to characterize stressful life event exposure in patients with and without DS as well as examine the impact of stressful life events on the clinical course of negative symptoms.
**METHODS:** Participants (N = 82) with a schizophrenia or schizoaffective disorder diagnosis within the first two years of illness onset were recruited from local hospitals or clinics. All participants received a long-acting injectable medication, individual psychotherapy, group social skills training, and case management. Participants were followed for a one-year period. Trained interviewers were routinely administered various clinical measures including the Brief Psychiatric Rating Scale, Psychiatric Epidemiology Research Interview for Life Events, and the Cognitive Appraisal of Life Events Scale to participants. The Proxy for the Deficit Syndrome was used to determine the presence of the deficit syndrome among participants.
**RESULTS:** Multivariate analyses of variance revealed that first-episode patients with the deficit syndrome reported fewer total life events and fewer negative life events. Deficit syndrome patients also reported muted appraisals of negative life events. There were no significant differences between deficit and non-deficit patients in coping. Further longitudinal analyses will be conducted to examine the impact of stressful life events on clinical outcomes including symptom relapse and functioning.
**DISCUSSION:** These findings have the potential to enhance our understanding of negative symptoms including the impact of stressful life events on the course of negative symptoms. Results will also be discussed in the context of treatment implications for treating negative symptoms and managing stress in both deficit and non-deficit patients.

### M64. Perception of Daily Stressors in Emerging Adults With High Schizotypy

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**BACKGROUND:** Schizotypy (SZY) refers to the spectrum of schizophrenia-like personality traits that may reflect latent illness vulnerability and serves as a general risk factor for psychopathology. The diatheses-stress model of psychosis holds that significant stress, frequently psychosocial stress, precipitates psychosis onset by triggering a neurochemical cascade preset by biological factors. Symptom onset of most psychological disorders, including schizophrenia, occurs during the adolescence to young adult transition, wherein significant changes and stressful experiences occur across multiple life domains. Thus, studying daily stressors that may contribute to psychosis onset in this age group is critical to elucidating potentially modifiable environmental contributors to the psychosis transition.

Indeed, existing cross-sectional data suggests daily stressors are more frequent in young people with SZY, and that perceived daily stress is associated with positive symptoms. However, there has been little investigation into whether there are specific types of daily stressors that

disproportionately confer stress in people high in SZY, and impacts of daily stressors on perceived stress on the momentary (vs. retrospective) basis are understudied. Understanding these connections will improve our ability to model daily stressors' contributions to neurochemical cascades in psychotic disorder development.

In an emerging adult sample, we used ecological momentary assessment (EMA) to assess incidence of perceived stress and related presence/absence of specific stressors throughout the day in groups of students high or low in schizotypal traits. We predicted that compared to the low SZY group, the high SZY group would encounter more stressors and have higher overall perceived stress. In addition, we expected interpersonal stressors would disproportionately relate to perceived stress given established interpersonal sensitivity in individuals with clinical high risk for psychosis.

**METHODS:** College students (age: M=19.0, SD=1.1) were categorized as either High SZY (N=133) or Low SZY (N=61) using cutoff scores on the Schizotypal Personality Question-Brief Revised Updated (SPQ-BRU). To assess momentary stressors and perceived stress, participants completed EMA via the Avicenna smartphone app over a 1- or 2-week period with 6 trials/day, totaling 42 or 84 maximum possible trials per person. Current perceived stress was rated from 0 (no stress) to 10 (extreme stress), and participants indicated which of 18 listed stressor(s) contributed to that rating, a subset of which were categorized as Interpersonal, Logistical/Practical, or Academic/Work. Group differences in stressor frequency and perceived stress were tested using non-parametric and independent t-tests, respectively. Unique impact of these 3 stressor types was tested using multilevel modeling predicting perceived stress from the presence or absence of the 3 stressor types as well as group membership (High/Low SZY).

**RESULTS:** Compared to the Low SZY group, the High SZY group encountered, on average, more stressors ($W=4900.0$, $p=0.02$, $d=0.78$) and more perceived stress ($t(192)=3.02$, $p=0.002$, $d=0.47$). No group differences were found in frequency of endorsed stressor types. Multilevel models also found High SZY group reported more stress than Low SZY group at within-person level (estimate = 0.89 [0.38-1.41], $p=0.001$). Moreover, all stressor types predicted increased perceived stress (all $p < 0.001$, estimates: Interpersonal 1.27 [1.04-1.50], Logistical/Practical 1.28 [1.04-1.52], Academic/Work 1.25 [1.13-1.38]). An interaction was found between Group and Academic/Work stressors (estimate = 0.67 [0.42-0.91], $p < 0.001$), such that Academic/Work stressors were more strongly associated with subjective stress in the Low SZY group than the High SZY group; no other interactions between group and stressor type were significant.

**DISCUSSION:** Young adults high in SZY encountered more stressors and reported greater perceived stress than those with low SZY. However, events themselves were not perceived as more stressful in high SZY group. Notably, the only Group x Stressor interaction indicated academic/work stressors were less stressful in the high SZY group, suggesting differences in perceived stress, thought to contribute to poor mental health and psychosis risk, are better explained by objective lifestyle, systemic, or environmental differences than by subjective differences in life event interpretations. Academic/work stressors may be a special case where differences in general motivation or occupational priorities cause these stressors to be less relevant for young adults with high SZY.

Buildup of stress can lead to chronic poor mental health, and one's ability to cope adequately with stressors is proposed to determine degree of biological stress response. Thus, this study's

finding that High SZY individuals experience both greater number of stressors and greater perceived stress supports the use of interventions specifically designed to reduce stress in individuals high on the SZY spectrum to prevent conversion to psychosis. Finally, these data highlight the need to explore stressor type in investigations of daily stressors in people at risk for psychosis.

## M65. Cognitive Behavioral Group Therapy in Early Psychosis, From High-Risk Individuals to First Episode of Psychosis: A Systematic Review of CBTP Group Therapy

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**BACKGROUND:** Over the past two decades, Group Cognitive Behavioral Therapy for Psychosis (GCBTp) has emerged as a therapeutic approach within early psychosis detection and intervention clinics. However, its inclusion in international clinical practice guidelines remains limited. This study aims to conduct a rigorous systematic review on the existing research on the effectiveness of GCBTp among individuals experiencing a first psychotic episode or at risk of psychosis with attenuated psychotic symptoms.
**METHODS:** The PRISMA 2020 guidelines were followed for systematic reviews. Five databases were searched including MEDLINE, EMBASE, EBM Review, APA PsycInfo, and CINAHL Complete, along with Google Scholar for relevant literature up to October 2023, with no restrictions on publication date, study design, or language.
**RESULTS:** A total of 1827 studies were screened, with 30 articles meeting the inclusion criteria. The quality of evidence ranged from low to moderate risk of bias, warranting cautious interpretation of the findings. Nonetheless, the results indicate significant improvements in individuals at clinical high risk for psychosis (CHR) and those with recent onset psychosis. These improvements were observed across multiple domains, including psychiatric symptoms, social functioning, cognition, self-esteem, and other measures. While methodological limitations exist, the findings are supported by evidence from multiple studies and suggest clinically meaningful progress in these populations.
**DISCUSSION:** Evidence suggests CBTp interventions are effective in group formats; however, GCBTp remains underexplored in randomized controlled trials, and dropout rates present a challenge. Still, findings remain promising. More studies on moderating processes in GCBTp are warranted, particularly examining interpersonal dynamics.

## M66. Widespread White Matter Microstructural Abnormalities in Recent-Onset Psychosis Compared to Individuals at Clinical High-Risk

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**BACKGROUND:** Diffusion MRI (dMRI) findings of lower fractional anisotropy (FA) in individuals with psychosis support the dysconnectivity hypothesis, supporting the notion that disrupted neural connections may underpin the development of symptoms and cognitive dysfunctions. Further, individuals at clinical high risk for psychosis (CHR) exhibit white matter microstructural alterations, though less extensive and inconsistently reported, likely due to varying progression rates and risk profiles. It remains unclear to which extent white matter abnormalities represent a predisposing vulnerability factor or are associated with the full-blown disorder. In the present study, we addressed this question by comparing FA abnormalities directly between individuals with recent onset psychosis (ROP) and individuals at CHR. Moreover, we explore associations with risk factors and clinical phenotypes, hypothesizing a gradient of FA abnormalities, with healthy control participants (HC) having higher FA in localized regions of interest (ROIs) than CHR, and CHR having higher FA than ROP.
**METHODS:** In the Personalized Prognostic Tools for Early Psychosis Management (PRONIA) study a total of 207 ROP (91F/116M), 183 CHR (95F/88M), and 297 HC (178F/119M) individuals were recruited across seven sites. dMRI data were pre-processed, site-harmonized, free-water corrected, and co-registered to calculate FA averages across 25 ROIs extracted from the JHU white-matter label atlas. Analysis of covariance (ANCOVA) tested FA differences among groups for each ROI separately, adjusting for linear and quadratic age and sex effects. Significant main effects corrected for false discovery rate (FDR) led to post-hoc comparisons on the marginal means. To explore brain-behaviour patterns, we used canonical correlation analysis (CCA) to identify linear combinations of region-wise FA and behavioural ("modes") across CHR and ROP groups. We used permutation analysis that randomly shuffled the data 1000 times to assess significance of the modes correcting for family-wise error rate (FWER).
**RESULTS:** Eighteen of the 25 ROIs yielded significant group differences. Post-hoc tests revealed lower FA across 18 ROIs in ROP compared to HC ($pFDR < .050$), with 10 of these also showing lower FA in ROP compared to CHR ($pFDR < .048$). Additionally, FA in 4 of these ROIs was lower in CHR compared to HC ($pFDR < .045$). CCA identified a first mode ($r=.450$, $pFWER=.001$) associated with widespread lower FA and a clinical phenotype characterized by a diagnosis of ROP rather than CHR, low global functioning, low overall intelligence quotient (IQ), and high severity of disorganized symptoms. The second mode ($r=.405$, $pFWER=.018$) revealed localized low FA within the fornix, genu and splenium of the corpus callosum linked to severe negative and positive symptoms, low verbal IQ and an absence of familial risk as indicated by amnestic information.

**DISCUSSION:** Our study reveals a gradient of FA reductions, with widespread changes in ROP and more localized ones in CHR, suggesting that microstructural white matter abnormalities intensify around psychosis onset. Our canonical correlation links stable trait-like factors like global functioning and IQ along with a full-blown diagnosis to broader white matter changes, while current state-like factors have more localized effects. Future research, including also longitudinal data in individuals pre- and post-psychosis onset will be crucial to specify the dynamics of white matter changes in psychosis as well as the driving neurobiological processes.

## M67. A Confirmatory Factor Analysis of Competing Panss Negative Symptoms Models

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**BACKGROUND:** The psychotic negative symptoms are heterogeneous, which complicates the understanding of their pathophysiology, precise inclusion in clinical trials and consequently development of effective treatments. Factor analytic studies of the Positive and Negative Syndrome Scale (PANSS) document the existence of two-factorial negative symptoms models: Expressive Deficit (ED) and Social-Amotivation (SA), albeit of different compositions. Whilst different models derived from other assessment scales were directly compared, to our knowledge, no study applied this approach to PANSS, the most widely used rating scale in psychosis research. Our aim was to determine the best PANSS derived negative symptom model.
**METHODS:** A cohort of medication naïve/minimally treated patients with first episode psychosis (n=446) were assessed with the PANSS. Confirmatory Factor Analysis (CFA) was performed using AMOS graphics version 24 program to test 6 empirically and theoretically driven PANSS models: the nine-item model (Liemburg Factor), the three eight-item models based on exploratory factor analysis, and the seven-item model (NSFS/Marder Factor).
**RESULTS:** A 9-item PANSS model comprising SA and ED dimensions outperformed the other models by providing the best fit for the data: CFI = 0.98, GFI = 0.97, TLI = 0.97 and RMSEA = 0.06 (CI 90%: 0.04–0.08), BIC =191.9, AIC = 101.7.
**DISCUSSION:** A 9-item model (Liemburg Factor) appears to best reflect the underlying structure of negative symptoms as assessed using the PANSS. Our findings suggest that when

using data collected with the PANSS, a 9-item, two-dimensional model may be optimal for investigations of negative symptoms.

### M68. Do Negative Symptom Profiles Differ Between Affective and Non-Affective Psychosis? A Two-Year Longitudinal Study of Individuals Having Experienced a First Episode of Psychosis

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**BACKGROUND:** From the early stages, the course of schizophrenia-spectrum disorders is marked by substantial negative symptoms with a detrimental functional impact. Hence, studies in this population confirmed the need to detect these symptoms early on to improve the functional trajectories of individuals and proposed to assess these using a more parsimonious approach with two main domains: motivation and pleasure (MAP) and expressivity (EXP). Recently, the transdiagnostic approach of severe mental illnesses highlighted that these symptoms are present across a broader range of conditions, notably in mood disorders, but their potential specific and/or shared characteristics across diagnoses are still unclear. This study aimed to examine the interplay between the two domains of negative symptoms and diagnoses of affective psychosis (AP) versus non-affective psychosis (NAP) in a large cohort of FEP patients over 24 months following admission into an early intervention service.
**METHODS:** Six hundred and seventeen individuals having experienced a FEP, recruited between 2003 and 2018 at PEPP-Montréal, were included in the study. All participants were either antipsychotic-naïve or had received < 1 month of antipsychotic treatment at baseline. Among those, 181 had a diagnosis of AP (i.e., unipolar depression or bipolar disorder) and 436 of NAP. Participants were assessed for sociodemographics, psychopathology (i.e., negative, positive, depressive, and manic symptoms), and functioning. Negative symptoms were computed into MAP and EXP domains at baseline, 6, 12, 18, and 24 months follow-up. Generalized estimating equations were used to explore MAP and EXP; domains of "Time" and "Group" were included a priori in the model. Sex and age were added as fixed domains.
**RESULTS:** At baseline, the groups did not significantly differ in age, sex, or severity of positive symptoms; mood symptoms were more severe in the AP group. A main "Time" effect was significant for both MAP and EXP domains, with a decrease in symptoms across time ($\chi2$ = 262.24, df = 4, $p < 0.001$; $\chi2$ = 115.49, df = 4, $p < 0.001$, respectively), especially in the first part of the follow-up (i.e., between baseline and M6 and between M6 and M12). A main "Group" effect was also detected for both domains, with the NAP group experiencing more severe negative symptoms than the AP group ($\chi2$ = 13.92, df = 1, $p < 0.001$; $\chi2$ = 18.41, df = 1, $p < 0.001$, respectively). A "Group x Time" interaction was only observed for the EXP domain ($\chi2$ = 10.63, df = 4, $p = 0.031$).
**DISCUSSION:** In this large FEP cohort, the severity and evolution of EXP and MAP domains differed depending on the diagnosis. More specifically, the NAP group presented more EXP symptoms over time and would benefit from a personalized approach to reduce these symptoms. Replication with other early intervention service datasets and later stages of severe mental illness would contribute to confirming these results and developing an appropriate framework for individualized care.

## M69. Identifying Clinical Characteristics of Young People With Treatment-Resistant Schizophrenia for Community vs Hospital Initiation of Clozapine

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**BACKGROUND:** The Early Psychosis Prevention and Intervention Centre (EPPIC) is a specialist service within Orygen (Melbourne, Australia), providing treatment to young people aged 15-25 presenting with first-episode psychosis (FEP). The prevalence of treatment resistance is 25% in first-episode schizophrenia. The need for hospital admission has consistently been identified as a barrier to clozapine treatment. Community initiation of clozapine increases accessibility for patients who otherwise would not agree to admission. We aimed to examine the pathway to, and treatment setting for clozapine initiation; ascertain frequency of hospital and community based clozapine initiation and examine demographic and clinical measures associated with clozapine treatment setting. We will describe clinicodemographic characteristics of treatment resistant schizophrenia (TRS) cases in the FEP cohort, including time to clozapine initiation, and characteristics of antipsychotic use prior to clozapine initiation.

**METHODS:** A retrospective chart review was completed on 1,220 cases of FEP in a cohort of 15-24 year olds attending EPPIC from 2011-2017. A subgroup of 521 cases of schizophrenia spectrum disorder was extracted and TRS cases were identified based on the TRRIP consensus guideline.

**RESULTS:** A total of 96 cases of TRS were identified, representing 18.4% of schizophrenia spectrum disorder cases and 7.9% of all cases of FEP; 58.5% of TRS cases were male and 41.5% female. Mean age was 19.1 (SD 2.7) with a median duration of untreated psychosis of 12 weeks (SD 61.43, range 0 – 364 weeks). Seventy-five percent (n = 72) were treated with clozapine. Two cases were excluded from analysis as they were prescribed clozapine prior to entering EPPIC; therefore 70 cases were included for analysis.

The treatment setting for clozapine initiation was available in 67 of 70 cases. Fifty-four percent (n=36) commenced clozapine in a community treatment setting, with 46% (n = 31) of clozapine initiations in hospital. Compared to hospital initiation, individuals with community initiation had decreased odds of involuntary admission at presentation (OR = 0.31, 95% CI [0.11 – 0.88] (36% vs 64%)) and during episode of care (OR = 0.22, 95% CI [0.08 – 0.63] (37.8% vs 62.2%)); and substance use during episode of care (OR = 0.36, 95% CI [0.13 – 0.99] (38.5% vs 61.5%)). Cases with community initiation had significantly lower mean delusion item scale scores on short form SAPS (mean 3.08 [SD 1.87] vs 3.87 [SD 1.20], t = 2.01, p = 0.024). Twenty-two percent of cases (n = 15) discontinued clozapine, with reduced odds of discontinuation among the community initiation group (OR = 0.22, 95% CI [0.06 – 0.78] (26.7% vs 73.3%)).

The median number of trials of antipsychotic medication was 3 (SD 1.19, range 1 – 7), with 74% (n = 66) of cases trialled on 3 or more antipsychotics, and 19.1% (n = 18) prescribed antipsychotic polypharmacy after meeting criteria for TRS. The median time from illness onset to clozapine initiation was 59 weeks (SD 41.46, range 9 – 238 weeks). Thirty percent of clozapine cases (n = 21) were prescribed depot/long-acting injectable antipsychotic for at least one trial.

**DISCUSSION:** In this sample of FEP cases there was a majority of cases with community clozapine initiation. Involuntary admission, substance use, and more severe delusions at first presentation are all associated with reduced likelihood of community initiation. Factoring in these clinical characteristics in relation to treatment considerations would be recommended to enhance access for community initiation to a wider cohort of FEP cases. Community initiation of clozapine increases accessibility for this effective treatment, and in this sample resulted in fewer patients discontinuing clozapine.

## M70. The Time Perception Accuracy Test (TPAT) – A Clinical Tool for Measuring Deficits in the Perception of Event Timing in Relation to Psychosis

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**BACKGROUND:** Despite a large amount of accumulated knowledge about brain abnormalities in schizophrenia, the neurobiological mechanisms responsible for producing psychotic symptoms remain unclear. Here we describe the preliminary stages of a new study to investigate a potential mechanism for specific types of paranoid delusions: reference, mind reading, persecution and external control. We postulate that these types of delusions arise from misperceptions of the timing of external events, which in social situations could form the kernel of some delusional beliefs. For example, perceiving incorrectly that a listener reacted to the patient earlier in conversation than anticipated could be interpreted as a mind reading event. There have been previous reports of timing perception deficits in schizophrenia, and so we have developed a computer task to assess timing perception. Cortical GABA interneuron deficits and disrupted EEG synchrony are well known deficits in schizophrenia, and we hypothesize that these give rise to the time perception deficits.

Hypothesis: We hypothesize that disrupted EEG synchrony in schizophrenia results in abnormal perception of the timing of events, which in turn contributes to the genesis of paranoid delusions.

**METHODS:** To test this hypothesis, this project will recruit participants with schizophrenia and analyze the association between the following variables: EEG gamma synchrony, timing perception and delusional symptoms. We have developed a computer task to measure event timing, consisting of viewing a series of simulated collisions between balls on a screen. These are much like billiard balls on a pool table, but some of the collisions have been deliberately altered so that the collision trajectories do not match the timing of ball impacts. This will allow us to generate an empirical measurement of each participant's average timing perception accuracy.

**RESULTS:** Here we present preliminary data on the validity of the ball bounce task in healthy controls (n=17), demonstrating that accuracy in detecting invalid collisions is correlated with the length of delay in the test collision. The longer the delay, the easier it is to detect it (n=17, R^2= 0.65 Pearson's r=0.80 p=0.000033. The mean percentage of correct collision perceptions was 58.2 (95% CI: 52.8-63.6). This suggests that the task we created is able to generate a read out of timing perception accuracy in human subjects. We are currently recruiting patients with schizophrenia at various stages of illness to complete this task, undergo EEG, and complete psychotic symptom rating scales.
**DISCUSSION:** We have demonstrated the potential utility of a novel task to measure time perception and plan to apply this to investigating the mechanisms underlying paranoid delusions in schizophrenia. This study will test a new hypothesis that could enhance understanding of these core symptoms of schizophrenia.

## M71. A Collaborative Care Model Integrated Within Primary Care for Early Psychosis Screening, Triage, and Referral to Improve Patient Access to Resources and Specialty Care

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**BACKGROUND:** To facilitate early identification and intervention for young adults experiencing early psychosis and ultimately improve long-term outcomes, brief screening in primary health care settings has potential to be used at-scale to facilitate rapid access and referral to care, especially for BIPOC and LGBTQ+ who have historically been underserved in traditional community care for psychosis. While screening for mental health conditions such as anxiety, depression and suicidality has become more commonplace in primary care, routine psychosis screening remains rare in the United States (see Woodberry et al. 2022; Savill et al. 2022, 2024).
**METHODS:** Penn Integrated Care (PIC) of the University of Pennsylvania Health System employs a collaborative care model to increase access to and engagement with mental health care to improve mental and physical health outcomes. Primary Care patients complete a behavioral health screening toolkit with the PIC team via phone or secure online survey. In June 2024, PIC added the PRIME-5 screener, a 5-item short form of the PRIME-Screen-Revised which we previously used computerized adaptive test simulation to develop, and then age norm and externally validate. Screening results are embedded into the Health System's electronic health record. Young adults in the peak age range (18-30) of risk for psychosis emergence scoring positive on the PRIME-5 (indicating possible clinical high risk for psychosis / early psychosis) are referred to Pennsylvania's First Episode Psychosis technical assistance and training center, HeadsUp, which connects with patients to conduct further phone screening to determine potential eligibility for clinical-high risk or first episode psychosis Coordinated Specialty Care programs.
**RESULTS:** PIC screening is ongoing to date; this preliminary report provides results between June and September 2024, during which time 506 patients (mean age=25.1, sd=3.4) completed the screening toolkit, of whom 30% (n=154) screened positive on the PRIME-5. Individuals screening positive on the PRIME-5 also endorsed significantly greater depression (PHQ-9) and

anxiety (GAD-7) than those screening negative (all p's < 0.001). Following PIC triage, 7% (n=38; BIPOC=58%; Female=87%) were referred to HeadsUp for further screening. Among them, 47% (n=18) were determined to be "true positives" for psychosis spectrum symptoms and offered referrals to coordinated specialty care (n=10) or other psychosis specific care, 45% (n=17) were determined to be "false positives" and offered referrals to other mental health services, and the remaining 8% (n=3) were unreachable. All contacted participants were receptive to mental health care referrals. At the current referral rate (approximately 3 per week), we anticipate that data presented at SIRS will reflect results from approximately 1500 PIC screenings occurring between June 2024 and February 2025.
**DISCUSSION:** Ongoing screening and follow-up will evaluate ultimate connection to care for referred participants. Results thus far are encouraging in demonstrating the feasibility and utility of a collaborative care model to expedite access to psychosis specialty services especially for historically underserved communities in the United States. Public availability of the brief age normed and validated PRIME-5 screening tool will allow future piloting and expansion in a wide range of medical care settings, such as pediatric primary care and obstetrics/gynecology.

## M72. "We Have Our Own Different Cultures": Exploring Latino/A Mental Health Experiences Accessing and Engaging in Early Psychosis Care

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**BACKGROUND:** In the U.S., the incidence rate of first-episode psychosis (FEP) is between 15-100 individuals per 100,000 annually. Studies have reported that Hispanic and Latino populations have higher prevalence rates of psychotic symptoms and are up to three times more likely to be diagnosed with certain psychotic disorders (e.g., affective psychosis diagnoses) than non-Hispanic White individuals. FEP is a critical period for intervention to alter the course of long-term outcomes associated with schizophrenia and other psychotic disorders, such as low employment rates and high rates of suicide. Coordinated specialty care (CSC) models provide early intervention for individuals experiencing FEP, by offering comprehensive services that include the delivery of psychosocial and pharmacological approaches by a multidisciplinary team of mental health professionals.
**METHODS:** This qualitative study examines the experiences of Latino/a individuals and their families navigating early psychosis care in Washington State. In-depth interviews were conducted with 13 participants recruited from a network of coordinated specialty care programs, including three service users and ten family members of those enrolled in services. Data were analyzed using a content analysis approach, and qualitative data coding was facilitated with Atlas.ti software.
**RESULTS:** All 13 participants identified as Latino, of which three were service users of CSC, and ten were family members of service users enrolled in CSC. Qualitative findings uncovered three themes that summarized experiences with mental health services, including CSC, among Latino families: (1) the limited guidance in navigating services leads to diminished trust, (2) the importance of cultural and linguistic understanding, and (3) the value of the CSC model in fostering engagement and support for participants.

**DISCUSSION:** The findings highlight the importance of CSC models that incorporate the diverse backgrounds and experiences of individuals affected by psychosis, specifically Latino individuals. By nurturing trust, cultural awareness, and strong support networks, providers can cultivate inclusive environments that promote the recovery and well-being of individuals experiencing psychosis. By fostering trust, cultural understanding, and robust support networks, coordinated specialty care can create inclusive and empowering environments that enhance the recovery journey for Latino/a individuals with psychosis and their families.

## M73. Atypical Neural Activation During Live Face Gaze in First Episode Psychosis

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**BACKGROUND:** Typical social cognitive studies in Schizophrenia rely on single subject paradigms using static images. Implicitly viewing images of fearful faces has revealed aberrant neural activation in Schizophrenia. Even though fruitful in understanding neurobiology, these paradigms hardly mimic the dynamic nature of real-world social interactions. In this pilot study, we introduce an ecologically valid method to study dyadic social interaction in First Episode Psychosis (an individual within 3 years of onset of a primary psychotic illness), its neural correlates and therapeutic implications. We hypothesized that neural responses to dyadic live emotive face gaze are atypical in First Episode Psychosis (FEP) and predict real world social function indices such as the Bureau of Labor Statistics (BLS) classification.
**METHODS:** 14 individuals (females: males= 2:12; mean age: 24.2 + 4.1 years) with FEP were recruited from Specialized Treatment Early in Psychosis (STEP) clinic at Yale University. Sociodemographic details (including Bureau of Labor Statistics codes) and PANSS (Positive and Negative Syndrome Scale) were collected prior to the experiment. BLS codes assess the status of employment and do not consider severity of symptoms. We used a novel paradigm in which the experimenter emotes natural facial expressions while watching a series of emotionally evocative short video clips, and the participant (FEP) observes the experimenter's face. After each run of the movie, the experimenter looks either at the participant's face (direct gaze) or at the shoulders (diverted gaze). Facial expressions of both were tracked as Facial Action Units (FAU) using Openface platform. Cortical hemodynamic responses of the participant, assessed as absorption rate of near infrared light by Oxy and deoxy Hemoglobin, were acquired by Functional Near Infrared Spectroscopy (FNIRS) and these data serves as proxy for cortical neural responses.
**RESULTS:** During live gaze with an emotive face, the auditory regions of left Temporal parietal junction (LTPJ) were activated in FEP, contrary to findings reported in healthy individuals where homologous regions are activated in the right hemisphere. The effects were higher with direct gaze. The neural responses strongly correlated with PANSS positive scores (r=0.49) and BLS linked classification (r=0.60).
**DISCUSSION:** Our study shows a shift in activation from right to left Temporal parietal Junction during live face gaze in FEP. This could represent a compensatory mechanism for dysfunction in the right social cognitive network. The neural systems activated while engaging in direct gaze with an emotive face are distinct enough to clearly differentiate between FEP and healthy individuals. Since ours is an early psychosis sample, this could be a potential neural

marker for Schizophrenia risk. The fact that the neural responses were significantly correlated with BLS codes underscores the ecological validity of our study. Since this links a real-world dysfunction with a neural response, neuromodulatory techniques targeting RTPJ may prove beneficial for social cognitive deficits in FEP.
This is the first study evaluating the neural responses of live emotive face gaze in FEP using FNIRS and facial classification. Future directions could include studies with larger samples, neuromodulatory trials and examining if similar findings are present in other disorders with social dysfunction, like autism spectrum disorder.

## M74. The Potential of AI for Scale Development: A Self-Report Psychosis Symptoms Measure Using ChatGPT

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**BACKGROUND:** Schizophrenia is a chronic condition marked by significant personal and societal burdens, necessitating reliable and cost-effective tools for symptom assessment. Traditional clinician-administered scales, such as the Positive and Negative Syndrome Scale (PANSS), are time-intensive and require specialized training, limiting their routine use in clinical practice. This study addresses these challenges by developing a brief, self-report psychosis measure using ChatGPT, an AI language model, to enhance accessibility and scalability in psychosis assessment.

**METHODS:** Participants for this study are being recruited from the Specialized Treatment Early in Psychosis (STEP) clinic in Connecticut. Eligible participants are aged 16–35 and experiencing first-episode psychosis (FEP) within three years of onset. The ChatGPT self-report psychosis scale assesses four dimensions—hallucinations, delusions, disorganized thinking, and impaired insight—each measured by three items designed to ensure high internal consistency and discriminant validity. While the self-report scale is administered online, the PANSS is conducted with patients by trained raters.
Psychometric properties of the self-report measure will be rigorously evaluated. Internal consistency will be assessed for each dimension, while construct validity will be examined through factor analysis. Criterion validity will be established by comparing self-report scores with PANSS ratings. Receiver Operating Characteristic (ROC) analyses will evaluate the sensitivity and specificity of the self-report scale in detecting varying severities of psychotic symptoms. Additionally, the study will investigate the role of insight, as measured by PANSS, in any discrepancies between self-reported and clinician-rated symptoms.

**RESULTS:** Eighteen participants have been recruited, with data collection ongoing. Preliminary findings indicate moderate alignment between self-reported and PANSS measures. Self-reported hallucination items show significant moderate correlations with PANSS (P3), while delusion items demonstrate moderate to strong alignment with PANSS (P1), including significant correlations. In contrast, disorganization items exhibit weak to moderate, non-significant correlations with PANSS (P2), suggesting limited alignment. Insight items show weak to moderate negative correlations with PANSS (G12). Due to the small sample size, interpretations

at this stage are limited; however, we aim to have 35 participants by the time of the conference, enabling us to present comprehensive results.
**DISCUSSION:** This study represents an innovative step in integrating AI into psychometric tool development for psychosis. Findings will provide insights into the efficacy of generative AI in creating cost-effective, scalable measures, with implications for improving early detection, monitoring, and management of psychotic symptoms across diverse clinical settings.

### M75. Rationale and Preliminary Findings for Strength-Based, Developmentally-Guided Modifications to Early Intervention Services for First Episode Psychosis

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**BACKGROUND:** Internationally-conducted randomized controlled trials (RCTs) demonstrate early intervention services (ElS) following a first episode of psychosis (FEP) enhance indices of recovery. ElS, however, consistently benefited only about 10% of FEP patients vs. usual care (UC), much fewer than the 30 to 40% needed to assure implementation. ElS evolved from evidence-based therapies for older disabled psychotic patients, whereas the primary goal of EIS and of FEP patients is to prevent disability? Secondary analyses indicate refocusing ElS on engagement, individualized steps to achieving patient goals, promoting developmental milestones and work/school participation could boost and extend benefits.
**METHODS:** A multi-step developmentally-informed approach to recovery was adopted by Northwestern Medicine's Recovery from Early Psychosis Program (REPP). Treatment was guided by occupational therapy-derived goals and evolving individualized treatment plans focused on assessing patient interests and increasing their capacity to assume adult responsibilities. Work and school participation was our primary outcome. Secondary outcomes were hospitalization, dropouts, and global functioning. Results were compared to functional outcomes of historical controls (2176 EIS and UC subjects of 10 RCTs).
**RESULTS:** Work and school participation increased by 75% (95% Cl: 88%, 62%) in REPP subjects. 38% and 45% benefited relative to ElS (NNT=2.6; Cl: 1.9,4.0), UC controls (NNT 2.2, Cl =1.7, 3.1), respectively. Findings could not be accounted for by baseline group differences assessed with regression/meta-regression analyses. Benefits for secondary outcomes were significantly greater for REPP than UC controls, and greater, but not significantly so, compared to ElS controls.
**DISCUSSION:** Preliminary results support the possibility that refocusing ElS to promote patient goals enhances work and school participation to levels that can help assure broader ElS implementation as an evidence-based intervention.

### M76. A Latent Profile Analysis of Psychosis Symptoms Among Individuals in an Early Phase of Psychosis Illness: Examinations of Distress and Depression as Pathways to Suicide Ideation

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**BACKGROUND:** Suicide rates are high among individuals in first episode psychosis and there is a critical need to better understand drivers of suicide risk to inform treatment efforts. This study identified profiles of psychosis symptoms and examined a mediation model of depression and distress as mechanisms in the relationships between psychosis symptoms and suicide ideation by latent profiles.
**METHODS:** Data were obtained from the Human Connectome Project for Early Psychosis (n=169) of individuals between 16 and 35 years of age who had onset of affective or non-affective psychosis within 5 years of consent. Data were analyzed using Latent Profile Analysis (LPA) and Structural Equation Modeling in MPlus.
**RESULTS:** LPA revealed the following groups: (1) relatively lower and more balanced levels of symptoms, (2) highest positive and general symptoms, and (3) highest negative symptoms. Findings indicated the relationships in the model differed between by LPA groups. Distress and depression functioned as mediators between psychosis symptoms and suicide ideation for Groups 1 and 2.
**DISCUSSION:** A better understanding of the roles that distress and depression play in the relationships between psychosis symptoms and suicide ideation can help inform modifiable targets of early intervention and subsequently decrease risk for suicide.

## M77. Cognitive and Clinical Profiles in First-Episode Psychosis and Their Relationship to Functional Outcomes Over Time

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**BACKGROUND:** Cognitive impairment is a core feature of psychosis. However, previous findings suggest that significant heterogeneity in cognitive and clinical outcomes exists in first episode psychosis (FEP). The aim of this study was to identify cognitive and clinical subgroups in FEP and determine if these profiles were linked to functional outcomes over time.
**METHODS:** 323 individuals with FEP were included. Two-step hierarchical and k means cluster analyses were performed using baseline cognitive and clinical variables. General linear mixed models were used to investigate whether baseline cognitive and clinical clusters were associated with functioning at follow-up time points (6-9, 12 and 15 months).
**RESULTS:** Three distinct cognitive clusters were identified: a cognitively intact group (N=59), a moderately impaired group (N=77), and a more severely impaired group (N=122). Three distinct clinical clusters were identified: a subgroup characterised by predominant mood symptoms (N=76), a subgroup characterised by predominant negative symptoms (N=19), and a subgroup characterised by overall mild symptom severity (N=94). The subgroup with more severely impaired cognition also had more severe negative symptoms at baseline. Cognitive clusters were significantly associated with later social and occupational function, and associated with changes over time. Clinical clusters were associated with later social functioning but not occupational functioning, and were not associated with changes over time.

**DISCUSSION:** Cognitive and clinical cluster analyses suggest those with the largest cognitive impairments and negative symptom severity are at higher risk for functional disability. Cognitive clusters at baseline were associated with both social and occupational functional outcomes at follow up time points, suggesting that identification of cognitive profiles at service entry can offer valuable information in terms of prognosis and treatment needs.

## M78. What Program-Level Factors and Strategies Improve Patient and Family Engagement in First-Episode Psychosis Coordinated Specialty Care?: A Mixed Methods Study

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**BACKGROUND:** Poor treatment engagement of individuals with first-episode psychosis (FEP) and their families adversely impacts the effectiveness of early intervention services. This study examined modifiable program-level determinants and engagement strategies associated with patient retention and family engagement across FEP coordinated specialty care (CSC) programs in Massachusetts.

**METHODS:** Out of the total number of active patients in their program from October 2022 to September 2023, program leaders reported the number of patients who prematurely discontinued services and number of families who participated in at least one session of any type of family intervention (e.g., family psychoeducation, multifamily group, family peer support). Program characteristics (EPINET Program-Level Core Assessment Battery) and independent-assessor ratings on an adapted version of the FEP Services Fidelity Scale 2.0 were explored as predictors of patient retention and family engagement rates using independent t-tests or univariate linear regressions. Group interviews with each program were thematically analyzed to identify successful engagement strategies programs used to retain patients and involve families in treatment.

**RESULTS:** Across nine participating programs (N=43 interviewed providers), mean patient retention rate was 86% (SD: 13) and family engagement rate was 40% (SD: 27). Higher overall fidelity in providing evidence-based family interventions had a significant, large, positive effect on patient retention (B (SE)=11.5 (2.7); AR2=.68, p=.004). Fidelity to family interventions was not associated with family engagement rates. Higher overall fidelity to recommended outreach and engagement practices (e.g., proactive outreach, flexible hours and location, shared decision making) had marginally significant positive effects on family engagement rates (B (SE)=19.8 (10.5); AR2=.24; p=.10), but not on patient retention rates. Congruent with quantitative findings, interviews highlighted several strategies that programs used to create more opportunities for and overcome barriers to patient and family treatment engagement, including: 1) conducting a program orientation with equal prioritization of all CSC elements during intake, 2) providing a range of recovery-oriented services beyond standard CSC elements (e.g., peer support, family partner/navigator, family support/educational groups, case management, milieu environment), 3) engaging in varied modes of treatment delivery (e.g., home/in-person community visits, family-

friendly office hours), and 4) holding frequent treatment reviews with patients and their families to encourage participation in underused CSC services.
**DISCUSSION:** Quantitative and qualitative results from Massachusetts FEP CSC programs underscore importance of delivering high-fidelity, evidence-based services and employing comprehensive yet flexible strategies for better patient and family engagement. Identified engagement strategies, ranging from diverse service offerings, modalities, and intake and treatment review procedures, provide actionable insights for improving patient and family engagement in first-episode psychosis care.

## M79. Genetic Susceptibility Across the Psychosis Continuum: Insights From Polygenic Scores

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**BACKGROUND:** The psychosis continuum model conceptualizes psychotic symptoms as existing on a spectrum, ranging from normal experiences to severe psychotic disorders. Evidence across this continuum reveals sociodemographic, cognitive, and neuroimaging similarities between subclinical and clinical states, highlighting shared risk factors and underlying aetiology. Genetic studies have provided mixed evidence, where some have found the genetic risk for schizophrenia and other mental disorders to be significantly associated with the development of psychotic experiences in the general population, while others have failed to replicate these findings. Additionally, the psychosis continuum challenges the traditionally categorical diagnostic framework, supporting a dimensional, transdiagnostic perspective.
Clinically, psychotic symptoms can present in diverse psychiatric disorders including but not limited to schizophrenia, bipolar disorder, and major depressive disorder (MDD). Genetic studies further substantiate this overlap, linking psychotic experiences to genetic risk for all three disorders and pointing to shared underlying biological mechanisms.

This study investigates the genetic risk for schizophrenia, bipolar disorder and MDD across the psychosis continuum to understand genetic contributions to psychosis dimensionally: across stages of psychosis and across psychiatric disorders.

**METHODS:** This study leveraged data from five samples recruited in South London. The psychosis continuum was defined as 0) controls that have not been diagnosed with psychotic disorder (n=606), 1) individuals that self-reported one or more psychotic experience in the past year using the Psychosis Screening Questionnaire (n=88), 2) those at clinical high-risk that did not convert to psychosis after 2-years follow up using the Comprehensive Assessment of At-Risk Mental States (n=139), and 3) individuals diagnosed with first episode psychosis (FEP) (n=427). Individual and combined effects of genetic risk for psychiatric disorders on the psychosis continuum were analysed using ordinal logistic regressions. ANOVAs were fit to explore pairwise differences in genetic risk between clinical stages.
**RESULTS:** Genetic liability for all three psychiatric disorders were significantly associated with the psychosis continuum in individuals of European ancestry. Among them, schizophrenia

polygenic scores explained the largest variance ($R^2$=0.085). Adding multiple psychiatric disorders into one model increased the variance explained by the model ($R^2$=0.104). Genetic liability for schizophrenia followed a gradient across stages, with clinical high-risk individuals who did not convert to FEP showing intermediate scores—significantly higher than controls and lower than those with FEP. In line with previous studies showing lower predictive power of polygenic scores in non-European samples, analyses in individuals of African ancestry were non-significant, highlighting the need for better representation of globally diverse population in genetic studies.
**DISCUSSION:** The findings support the psychosis continuum model, demonstrating shared biological mechanisms underlying psychotic symptoms across subclinical and clinical stages. Further, they support a dimensional, transdiagnostic perspective, showing that genetic risk for multiple disorders are associated with the psychosis continuum. The significant difference in genetic risk between high-risk populations that did not advance to FEP and those with established psychotic disorder shows potential for clinical utility in aiding diagnostic stratification and resource allocation in early interventions for psychosis.

## M80. Genome-Wide Association Analysis of Social Participation and Occupational Engagement in the UK Biobank

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**BACKGROUND:** Psychosis is a leading cause of disability worldwide. Although generally characterised by hallucinations and/or delusions, psychosocial disability(PD) in the form of impaired social participation(SP) and occupational function(OF), is also a key feature. While several environmental and cognitive factors have been identified as predictors of PD, the biological contribution to PD remains unclear. Here, we sought to identify genetic determinants of variability in SP and OF in the UKBiobank(UKB).
**METHODS:** SP(N=404,403) was defined as a summed index of responses from frequency of friend and family visits and leisure/social activity questionnaires from UKB. OF was derived from individual employment status response(N=405,569). Mixed-linear-model genome-wide association (GWA) analysis was conducted on all phenotypes using fastGWA.
**RESULTS:** GWA analysis of SP and OF revealed 17 and 1 independent loci respectively. Gene-based FUMA analysis of SP indicated 17 significant gene-phenotype associations at a Bonferroni correction threshold ($p < 2.62e-6$). The top genes identified for SP include CDH7(p=5.57e-12), GBE1(p=5.90e-11), and ZNF536(p=1.20e-10). Tissue expression analysis revealed brain tissues, including cerebellar, frontal lobular, and amygdalar were most specific to implicated genes in SP. Genetic correlations showed that lower SP was associated with increased risk for schizophrenia, socioeconomic deprivation, and loneliness.
**DISCUSSION:** Our findings propose that SP has a stronger genetic component than OF in a healthy population. Of the tissues implicated in this analysis, both the amygdala and frontal lobe have been linked to social behaviours in previous neuroimaging research. Overall, we outline genetic loci and tissue types with possible roles in PD and phenotypes with a shared genetic basis.

## M81. Aspects of Cognitive Control Related to Polygenic Risk for Schizophrenia

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**BACKGROUND:** Schizophrenia spectrum disorders are associated with impairments in cognitive control. Trial-level analyses of responses on cognitive control tasks using drift diffusion modeling (DDM) have shown that people with psychosis (PwP) display slower drift rate and longer non-decision time in comparison to unaffected controls indicative of slowed perceptual and information processing in determining a response. To investigate what aspects of cognitive control deficits are associated with additive genetic risk for schizophrenia, we computed polygenic risk scores (PRSs) for a sample of individuals with a history of psychotic symptomatology (schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis), their first-degree biological relatives, and healthy controls, and examined associations of PRSs with DDM parameters derived from responses during the Dot Pattern Expectancy (DPX) task.
**METHODS:** Data for this preliminary analysis were derived from three family studies of severe psychopathology at the Minneapolis VA Health Care System and included 36 probands with a history of psychotic symptomatology (PwP); 35 first-degree relatives of PwP; and 33 healthy controls with no family history of psychosis. Hierarchical DDMs were fitted to DPX task data for each group (proband, relative, control) using the HDDM 0.9.1 Python package. Biospecimen samples were genotyped using Illumina PsychArray microarrays and their data were imputed using the TOPMed Imputation Server. PRSs were calculated with the Psychiatric Genomics Consortium Wave 3 Schizophrenia GWAS using Plink. We carried out linear regression analyses to test if PRSs explained any of the variability in drift rate and non-decision time for all trial types (AX, AY, BX, BY), as well as conventional measures of cognitive control (BX trial errors, proactive behavioral index [PBI-RT]).
**RESULTS:** Linear regression analyses of BX errors and PBI-RT failed to yield any associations with PRSs; however, select DDM parameters were associated with polygenic risk for schizophrenia. Specifically, analyses revealed that PRS was positively correlated with non-decision time for BX ($t(102) = 1.99$, $p = 0.049$) and BY ($t(102) = 2.13$, $p = 0.035$) trials. Additionally, PRS was negatively correlated with the drift rate of BY trials ($t(102) = -2.30$, $p = 0.023$). PRS also showed a similar negative trend with the drift rate of AY trials ($t(102) = -1.70$, $p = 0.092$).
**DISCUSSION:** The current investigation provides evidence that select subprocesses of cognitive control map onto additive genetic contributions to schizophrenia. Greater genetic risk for schizophrenia was associated with protracted perceptual processing (i.e., non-decision times) and slower information processing (i.e., drift rate) during proactive and reactive control. A negative trend between PRS and drift rate for AY trials raises the possibility of additional evidence for additive genetic risk being related to reactive control deficits. Overall, findings support the idea that additive genetic contributions to schizophrenia are associated with select perceptual and information processing deficits that contribute to impairments in proactive and reactive cognitive control. Results also suggest that trial-level characterization of cognitive control is necessary to capture elements of cognitive control related to genetic risk for

schizophrenia. These findings will be tested for replication in an analysis of an independent sample of similar size.

## M82. FOXP1 Dysregulation and its Association With Schizophrenia and Cognitive Function

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**BACKGROUND:** Rare mutations in FOXP1 (Forkhead-box protein P1), a transcription factor crucial for cortical neural development, cause FOXP1 syndrome, characterized by developmental delays, intellectual disability, with or without autistic features. Common SNPs in the gene are associated with schizophrenia (SCZ) and cognitive function. This study explores FOXP1's contribution in these conditions using RNA-seq data from FOXP1 knockout (KO) models, including neural stem cells from embryonic mice and human brain organoids, and cortical tissues from different postnatal stages; postnatal day 0 (P0), P7, and P47.
**METHODS:** For these prenatal and postnatal FOXP1 KO models, FOXP1 function had previously been disrupted in the cortical tissue/cells and gene expression assayed using RNA-seq. We performed pairwise comparisons and time-course expression analysis on the RNA-seq data. Linkage disequilibrium score regression was used to determine if differentially expressed genes (termed gene-sets) were enriched for heritability related to SCZ and cognitive function. To identify the affected cell types by FOXP1 KO and its association with SCZ, gene-set enrichment analysis was conducted using data on SCZ-associated gene-sets generated from snRNA-seq analysis of the port-mortem samples from the cortical region from SCZ patients with controls. SynGO analysis was performed to identify FOXP1 KO impacts on genes enriched in presynaptic and postsynaptic components.
**RESULTS:** Our findings show that FOXP1 gene-sets across all stages are enriched for SNP-based heritability related to cognitive function. Most FOXP1 gene-sets are enriched for SCZ heritability, with the highest enrichment at the P7 stage followed by P47 stage. Gene-set from P7 exhibits the broadest enrichment for SCZ-related genes across various cortical cell types. Both FOXP1 gene-sets from later stages of development (P7 and P47) were enriched mainly within glutamatergic excitatory neurons, with P47 also showed enrichment for GABAergic inhibitory neurons across regions of the prenatal and postnatal cortex. These stages exhibited a significantly stronger association with both pre- and postsynaptic components and biological processes compared to the earliest postanal stage (P0).
**DISCUSSION:** FOXP1 disruption affects genes linked to SCZ risk and cognitive function, influencing different cortical cell types and synaptic signaling. The genetic risk for SCZ associated with FOXP1 displays a dynamic trajectory across developmental stages. FOXP1 regulates distinct gene sets at various points in development, with its impact being relatively minor during prenatal and perinatal stages and more significant during childhood and adolescence.

**M83. Elevated Polygenic Risk Score in Patients and Their Non-Affected Relatives in Multigenerational Families Affected by Schizophrenia and Bipolar Disorder in the Quebec Founder Population**

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**BACKGROUND:** Over the past two decades, there has been a notable shift in focus from family studies to genome-wide association studies (GWAS) in large samples of unrelated patients and controls. As a result, little is known about the transmission of PRS among highly familial cases of schizophrenia (SZ) or bipolar disorder (BP) and sporadic cases. Our prior research, along with others, has shown that polygenic risk scores (PRS), which sum the small effects of millions of genetic variants identified in GWAS, are elevated in both patients and young individuals at familial risk for BP and SZ. This raises the question of how elevated PRS would be transmitted across generations and along which mode.
In affected multigenerational families, our objective was first to test whether elevated PRS can be observed in such families and along what transmission architecture. First, we sought to distinguish the predictive power of the PRS for different groups of non-affected adult relatives (NAARs). In a subsequent phase, the objective is to characterize the PRS transmission among the generations of densely affected families and to differentiate its within- and between-family effects.

**METHODS:** We genotyped 1177 participants divided in 48 families from the Eastern Quebec Schizophrenia and Bipolar Disorder Kindreds (DSM-IV BP n=208; SZ n=128). Of these, 677 genotyped-only participants were imputed (combination of family- and population-based methods) using the whole genome sequences of the other 500 participants and of 1,886 subjects of European ancestry from the Québec CARTaGENE (CaG) population panel. After quality control, 3,716,258 autosomal SNPs were also reported in the most recent Psychiatric Genomics Consortium BP and SZ GWAS. PRSs for both SZ and BP were computed using the Multivariate Lassosum software, which employs a penalized regression framework, leveraging the well-established genetic correlation between the two traits. We compared the PRS distributions of BP and SZ to those of CaG and to the ones of their NAARs stratified by the presence or not of other non-mood non psychotic DSM-IV diagnoses. We employed logistic regressions with generalized estimating equations, to account for familial structures, to estimate odds ratios (OR) of these disorders for an increase of 1 PRS standard deviation. Analyses were corrected for sex and population structure using principal component analysis.
**RESULTS:** BP and SZ PRSs distinguished patients from NAARs(OR BP=2.12, 95%IC=[1.7-2.6], p=5.3x10-11; OR SZ=1.78, 95%IC=[1.4-2.2], p=2.4x10-7). It is noteworthy that these results remained regardless of the presence of other DSM-IV diagnoses. Patients and NAARs presented higher SZ PRS compared to the CaG control panel (OR patients=2.57, 95%IC=[2.0-3.2], p=2.9x10-15; OR NAARs=1.55, 95%IC=[1.3-1.9], p=7.8x10-5). The results did not significantly differ when stratifying by sex. We also examined segregation to assess how family structures impact the PRS transmissions.
**DISCUSSION:** This study reinforces the importance of family-based genetic and genomic research in psychiatry. Consistent with prior findings, we reaffirm the importance of PRS in multigenerational families for both BP and SZ patients. Notably, we also demonstrate that

NAARS exhibit higher PRSs compared to population controls, irrespective of whether they report other mental health vulnerabilities. This suggests that the mechanisms underlying PRS are shared among members of multigenerational families, regardless of the presence of SZ, BP or other psychiatric conditions. These findings support the need to explore additional familial genetic susceptibilities and possibly integrate PRSs with rare variant studies.

## M84. Incidence of Non-Affective Psychotic Disorders Among First- and Second-Generation Migrant Groups in Canada: New Findings From a Population-Based Birth Cohort

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**BACKGROUND:** Migration is a risk factor for psychotic disorders, with persistence of risk into the second generation; however, there has been a lack of evidence from a Canadian context, particularly for second-generation migrants. We sought to examine the risk of psychotic disorder among migrant groups in Ontario (Canada), and explore the role of region of birth, generation status, and migrant class.

**METHODS:** We constructed a retrospective birth cohort using health administrative data, which included 560,262 children born in Ontario between 1992 and 1996 and followed to age 25-30 years. Linkages with immigration data and hospital birth records allowed us to identify first- and second-generation migrants. We estimated incidence rate ratios (IRR) and 95% confidence intervals (CI) for the association between migrant status and the incidence of non-affective psychotic disorder.

**RESULTS:** The risk of psychotic disorder among first-generation migrant groups was lower than the Canadian-born population (IRR = 0.64, 95%CI = 0.80, 0.94), with no difference in risk for second-generation migrants (IRR = 0.97, 95%CI = 0.92, 1.03). However, we found distinctive patterns of risk by region of birth, with both first- and second-generation migrants from Africa and the Caribbean having elevated rates of psychotic disorder.

**DISCUSSION:** Our population-based health administrative datasets that include migrants from a wide range of countries have produced the first Canadian evidence on psychosis among second-generation migrant groups. Our unique migration context can inform international efforts to ameliorate known disparities for migrant groups with psychosis.

## M85. Clinician-Reported Impact of Tardive Dyskinesia in Individuals who Were not Using a VMAT2 Inhibitor: Interim Analysis of the Impact-TD Registry

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**BACKGROUND:** Tardive dyskinesia (TD) can have a profound negative impact on an individual's daily functioning and may lead to negative physical, cognitive, and psychosocial outcomes. Current American Psychiatric Association guidelines for treating schizophrenia recommend the use of vesicular monoamine transporter 2 (VMAT2) inhibitors as first-line

treatment for individuals who have moderate to severe or disabling TD. The current analysis examines the impact of TD in individuals with TD symptoms who were not receiving VMAT2 inhibitor treatment at baseline.
**METHODS:** The IMPACT-TD Registry, an ongoing, phase 4, 3-year longitudinal study with visits every ≈3 months, includes individuals aged ≥18 years with a score of ≥2 on at least one item of the Abnormal Involuntary Movement Scale (AIMS) and with probable TD or, alternatively, who are receiving treatment with a VMAT2 inhibitor. No formal TD diagnosis is required; clinicians report whether the included individual has a formal diagnosis of TD. TD severity was assessed by AIMS scores, and multidimensional impact of TD was assessed with the clinician-reported IMPACT-TD (ClinRO) scale. This interim analysis includes those enrolled in the IMPACT-TD Registry as of December 31, 2023, who were not receiving VMAT2 inhibitor treatment at baseline.
**RESULTS:** Among 286 individuals included in the IMPACT-TD Registry at the time of this interim analysis, 208 (72.7%) were not receiving VMAT2 inhibitor treatment at baseline. In this subgroup, mean (SD) age was 50.0 (15.3) years, most (83.2%) individuals were aged < 65 years, 54.3% were male, 47.6% were White, 25.5% were Black/African American, and 33.2% were Hispanic/Latino. The majority (89.4%) of individuals in this population reported a history of antipsychotic (AP) use, most commonly second-generation APs and beyond (58.2%). The most common baseline psychiatric diagnoses were bipolar disorder (44.4%), depression (37.7%), and schizophrenia (36.7%). Median time since TD movements were first recognized was 5.5 years, yet the majority (74.5%) of individuals did not have a formal TD diagnosis, and 88.9% had never tried any TD treatment for their symptoms. Among individuals in this population, 190 had AIMS scores recorded (AIMS score: 0–6, 46.8%; 7–14, 44.7%; ≥15, 8.4%), with a mean (SD) total motor AIMS score of 8.0 (4.6). ClinRO scores were available for 191 individuals, with 99.0% experiencing some impact (mild/moderate/severe) in any domain of the ClinRO assessment. In each ClinRO domain, most individuals experienced at least mild impact of TD (social, 93.7%; psychological/psychiatric, 92.1%; physical, 94.8%; vocational/educational/recreational domain, 86.9%). Moderate/severe global ClinRO scores were seen in 84.3% of individuals, with the highest rate of moderate/severe impact on individual domains seen in the psychological/psychiatric domain (73.3%).
**DISCUSSION:** In this real-world study, most individuals who were not receiving a VMAT2 inhibitor did not have a formal TD diagnosis, despite 5.5 median years since TD movements were first recognized, suggesting that clinicians may wait to diagnose people with TD until they are preparing to prescribe a medication to treat TD symptoms. Most individuals without VMAT2 inhibitor treatment at baseline experienced some impact of TD in any domain, with high rates of moderate/severe impact in the psychological/psychiatric domain, indicating that clinicians may not be factoring impact when making decisions about diagnosis and treatment. These findings merit further investigation into how factors such as age, sex, race, underlying condition, and severity of movements contribute to diagnosis and treatment patterns.

## M86. A Non-Interventional Observational Study to Describe Demographic and Clinical Features of Patients With Negative Symptoms in Schizophrenia

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**BACKGROUND:** Schizophrenia is marked by positive and negative symptoms and cognitive impairment. The clinical course typically includes periods of relapsing psychosis and periods where patients experience a reduction of these symptoms. Negative symptoms may be experiential or expressive and are associated with poor clinical and functional outcomes, contributing to the emotional and socioeconomic burden associated with schizophrenia. In this study, we describe clinical and demographic characteristics of patients with schizophrenia who are in a stable phase related to positive symptoms and antipsychotic medication with or without negative symptoms.

**METHODS:** This observational study used electronic health records available in the NeuroBlu v23r6 database. Adult patients with a schizophrenia diagnosis were included. Two definitions of stability were considered: no documented evidence of positive symptoms (cohort 1) and presence of a stable antipsychotic treatment regimen (cohort 2). Evidence of negative symptoms was identified via mental state examination (MSE) data. Patients were categorized as having negative symptoms if ≥1 MSE label indicative of negative symptomatology was present. Demographic and clinical characteristics at the point of first recorded schizophrenia diagnosis and stability were described (index date). Baseline period was the index date ±14 days.

**RESULTS:** Overall, 5918 and 1470 patients were identified with schizophrenia in a stable phase in cohorts 1 and 2, respectively. Mean (standard deviation [SD]) age was 45.8 (16.3) and 45.1 (15.6) years, and 60.8% (n=3596) and 59.2% (n=870) were male. Index visit occurred in outpatient (cohort 1: 44.2%; cohort 2: 67.3%), inpatient (21.8%; 21.1%), and emergency settings (32.3%; 9.8%). Evidence of negative symptoms was seen in 2161 (36.5%) and 698 (47.5%) of patients in cohorts 1 and 2. Of these, expressive negative symptom features were seen in 1800 (83.3%) and 610 (87.4%) patients and experiential negative symptom features were seen in 1034 (47.8%) and 352 (50.4%) patients. Frequency of negative symptoms was similar in males and females (36.6% vs 36.3%) in cohort 1 but higher in males in cohort 2 (51.1% vs 42.2%). Patients with negative symptoms were more likely to have cognitive impairment (cohort 1: 57.3% vs 22.5%; cohort 2: 74.1% vs 25.4%) and antipsychotic polypharmacy at baseline (23.2% vs 17.6%; 18.6% vs 12.3%). In cohort 1, negative symptom frequency was similar in patients receiving long-acting injectable (LAI; 37.5%) and oral (36.6%) antipsychotics; in cohort 2, patients on LAIs (58.9%) had a greater negative symptom frequency than those on oral antipsychotics (47.2%). Patients with negative symptoms more frequently had comorbid psychiatric diagnoses (cohort 1: 71.4% vs 65.8%; cohort 2: 69.5% vs 59.2%) and a non-antipsychotic pharmacological prescription (87.4% vs 79.6%; 81.5% vs 76.4%). Substance use disorder was the most common comorbid psychiatric diagnosis and was more common in patients with negative symptoms (cohort 1: 38.3% vs 33.8%; cohort 2: 32.8% vs 22.2%). In cohort 1, patients with negative symptoms were more frequently seen in inpatient settings (25.7% vs 18.2%) and emergency settings (38.6% vs 28.6%); in cohort 2, patients with negative symptoms were more frequently seen in inpatient settings (25.5% vs 16.6%).

**DISCUSSION:** Patients with schizophrenia in a stable phase with negative symptoms had greater cognitive impairment at index and had evidence of increased number of prescribed antipsychotics, a higher number of psychiatric comorbidities, and greater acute healthcare burden than those without negative symptoms.

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## M87. What is the Efficacy of the Major Psychiatric and General Medicine Treatments: An Umbrella Review

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**BACKGROUND:** Understanding the efficacy of psychiatric drugs is crucial for improving treatments, especially considering the increasing global burden of mental disorders. Integrating psychiatric medications into mainstream general medical practice enhances treatment effectiveness and public awareness. With medicine becoming increasingly specialized, few psychiatrists are well-versed in evidence concerning both general medicines and psychiatric drugs. For example, how do schizophrenia drugs compare to the many effective medical medications? A pervasive distrust of psychiatry has emerged due to reports suggesting minimal efficacy of psychiatric drugs. In fact, the efficacy of psychiatry drugs is far undervalued compared with the general medicines(Leucht S, et al. Br J Psychiatry. 2012). Against this backdrop, we conducted a new update review to assess the efficacy of psychiatric pharmacotherapy in the context of standard medical drugs, marking the comprehensive attempt to provide an overarching view of major drugs.
**METHODS:** We included systematic reviews with meta-analysis of randomised controlled trials (RCTs) in the form of pairwise meta-analysis, individual-patient-data meta-analysis or network meta-analysis. We searched Pubmed and the Cochrane Library for meta analysis and systematic reviews on the efficacy of drugs compared with placebo/control for major medical diseases(according to the WHO disease burden) and psychiatric disorders from May 2009 to October 2023. The following medical diseases will be addressed: hypertension, myocardial infarction, chronic heart failure, stroke, chronic hepatitis C, multiple sclerosis, back and neck pain, lung cancer, diabetes, Covid-19, pneumonia, chronic obstructive pulmonary disease and cystitis. And we selected the following major psychiatric disorders listed in DSM-5 or ICD-10/11: schizophrenia, bipolar disorder, major depressive disorder, obsessive compulsive disorder, panic disorder, generalised anxiety disorder, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), insomnia disorder, alcohol dependence and Alzheimer's disease. For participants, to enhance generalisability, we chose meta-analyses which included broad populations (usually adults). For Interventions, We identified the major pharmacological treatments for the chosen diseases using "UpToDate" which is a recognised source of evidence. For reasons of generalisability we chose broad meta-analyses, i.e. we prefered meta-analyses of drug classes rather than single agents. For comparators, control conditions are placebo or no treatment. For continuous outcomes we mainly extracted effect sizes, presented both as differences in original units (mean difference) and as standardised mean differences (SMD). For dichotomous outcomes we mainly presented the percentage of participants improved in the drug and placebo groups, the absolute risk/response

difference(ARD); the relative risk reduction or relative response ratio(RR or RRR). The data which were not reported in the studies, we transformed the existing data with appropriate formula, or we recalculated meta-analyses by entering single study results using Review Manager or R.
**RESULTS:** We ultimately included medications for 11 psychiatric disorders and 13 medical disorders.The psychiatric drugs were not generally less efficacious than other medical drugs, even some psychiatric drugs are very effective. Since it is not possible to show a complete chart here, here are only some examples of disease data. For example, our result shows that for the acute treatment of schizophrenia, antipsychotics increased the percentage responding from 30% with placebo to 51.9%(ARD 21%, RR 70%). Antipsychotic maintenance treatment reduced schizophrenia relapse rates from 60.3% to 23.9% within approximately 29 weeks (ARD 36.4%, RRR 60%). In obsessive compulsive disorder, SSRIs (SMD 0.51) showed good effect sizes by Yale Brown Obsessive Compulsive Scale (YBOCS) scoring reduction of obsessive compulsive disorder symptoms. In prevention of cardiovascular events, Aspirin reduced such events from 5.0% to 4.8% (ARD 0.2%, RRR 4%). Statins(SMD 1.23) showed robust effect sizes in overall reduction of Low-density lipoprotein(LDL).
**DISCUSSION:** Our results so far show that the differences between psychiatric drugs and placebo compared with general medicines and placebo are smaller than expected. Among the data, Schizophrenia medications are more effective than many general medical drugs. Comparing treatments across various diseases is inherently qualitative, thus, our data help place psychiatric drugs within the broader context of general medical treatments. While certain general medical drugs exhibit high effect sizes, psychiatric medications typically demonstrate effect sizes comparable to most general medical pharmacotherapies. However, the degree of improvement achieved with a drug should also be interpreted considering factors such as disease severity, associated suffering, specific outcomes measured, societal values, and the natural progression and duration of the illness.

## M88. Antipsychotic Effects on Cognitive Functioning Emerge After the First Decade of Treatment: A Cross-Sectional Analysis of Treated vs Never-Treated Schizophrenia Across Early and Chronic Stages in China

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**BACKGROUND:** Clinical trials suggest antipsychotic (AP) treatment provides modestly improved cognitive functioning among individuals with schizophrenia (IWS). However, cognitive impairment may worsen in never-treated IWS in the later stages of illness ( > 10 years), particularly in low- and middle-income countries (LMICs), due to the combined effects of aging and prolonged untreated illness. In this context, AP treatment could mitigate cognitive decline that may otherwise worsen over time. Leveraging a unique sample from rural China, this study compares cognition among a community-sample of chronic, treated IWS vs. never-treated

IWS to assess AP treatment effects on cognition and whether this varies by duration of illness (DOI).
**METHODS:** The Flexible Adapted Cognitive Test battery for Schizophrenia (FACTS), tailored for older, under-educated IWS, was administered to 134 treated and 134 never-treated IWS, matched on gender, age, ethnicity, education, urban/rural residence, and DOI. The sample included 95% rural residents and 60% females, with a mean age of 49.2 years, 4.2 years of education, and a mean DOI of 20.5 (SD = 12.5) years. Domain-level T scores for: a) speed of processing (SpProc); b) attention/problem-solving (Att/Prob), and c) learning, were normed using matched healthy controls and then demographically-adjusted. Group differences in the standardized effect size of domain T scores were examined using a regression model with treatment status (treated vs. untreated), DOI epoch (i.e., 1-9, 10-19, 20-29, and 30-50 years), and their interaction, as predictors. Regression coefficient contrasts tested group differences across DOI epochs. Analyses controlled for positive and negative symptoms.
**RESULTS:** Differences between treated and untreated IWS were found only in the 10-19 year DOI epoch, where never-treated IWS showed significantly poorer performance in SpProc (M group difference = 0.55, SD = 0.23; t[258] = 2.36, p = 0.02) and trend-level differences in Att/Prob (M group difference = 0.42, SD = 0.23; t[258] = 1.79, p = 0.07). The significant interaction between DOI and treatment status for the 1-9 year vs. 10-19 year epochs reveals that performance among IWS with 10-19 years DOI diverged significantly from those observed in the 1-9 year DOI group, with significant effects for SpProc (p = 0.01) and trend-level effects for Att/Prob (p = 0.08). Thus, while treated IWS showed improvements in cognition between the 1-9 year and 10-19 year epoch; untreated IWS showed greater impairments in the 10-19 year epoch compared to the 1-9 year epoch. In contrast, cognitive performance patterns among treated vs. untreated IWS in the later stages of illness (30-50 years DOI) showed no differences, suggesting a diminished AP treatment effect beyond the third decade of illness.
**DISCUSSION:** Cognitive differences by treatment status were not evident in the early stages of illness (1-9 years DOI) and only emerged in the 10-19 year DOI epoch, particularly in the area of SpProc, with trend effects observed for Att/Prob. This is further supported by the significant interaction between early (1-9 years) and mid-stage (10-19 years) epochs and treatment status on cognitive performance. However, AP treatment does not appear to mitigate cognitive impairments as DOI progresses beyond 30 years. Results suggest that while the cognitive benefits of AP treatment may persist through the early and mid-stages of illness (compared to continued cognitive decline as illness remains untreated up to 20 years), AP effects may diminish as illness progresses into the chronic phases of > 30 years DOI.

## M89. Patient and Healthcare Professional Attitudes and Trial Experiences With a Subcutaneous Long-Acting Injectable Olanzapine (TV-44749) for the Treatment of Schizophrenia

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**BACKGROUND:** Poor treatment adherence is a clinical challenge for those living with schizophrenia, leading to increased risk of relapse and hospitalization. Compared with oral formulations, long-acting injectables (LAIs) are associated with improved adherence and lower healthcare resource utilization. Olanzapine, an antipsychotic with a well-known safety and efficacy profile, is available in both oral and intramuscular (IM) LAI formulations; however, the clinical use of the IM LAI formulation is limited due to risk of post-injection delirium/sedation syndrome (PDSS) and the corresponding Risk Evaluation and Mitigation Strategy (REMS) requirement that healthcare professionals (HCPs) educate patients about risks and monitor them accordingly. An additional barrier to LAI use is low acceptance among patients and HCPs owing to negative opinions of IM LAIs. TV-44749 is an investigational subcutaneous (SC) olanzapine LAI for once-monthly administration designed to provide sustained efficacy without the risk of PDSS.
**METHODS:** This attitudes and experiences study was a prospective, cross-sectional, observational, online survey study intended to complement the SOLARIS trial. SOLARIS is a double-blind, placebo-controlled phase 3 clinical trial to assess the efficacy, safety, and tolerability of TV-44749 in adults with schizophrenia (NCT05693935). This study recruited participants (patients and HCPs) taking part in the SOLARIS trial who had 2 or more experiences with TV-44749. Surveys collected information on participants' demographics and clinical characteristics as well as their attitudes on and experiences with LAI treatment attributes, delivery of care, and treatment satisfaction. Descriptive analyses were conducted for all survey items and select stratified analyses were performed using pertinent characteristics.
**RESULTS:** Overall, 70 patients (65.7% identified as male; 77.1% Black; mean age 44.4 years [SD=10.7]) and 35 HCPs (11 physicians and 24 nurses) completed the survey. Patient characteristics mirrored the larger SOLARIS population.

Injection-type preference. Patients preferred SC vs IM injections (78.6% vs 21.4%, respectively), with 67.3% of patients indicating the shorter and thinner SC needle as the main reason for their preference. Of those who chose IM, familiarity was the main reason for their preference (46.7%). For HCPs, SC vs IM preference was balanced for physicians (54.6% vs 45.5%, respectively) and nurses (both 50.0%). Among HCPs preferring SC, the main reason was SC being perceived as less threatening for the patient (physicians 83.3%; nurses 91.7%). The main reason for IM preference was patient familiarity (physicians 100%; nurses 75.0%).

Post-injection monitoring requirements. < half of patients indicated that an LAI requiring a 3-hour post-injection monitoring period (45.7%) or caregiver accompaniment (44.3%) would have a time, financial, social, or emotional impact on them. Patients who were employed or looking for work noted a higher impact of the post-injection monitoring period requirement than those who were unemployed (51.4% vs 38.7%, respectively). Despite reporting low levels of impact, nearly all patients noted it would be helpful to have an LAI without a post-injection monitoring period (90.0%) or caregiver accompaniment requirement (92.9%). Most physicians ( > 90%) and > 66% of nurses responded that the post-injection monitoring period may present potential treatment barriers and clinical challenges that could impact patients' use of LAIs.

Initiation regimen and dosing schedule. When starting an LAI, most participants preferred an initiation regimen requiring only 1 injection vs more complex regimens requiring concomitant oral medications or multiple injections (patients: 72.9% vs 27.1%; physicians: 90.9% vs 9.1%;

nurses: 79.2% vs 20.8%). Most participants valued a monthly dosing schedule "a lot" (patients: 61.4%; physicians: 72.7%; nurses: 66.7%).

TV-44749 satisfaction. Most participants had favorable responses (satisfied or very satisfied) regarding the initiation regimen, dosing schedule and trial medication overall (patients: > 92%; physicians: > 72%; nurses: > 87%), and responded favorably regarding continuing TV-44749 (patients: 82.9%; physicians: 63.6%; nurses: 70.8%). Patients who had prior experience with LAIs were more likely to indicate they were "very satisfied" with trial medication overall (61.9% vs 53.1%). HCPs with more (≥10) TV-44749 experiences were more likely to rate it favorably (88.9% vs 76.5%) and be willing to continue treatment with TV-44749 (83.3% vs 52.9%).

**DISCUSSION:** Overall, patients and HCPs reported favorable opinions of TV-44749's single-injection initiation regimen, monthly dosing schedule, and the trial medication overall. Further, HCPs who had more experiences with TV-44749 reported higher rates of satisfaction and a desire to continue treating their patients with TV-44749. These results show participants would value an LAI that does not require a post-injection monitoring period or caregiver accompaniment. Collectively, these results offer insight into attitudes about LAI treatments and highlight opportunities for TV-44749 to address barriers to LAI adoption.

## M90. Healthcare Resource Utilization and Cost Burden in Schizophrenia Patients With and Without Evidence of Tardive Dyskinesia

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**BACKGROUND:** Antipsychotics (APs) are known for causing extrapyramidal side effects, and prolonged treatment (particularly with 1st-gen APs) may lead to tardive dyskinesia (TD). VMAT-2 inhibitors may be used to treat TD. AP-related side effects are linked to low treatment adherence, leading to poor clinical outcomes. We analyzed real-world data to examine evidence of TD, AP use among patients with and without TD, healthcare resource utilization (HCRU), and the economic burden of TD among patients with schizophrenia (SCZ).

**METHODS:** A retrospective analysis using the Marketscan Medicaid (01/2014 to 12/2022) and PharMetrics Plus (01/2009 to 9/2023) claims databases was performed. Patients aged ≥18 years with SCZ diagnosis and ≥12 months of continuous enrollment before and after the earliest SCZ diagnosis (index date) were included. Patients diagnosed with Huntington's Disease before the index date were excluded. Age, gender, race (Marketscan Medicaid only), Elixhauser comorbidity index (ECI), and index year were included in a propensity score matched analysis between patients with and without TD evidence, defined by a TD diagnosis or VMAT-2 inhibitor use. Distribution of and treatment persistence to APs, as well as healthcare costs and HCRU during the 1-year follow-up since the index date, were compared between patients with and without TD evidence (i.e., TD vs. no TD groups).

**RESULTS:** In PharMetrics Plus and MarketScan Medicaid, 43,411 and 47,796 individuals with SCZ were identified, with 2.2% and 2.6% showing evidence of TD, respectively. At baseline, the TD group was older, more often female, and had a higher mean ECI score than the no TD group

in both databases. After matching, 16.7% of the 5,784 and 7,230 SCZ cohorts in PharMetrics Plus and Marketscan Medicaid, respectively, had evidence of TD. In both databases, the matched TD and no TD groups had a mean age of 50 years, a greater proportion of females, and a mean ECI score of 4. In both datasets, the matched TD group had a higher proportion of patients using APs during follow-up than the matched no TD group (PharMetrics Plus: 1st-gen APs = 27.9% vs. 15.8%; 2nd-gen APs = 85.8% vs. 72.9%; Marketscan Medicaid: 1st-gen APs = 30.7% vs. 15.1%; 2nd-gen APs = 97.4% vs 83.7%). In Marketscan Medicaid, the matched TD group had a higher proportion of those with treatment persistence (defined as a proportion of days covered of ≥80% during follow-up) to any APs (66.8% vs. 61.2%), 2nd-gen oral APs (66.5% vs. 60.9%), and 2nd-gen LAI APs (78.5% vs. 72.0%), and a lower proportion of those with adherence to 1st-gen LAI APs (55.2% vs. 64.8%) and 1st-gen oral APs (64.5% vs. 65.3%) compared to the matched no TD group. Similar results were observed in PharMetrics Plus, except that their matched TD group had a higher proportion of those with adherence to 1st-gen oral APs (71.6% vs. 67.5%) and a similar proportion of those with adherence to 2nd-gen oral APs (68.0% vs. 68.3%). Additionally, the matched TD group had higher total all-cause and psychiatric-related HCRU and health-related costs during follow-up in both databases.
**DISCUSSION:** The matched TD group was more likely to use any type of AP and had a greater proportion of patients with adherence to 2nd-gen oral/LAI APs and a lower proportion with adherence to 1st-gen LAI APs during follow-up compared to the matched no TD group. Among AP types, while the 2nd-gen oral AP was the most common AP used, adherence to 2nd-gen LAI was the greatest in both TD and no TD groups. Additionally, the matched TD group incurred a greater burden in terms of healthcare costs and HCRU relative to the matched no TD group, underscoring the need for increased attention to these cohorts among patients with SCZ.

## M91. Cannabis use Patterns in First Episode Psychosis and Schizophrenia: An Integrative Review and Case Series

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**BACKGROUND:** The 2024 US Monitoring the Future Study showed record-high past-year cannabis use – 42% for young (19–30 years) and 29% early mid-life adults (35–50 years). Cannabis use is even more common in persons with first-episode psychosis (FEP) and schizophrenia (SCZ) spectrum disorders. Early, high level cannabis use is associated with developing psychosis and continued use after psychosis onset predicts symptoms and relapse. With increasing potency of street cannabis and legally available THC products, understanding cannabis use patterns in SCZ is crucial. This project aims to synthesize research on cannabis use patterns in FEP and SCZ since the expansion of US cannabis legalization and describe use patterns in a case series of psychosis patients.
**METHODS:** Using an integrative review framework, we searched PubMed with terms for cannabis and SCZ-related diagnoses for studies of FEP or SCZ patients describing cannabis use characteristics collected after 2016. We also assessed the type and frequency of past 30-day cannabis use in six consenting psychiatric inpatients with psychosis and recent cannabis use during 2022–23 using the Cannabis Engagement Assessment. The parent study was reviewed

and approved by the New Hampshire, U.S., Department of Health and Human Services Committee for the Protection of Human Subjects.
**RESULTS:** Integrative Review: Of 672 articles, nine studies met the inclusion criteria; four had control conditions, two used US samples, five required cannabis use for inclusion. Sample sizes ranged from 15 to 207. Structured clinical interviews were the most common cannabis assessment method (four studies). Four studies reported SCZ groups with at least daily use within the past three months. Among the three studies with comparison cannabis use disorder (CUD) participants, there was not a consistent pattern as to whether patterns of use among participants with SCZ were different than those with CUD without psychosis. Two studies (Germany and Canada) showed similar calculated daily joint use in SCZ groups with and without CUD compared to control conditions with CUD. One US study showed participants with SCZ and CUD used fewer joints and fewer days than participants with CUD only (14.7±10.1 vs 26.4±11.5 days in the past 35). Reported amount of use varied ranging from 0.4±0.5 to 4.3±3.4 (mean daily joints). Studies requiring cannabis use for inclusion showed heavier use among SCZ participants. Only one study detailed cannabis product types. This recent qualitative study of 15 Canadian cannabis users with recent-onset psychosis reported high rates of concentrate (60%) and edible (80%) use. Products included flower, edibles, concentrates, topicals, and oil. Flower (93.3%), edibles (80%), and concentrates (60%) for THC and flower (40%) for CBD were most used.

Case Series: Participants' mean age was 32.0±14.4, 66.7% were male, 83.3% had SCZ, mean PANSS-6 score was 15.8±3.3, and age of first cannabis use was 14.2±4.9. All used cannabis leaf (mean 3.1±2.3 joints per day on use days) and used 2.7±2.1 days per week. Half of participants (all heavy users) also used concentrates (33.3%) or edibles (16.7%). Half (50%) obtained cannabis from a dealer, and all used cannabis "mostly alone." Most (83.3%) tried to reduce use, but none had sought support for reduction.

**DISCUSSION:** Recent research using various methods has reported a wide range of cannabis use frequencies and quantities in persons with FEP and SCZ, with many reporting heavy use. Similar to one small study showing high rates of concentrate use, half of our case series subjects used high-potency products as well as leaf. As cannabis legalization expands, further research should examine the extent of risky high-potency product use in people with psychosis.

## M92. Prevalence and Characteristics of Patients Living With Schizophrenia in Medicaid: National and State Levels

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**BACKGROUND:** Schizophrenia (SCZ) is a chronic mental health disorder characterized by positive symptoms, negative symptoms, and cognitive impairments. It significantly impacts quality of life and functioning, often leading to long-term disability. The prevalence of SCZ in the general population is approximately 0.5%. There are limited published data indicating higher prevalence of patients living with SCZ among the Medicaid population. Additionally,

comprehensive details on the prevalence and characteristics of these patients are lacking. This study aims to estimate the prevalence and describe characteristics of individuals living with SCZ covered by Medicaid programs at national and state levels.
**METHODS:** This retrospective cohort study utilized data from the Transformed Medicaid Statistical Information System Analytic Files (T-MSIS; 2016-2022). The study population comprised adults aged 18 years and older with at least two documented SCZ diagnoses, who were continuously enrolled in Medicaid for a minimum of 12 months before and after the most recent claim associated with a SCZ diagnosis (index date). Data from 2016-2022 were analyzed to assess overall prevalence in annual number of patients living with SCZ at a national level. For state-level number of patients living with SCZ, 2020-2022 data were utilized to understand regional variations. Sociodemographic variables were based on those with Medicaid only, excluding dual-eligibles, with an index year of 2021.
**RESULTS:** The study analyzed data from over 55 million Medicaid enrollees with an average annual national prevalence of 2.3% over 2016-2022. In 2022, approximately 956,023 individuals with Medicaid (including those with dual-eligibility) had a diagnosis of SCZ. The number of Medicaid patients living with SCZ in 2022 exhibited state-level variations, with California having the highest number of Medicaid patients (130,182), followed by New York (85,047). In 2022, among 143,970 patients living with schizophrenia (SCZ), excluding dual-eligible individuals, 56.4% were male, with an average age of 41.9 years. The majority of patients were in younger age groups, with 14.7% aged 18-24, 24.7% aged 25-34, and 20.3% aged 35-44, accounting for 59.7% of the total SCZ population. Non-Hispanic White individuals accounted for 41.8% of the patients, followed by non-Hispanic Black individuals at 26.1%. Among patients with poverty data, almost half (48.5%) were under the federal poverty level.
**DISCUSSION:** The study highlights key findings on SCZ prevalence and characteristics among Medicaid enrollees. The prevalence of Medicaid enrollees living with SCZ was higher (2.2%) than that of the US general population (0.5%), potentially reflecting the lower socioeconomic status of this patient population. Variations in the number of patients living with SCZ across states highlight differing levels of schizophrenia burden among states. The data also reveals that nearly half of the patients living with SCZ fall within the lowest family income poverty level, underscoring the socioeconomic challenges faced by this population. Limitations include potential misclassification, underestimation of prevalence from claims data, and missing data. Despite these limitations, the study provides valuable insights into the national and state-level characteristics of patients living with SCZ. Future research should focus on identifying the underlying factors contributing to these regional differences and developing strategies to mitigate the burden of SCZ on Medicaid programs.

## M93. Consensus in Psychiatric Emergencies Using the Delphi Technique

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**BACKGROUND:** his study aimed to elicit expert consensus on the necessary components of a seclusion room module required to accommodate and manage psychiatric emergency patients requiring both medical and surgical interventions in infectious disease situations.

**METHODS:** A two-round Delphi survey was conducted among 38 medical professionals, architects, and spatial design experts. The survey assessed the effectiveness, feasibility, and urgency of spatial scales, spatial organization, and movement system domains related to the necessary elements of a seclusion room.
**RESULTS:** In the spatial scale domain, items such as "sufficient width to comply with disability standards (wheelchair accessible)" and "larger space should be provided for patients with a large range of motion or requiring special medical procedures" emerged as priorities. In the movement system domain, priorities included "anticipating situations where stable patients need to be pushed on a stretcher cart from both sides, necessitating a wider passage." In the spatial organization domain, priorities included "installing interior elements (wall images, media panels, etc.) that aid patient stability, although a separate area for patients' activities reflecting psychiatric characteristics is not necessary."
**DISCUSSION:** Expert consensus was achieved regarding the spatial scales, spatial organization, and movement system domains related to the necessary elements of a seclusion room for psychiatric emergency patients.

## M94. Digital Environments for Anxiety Reduction in Individuals With Psychotic-Like Experiences (PLE): Preliminary Findings and Future Directions

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**BACKGROUND:** Past literature has largely focused on risk-factors of urban environments (e.g. city-dwellers are more prone to symptoms of anxiety and are more likely to have transient symptoms of psychosis), very little work has looked at aspects of the environment that may be protective against mental health concerns. Recent research has shown that more exposure to greenspace is associated with fewer psychopathology symptoms and less incidence of psychological disorders. While greenspace may be associated with positive mental health, not everyone has equal access to greenspace. Thus, this study proposed to explore the impact of virtual exposure to greenspace on reducing anxiety in individuals with co-occurring psychotic-like experiences, with or without a history of trauma. Bivariate correlations revealed positive relationships between age and total traumas experienced, PLE, and trait anxiety, and moderate positive associations between total traumas and trait anxiety.
**METHODS:** Participants were recruited from a suburban undergraduate and graduate institution (N=193) using the Sona online study recruiting tool. Participants were English speaking, at least 18 years old (M= 20.79; SD=4.05), and endorsed at least one item on the CAPE-P15 screener for psychotic-like experiences (PLE) and randomized into one of two digital intervention conditions: 1) a virtual walk through a green area (experimental) or 2) a virtual walk around an indoor track (control). After randomization, participants completed baseline questionnaires then were exposed to a modified Trier Social Stress Test (TSST), followed by one of two virtual interventions, and post-experimental questionnaires.
**RESULTS:** Analyses did not yield significant differences in state anxiety nor in measures of cognitive performance between experimental groups, however, anxiety was observed to decrease over time in both the greenspace and control conditions. Higher PLE scores and higher number of total traumas were observed in those who were raised in urban settings as compared to those

in suburban settings. Additionally, participants currently living in rural and urban settings reported a higher number of PLE than those in suburban settings and those currently living in urban settings reported a higher number of traumas than those in suburban settings.
**DISCUSSION:** Further research is needed to understand the impact of virtual and in vivo environments on psychopathology, with particular emphasis on its impact on individuals with PLE who may be at greater risk for more serious psychotic disorders.

## M95. SCID Diagnosed Prevalence of Schizophrenia and Other Mental Health Disorders Among US Homeless Adults: Results From the Mental and Substance use Disorders Prevalence Study, Fielded 2020-2022

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**BACKGROUND:** Two percent of US adults experienced past-year homelessness. Schizophrenia is disproportionately represented in homeless populations, but accurate prevalence estimates of mental health disorders (MHD) are challenging to obtain; little is known about the sheltered subset of the homeless population. The Mental and Substance Use Disorders Prevalence Study (MDPS), fielded 2020-2022, estimated the prevalence of mental and substance use disorders (SUD) in the US. Trained clinicians administered the Structured Clinical Interview of the DSM-5 (SCID) to identify past-year MHD and SUD among individuals from households, prisons, shelters and state psychiatric hospitals. We identified the prevalence of MHD, SUD, service use and demographics of MDPS participants experiencing homelessness in the past year and compared those who currently/recently lived in a shelter to those who were not homeless.
**METHODS:** The MDPS household sample was nationally representative, and the shelters and hospitals were convenience samples selected from rural, suburban and urban regions to encompass the breadth of shelter/hospital types. In the shelter/hospitals a random sample of adults (aged 18-65) was selected to participate. Due to over-representation of MHD in these settings survey weights reduced the oversampling back to the relative size of these US populations. Participants in the household and hospital samples were defined as homeless if they reported homelessness in the past year; the subset who reported time in a shelter were included in the “sheltered” subsample. The shelter sample was included in both homeless and sheltered groups. Prevalence of schizophrenia (12-month and lifetime), and 12-month bipolar 1 (BP-I), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and anorexia nervosa were determined. SUD included alcohol, cannabis, stimulant, opioid and sedative/hypnotic/anxiolytic use disorders. Logistic regressions identified the odds of being homeless and separately of being in a shelter, versus not homeless in the past year, adjusting for age, birth sex, race and ethnicity.
**RESULTS:** 2% of MDPS participants were homeless and 0.4% were sheltered in the past year. Notably, Black individuals were 2 times more likely to be home< White individuals (AOR 2.1, 95% CI=1.1-3.7), but there were no ethnoracial differences among sheltered individuals. Over half of homeless individuals had a MHD and over one third had a SUD; over 50% of sheltered individuals had a SUD. The prevalence of schizophrenia in sheltered individuals exceeded that of the overall homeless sample, 15% (95% CI=0%-32%) versus 7% (95% CI=2%-12%). While all

other MHD were more likely to have been homeless, only individuals with schizophrenia (AOR 10.1, 95% CI=2.1-50.2) and PTSD (AOR 15.1, 95% CI=5.7-40.5) were more likely to be sheltered in the past year. Individuals with SUD were more likely to be homeless and sheltered in the past year. More individuals with inpatient mental health treatment in the past year were in shelters than the overall homeless sample,15% (95% CI=6%-25%) versus 7% (95% CI=4%-10%). Any SUD treatment was more likely in the homeless sample, while only inpatient SUD treatment was more likely in the shelter sample, compared to those not homeless.
**DISCUSSION:** Findings provide prevalence estimates of rigorously SCID diagnosed MHD among individuals experiencing homelessness. MHD and service use of those living in shelters was different than in the overall homeless sample. Schizophrenia was more prevalent in the sheltered than overall homeless population. This suggests substantial unmet needs unique to unsheltered homeless populations.

## M96. Do Neighborhood Factors Make You Paranoid? Using Virtual Neighborhood Visits to Examine Threat Response to Adverse Neighborhood Characteristics

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**BACKGROUND:** Paranoid ideation, the unsubstantiated belief that intentional harm has or will occur, is a major contributor to impairment in psychosis (Fan et al., 2022; Pinkham et al., 2016). Neighborhood characteristics play a role in paranoid ideation with findings indicating that neighborhood deprivation and crime contribute to increased stress and negative affect (Anglin et al., 2021; Newbury et al., 2018) which then increase paranoid ideation (So et al., 2018). Neighborhood deprivation and crime also drive interpersonal mistrust and threat (Vargas et al., 2020), potentially increasing paranoid ideation. It is unclear whether increases in perceived threat in response to neighborhood factors are unique to psychosis or represent warranted wariness (Wilson et al., 2016).
**METHODS:** Utilizing a novel Street View paradigm, the current study examined how neighborhood factors contribute to paranoid ideation in both a transdiagnostic sample (based on administrative assessments of their own neighborhood) and in naïve raters (based on a virtual Street View visit to those same neighborhoods). We tested the hypothesis that exposure to adverse neighborhood environments is sufficient to drive increases in threat perception in both residents and visitors to these neighborhoods. Specifically, we predicted that 1) participant clinical ratings of depression-anxiety and paranoid ideation along with reports of momentary negative affect and paranoid ideation will be related to neighborhood deprivation and crime and 2) naïve raters reports of momentary negative affect and paranoid ideation experienced during a virtual visit to participants' neighborhoods will relate to neighborhood deprivation and crime.

Data were collected from a transdiagnostic sample of individuals with psychosis. Baseline paranoid ideation was measured using the Revised Green Paranoid Thoughts Scale (R-GPTS; Freemen et al., 2021) and anxiety-depression was measured using the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993). Momentary paranoid ideation and negative affect were calculated using aggregate ecological momentary assessment (EMA) responses (Orth et al., 2022) from a 7-day period. Neighborhood data were assessed at the census block group level

using Area Deprivation Index (Kind and Buckingham, 2018) national percentile and CrimeRisk (Goldman-Mellor et al., 2016). Using CANVAS Google Street View (Bader et al., 2015) naive raters reported their negative affect and paranoid ideation while completing virtual neighborhood visits.

**RESULTS:** Analyses (N = 47) indicated that BPRS anxiety-depression was related to EMA negative affect ($r = .41$, $p = .02$) and that R-GPTS total score was related to EMA paranoid ideation ($r = .72$, $p < .001$), validating our EMA approach. Analyses also indicated that greater EMA paranoid ideation was related to greater neighborhood deprivation ($r = .30$, $p = .05$). No other symptom measures were related to neighborhood factors. Naive raters (N = 5) reports of negative affect and paranoid ideation during virtual neighborhood visits were unrelated to neighborhood factors.

**DISCUSSION:** Increased momentary paranoid ideation assessed during EMA was related to living in a more deprived neighborhood. This finding replicates previous research on the relation between neighborhood deprivation and paranoid ideation. Contrary to hypotheses, naive raters' reports of negative affect and momentary paranoid ideation during virtual neighborhood visits were unrelated to neighborhood factors. This finding raises questions about whether a singular exposure to a neighborhood is sufficient to drive increases in paranoid ideation or if chronic exposure is necessary. Implications of these findings will be discussed further at the time of presentation.

## M97. The Impact of Negative Symptoms on Language: A Lexical Analyses of Social Speech

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**BACKGROUND:** Negative symptoms of schizophrenia manifest as deficits in motivation and pleasure (MAP) and emotional expression and are related to functional impairments and deficits in social skills. Anhedonia, a core negative symptom characterized by a marked decrease in pleasure, has been linked to increases in usage of negative emotion expression and sadness words. Understanding the impact of negative symptoms on word valence is important when looking at how individuals with schizophrenia communicate with others, and how they develop and maintain social relationships- prior studies have shown that language production is severely impacted by psychosis symptoms, both positive and negative. The current study aims to expand on existing literature by examining word valence and count during a video-prompted social interaction task, aiming to explore the relationship between clinical symptoms, word valence, and word count. We hypothesize that 1) Greater motivation and pleasure deficits will be associated with diminished positive, affiliative and social word use; 2) Greater paranoia, agitation, and depressive symptoms will be related to greater negative words and lower word count.

**METHODS:** Data (N = 113) was collected from a transdiagnostic sample of adults with psychotic disorders and non-clinical participants living in the Baltimore and D.C. areas. Negative symptoms were measured using the MAP subscale of the Clinical Assessment Interview for Negative Symptoms (CAINS). Positive and agitation symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). Participants watched a short video of an individual introducing

themselves and were then asked to introduce and talk about themselves. These participant responses were then transcribed and analyzed with the Linguistic Inquiry and Word Count (LIWC) to assess for positive, affiliative, social words, and word count.
**RESULTS:** Results indicate that more severe MAP symptoms were associated with fewer positive emotions (love, nice, etc.) ($r = -.19$, $p = .04$). There were no significant correlations between severe MAP symptoms and affiliative words (ally, friend, etc.) ($r = -0.16$, $p = 0.08$), nor between MAP symptoms and social words (mate, talk, etc.) ($r = -0.11$, $p = 0.20$). Depressive symptoms and paranoid ideation were not correlated with word count ($r = -.04$, $p = 0.62$) or negative emotion (hurt, ugly, etc.) ($r = 0.09$, $p = 0.35$). There were no other significant correlations between word count or social speech and clinical symptoms.
**DISCUSSION:** Results indicated that motivation and pleasure deficits manifest in language with the use of fewer positive emotion words. These results were specific to MAP symptoms as no other symptom domain was related to lexical results. These results indicate that individuals with more severe MAP symptoms are less likely to engage in socially affiliative behaviors causing further problems for social interactions. Future studies should expand on the current findings and examine how negative symptoms and language impact social interactions for those with psychosis. Results will be discussed further at the time of presentation.

## M98. Comprehensively Assessing Cognition in Individuals With Schizophrenia 60 Years of age and Older Using the Flexible Adapted Cognitive Test Battery for Schizophrenia (FACTS)

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**BACKGROUND:** The number of persons with schizophrenia 60 years of age or older is estimated to double by 2050. However, this cohort has long been overlooked compared to their younger counterparts and is often excluded from studies that administer comprehensive neuropsychological batteries. To better understand cognitive functioning in this population, we developed the Flexible Adapted Cognitive Test battery for Schizophrenia (FACTS), which includes nine separate tests that assess seven distinct cognitive dimensions.
**METHODS:** We administered FACTS to 208 participants 60+ years of age in Ningxia and Guangxi, China, including 92 with untreated schizophrenia [UT], 36 with treated schizophrenia [TC], and 80 healthy controls [HC]. Participants' mean (SD) age was 67.3 (5.2) years; their mean years of education was 2.1 (2.6) years; 59% were female; 90% lived in rural areas; 44% were from minority (non-Han) ethnic groups; and the mean duration of illness (DOI) in the participants with schizophrenia was 32.6 (13.2) years. Test comprehension scores and test completion scores for each test were assessed by FACTS interviewers based on the difficulty participants had learning the requirements of the tests and their performance during the formal (scored) tests. The nine test comprehension scores were combined into a composite learning score (with a range of 0 to 100).
**RESULTS:** The gender, years of schooling, ethnicity and residency (rural vs urban) of the three groups of participants were similar, but the mean (sd) ages of UT (69 [6.0]) and HC (67 [4.3])

were significantly > that of TC (64 [3.2]) (F=11.18, p < 0.001; multiple comparisons: UT, HC > TC). The UT has a significantly longer DOI than the TC (34.1 [13.1] vs 28.9 [12.7] years, t=2.07, p=0.043) and significantly more severe symptoms (PANSS total score: 78.9 [20.0] vs 62.0 [21.9], t=4.02, p < 0.001).

Test comprehension scores (i.e., ability to learn the task assessed in the test) were significantly higher in HC than UT in all nine tests and than TC in three tests, and significantly higher in TC than UT in seven tests. The mean (sd) composite learning score was lowest in UT (35.6 [30.01), intermediate in TC (62.4 [30.0]) and highest in HC (72.1 [17.4]) (Kruskal-Wallis chi2=61.80, p < 0.001; multiple comparisons: HC > TC > UT). For all nine tests, rates of successful test completion were the lowest in UT (26.1-70.7%), intermediate in TC (62.9-97.2%) and highest in HC (86.3-100.0%). Successful test completion rates were significantly higher in HC than UT in all nine tests and than TC in two tests, and significantly higher in TC than UT in eight of the nine tests.

Most of these differences in the test comprehension results between the three groups of participants remained significant after adjustment for demographic and clinical variables; all of the differences in test completion rates remained significant after adjustment. In the multivariable analyses, younger age, male gender, more years of schooling, urban residency, duration of illness, and current symptom severity were associated with some test-specific test comprehension and successful test completion results.

**DISCUSSION:** It is feasible to use FACTS to comprehensively assess cognitive functioning in individuals with schizophrenia aged 60 and older. The meta-measures developed for FACTS—test comprehension and test completion scores—can distinguish UT from TC and HC, indicating their potential value as additional measures of cognitive functioning. The differences between UT and TC suggest that treatment might decrease the magnitude of cognitive impairment in older individuals with schizophrenia.

## M99. Genetic Susceptibility to Schizophrenia Through Neuroinflammatory Pathways is Associated With Retinal Thickness: Findings From the UK-Biobank

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**BACKGROUND:** Schizophrenia is associated with structural and functional changes in the central nervous system, including the most distal part of it: the retina. However, the question of whether retinal atrophy is present before individuals develop schizophrenia or is a secondary consequence of the disorder, caused for example, by pathophysiological processes or other confounders (e.g. antipsychotics) remains unanswered. We aimed to address this question by examining the association between polygenic risk scores for schizophrenia and retinal morphologies in individuals without a schizophrenia diagnosis.

**METHODS:** We used population data for white British and Irish individuals from the UK Biobank and estimated a polygenic risk score for schizophrenia based on the genome wide

association data (PGC release 2022). We hypothesized that greater genetic susceptibility to schizophrenia is associated with thinner retinal tissue, specifically within the macula. To gain additional mechanistic insights, we conducted pathway-specific polygenic risk score associations analyses for gene pathways related to schizophrenia. Analyses were conducted for individual retinal layers as this provided the opportunity to distinguish between neurodevelopmental and neurodegenerative processes.
**RESULTS:** Of 64283 individuals recruited, 34939 participants with available matching imaging- genetic data were included in the analysis, of whom 19070 (54.58%) were female and 15869 (45.42%) were male. According to our robust regression results, higher polygenic risk scores for schizophrenia were associated with thinner overall macular thickness while controlling for confounding factors ($b = -0.17$, $p = 0.018$). Similarly, we found that greater polygenic risk scores for schizophrenia specific to neuroinflammation gene sets were associated with thinner ganglion cell-inner plexiform layers ($b = -0.10$, self-contained $p = 0.014$; reflecting the level of association, competitive $p = 0.02$; reflecting the level of enrichment).
**DISCUSSION:** These results provide new evidence for genetic factors that could predispose individuals to heightened neuroinflammatory responses. Over time these responses could contribute to progressive neurodegeneration, manifesting in part as retinal thinning. The results also suggest the involvement of inflammatory biomarkers in structural changes in the retina.

## M100. Post-Mortem Cerebrovascular Disease is Associated With Cognitive Impairment in a Subtype of Chronic Schizophrenia

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**BACKGROUND:** Cognitive impairment affects up to 98% of chronic schizophrenia (SCZ) patients but is not addressed by current therapies. The underlying neuropathology in SCZ only occasionally exhibits pathologies such as Alzheimer's disease (AD) in elderly patients. This study explores potential SCZ-specific mechanisms for cognitive impairment.
**METHODS:** Clinical and demographic data were analyzed for 55 SCZ patients who underwent autopsy. Neuropsychological evaluations (Positive and Negative Syndrome Scale, Mini-Mental Status Examination or MMSE, and Frontal Assessment Battery) were conducted on 34 subjects. 15 brain tissue blocks per subject were evaluated for AD using the NIA-Reagan Criteria and for cerebrovascular disease (CVD) using 2 scoring systems (one in-house, one externally validated). Dimensionality reduction and clustering analysis (Uniform Manifold Approximation and Projection and k-means clustering) were conducted to explore heterogeneity and extract potential subgroups. Continuous variables were analyzed using Pearson correlations and linear regression with age and education as covariates. Cluster differences were assessed using the Mann-Whitney U-test (continuous variables) and the chi-squared test (categorical).
**RESULTS:** The mean (SD) age of death in our cohort was 78.2 (9.4) years, and the mean disease duration 53.9 (10.6) years. 14 (32.6%) had completed primary school or higher education, 42 (81.1%) were heavy smokers, and 37 (74.0%) were on antipsychotics. The mean PANSS score was 100.3 (30.0). The mean MMSE score was 17.4 (8.3), with 27 (71.1%) of

patients reaching the cutoff for impairment. Among those impaired, 42% did not show pathological changes on autopsy that would explain the impairment. AD pathology was found in 20 (37%) patients, and CVD in 46 (85%). The primary autopsy diagnoses included CVD, primary age-related tauopathy, and AD. Neuropathological severity was not associated with any domain-specific cognitive testing. The association between MMSE score and neuropathology appeared to be driven largely by CVD specifically (Pearson $r = -0.44$, $p = 0.007$). Clustering by test scores revealed 3 subgroups, distinct in symptom severity and age. The mean MMSE score in Cluster 2 (26, above the impairment cutoff of 24) was significantly higher than the mean of 10 in Cluster 1 ($p < 0.001$). CVD severity was associated with MMSE score only in Cluster 3 (Pearson $r = -0.74$, $p = 0.01$). Neither tangles nor amyloid beta plaques predicted MMSE score in any cluster.

**DISCUSSION:** This dataset represents a cohort of elderly patients with chronic SCZ characterized by significant impairment. Cognitive dysfunction was not fully explained by neuropathology, suggesting novel underlying mechanisms. While AD prevalence here was comparable to the general population, CVD was more frequent and not associated with typical vascular risk factors such as smoking or antipsychotic use. This suggests that the CVD in SCZ may be driven by an inherent metabolic or vascular etiology rather than by common external risk factors. The association between MMSE score and CVD severity in Cluster 3 suggests that CVD may drive cognitive decline in certain SCZ subtypes. In contrast, Cluster 1 showed impairment without clear pathology, while Cluster 2 was largely cognitively preserved. These findings highlight the heterogeneity of SCZ and the importance of considering patient subtypes when studying the disease. Despite limited subgroup sample sizes, these data suggest that subtyping patients based on clinical features could help uncover distinct disease mechanisms and guide tailored interventions. Larger studies are needed to clarify the role of CVD and other pathologies in chronic SCZ.

## M101. An in Vitro Cell Model to Study Antipsychotic-Induced Metabolic Syndrome

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**BACKGROUND:** Second-Generation Antipsychotics (SGAs), including olanzapine (OLZ), represent first-line treatments for major psychoses. However, such agents may induce Metabolic Syndrome (MetS). In the current study, we investigated the effect of individual-specific adipocyte exposure to OLZ in order to assess the role of this SGA on insulin resistance’s onset, a core mechanism supporting MetS. Importantly, since MetS arises from both environmental and genetic factors, also genetic variants impacting both MetS and major psychoses, by setting up this individual-specific adipocyte model, we aimed at preserving the whole genomic background of the original donors, whose in vivo metabolic status was known.

**METHODS:** We collected Urine-Derived Cells from 6 healthy subjects, therefore carrying an epigenetic signature that was not biased by any previous pharmacological treatment, and isolated CD133+ multipotent stem cells using an immunomagnetic approach. Finally, we differentiated stem cells into individual-specific mature adipocytes.
We assessed the successful differentiation process with an Oil Red O Solution staining along with an immunofluorescence assay. Then, we exposed the adipocytes to increasing concentrations of OLZ (0.02, 0.2, 2, 10, 20 μM) for 24 and 72 hours controlling for cytotoxicity. Finally, we exposed the cells to 10 and 20 μM OLZ (as reported in literature) for 24 and 72 hours to analyze the drug impact on cell levels and function of GLUT4 and AKT proteins, central players in the insulin cascade transduction signaling, using Western Blotting and Glucose Uptake assays. Also, a transcriptome-wide analysis on these cell lines was used to identify OLZ-induced gene expression modification of relevance to MetS.

**RESULTS:** We found that OLZ affects GLUT4 and phosphorylated-AKT (p-AKT) levels. More specifically, in our cells after 24 hours of 10 μM OLZ treatment, GLUT4 expression levels significantly decreased, while p-AKT levels were enhanced. On the other hand, after 72 hours of treatment, GLUT4 expression was significantly increased and p-AKT levels were significantly decreased. Glucose Uptake assay revealed that cell exposure to 20 μM, but not 10 μM, OLZ concentration significantly reduced glucose uptake. Finally, transcriptome analysis showed that 95 genes were differently expressed in treated and untreated cells. The vast majority of these Differentially Expressed Genes (DEGs) belonged to lipid and glucose metabolism along with Neuregulin pathways.

**DISCUSSION:** Our results suggest that the increase of p-AKT levels after 24 hours exposure to OLZ may represent a compensatory mechanism counterbalancing the reduced amount of GLUT4 on the plasma membrane. Coherently with this hypothesis, after 72 hours of OLZ exposure, the increased levels of GLUT4 expression were counterbalanced by a decrease in p-AKT levels. The transcriptome analysis confirms the potential peripheral effect of OLZ in inducing metabolic alterations typically related to MetS, while suggesting that one putative core molecular mechanism mediating such effect involves the upregulation of neuregulin-2 pathway, potentially correlated to adipogenesis.

In conclusion, our results suggest that future treatments to reduce the impact of SGAs on metabolism, including OLZ, should take into account the importance of the peripheral processes involved in AP-induced-MetS and could benefit from targeting the molecular mechanisms here identified underlying the pathophysiology of this condition.

## M102. Genetic Interaction of DISC1 and FMR1 in Glutamatergic Synaptogenesis

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**BACKGROUND:** Schizophrenia is a severe mental disorder that impacts about 1% of the population. Although the molecular and pathological mechanism of schizophrenia remains elusive, genome-wide and familial lineage studies of schizophrenia patients indicate multiple genetic risk factors contributing to the pathological condition. An increasing number of potential

risk factor loci have been identified to date. These studies also indicate that numerous genetic risk loci associated with schizophrenia are shared with other psychiatric disorders, including bipolar disorder, autism spectrum disorder, and intellectual disability. Many of these shared risk loci encode genes for synaptic proteins, indicating a convergence in their biological functions toward pathways that regulate synaptic development and plasticity. Fragile X syndrome is one of the most prevalent forms of intellectual disability and autistic abnormality. Molecular studies have shown that fragile X syndrome (FXS) is caused by loss-of-functions of the < i > Fragile X Mental Retardation 1 (FMR1) < /i > gene, which encodes an RNA-binding protein (FMRP) that controls the translation of diverse synaptic proteins.
**METHODS:** The larval neuromuscular junction (NMJ) of the fruit fly ( < i > Drosophila melanogaster < /i > ) shares several important characteristics with the excitatory synapses found in the vertebrate brain. The NMJ fly uses glutamate as its primary transmitter and contains ionotropic glutamate receptors that are homologous to those found in humans. The fly NMJ's stereotypic synaptic connections, with distinct and identifiable presynaptic motoneurons and postsynaptic muscles, make this system highly valuable for investigating the molecular genetic mechanisms of synaptogenesis and functions. As a way to analyze interactions between diverse psychiatric risk factor genes in synaptogenesis, we introduced the human < i > Disrupted-in-Schizophrenia-1 (DISC1) < /i > gene in fruit flies. A balanced chromosomal translocation affecting < i > DISC1 < /i > locus was initially identified in a large Scottish family with schizophrenia. We showed that overexpression (OE) of < i > DISC1 < /i > causes anatomical alteration of synaptic structures in the larval NMJ, resulting in suppression of the total bouton area. Based on this finding, we have genetically screened other schizophrenia risk factor genes for functional interactions with < i > DISC1 < /i > in the developing glutamatergic synapses and identified several interacting genes, including < i > dfmr1 < /i > , the fruit fly < i > FMR1 < /i > homolog. It has been reported that the ortholog of the vertebrate < i > FMRP (dFMRP) < /i > in fruit fly NMJ is expressed in both presynaptic motor neurons and in postsynaptic muscles in larvae. To evaluate genetic modifications, we examined the synaptic anatomy of NMJ, focusing on the three morphological parameters (bouton area, number of boutons, and number of axonal branch points). To further understand the morphological phenotypes at the molecular level, we next investigated the protein expression levels of potential interactors of < i > DISC1 < /i > and < i > FMR1 < /i > in synaptogenesis.
**RESULTS:** We showed that loss of < i > dfmr1 < /i > modifies the < i > DISC1 < /i > OE phenotype in synaptogenesis, suppressing the formation of synapse boutons. We also demonstrate that < i > dfmr1 < /i > mutations suppress the < i > DISC1 < /i > -mediated upregulations of the expressions of a glutamate receptor (DGluRIIA) in postsynaptic cells and a ELKS/CAST protein, Bruchpilot (Brp) in presynaptic cells. Moreover, < i > DISC1 < /i > OE in the < i > dfmr1 < /i > heterozygous null background causes the downregulation of a MAP1 family protein, Futsch. In this study, we have found that dfmr1, the Drosophila homolog of FMR1, exhibits functional interactions with DISC1 in synaptic development. We have shown that mutations of dfmr1 modify the < i > DISC1 < /i > OE synaptic phenotypes at the molecular and morphological levels. In summary, the various synaptic phenotypes were uniquely detected in the presence of both < i > DISC1 < /i > OE and < i > dfmr1 < /i > null heterozygous mutations, which includes, for the NMJ morphology, 1) neutralization of decreased bouton area induced individually by < i > DISC1 < /i > OE and < i > dfmr1 < /i > null mutations, 2) decreased numbers of boutons and branches. For the protein expression level, the dual mutants displayed 3) neutralization of increased DGluRIIA and Brp levels induced by < i > DISC1 < /i >

OE mutations, and 4) decreased Brp expression level. These results suggest an intriguing converging mechanism controlled by < i > FMR1 < /i > and < i > DISC1 < /i > in the developing glutamatergic synapses.
**DISCUSSION:** Focusing on genetical interactions in synaptic development, our study highlights a common molecular underpinning regulated by < i > FMR1 < /i > and < i > DISC1 < /i > that contribute to the pathological process of neuropsychiatric disorders. A part of this work has just been published in Honda T et al., < i > Schizophrenia < /i > , 10(1) 112, (2024). In the SIRS 2025, we plan to present further our ongoing progress in screening results of < i > DISC1 < /i > interacting genes in glutamatergic neurons and synapses. Our research potentially provides insights into the genetic and cellular mechanisms and pathophysiology of schizophrenia.

## M103. The Moderating Role of Schizotypy in the Association of Subclinical Psychotic-Like Symptoms and Distress: A Time-Lagged Daily-Life Examination

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**BACKGROUND:** Schizotypy is a heterogenous and spans across a broad spectrum of traits, subclinical and clinical features, including psychotic symptoms and psychotic-like experiences (PLE). PLE may be relatively frequent and innocuous for some individuals while for others, they can be distressing and lead to a heightened risk of psychosis. Further research is warranted to explore the factors that moderate the distress associated to PLE. This study aimed to (1) examine whether schizotypy dimensions are associated with psychotic-like manifestations in daily life, (2) explore the differential association of momentary psychotic like experiences and paranoia are associated to subsequent distress in daily-life, and (3) investigate whether this association was moderated by positive, negative or disorganized schizotypy dimensions.
**METHODS:** The sample belongs to the Barcelona Longitudinal Investigation of Sensitivity and Schizotypy (BLISS 2) comprised of n = 301 non-clinical adults. Participants completed the Multidimensional Schizotypy Scales-Brief and participated in a 10-day ambulatory assessment using Experience Sampling Methodology. Individuals were randomly signaled six times daily to complete brief questionnaires assessing paranoia, PLE, and distress. Linear mixed models tested the associations between schizotypy dimensions, psychotic-like manifestations and stress-appraisals in daily life. Cross-level interactions were conducted to explore whether schizotypy moderated the relationship between psychotic-like expressions and subsequent distress. Significant interactions were examined using simple slopes analyses.
**RESULTS:** Positive and disorganized schizotypy were associated with increased paranoia (positive: $\beta = .034$, SE = .017, $p < .05$; disorganized: $\beta = .080$, SE = .015, $p < .001$), and PLEs (positive: $\beta = .070$, SE = .014, $p < .001$; disorganized: $\beta = .033$, SE = .013 $p < .01$) in daily life. Paranoia ($\beta = .580$, SE = .014, $p < .001$) and PLEs ($\beta = .479$, SE = .021, $p < .001$) predicted subsequent levels of stress appraisals. Positive schizotypy moderated the relationship between paranoia and subsequent stress ($\beta = .007$, SE = .004, $p < .10$). This effect was more pronounced for individuals with higher levels of positive schizotypy ($\beta = .083$, SE = .018, $p < .001$), who also displayed greater levels of distress after experiencing paranoia.

**DISCUSSION:** Findings showed that schizotypy dimensions are differentially expressed in daily-life, suggesting that stable trait-like schizotypy may translate to differences in daily-life fluctuations. Paranoia and PLE predicted subsequent stress appraisals, underscoring their potential for causing distress in non-clinical populations, which may contribute to a heightened risk for developing psychosis spectrum pathology. Importantly, findings also revealed the different moderating effects of schizotypy dimensions: positive schizotypy lead to increased stress after paranoia. These results reflect the role that schizotypy plays in shaping the appraisal of psychotic expressions in everyday life, providing valuable insights that could inform tailored ecological momentary interventions.

## M104. The Interaction Between Genetic Risk for Schizophrenia and for Bipolar Disorder is Associated With Structural and Functional Brain Phenotypes Linked With Mood-Related Symptoms in Patients With Schizophrenia

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**BACKGROUND:** The risk for schizophrenia (SCZ) and bipolar disorder (BD) is characterized by complex genetics with an estimated heritability of nearly 80%. Importantly, recent literature has highlighted that several genes are implicated in the risk for SCZ and for BD, and that genetic variation associated with BD is also heavily present in individuals with SCZ. In addition, SCZ and BD have shared clinical features, including mood dysregulation, which is pervasive in BD but is also commonly observed in SCZ. Thus, it is possible that a combined effect of altered genetic background relevant to SCZ and BD influences the structure and function of brain regions implicated in emotion processing, which is at the basis of mood regulation, and that this modulation is relevant to the mood-related symptoms in SCZ. In this study, we investigated the interaction between the cumulative genetic risk for SCZ and BD on brain phenotypes in healthy subjects. In addition, we tested the relationship between brain phenotypes modulated by such an interaction and mood-related symptoms in SCZ.
**METHODS:** 263 healthy participants (HP) (males=137, age=26.6 ± 7.1) were included. All HP were genotyped for variations associated with SCZ and BD. Polygenic Risk Scores (PRS) for SCZ and for BD, based on the last GWAS results, were computed using single nucleotide polymorphisms at the genome-wide level ($p < 5e-08$ - PRS_GWA_SCZ, PRS_GWA_BD) or at $p < 0.05$ (PRS_05_SCZ, PRS_05_BD). We also included 43 individuals with SCZ (males=34, age=35.7 ± 8.7) derived from the Consortium for Neuropsychiatric Phenomics database. Mood symptoms in individuals with SCZ were evaluated with the Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (YMRS). We calculated whole-brain voxel-based morphometry (VBM) on magnetic resonance imaging (MRI) data, as well as Amplitude of Low Frequency Fluctuations (ALFF) and fractional Amplitude of Low Frequency Fluctuations (fALFF) on resting-state functional MRI data in HP and SCZ. A multiple regression was used to investigate the association between PRS_SCZ and PRS_BD and their interaction on structural

and functional MRI measures, using age, sex, intracranial volume and scanner as covariates for VBM analyses and age, sex and scanner for ALFF and fALFF analyses. Significance was set at pFWE < 0.05. Spearman's correlation tests were used to investigate the relationship between signal change of the regions of interest identified in the HP sample and mood symptoms in SCZ, using age and sex as covariates.
**RESULTS:** VBM analyses in HP showed a significant interaction between PRS_GWA_SCZ and PRS_GWA_BD on the volume of the bilateral dorsolateral prefrontal cortex (DLPFC) and right primary auditory cortex. In SCZ, VBM values of the left DLPFC presented a marginally significant negative correlation with YMRS scores (rho=-0.313; p=0.046).
Functional results indicated a significant interaction between PRS_05_SCZ and PRS_05_BD in the fALFF of the left DLPFC in HP. In SCZ, fALFF values of the left DLPFC were negatively correlated with HAM-D scores (rho=-0.380; pFDR=0.038).

**DISCUSSION:** Our results suggest that the genetic risk for SCZ converges with the genetic risk for BD in affecting structural and functional measures of prefrontal areas, which are associated with mood dysregulation in SCZ. These findings could aid in identifying subgroups of individuals with high risk for schizophrenia who could benefit from treatments specifically designed to improve mood symptoms.

## M105. Effects of Δ9-THC on EEG Measures of Excitatory-Inhibitory Balance and Their Relationship to Subjective Effects

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**BACKGROUND:** There is a balance between the excitatory and inhibitory (E/I) inputs driving pyramidal cell activity that is essential for brain function and is altered in various neuropsychiatric disorders including schizophrenia. The aperiodic component of EEG signals underlies the 1/f^α (α > 0) exponential relationship between frequency and the power spectral density (PSD) of the signals. The exponent α has been shown to be inversely correlated with E/I ratio. The activation of cannabinoid type I receptors (CB1Rs) is known to disinhibit pyramidal cell activity. We hypothesized that Δ9-THC, the main active constituent of cannabis, will disinhibit neural circuits and lead to increased E/I ratio, which will be associated with the subjective effects of Δ9-THC.
**METHODS:** In this double-blind, placebo-controlled, randomized, within-subject study, 25 participants received intravenous Δ9 -THC (0.015 mg/kg, 0.03 mg/kg, and placebo) on three test days while they completed an EEG auditory oddball task. Behavioral effects were captured with the Positive and Negative Syndrome Scale (PANSS). To estimate brain circuit disinhibition, α was calculated for the pre-stimulus, attentional period of the oddball task. Generalized estimating equations (GEE) were used to assess the effect of drug condition on α, and the relationship between α and PANSS scores. Covariates were added to the models.
**RESULTS:** The analyses showed a significant effect of drug condition on the α exponent (Wald X2 =75.729, p < 0.001). Pairwise comparisons revealed significantly lower α values in both active drug conditions compared to placebo (both pAdj < 0.001). No differences between high and low doses were observed (pAdj > 0.05). The GEE longitudinal regression showed a

significant negative relationship between α and both positive (β = -0.288, Wald X2 = 5.978, pAdj = 0.014) and total (β = -0.196, Wald X2 = 3.870, pAdj = 0.049) log transformed PANSS scores. The association between α and PANSS positive scores was strengthened when pre-infusion α (β = -0.425, Wald X2 = 9.065, pAdj = 0.003) and beta-band power (β = -0.404, Wald X2 = 13.078, pAdj < 0.001) were included as covariates. Importantly, age of first cannabis use was significantly associated with preinfusion α (β = -0.101, Wald X2 = 3.901, pAdj = 0.048) in subjects who started using cannabis before the age of 18 years.
**DISCUSSION:** At psychotomimetic doses, Δ9-THC reduced the aperiodic exponent during the prestimulus period of an oddball task. Furthermore, there was a negative relationship between exponents and both PANSS positive and total scores. In view of the relationship between aperiodic exponent and E/I ratio, these results suggest that THC induces a state of circuit disinhibition that is related to the psychoactive effects of the drug. Importantly, the relationship between preinfusion exponent and age of first cannabis use suggests that baseline E/I ratio is affected by adolescent cannabis exposure and modulates the disinhibitory effect of Δ9-THC. Further studies are required to understand the acute and chronic effects of THC on E/I ratio during development and pathological states like schizophrenia.

## M106. DMRI-FLOW: Containerized Diffusion MRI Analysis Pipeline for Processing Decentralized Datasets

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**BACKGROUND:** Diffusion magnetic resonance imaging (dMRI) is a pivotal noninvasive technique for examining brain white matter. dMRI is particularly suited for detecting subtle microstructural pathologies often associated with psychiatric conditions that are typically undetectable using other structural MRI modalities. Since the pathologies are subtle, multi-site studies are needed to enhance the statistical robustness of dMRI research. However, multi-site studies face challenges such as data-sharing restrictions and the need for standardized data processing across sites. To address these challenges, we present dMRI-flow, a containerized and automated pipeline designed for decentralized dMRI analysis. By ensuring consistent preprocessing and enabling collaborative research, dMRI-flow supports projects like the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium, which adopts a decentralized approach to integrating multi-site data.
**METHODS:** dMRI-flow employs containerization technologies, specifically Docker and Singularity, to encapsulate all necessary software dependencies and configurations into a single executable package. This design allows for seamless deployment across various computational environments, eliminating compatibility concerns. The pipeline processes raw dMRI data through several automated steps: 1) Data Conversion: Converts DICOM files to NIfTI format

and organizes them into the Brain Imaging Data Structure (BIDS) 2) Artifact Correction: Removes Gibbs ringing artifacts and corrects for EPI distortions, head motion, and eddy-current artifacts using tools like FSL's Topup and Eddy 3) Brain Masking: Utilizes a machine learning-based tool to distinguish between brain and non-brain voxels 4) Diffusion Tensor Imaging (DTI) Metrics Calculation: Computes scalar maps such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) 5)Tract-Based Spatial Statistics (TBSS): Registers diffusion metrics to a standard template and projects values onto a white matter skeleton for region-of-interest analysis.
Comprehensive quality control (QC) measures are integrated throughout the pipeline, including the generation of visual aids and an interactive HTML dashboard for data inspection and sharing.

The pipeline was tested on the following hardware setups: 1) MacBook Pro: macOS Sonoma 14.6, 2.4 GHz 8-core Intel i9 processor, 32 GB RAM. 2) Windows 11 Home virtual machine: Hosted on a system with a 2.5 GHz 16-core Intel i7-11700 processor, 32 GB RAM. The virtual machine was allocated 4 virtual CPUs and 8 GB of memory. 3) Ubuntu 24.04 virtual machine: Hosted on the same hardware as the Windows setup, with the same virtual resource allocation. All tests utilized a container configured with 4 virtual CPUs and 8 GB of memory, ensuring consistent performance across platforms.

**RESULTS:** Applying dMRI-flow to a sample dMRI dataset, comprising one b=0 volume and 64 diffusion-weighted volumes at a b-value of 1000 s/mm² with a resolution of $1.75 \times 1.75 \times 3.5$ mm³, demonstrated its efficiency, reliability, and cross-platform compatibility. Processing dMRI data from two subjects took approximately 65 minutes on the MacBook Pro, 68 minutes on the Windows virtual machine, and 37 minutes on the Ubuntu virtual machine. The pipeline produced average diffusion measures of major white matter bundles in addition to detailed QC reports, including screenshots of raw images, brain masks, FA maps, and summaries of head motion and outlier slices. The resulting data were organized systematically, facilitating straightforward sharing and further analysis.
**DISCUSSION:** dMRI-flow addresses key challenges that make decentralized dMRI studies more feasible and robust by providing a standardized, automated preprocessing pipeline that is easily deployable across diverse computational environments. Its containerized nature ensures reproducibility and simplifies installation, making advanced neuroimaging techniques accessible to researchers with varying levels of technical expertise. Integrating comprehensive QC measures enhances data integrity and facilitates collaboration among multi-site research groups. The tool is currently being applied on the ENIGMA-CHR project and is available for other project through GitHub. Future developments include incorporating site-harmonization techniques to address data heterogeneity and the expansion of analysis modules to encompass multi-modal imaging data.

## M107. Clarifying Cognitive Control Deficits in Psychosis via Drift Diffusion Modeling and Functional Magnetic Resonance Imaging

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**BACKGROUND:** Previous research using drift diffusion models (DDMs) has identified that slower evidence accumulation rates and longer preparatory periods are key contributors to

cognitive control deficits in individuals with psychotic psychopathology. The triple network theory proposes that cognitive and affective disturbances in psychopathology may be driven by dysregulation in large-scale brain networks, including the default mode network (DMN), the salience network (SN), and the central executive network (CEN). However, it remains unclear how DDM parameters estimated from full DDMs reflect aberrant neural processes within the triple network during cognitive control tasks in psychotic psychopathology.
**METHODS:** People with psychosis (PwP; N=119), their first-degree biological relatives (N=77), and healthy controls (N=49) from the Psychosis Human Connectome Project each completed 120 trials of the Dot-Pattern Expectancy (DPX) cognitive control task. We fit full hierarchical Drift Diffusion Models (DDM) to response and reaction time (RT) data for individual trials to examine proactive and reactive control. We performed region-of-interest (ROI) analyses of the triple network to investigate task-related neural activation during proactive and reactive control. Mixed-effects linear regression analyses were performed to examine the association between DDM parameters estimated from participants' responses with brain activation during proactive (B vs. A) and reactive (AY vs. AX) contrasts within the triple network, while controlling for age, sex, and family-level dependencies, as well as multiple comparisons.
**RESULTS:** There were no significant group differences in brain activation during the proactive (B vs. A) contrast across the triple network ROI. However, compared to controls, PwP demonstrated significant hypoactivity during the reactive (AY vs. AX) contrast across several regions: the bilateral prefrontal cortex, anterior cingulate cortex (ACC), medial frontal gyrus, posterior cingulate cortex, precuneus, and supramarginal/angular gyrus. Relatives showed significant hypoactivity in the left prefrontal cortex, left ACC, and right supramarginal gyrus compared to controls during the reactive contrast. The drift rate difference between B and A cue trials was significantly negatively associated with left dorsolateral prefrontal cortex activation during the proactive contrast. Exploratory analysis revealed that the drift rate difference between AY and AX trials was significantly negatively associated with activation in the bilateral prefrontal cortex, supramarginal gyrus, and ACC.
**DISCUSSION:** We found that the triple network, especially DMN, CEN, and the insula, is also heavily involved in the less discussed reactive control processes. Despite comparable behavioral performance during reactive control trials, individuals with a history of psychosis exhibit greater deactivation in the DMN and reduced activation in the CEN compared to healthy controls. This suggests that the similar performance during reactive control trials in individuals with psychosis may be driven by a neural compensatory mechanism, as well as decreased demand during reactive control trials given lower established bias. Additionally, our RESULTS: indicate that DDM parameters capture inefficiencies in both proactive and reactive control processes, as evidenced by their neuroimaging correlates. This finding suggests the potential of using DDM parameters as proxies for neural activation in cognitive control studies.

## M108. Elevated Ocular TNF-Alpha Levels and Altered Visual Processing: Implications for Schizophrenia

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**BACKGROUND:** Schizophrenia is a severe neuropsychiatric disorder that is characterized by multiple visual system changes, including retinal atrophy, reduced retinal signaling, reduced visual evoked potentials, altered contrast sensitivity, and structural and functional changes in the occipital lobe. The causes of these changes are unknown, but findings in unmedicated patients and at-risk populations suggest that they are related to the disease process and are not secondary to lifestyle or treatment effects. Additionally, elevated systemic levels of TNFα, an inflammatory cytokine, have been reported in drug-naïve, first-episode schizophrenia patients and these elevated levels have also been shown to decrease with long-term antipsychotic treatment. When released by microglia in the retina, TNFα is known to promote the death of retinal ganglion cells which in turn has been linked to degenerative effects within the sequential structures of the feedforward visual system pathway, some of which are consistent with altered contrast sensitivity and altered visual response properties frequently observed in people with schizophrenia. Moreover, a recent study revealed a link between genetic variations in neuroinflammatory pathways and retinal atrophy relative to schizophrenia (Rabe et al, 2024, in pre-print).
**METHODS:** In this study, we report on a new animal (ferret) model that tests the hypothesis that neuroinflammation can generate many of the visual system changes observed in people with schizophrenia. Using optical coherence tomography, electroretinography, and single-neuron recordings, we are assessing the structural and functional alterations to early visual structures (retina, visual thalamus, primary visual cortex) following the elevation of TNFα levels in the eye after intravitreal injection.
**RESULTS:** Preliminary results suggest that loss of retinal cells depends on the concentration of TNFα injected as well as the time between injection and neuronal recordings. Moreover, following intravitreal injection of TNFα, significant retinal atrophy was observed as well as altered visual response properties including reduced firing rates, reduced contrast sensitivity, and altered spatial and temporal frequency preferences among neurons in the contralesional visual thalamus.
**DISCUSSION:** Our results suggest that our ferret model of elevated ocular inflammation will allow us to explore the neural mechanisms underlying perceptual deficits in schizophrenia at different stages of disease progression.

## M109. Neurofunctional Correlates of Working Memory in Psychosis Spectrum: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Working memory (WM) impairment is a core cognitive deficit in schizophrenia, for which there are currently no treatments. Meta-analytic findings show consistent WM performance deficits across the psychosis spectrum, including individuals at clinical high-risk for psychosis (CHR-P), at familial high-risk (FHR), first-episode psychosis (FEP) and schizophrenia spectrum disorders (SSD). Neuroimaging meta-analyses have explored functional MRI (fMRI) patterns underlying WM deficits separately in FHR, CHR-P and SSD. However, meta-analytical evidence of such fMRI patterns across the psychosis-spectrum, which may reveal distinct and overlapping brain mechanisms, is lacking.

**METHODS:** We conducted a systematic search of PubMed, Ovid, and Web of Science to identify fMRI studies comparing WM-related brain activation in psychosis spectrum groups (CHR-P, FHR, FEP, SSD) and healthy controls. Studies reporting whole-brain WM load-dependent case-control differences during the n-back task were included in a seed-based D-mapping (SDM) meta-analysis, while studies reporting region-of-interest (ROI) findings or used other WM tasks were included in a systematic review. Meta-analysis results were considered significant after family-wise error correction $p < 0.05$ at the cluster level.
**RESULTS:** A total of 93 studies were included in the systematic review (n=2,966 psychosis spectrum, n=2,815 healthy controls). From these, 69 studies involved SSD patients, while FEP, CHR-P and FHR were involved in 9, 12, and 13 studies respectively. The meta-analysis included 53 studies that met the eligibility criteria (n=1,621 psychosis spectrum, n=1,489 healthy controls). The meta-analysis revealed one significant cluster (208 voxels) showing greater activation in the superior frontal gyrus/anterior cingulate cortex (BA10/11) across psychosis spectrum groups compared to healthy controls (MNI coordinates: 6, 42, -4; $Z = -3.674$, $p = 0.019$). Analyses including only SSD participants revealed a smaller cluster (81 voxels) located at the same peak maxima, while no significant clusters were found for FHR, CHR-P and FEP analyses. The systematic review of ROI and alternative WM tasks revealed inconsistent results. The most reported region was the dorsolateral prefrontal cortex, showing hyperactivation in psychosis spectrum vs controls in 14/32 reports, hypoactivation in 12/32 reports, and no differences in 7/32 reports. Studies reporting WM stage-specific findings consistently indicated hyperactivations in regions of the default mode network.
**DISCUSSION:** Our novel whole-brain meta-analytic findings indicate a potentially shared neural mechanism underlying WM dysfunction across the psychosis spectrum. The cluster in the superior frontal gyrus/anterior cingulate cortex was likely driven towards significance by the SSD findings, as there were no sufficient findings from FHR, CHR-P, and FEP based meta-analyses that could reach significance. The systematic review including ROI-based studies showed mixed results, with little consistency across regions or groups, indicating a high heterogeneity in the WM task-based neuroimaging literature. The findings of hyperactivations in regions of the default mode network during WM retrieval warrant further investigation into differential mechanisms by WM stage in the psychosis spectrum.

## M110. Olfactory Subnetwork Abnormalities in Patients With Psychotic Disorders: A Resting State Functional Connectivity Study

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**BACKGROUND:** Patients with psychotic disorders have demonstrable impairments on many aspects of olfactory processing. Research has consistently documented higher-order olfactory deficits in these patients while decrements in basic sensory (detection threshold) performance has been less commonly observed. There is significant overlap between the olfactory pathways and psychosis neuropathology; however, the underlying brain regions responsible for these deficits has not yet been identified. Using resting state functional MRI (rsMRI) data from the Human Connectome Project, Arnold et al., (2020) identified three separable olfactory subnetworks that

they termed the sensory subnetwork, the limbic subnetwork and the frontal subnetwork. To date, these subnetworks have not been examined in patients with olfactory deficits, including in individuals with psychotic disorders. The aim of this study was to examine the olfactory subnetworks, using rsFMRI, in patients with psychotic disorders compared to a group of similarly aged healthy participants. We hypothesized that aberrant connectivity would be noted in the two higher level olfactory subnetworks (limbic subnetwork and the frontal subnetwork), but normal connectivity was anticipated in the sensory subnetwork.
**METHODS:** rsFMRI was conducted on a 1.5T GE Signa scanner in two participant groups- one group diagnosed with a psychotic disorder(n=20), the other with no known psychiatric history (n=52). Regions of interest were identified based on Arnold et al (2020) study and functional connectivity (temporal cohesion across spatially distinct regions) was computed across nodes (only within the right hemisphere). Using t-tests, the resulting activity patterns were compared across groups within each olfactory subnetwork.
**RESULTS:** As predicted, reduced functional connectivity was observed in the patient group (relative to controls) within the frontal subnetwork (anterior insula to anterior piriform/orbitofrontal cortex (OFC; $p < 0.001$)) and within the limbic subnetwork (posterior hippocampus ($p < 0.01$) and entorhinal cortex to OFC; $p < 0.04$). Within this same subnetwork, enhanced connectivity was observed between the olfactory tubercle and two subregions of the OFC ($p < 0.03$; $p < 0.019$) in the patient group relative to controls. No between group differences were observed within the sensory subnetwork.
**DISCUSSION:** These findings suggest that the impairment in olfactory performance may be associated with altered connectivity across brain regions that subserve olfactory processing. The anterior insula, the hippocampus, entorhinal cortex, and the OFC are documented to be abnormal in psychosis patients. As such, abnormalities in these regions may underlie the aberrant communication within these networks. The lack of sensory subnetwork differences was expected as lower order olfactory processing appears to be intact in these patients, while higher order olfactory processing is impaired. The reason for enhanced connectivity between the olfactory tubercle and the OFC is unclear but given the potential role of the olfactory tubercle in parallel processing of odours, this pathway may be compensating for abnormalities within the indirect (piriform cortex) olfactory pathway.

One limitation of this study was the lack of olfactory testing and as such these results may not be specific to olfaction, but to psychotic disorders. Further, these findings may permit identification of those at risk of developing a psychotic disorder. Future research should replicate these findings in a larger sample, using a more powerful magnet and extrapolating across both hemispheres.

## M111. Understanding Interoception and Emotion in Schizophrenia Using Psychophysiology and Heartbeat-Evoked Potential

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**BACKGROUND:** Interoception refers to the processing, integration, interpretation, and regulation of bodily signals by the brain. It is crucial to motivational and affective functioning

such as subjective experience of arousal (i.e., intensity of emotion). Previous studies found that people with schizophrenia reported higher arousal than healthy controls in response to neutral stimuli, and higher levels of aversive emotion in response to positive and neutral stimuli. However, it's unclear if this difference in subjective experience is due to altered interoceptive processing of normative bodily responses, or normative interoceptive processing of elevated baseline arousal state/negative emotion. This study aimed to investigate interoceptive processing and emotional experience in schizophrenia by examining heart rate changes and heartbeat-evoked potential (HEP) during varying emotional states. HEP is an event-related potential that is time-locked to heartbeats and reflects cortical processing of heartbeats. We hypothesized a potential disconnect between physiological signals, HEP, and subjective emotional experience in schizophrenia.
**METHODS:** Data collection and analysis are ongoing. The preliminary sample includes 19 participants with schizophrenia or schizoaffective disorder (SZ) and 17 healthy controls (HC). Participants viewed images while their electroencephalogram (EEG) and electrocardiogram (ECG) were being recorded, and rated their feelings of valence (i.e., pleasantness) and arousal after each image. We used multilevel modeling for group comparisons of subjective rating and heart rate changes. HEP were averaged within different stimuli conditions (negative, neutral, positive) per participant.
**RESULTS:** HC and SZ were matched on age and sex. For subjective rating during image viewing, there were significant group by condition interaction effects on both valence and arousal. Specifically, SZ rated the negative images as less unpleasant, and less intense than HC. Participants had a transient decrease in heart rate only when viewing negative images. There was no group or group by condition interaction effects for heart rate changes. When looking at the association between subjective rating and heart rate change, we found a significant effect of valence rating, and a significant group by valence rating interaction effect. Specifically, as valence rating decreases (i.e., becomes more negative), heart rate decreases in HC, but this association is not significant in SZ. Similarly, we found a significant effect of arousal rating on heart rate, but no group by arousal rating interaction effect. Lastly, for HEP amplitude, we found a positive shift in SZ relative to HC when viewing neutral images across many frontal-central channels.
**DISCUSSION:** The finding of a transient decrease in heart rate in response to negative images is consistent with previous literature. Moreover, HC's valence rating of each image was predictive of their heart rate change while viewing the corresponding image, but this relationship was not significant in SZ. In other words, SZ exhibited normative heart rate changes in response to negative images, but such physiological signals were less informative when reporting their subjective emotional experience, resulting in different ratings. We also found a positive shift in HEP amplitude when SZ viewed neutral images, despite no group differences in either subjective rating or heart rate changes. In sum, preliminary results support a disconnect between physiological, subjective, and cortical processing in SZ, suggesting that differences in emotional experience may be a result of altered cortical processing instead of abnormal physiological responses.

### M112. The Impact of Gender Inequality on Cortical Thickness in Individuals With Psychosis and Healthy Controls

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**BACKGROUND:** First-episode psychosis (FEP) patients have decreased cortical thickness (CT) compared to healthy controls (HC) as demonstrated in previous studies. However, it has been consistently demonstrated that gender is also associated with CT differences. Despite the demonstrated impact of gender inequality on mental health, the nature of possible structural brain mechanisms remains unclear, particularly in individuals with psychosis who belong to an even more vulnerable population. The purpose of this study was to explore the distinct effects of gender inequality on CT in both FEP and HC populations.

**METHODS:** One hundred twenty-five antipsychotic-naïve FEP patients and 90 healthy controls (HC) were screened and evaluated. Gender inequality and marginalization indexes were assigned to participants based on their current living address and the Mexican government report by municipality. T1-weighted MRI images were processed using the CIVET pipeline to measure CT. CT measures were compared between groups using vertex-wise diagnosis contrast analyses with gender inequality and marginalization indexes as covariates. For spatial distribution visualization, t-values were projected into a brain map of the participants' average surface. CT means were used in linear models to explore possible correlations with socio-clinical demographic variables.

**RESULTS:** The final sample included 56 FEP patients (DUP mean in weeks=145.79) and 52 HC. The mean CT was lower in FEP (t=2.56, p=0.01). Comparisons by gender revealed a lower mean CT in females both in FEP (t=2.84, p=0.01) and in HC (t=2.55, p=0.01). Right and left hemisphere mean CT were inversely correlated with the gender inequality index in HC (left hemisphere r=-0.39, p=0.01, right hemisphere r=-0.36, p=0.01) but not in FEP (left hemisphere r=-0.26, p=0.05, right hemisphere r=-0.25, p=0.06). Worse marginalization index also correlated with mean CT in HC (left hemisphere r=0.46, $p < 0.01$, right hemisphere r=0.45, $p < 1$) but not in FEP (left hemisphere r=0.08, p=0.58, right hemisphere r=0.05, p=0.72). In vertex-wise analysis with the full sample, higher gender inequality index was associated with lower CT in the right middle frontal gyrus, left inferior and orbital frontal gyri, left superior temporal gyrus, right superior, middle and inferior temporal gyri, bilateral anterior and posterior cingulate cortex at a 10% FDR. Worse marginalization index was associated with lower CT in the medial right temporal lobe at a 10% FDR.

**DISCUSSION:** Worse gender inequality and marginalization are associated with decreased CT with specific neuroanatomical distributions. Furthermore, the relationship of overall mean CT with gender inequality and marginalization is not as straightforward for FEP as it is for HC, possibly implying more complex variables in the FEP population. Further studies are needed to explore the potential consequences of detrimental sociocultural factors on brain structure, especially in vulnerable populations such as FEP.

## M113. Theta Oscillatory Activity is Associated With Modulation of Sensory Cortical Activity in Psychotic Psychopathology

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**BACKGROUND:** During processing of ambiguous visual stimuli, high-level information such as the contours of known objects can guide perception and facilitate object identification. The influence of high-level (i.e., top-down) information may be evident in the activation of early visual areas. It has been proposed that oscillations in the electrical fields of the brain are a mechanism by which top-down information is conveyed to sensory areas to guide perception. Psychotic psychopathology may result, in part, from aberrations in the interactions between these top-down and low-level (i.e., bottom-up) perceptual processes. Indeed, aberrant activation in sensory brain regions and reduced oscillatory signaling have both been associated with psychotic illness. The present investigation seeks to link these effects in a sample of probands with psychosis, their biological siblings, and healthy controls.

**METHODS:** Probands with psychosis (schizophrenia spectrum (SZ = 27) and bipolar disorder (BP = 13)), their biological siblings (REL = 17) and healthy controls (HC = 27) completed the Fragmented Ambiguous Object Task, which varies high-level features by presenting meaningful (MF) vs meaningless (ML) ambiguous objects while controlling for bottom-up visual features. This task was completed twice: first while MEG data were collected, with oscillatory power to MF and ML stimuli quantified using Morlet wavelet convolution in theta and alpha frequency bands. Second, 7T fMRI data were collected on a subset of participants (probands = 15, REL =12, HC = 23), and top-down modulation of BOLD activity was assessed using MF – ML contrasts. Regions of interest (ROIs) were functionally defined from cluster corrected ($p < .001$) thresholds in an all-subjects MF – ML contrast.

**RESULTS:** Analyses of MEG data revealed a group difference in occipital theta ($F(3,74) = 4.21$, $p=.008$), which was reduced in SZ and marginally reduced in REL compared to HC, but no significant impact of condition (MF vs ML) on theta power. No effects emerged for occipital alpha power. Analyses of fMRI data revealed group differences in condition-dependent modulation of BOLD activity in the left fusiform ($F(3,46)=3.08$,$p=.036$), parietal ($F(3,46)=4.2$,$p=.01$), and precentral ROIs ($F(3,46)=3.1$, $p=.036$), with the greatest condition-dependent modulation in REL and the least in HC. The same direction of effects was found in these areas in the right hemisphere, but without significant differences (p's = .09, .10, and .11). Bivariate correlations revealed associations between condition-dependent modulation of MEG theta power and condition-dependent BOLD modulation of the left and right fusiform (L: $r=-.328$, $p = .02$, R: $r=-.305$, $p = .03$) and intraparietal sulcus (L: $r =-.359$, $p =.01$, R: $r =-.294$, $p = .04$) and right sensorimotor ($r=-.291$, $p = .04$) ROIs. No associations emerged with alpha.

**DISCUSSION:** We used fMRI and MEG to quantify the modulation of neural activity in response to visual stimuli with embedded ambiguous objects that were either identifiable (i.e., meaningful [MF]) or unidentifiable (i.e., meaningless [ML]). We specifically contrasted activity for MF and ML to determine neurophysiological responses that were associated with high-level (i.e., top-down) processes elicited during object detection. RESULTS: support a reduction of occipital theta power in SZ and, to a lesser extent, REL. We also found group differences in condition-dependent modulation of BOLD activity in left hemisphere fusiform, parietal, and precentral regions. Furthermore, condition-dependent modulation of theta power was negatively associated with condition-dependent modulation of BOLD activity. Such findings support theta power as a possible mechanism of bottom-up communication rather than as a top-down signal.

**M114. ALTO-101 Modulates EEG Biomarkers Linked to Cognitive Impairment in Schizophrenia: Evidence From a Phase 1 Trial and BSNIP Studies**

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**BACKGROUND:** Cognitive impairment associated with schizophrenia (CIAS) is a major determinant of long-term outcomes, yet no approved pharmacological treatments are currently available. Drugs that increase intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling have shown promise as pro-cognitive and mood-enhancing therapeutics in animal models and early-stage clinical trials. ALTO-101 is an inhibitor of phosphodiesterase-4 (PDE4) and has been shown to increase cAMP levels in brain regions critical for cognition, memory, and mood, suggesting its potential as a novel treatment for CIAS. In this study, we aimed to identify electroencephalography (EEG)-based pharmacodynamic (PD) biomarkers for ALTO-101 that may indicate its effects on CIAS.

**METHODS:** We integrated findings from our Phase 1 study of ALTO-101 with data from the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP 1 and 2) studies. In the Phase 1 study, 40 healthy adult volunteers aged 40–64 were enrolled in a randomized, double-blind, placebo-controlled trial. Each participant received a single oral dose of placebo, 0.5 mg ALTO-101, and 1.5 mg ALTO-101 in a three-way counterbalanced crossover design, with a 7-day washout period between doses. During the evaluation of the acute phase of drug effects, participants underwent EEG assessments, including resting-state EEG (rsEEG) and event-related potentials (ERPs). In the BSNIP data, we conducted analyses on a participant group that mirrored the population used in CIAS trials, involving 625 patients with schizophrenia or schizoaffective disorder and 641 healthy controls. We assessed various schizophrenia-related EEG/ERP features in terms of patient-control differences and their associations with cognitive performance. To emphasize reproducibility, we divided the data into discovery and test sets for replication.

**RESULTS:** Regarding ERP outcomes, ALTO-101 enhanced the magnitude of mismatch negativity ($d = 0.53$, $p = 0.02$ for 1.5 mg; $d = 0.38$, $p = 0.07$ for 0.5 mg) and increased inter-trial coherence (ITC) in the theta ($d = 1.05$, $p < 1e\text{-}4$ for 1.5 mg; $d = 0.33$, $p = 0.09$ for 0.5 mg) and gamma bands ($d = 0.68$, $p < 0.01$ for 1.5 mg; $d = 0.35$, $p = 0.08$ for 0.5 mg) in response to standard auditory stimuli. For rsEEG, ALTO-101 decreased relative theta power ($d = 0.88$, $p < 0.001$ for 1.5 mg; $d = 0.51$, $p = 0.02$ for 0.5 mg). In the BSNIP data, we found that task-related theta responses, including theta ITC and event-related spectral perturbation (ERSP), exhibited the largest patient-control differences and best correlated with cognitive performance. Specifically, theta ITC to standard auditory stimuli correlated positively with global cognition ($r = 0.13$, $p = 0.04$) and processing speed ($r = 0.25$, $p < 1e\text{-}4$) within the patient group. These correlations were successfully replicated in the test set ($r = 0.15$, $p = 0.026$ for global cognition; $r = 0.18$, $p < 0.01$ for processing speed).

**DISCUSSION:** These findings demonstrate strong PD effects of ALTO-101 in modulating key brain processes associated with CIAS as measured by EEG. The data support further development of ALTO-101 for the treatment of CIAS.

## M115. Along-Tract White Matter Abnormalities and Their Clinical Associations in Recent-Onset and Chronic Schizophrenia

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**BACKGROUND:** Structural impairments in white matter tracts are well-documented in schizophrenia, though their clinical implications remain limited. Most previous studies using diffusion-weighted MRI (dMRI) and tractography relied on averaged diffusion indices, potentially obscuring localized changes in white matter tracts. Tractometry enables the investigation of localized changes at specific points along white matter tracts.
**METHODS:** We used dMRI and centerline tractometry to examine along-tract white matter abnormalities in 55 patients with recent-onset schizophrenia, 69 with chronic schizophrenia, and 77 healthy controls. Fractional anisotropy (FA) and peak length were measured at individual points along tract trajectories. Group differences in diffusion indices and their associations with clinical variables, including the Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF), were analyzed using linear mixed models and Spearman's rho.
**RESULTS:** In recent-onset schizophrenia, deviations in peak length were identified in multiple white matter tracts, and reduced FA in the genu and splenium of the corpus callosum correlated with PANSS positive, negative, general, and total scores, as well as GAF scores. In chronic schizophrenia, widespread FA reductions were observed across various white matter tracts, while peak length in projection tracts was significantly associated with PANSS general and GAF scores.
**DISCUSSION:** This study identified along-tract white matter abnormalities in recent-onset and chronic schizophrenia and revealed their associations with clinical symptoms. Localized measurements along tract trajectories enhance the detection of clinically relevant abnormalities compared to traditional methods relying on averaged diffusion indices.

## M116. Reduced Segregation in Social Brain Networks Related to Social Cognitive Performance Across Autism, Schizophrenia Spectrum Disorders, and Controls

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**BACKGROUND:** Schizophrenia (SSD) and autism spectrum disorders (autism) are characterized by atypical social cognition, which includes lower-level (e.g., emotion recognition) and higher-level (e.g., theory of mind) social cognitive domains. Lower-level social cognition has been related to connectivity in the limbic system and right frontoparietal regions (i.e., the mirror neuron system [MNS]), and higher-level social cognition has been related to connectivity

in the cortical midline structures and lateral temporoparietal regions (i.e., the mentalizing network [MENT]). In this study, we examined how the configurations of these two network systems relate to social cognition across a transdiagnostic sample including autism, SSD, and typically developing control (TDC) participants.
**METHODS:** fMRI derived functional connectivity metrics collected during empathic accuracy (EA) fMRI task performance from 454 participants (autism: N=86; SSD: N=189; TDC: N=179) was analyzed by covSTATIS (i.e., multi-table multidimensional scaling) followed by a 2-dimensional varimax rotation to extract latent dimensions that characterize brain configurations during EA task performance. With NeuroSynth, we categorized brain regions as MNS or MENT according to previous findings related to "mirror" or "empathy" (for MNS) or "mentalizing" (for MENT). As NeuroSynth did not identify the complete MNS, we further used the activation map from an imitation/observation task to identify additional MNS regions. The factor scores of regions from MNS and MENT were then analyzed by partial least squares correlation (PLSC) to examine their associations with 11 social cognition measures, including 4 subscales (i.e., angry, fear, happy, sad) from the Penn Emotion Recognition Test (ER40), Reading the Mind in the Eyes Test (RMET), and The Awareness of Social Inference Test – Revised (TASIT), including 6 subscales: TASIT 1, identifying emotions; TASIT 2 minimal social inferences including sincere, simple sarcasm, and paradoxical sarcasm; and TASIT 3 measuring social inferences (lies and sarcasm) with enriched contextual cues. The reliability and stability of the PLSC results were examined with permutation (1000 iterations), bootstrap (1000 iterations), and 10-fold cross-validation.
**RESULTS:** The first two covSTATIS dimensions explained 16.84% of the signal with Dimension 1 identifying the visual-auditory (perceptual) axis and Dimension 2 identifying the MNS-MENT (social) axis. The multivariate associations between these two dimensions and the 11 social cognitive measures were examined by PLSC and revealed one significant dimension ($p < .001$; explaining 73.43% of covariance). This PLSC dimension identified general associations between social network configuration and social cognitive performance. Across our transdiagnostic sample, better social cognitive performance was related to more segregation along the visual-auditory axis, specifically more distinct language and default mode networks from the visual end of the axis (bootstrap test with $p < .05$). Interestingly, better social cognitive performance was related to less segregation along the MNS-MENT axis, specifically the regions in the language and the visual canonical networks (bootstrap test with $p < .05$).
**DISCUSSION:** Using covSTATIS to examine network configuration using brain connectivity data derived during EA fMRI task performance, we identified a latent brain dimension of social network systems that map onto the MNS and MENT networks. The PLSC results provide insights into the transdiagnostic relationship (i.e., across our sample of autism, SSD, and TDC participants) between the configuration of social brain networks and social cognition. Results showed that better social cognition is related to the segregation of networks involved in perceptual and social processing.

### M117. Physical Neglect and Neuroconnectivity in Emotional Regulation of Schizophrenia

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**BACKGROUND:** Emotional regulation (ER) is essential for social functioning and is severely impaired in schizophrenia (SZ), affecting social cognition and emotional processing. Top-down control processes and bottom-up phenomena, where the amygdala plays a key role, may be involved in these ER deficits. Adverse childhood experiences (ACEs) have been shown to influence the brain circuits responsible for ER, though their impact on the functional connectivity (FC) of these circuits in SZ is not fully understood. This study aims to explore the relationship between ACEs, amygdala functional connectivity, and emotional regulation in patients with SZ.
**METHODS:** The study included 41 participants (20 SZ patients and 21 healthy controls, HC) aged 18 to 60 years. Resting-state fMRI imaging and seed-based analysis were used to evaluate the amygdala's FC with the rest of the brain, while questionnaires were employed to measure ACEs (CTQ), emotional regulation difficulties (DERS), and cognitive regulation strategies (CERQ).
**RESULTS:** Results showed that SZ patients were exposed to a higher number of ACEs ($p = 0.031$) compared to controls, had greater difficulties in emotional regulation ($p < 0.001$), and exhibited a more maladaptive ER strategy profile ($p < 0.001$). FC analyses revealed that greater exposure to physical neglect was associated with lower amygdala connectivity to brain regions involved in ER ($p < 0.001$), such as the frontal pole, orbitofrontal cortex, middle frontal gyrus, and anterior cingulate cortex. This connectivity deficits between amygdala and prefrontal regions was associated with higher emotional dysregulation and lower use of adaptive strategies in SZ. In contrast, HC showed an opposite pattern.
**DISCUSSION:** These results suggest that ACEs may disrupt the top-down control mechanisms necessary for adaptive ER in SZ. Furthermore, higher FC between the amygdala and prefrontal regions in SZ was associated with less emotional dysregulation and better use of adaptive ER strategies. These findings highlight the role of fronto-limbic connectivity in supporting compensatory ER strategies in SZ and underscore the clinical potential of addressing ER difficulties in this population.

## M118. Shared Genetic Effects Among Schizophrenia, Substance use Disorder, and Hippocampal Volume in a Multiplex Extended Pedigree Sample

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**BACKGROUND:** Individuals with schizophrenia are at increased risk for substance use disorders (SUD; 28-47% versus 14.6% in the general population) and comorbid SUD is associated with a host of negative clinical and functional outcomes. The reasons for this comorbidity are largely still unknown, though overlapping genetic effects may increase risk for both disorders. Such genetic effects may manifest in variations in brain structure phenotypes, which have been consistently observed independently in both schizophrenia and SUD; however,

no studies have identified how genetic effects that are shared between schizophrenia and SUD may impact brain structure. The current study examined if shared genetic effects jointly increase risk for both schizophrenia and SUD and if shared genetic effects on brain structure phenotypes mediate this relationship.
**METHODS:** Data were collected using a multiplex extended pedigree design ascertained through schizophrenia probands (total sample N=1,306, with N=789 relatives ascertained from 52 multigenerational families and N=517 unrelated controls) and a subsample of participants completed structural imaging scanning (total N = 506, with N=230 relatives and N=276 unrelated controls) to investigate the degree to which genetic effects are shared among schizophrenia, four SUDs (any SUD, alcohol use disorder, cannabis use disorder, and daily nicotine use) and structural MRI measures of surface area, cortical thickness, and subcortical volumes.
**RESULTS:** As predicted, schizophrenia was significantly genetically correlated with any SUD (Rg = 0.27, p = 0.033), alcohol use disorder (Rg = 0.35, p = 0.006), and cannabis use disorder (Rg = 0.24, p = 0.011). Next, using a subset of the sample that underwent structural magnetic resonance imaging (N=506), brain structure phenotypes genetically correlated with both schizophrenia and SUD were identified. Only hippocampal volume was significantly genetically correlated with both schizophrenia (Rg = -0.53, p = 0.001) and any SUD (Rg = -0.57, p = 0.043). Furthermore, genetic effects shared between schizophrenia and SUD were significantly statistically mediated by the genetic effects on hippocampal volume (standardized indirect effect, ab = 0.32; 95% CI = 0.25, 0.38; standardized direct effect, c' = -0.05; 95% CI = -0.13, 0.04).
**DISCUSSION:** These findings indicate that shared genetic effects play a significant role in the comorbidity between schizophrenia and SUD and suggest a unique role of the hippocampus in the pathophysiology of both schizophrenia and SUD.

## M119. Formal Thought Disorder Characteristics of Schizophrenia Patients Using Clozapine, Other Oral and Long Acting Injectable Antipsychotics

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**BACKGROUND:** Formal thought disorder (FTD), a core symptom of schizophrenia, is a dimensional construct that can be grouped into positive vs. negative and objective vs. subjective symptom domains. Detailed evaluation of these subdimensions is important to better understand FTD. Although FTD is thought to partially improve after psychotic episodes, knowledge about how various FTD characteristics manifest in patients receiving different treatments is limited. This study aims to compare FTD dimensions in schizophrenia patients treated with clozapine, other oral and long acting injectable antipsychotics (LAI).
**METHODS:** Participants consisted of N=170 schizophrenia patients. The sociodemographic and clinical information were recorded. The Positive and Negative Syndrome Scale (PANSS) and the Turkish version of Thought and Language Disorder Scale (TALD) were administered. Comparisons of TALD factor (objective positive [OP], objective negative [ON], subjective positive [SP], subjective negative [SN]) and item scores were made between clozapine (N=80) and other antipsychotic (N=90) groups. Additionally, binary comparisons were conducted

between LAI users (N=37) and clozapine users (N=74), between LAI users (N=37) and non-clozapine oral antipsychotic users (N=49), and between LAI users (N=37) and all oral antipsychotic users (N=123). Binary group comparisons were analyzed with Student's t and Mann-Whitney U tests. When comparing TALD items, the Bonferroni correction method was used (adjusted $p \leq 0.001$). After univariate analyses, binary logistic regression analysis was made using backward elimination for variables with $p < 0.25$.
**RESULTS:** Clozapine-users did not differ from non-clozapine antipsychotic users in PANSS scores, TALD total and factor scores. However, they had significantly higher concretism scores (TALD-ON) compared to non-clozapine antipsychotic users (p=0.001). In regression analysis, younger age at illness onset (OR=0.93, 95% CI=0.88 – 0.98), higher concretism (OR=1.69, 95% CI=1.18-2.43) and rupture of thought (OR=1.86, 95% CI=1.11 – 3.10) scores in TALD-ON, and lower inhibited thinking (OR=0.57, 95% CI=0.36 – 0.91) score in TALD-SN and lower verbigeration score (OR=0.45, 95% CI=0.21 – 0.98) were associated with clozapine use. In paired comparisons according to LAI use; LAI users had lower TALD-SP scores than all oral antipsychotic users (p=0.006), clozapine users (p=0.024) and non-clozapine oral antipsychotic users (p=0.003). Regression analyses further showed that higher poverty of thought scores (TALD-SN) were significantly associated with LAI use compared to non-clozapine oral antipsychotics (OR=0.29, 95% CI=0.14–0.58), clozapine (OR=0.49, 95% CI=0.29–0.87), and all oral antipsychotics (OR=0.49, 95% CI=0.31–0.78).
**DISCUSSION:** Considering that clozapine was started due to treatment resistance and patients on clozapine may be more severely ill, these results suggest that while clozapine may have a positive effect on positive FTD, its effect on negative FTD is limited. This is consistent with previous studies reporting that negative FTD is less responsive to treatment. The association between clozapine use and lower inhibited thinking scores in subjective negative FTD suggests that clozapine may be associated with improvement in subjectively experienced thought disorders. Based on comparisons with patients using LAI, subjective positive FTD scores were lower in LAI users than other groups. Also, higher poverty of thought scores in subjective negative FTD were associated with LAI use. The majority of studies evaluating the response of FTD to treatment, focus on total scale scores rather than specific FTD subdimensions. Comparisons between different antipsychotics are also limited. Additionally, while studies suggest that LAI use improves disorganized thought, there is a lack of detailed research on its effects on FTD subdimensions. This study's cross-sectional design and lack of side-effect evaluation are notable limitations. As FTD correlates with functioning, treatment effects on FTD warrant further investigation and longitudinal studies are needed in this matter.

## M120. The Totems Phase II Clinical Trial Targeting Cognitive Impairment Associated With Schizophrenia: Acute Effects of Partial Positive GABA(A)-Receptor Modulation by GT-002 on Psychophysiological Measures

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**BACKGROUND:** Cognitive impairment associated with schizophrenia (CIAS) significantly influences patients' functioning and quality of life, while effective treatments are lacking. Disruptions of the GABAergic system may contribute to hypofrontality, which is considered a key mechanism underlying CIAS. GT-002, a novel orally available drug candidate developed by Gabather AB acting as a GABA(A) receptor partial positive allosteric modulator, has shown promising preclinical results in schizophrenia models and demonstrated safety and tolerability in Phase I clinical trials involving healthy volunteers.
We present the design of the first Phase II clinical trial using GT-002 in a patient population.

**METHODS:** This single-center, double-blind, placebo- and active-comparator-controlled, randomized, four-way crossover trial will investigate the effects of GT-002 in 20 patients with schizophrenia spectrum disorders (SSD) and 30 healthy controls. We will assess the psychophysiological and cognitive effects of GT-002 (1 mg and 2 mg) compared to Oxazepam (15 mg), and placebo. Each participant will complete four study drug exposure sessions, in each session receiving one dose of each of the four study drugs in a randomized sequence, with at least a 7-day interval between sessions. Psychophysiological measures, including event-related electroencephalography (EEG) and electromyography (EMG), as well as resting-state EEG, will serve as proxy measures of hypofrontality. Cognitive tests will include the Trail Making Test, selected subtasks from the Brief Assessment of Cognition in Schizophrenia (BACS), and selected tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB).
**RESULTS:** This trial’s primary endpoint is the change in pre-pulse inhibition of the startle reflex (PPI) in patients with SSD following exposure to GT-002, placebo, or oxazepam. Secondary endpoints include alterations in psychophysiological measures from the mismatch negativity (MMN), selective attention (SA), 40-Hz auditory steady-state response (40-Hz ASSR) and resting-state EEG paradigms in SSD patients after experimental study drug exposures. Exploratory endpoints assess the safety and tolerability of GT-002, the differential acute effects of GT-002, oxazepam, and placebo on cognition, and their effects on EEG paradigms in healthy controls.
**DISCUSSION:** This Phase II clinical trial represents the first investigation of the acute effects of partial positive GABA(A) receptor modulation by GT-002 on psychophysiological and cognitive measures in SSD patients and marks an important step toward identifying effective pharmacological treatments for CIAS. If GT-002 demonstrates favorable effects, it could represent a novel therapeutic option for this highly vulnerable population.
The TOTEMS Phase II Clinical Trial is an investigator-initiated collaborative study between the Center for Neuropsychiatric Schizophrenia Research (CNSR) as the investigator and Gabather AB as the pharmaceutical partner. The trial is funded by a Grand Solutions grant from the Innovation Fund Denmark (IFD, grant ID: 3146-00002B), awarded to the sponsor.

## M121. Chemical Chaperones for the Prevention of Antipsychotic-Induced Impairments in Glucose Metabolism

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**BACKGROUND:** Antipsychotic medications are used to treat schizophrenia and often prescribed on- and off-label for other psychiatric disorders. However, their use increases the risk of type 2 diabetes. While antipsychotics induce weight gain, a risk factor for type 2 diabetes, they can also cause pronounced glucose dysregulation independent of weight gain. This effect is mediated in part through the central nervous system. Specifically in the hypothalamus, insulin and nutrients, including glucose and lipids, act to suppress glucose production by the liver (endogenous glucose production, EGP). This ordinarily helps maintain glucose homeostasis in the body. We have previously found that the antipsychotic olanzapine (OLA) blocks the ability of intracerebroventricular (ICV) insulin to suppress EGP, in association with endoplasmic reticulum (ER) stress, accompanied by impaired insulin via the PI3K pathway. ER stress, when localized to the hypothalamus, is known to disrupt glucose metabolism, including elevated glucose production by the liver. Chemical chaperones such as sodium 4-phenylbutyric acid (PBA) and tauroursodeoxycholic acid (TUDCA) assist in protein folding and have been shown to improve insulin sensitivity and overall glycemic control. Therefore, the objectives of this project are to examine if olanzapine's acute inhibition of central insulin action can be reversed via the co-administration of peripheral chemical chaperones and to examine if this effect occurs via the reversal of hypothalamic ER stress.

**METHODS:** Pancreatic euglycemic clamps, the gold standard technique to assess in vivo glucose metabolism, were used in this study. Sprague Dawley rats underwent two surgeries; first, cannulae were implanted into the third ventricle for intracerebroventricular administration of hormones. Second, after a 7-day recovery, the jugular vein and carotid artery were cannulated for infusions and blood sampling, respectively. On the study day, insulin, at a concentration established to suppress EGP or a vehicle, was administered via ICV, while OLA, or a vehicle, were delivered subcutaneously. Plasma insulin was replaced with a constant intravenous infusion, along with a glucose solution to regulate blood glucose levels. Intravenous chemical chaperones began along with the ICV infusate and continued for the whole duration of the experiment, at a dose previously determined to restore insulin sensitivity. Groups included (central-subcutaneous-intravenous): vehicle-vehicle-vehicle (n = 8), insulin-vehicle-vehicle (n = 5), vehicle-OLA-vehicle (n = 4), insulin-olanzapine-vehicle (n =7), vehicle-vehicle-PBA (n = 5), and insulin-OLA-PBA (n = 6). Following the experiment, tissues were collected including the hypothalamus, which to be used for western blot analysis of ER stress markers.

**RESULTS:** There were no differences in peripheral glucose levels. As expected, ICV insulin increased the infusion rate of glucose required to maintain euglycemia, a measure of whole-body insulin sensitivity, relative to ICV vehicle (vehicle-vehicle-vehicle: 3.51 SE = 1.32, insulin-vehicle-vehicle: 9.85 SE = 0.82; $p < 0.0001$). In agreement with past literature, this effect was then abolished via administration of OLA (insulin-OLA-vehicle: 3.40 SE = 0.75; $p < 0.0001$). However, there was no treatment effect noted with intravenous 4-phenylbutyric acid administration (insulin-OLA-PBA: 3.87 SE = 1.52; $p > 0.1$), suggesting that chemical chaperones on their own are not able to recapitulate central insulin action in the presence of olanzapine. Remaining groups did not demonstrate significance from vehicle-vehicle-vehicle (vehicle-OLA-vehicle: 3.81 SE = 0.90, vehicle-vehicle-PBA: 4.43 SE = 1.57; $p > 0.1$).

**DISCUSSION:** We replicate that effects of ICV insulin administration on whole body insulin sensitivity are abolished by OLA. We did not report an effect of chemical chaperone (PBA) administration, suggesting that this novel treatment is not effective at relieving the OLA-induced impairments of glucose homeostasis. This study was however not without limitations, some of which including the acute administration of OLA and chemical chaperones, as well as the use of only male rats.

## M122. The Acute Effect of Cannabinoids on Cognitive Task Performance: A Bayesian Meta-Analysis

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**BACKGROUND:** Cannabis use is frequently associated with cognitive impairment. However, the differential effects of different cannabinoids on cognition remain unclear. Delta-9-tetrahydrocannabinol (THC), the major psychoactive and psychotomimetic component of cannabis has been reported to have a negative impact on memory and learning (Paul and Bhattacharyya, 2020; Ranganathan et al., 2017; Schoeler et al., 2016). Interestingly, CBD, another major (but non-intoxicating) component of cannabis, has shown opposite effects to THC in numerous brain regions during a variety of cognitive fMRI tasks. If the opposing neuroimaging effects of CBD vs THC are also reflected in differential effects on cognition, it is possible that CBD could improve cognitive functions that are impaired by THC. However, whether CBD and THC have opposite effects on cognition itself remains inconclusive, due to the limited sample sizes and the highly heterogeneous task designs implemented in previous studies.
**METHODS:** This is a Bayesian meta-analysis aimed to evaluate the effects of cannabidiol on response time and accuracy of cognitive tasks compared to placebo, synthesizing data from both between-subject and within-subject study designs. After the searching of papers on PubMed and PsycINFO, eligible studies were selected if it is randomized controlled trials (RCTs) involving human participants and reporting quantitative outcomes of response time and accuracy on cognitive tasks. Effect-size estimates (Hedges' g) were then extracted from each included study to quantify the standard mean differences in task performance between THC and placebo (PLB) or CBD and PLB. Meta-analyses were conducted separately on the accuracy rate and response time of tasks on all domains and separate domains of cognition.
**RESULTS:** The estimated effect size of CBD studies indicated no significant impact on individual cognitive domains or overall cognitive performance. In contrast, THC demonstrated significant impairments, with a decrease in accuracy rate across pooled cognitive tasks ($g = -0.46$) and a slower response time ($g = -0.26$). Significant domain-specific negative effects were observed in accuracy rates of non-working memory tasks ($g = -0.40$), working memory tasks ($g = -0.79$), executive function tasks ($g = -0.79$), processing speed tasks ($g = -0.35$), attention tasks ($g = -0.43$), and language tasks ($g = -0.38$). However, THC showed no significant effect on the motor/construction domain. When examining the effects of paper tested effect of THC across multiple domains within the same cohort, working memory was significantly impaired ($g = -0.54$), whereas executive function ($g = -0.33$) and non-working memory ($g = -0.44$) did not show significant effects. Within the non-working memory, working memory, executive function,

and attention domains, the effect of THC has more than a 90% probability of exhibiting a medium effect ($g \leq -0.3$) or worse compared to placebo on the accuracy rate of tasks.
**DISCUSSION:** The findings suggest that CBD does not significantly affect cognitive function across various domains, supporting its safety for use. In contrast, THC was found to impair cognitive abilities in six areas, with particularly strong effects on working memory and executive function. However, there is currently insufficient evidence to directly compare the effects of THC and CBD on specific cognitive abilities. Additionally, studies using intravenous methods showed more consistent results, indicating that this approach may be more reliable for future research.

## M123. Comparative Efficacy, Safety, and Tolerability of Xanomeline and Trospium Chloride Versus Eight Atypical Antipsychotics for the Acute Treatment of Adults With Schizophrenia – A Network Meta-Analysis

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**BACKGROUND:** To expand prior network meta-analyses investigating the relative efficacy, safety, and tolerability of xanomeline and trospium, for the acute treatment of schizophrenia.
**METHODS:** An updated systematic literature review (SLR) was undertaken, building on a 2019 SLR, to identify RCTs of eight oral antipsychotics for acute treatment of adults with schizophrenia. Our SLR identified new publications from January 1st 2019 to March 20th 2024 and re-evaluated previously identified records against new inclusion criteria.
Bayesian NMAs were conducted for eleven outcomes: clinical response (≥30% decrease in Positive and Negative Syndrome Scale [PANSS] total score), all-cause discontinuation, discontinuation due to adverse events, sedation, somnolence, clinically significant weight gain (≥7% increase), change from baseline (CFB) PANSS scores (total, positive symptoms, and negative symptoms), CFB Clinical Global Impressions – Severity (CGI-S) score, and CFB weight.

**RESULTS:** Xanomeline/trospium treatment significantly improved odds of clinical response versus aripiprazole (odds ratio [OR]: 1.85; 95% credible interval [CrI]: 1.11, 3.11), brexipiprazole (OR: 2.23; 95% CrI: 1.34, 3.83), and cariprazine (OR: 2.05; 95% CrI: 1.19, 3.57), increased odds of all-cause discontinuation versus all comparators except cariprazine, and reduced odds of clinically significant weight gain versus aripiprazole, brexipiprazole, cariprazine, lumateperone, olanzapine, quetiapine, and risperidone. Further favorable RESULTS: for xanomeline/trospium included improvements in: CFB CGI-S versus aripiprazole, brexpiprazole, cariprazine, and olanzapine, CFB PANSS positive symptoms score versus brexpiprazole, and CFB weight versus brexiprazole, clozapine, olanzapine, quetiapine, and risperidone.
**DISCUSSION:** Xanomeline/trospium demonstrated improved clinical response and reduced weight gain compared with several existing oral antipsychotics.

## M124. The Impact of Prescriber Attitudes in Germany on Early Detection and Intervention for Treatment-Resistant Schizophrenia – An Online Survey

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**BACKGROUND:** Thirty percent of all patients with schizophrenia develop resistance to standard antipsychotic treatment (treatment-resistant schizophrenia, TRS). Approximately 80% of these cases emerge during the first episode. Clozapine remains the only effective antipsychotic drug for TRS but is severely underused. Notably, mirroring findings for the duration of untreated psychosis, a delay in initiating clozapine has a detrimental impact on response rates and long-term outcome. Clozapine underutilization is mainly attributable to a widespread fear of potential side-effects, perceived obstacles regarding monitoring requirements and lack of experience regarding clozapine use and TRS detection among prescribers. However, due to differences in health-care settings these factors cannot be applied directly to Germany. Consequently, we assessed factors contributing to clozapine underutilization among prescribers in Germany.
**METHODS:** Employing an online survey, we assessed attitudes towards clozapine. This included clinicians' experience regarding clozapine use, and TRS detection, perceived barriers, familiarity with guidelines, and presumptions regarding patients' attitudes towards clozapine.
**RESULTS:** Of 116 psychiatrists who completed the survey, the majority were board certified psychiatrists. All participants reported regularly using clozapine and expressed confidence in its management. Approximately, 84% of respondents were familiar with current national guidelines. However, a significant proportion did not adhere to these guidelines, often conducting at least one trial of polypharmacy before initiating clozapine. Interestingly, respondents who had attended additional training on clozapine use were less likely to prefer polypharmacy before clozapine. Regarding clozapine's efficacy, most participants agreed that clozapine is superior in reducing all-cause mortality, aggressive behavior, suicidality and both positive and negative symptoms. However, only one-third of participants believed that clozapine reduces cardiovascular mortality. A notable portion of participants indicated that they presumed patients would decline clozapine. Monitoring requirements, weight gain and blood dyscrasia were regarded as the main barriers.
**DISCUSSION:** Our preliminary findings provide a better understanding of factors contributing to clozapine underutilization in Germany. Despite familiarity with guidelines, many participants preferred polypharmacy prior initiating clozapine. Additionally, only one-third of participants believed that clozapine reduces cardiovascular mortality. Our findings regarding perceived barriers align with findings from other developed countries. Implementing targeted training programs and a widespread establishment of early detection and intervention services might facilitate a timely diagnosis of TRS and clozapine initiation.

## M125. Mono-Clonal Antibodies for Schizophrenia: Preliminary Results of an Individual Patient Data Meta-Analysis

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**BACKGROUND:** One of the hypotheses regarding the etiology of schizophrenia is that inflammatory mechanisms are involved in its pathophysiology. This is supported by studies showing that patients with schizophrenia have increased brain, plasma and serum levels of Interleukin-6 (IL-6) and Interleukin 1-beta (IL-1β). The Stanley Medical Research Institute funded three RCTs administering monoclonal antibodies for the treatment of schizophrenia: canakinumab: a monoclonal antibody that interferes with the bioactivity of IL-1β; tocilizumab: a monoclonal antibody against the IL-6 receptor; and siltuximab, a monoclonal antibody that binds IL-6. This study presents an individual patient data meta-analysis of these three studies together.
**METHODS:** In our preliminary analysis, we performed an individual patient data meta-analysis combing the data of three RCTs. We examine the end points of the Positive and Negative Syndrome Scale (PANSS) Total, Positive, Negative, and General symptoms scores by ANCOVA, with baseline score as a covariant , and monoclonal antibody and study as factors. We will also evaluate the early time point, and a mid-time point, and explore other variables that might alter psychopathology.
**RESULTS:** The monoclonal antibodies non-significantly decreased PANSS total, by -2.5 points (se=1.9, t=-1.3, p=.19 ns), positive symptoms by -.84 points (se=.90, t=-.94, p=35), and negative symptoms by -.42 points (se=.80, t=-.52, p=.60 ns), but non-significantly increased general symptoms, by .42 points (se=1.4, t=.31, p=76 ns).
**DISCUSSION:** The results of this preliminary meta-analysis did not find efficacy of monoclonal antibodies in the treatment of the symptoms of schizophrenia. Whereas some of the blood-based markers were changed by these monoclonal antibodies, this did not translate to reduction in clinical symptomatology . One potential reason for these results might be that these drugs do not cross the blood-brain barrier, hence while they have an effect on peripheral blood-based immune markers, they do not lead to change in symptoms. These results do not encourage further studies on monoclonal antibodies in reducing the symptoms of schizophrenia

## M126. Using Active and Passive Digital Phenotyping to Index 12-Month Treatment Effects of Xanomeline and Trospium Chloride on Physical Activity in Outpatients With Schizophrenia

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**BACKGROUND:** Sedentary behavior and associated negative health consequences are common in schizophrenia. Negative symptoms, such as avolition, share multiple features with sedentary behavior, including prolonged periods of sitting, resting, watching television, and doing nothing, to the exclusion of more productive, physically active behaviors. In a 12-month study of xanomeline/trospium (XT) in schizophrenia, ecological momentary assessment (EMA) and fit bit actigraphy to were used to capture active and passive digital phenotyping information. We examined changes in behavioral topography indexed by the frequencies of activities such as

sleeping or resting (recumbent), sitting, standing, and moving, as well as step counts from the actigraphy.
**METHODS:** Participants completed EMA surveys 7 days a week, three time per day, one week per month for 12 months. Participants wore their actigraphs on the 7 survey days. EMA surveys queried about activities such as sitting, resting, watching television, performing household chores, and engaging in away from home activities. Proportions of surveys reporting engagement in each activity and step counts at that same observation were analyzed using a mixed effects model for repeated measures (MMRM). Time since baseline was the repeated-measures factor. We also performed concurrent covariate analyses, examining influences of momentary positive affect (PA) on the activities, including steps, and examining the covariance of the growth curves for activities and step counts.
**RESULTS:** Data from 350 participants who answered at least 33% of their EMA surveys during the first month were analyzed. There were significant treatment-related reductions in recumbent and seated activities, as well as significant increases in activities that required standing or movement both at home and away from home, all $X2 > 54.5$, all $p < .001$. Steps also significantly increased over the 12 months, $X2=22.84$, $p=.019$. Higher momentary PA was associated with more steps that day, $X2=91.83$, $p < .001$, and the significant interaction of month x PA, $X2=144.99$, $p=.009$, suggested an increasing impact of PA on step counts over the course of study. Higher step counts predicted lower occurrence of recumbent and seated activities, with very large associations, $X2 =1874$, $p < .001$ and $X2 =1503$, $p < .001$, respectively.
**DISCUSSION:** X/T treatment was associated with broad reductions in sedentary behavior, indexed by decreased recumbent and seated activities and increased physical activity both at home and away. Step counts also increased, and these increases in steps aligned with shifts from inactive to more active activities. PA played a substantial role in mediating these changes, and further investigation of the origins and dynamics of the role of PA and sedentary behavior is warranted.

## M127. Preliminary Results of a Cognitive Enhancement Therapy Protocol for Persistent Negative Symptoms in Schizophrenia Spectrum Disorders

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**BACKGROUND:** Schizophrenia spectrum disorders (SSDs) are characterized by a complex interplay of positive, negative, and affective symptoms, which can contribute to poor quality of life, functioning, and overall life experiences. While advances in psychosocial interventions and pharmacotherapy have demonstrated capacity to ameliorate positive symptoms, many individuals with schizophrenia still experience significant negative symptom burden, which have been less responsive to treatment. Prior research in negative symptomatology has suggested that cognition and negative symptoms are linked and could prove to be a potential treatment target. This study reports on preliminary findings from a randomized trial of a cognitive remediation intervention designed to target severe and persistent negative symptoms.
**METHODS:** A total of 26 participants diagnosed with SSDs were randomly assigned to either Cognitive Enhancement Therapy (CET), a cognitive remediation treatment, or Enriched Supportive Therapy (EST), a field standard psychosocial intervention, for 18 months.

Assessments of cognition and symptomatology were collected at six-month intervals starting at baseline, and three months post study completion. Intent-to-treat linear mixed-effects models were conducted to examine differential cognition and negative symptom change trajectories between CET and EST.
**RESULTS:** Differential treatment effects were detected for problem-solving neurocognitive domains at post-completion assessments (B = 42.31, p = .002), as well as a trend level effect (B = 7.24, p = .087) for overall neurocognition, with CET outperforming EST. Additionally, an emerging effect on the expression negative symptom domain indicates a potential post-treatment improvement in CET vs. EST. While models indicate improvement in social cognition and reduction of other negative symptom domains across the trial, no significant differential treatment effects were detected in the preliminary sample.
**DISCUSSION:** While these findings are preliminary and will require further interpretation across the full study population, CET has shown efficacy in improving cognition as well as key components of negative symptomatology. The absence of a social cognition effect may suggest difficulty in engaging this target in those experiencing persistent negative symptoms. Analysis of 1-year post intervention assessments will provide crucial insight into the durability and lasting impact of negative symptom improvement and cognitive gains.

## M128. Improved Cognitive Control and Reward Learning After Brief Cognitive Training Intervention in Early Psychosis Highlights Unaddressed Cognitive Processes

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**BACKGROUND:** People with psychosis experience impaired cognition and motivation, which negatively impacts their ability to persist in goal-directed behaviors and respond adaptively to changing environments. Such impairments emerge early in illness and impact real-world functioning. Two key cognitive processes implicated in psychosis spectrum illnesses are cognitive control deficits and reward learning deficits. We tested whether these cognitive processes are malleable and improve with a brief cognitive training intervention.
**METHODS:** We leveraged computational modeling to capture latent cognitive processes during two behavioral tasks assessing cognitive control and value-based decision-making. In the first sample (n=85 early psychosis, n=71 control), the tasks were administered during two sessions three weeks apart in a parent fMRI study. In an independent sample of 29 participants with early psychosis, the tasks were administered before and after a brief 10-hour cognitive training intervention. The intervention involved computerized exercises to train visual discrimination and attentional control. Linear mixed models and paired t-tests were used for analyses.
**RESULTS:** At baseline, hierarchical sequential sampling modeling revealed that participants with psychosis had lower drift rates on proactive cognitive control trials compared to controls, indicating slower and less accurate responding ($F(1,154) = 117.44$, $p < .001$). Across baseline sessions on the value-based decision-making task, participants with psychosis switched between options more often than controls ($F(1,141) = 7.67$, $p = .006$), regardless of feedback, resulting in suboptimal transitions from exploiting high-reward options to exploring other options ($F(1,141) = 8.32$, $p = .005$). Bayesian modeling suggested that this over-exploration among participants

with psychosis was driven by overweighting environmental uncertainty ($F(141) = 7.20$, $p = .008$) and a trend for more decision noise, indicating less reliance on learned value ($F(141) = 3.82$, $p = .053$). Over-exploratory task strategy was associated with negative symptom severity (rho = .34, $p = .004$) and real-world functioning at baseline (rho = -0.40, $p < .001$).

In an independent sample tested before and after a brief cognitive training intervention, participants with psychosis showed a significant increase in the drift rate parameter on proactive cognitive control trials after intervention ($t(27) = -3.87$, $p < .001$). This suggests faster and more accurate decision-making after brief intervention. Further, behavior on the value-based decision-making task became more value-driven after intervention, as measured by increased stay choices ($t(27) = 2.66$, $p = .013$) and a trend for stay choices for the optimal stimulus ($t(27) = 1.95$, $p = .062$). Reinforcement learning modeling revealed a trend for increased learning rate after intervention ($t(27) = 1.80$, $p = .084$) and Bayesian learning modeling revealed improved decision noise after intervention ($t(26) = 2.43$, $p = .022$) but not uncertainty weighting ($p = .266$).

**DISCUSSION:** We found impaired cognitive control and uncertainty-driven over-exploration during value-based decision-making among participants with early psychosis at baseline. Parameters improved after a brief cognitive training intervention, with the exception of uncertainty weighting, suggesting this is a currently unaddressed cognitive process in psychosis which contributes to persisting in goal-directed strategies and warrants clinical attention. Our preliminary results suggest neuroplasticity in cognitive processes early in the course of illness and highlight latent cognitive processes as future treatment targets to further improve outcomes.

## M129. Exploration of Negative Symptoms and Digital Application use in People With Schizophrenia

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**BACKGROUND:** Negative symptoms of schizophrenia have a profound impact on functional outcomes. As there are currently no US Food and Drug Administration (FDA)-approved pharmacological treatments for negative symptoms, innovative treatments are needed. One potential innovation is digital therapeutics, which are increasingly considered as scalable, flexible, and accessible approaches to support mental health. Prescription digital therapeutics (PDTs) are a subset of these therapies that are rigorously evaluated for efficacy and safety and are subject to FDA authorization and regulatory control. This study aimed to understand the potential of PDTs for negative symptoms from the perspectives of those living with schizophrenia, focusing on their experience and conceptualization of negative symptoms, and their patterns and preferences of smartphone app use.

**METHODS:** An initial survey was completed by 49 people with schizophrenia recruited through a US-based non-profit schizophrenia advocacy organization. A subset of 29 respondents were asked to participate in a 90-minute focus group (n=26) or individual interview (n=3). To support diverse representation, those with more severe self-reported symptoms and people of

color were prioritized for focus group/interview inclusion. Anonymized transcripts were coded using a hybrid analytic approach.
**RESULTS:** The survey population had a mean (range) age of 42 (21–71) years. Almost half of the survey population were women, 61% White, and 16% Hispanic. Overall, 94% of survey participants reported using a smartphone and 39% used mental health apps. Focus group participants had difficulty defining negative symptoms; when defined, they were described as profoundly challenging across multiple life domains. Seventy-nine percent reported that it is very or extremely important to treat negative symptoms. Participants reported trying different coping skills (e.g., mindfulness, distraction, helping others), but reported a need for more effective strategies. When asked about health apps, participants expressed preference for ease of log-in/use, interactivity, therapist integration, and being informative and positive. Participants expressed dislike of apps being complicated, costly, or sending too many reminders; some were concerned about privacy. Participants were open to a theoretical PDT, expressing they would like help with symptoms, education, independence, and daily living skills, and to set goals related to social interactions. Participants were confident in their ability to use a theoretical PDT.
**DISCUSSION:** Negative symptoms, once defined with relatable language to persons living with schizophrenia, were self-reported as common and detrimental to quality of life with need for novel treatments. PDTs hold promise as novel, scalable ways to treat negative symptoms in schizophrenia, though these participants may be more digitally literature than average.

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### M130. Exploration of Factors Associated With Treatment Completion in Cognitive Enhancement Therapy (CET)

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**BACKGROUND:** Prior research has extensively examined differences between individuals who do and do not complete psychosocial interventions for schizophrenia, with findings primarily highlighting disparities in social support and clinical presentation. However, there is limited research exploring factors associated with treatment completion in cognitive remediation interventions. The present study explores differences between individuals who discontinued and those who completed CET.
**METHODS:** A total of 49 participants, predominantly male (81.6%), with a mean age of 43.43 years (SD = 13.04), and diagnosed with a Schizophrenia Spectrum Disorder (SSD), were included in the analysis. Participants were invited to take part in CET as part of their participation in a psychosocial rehabilitation program offered at a community-based mental health center. Of the 49 participants, 24 completed the intervention and 25 discontinued early. Participants completed a comprehensive series of assessments at baseline, including measures of schizophrenia symptoms (Scale for the Assessment of Negative Symptoms [SANS] and Scale for the Assessment of Positive Symptoms [SAPS]), anxiety symptoms (State-Trait Anxiety Inventory [STAI] and Liebowitz Social Anxiety Scale [LSAS]), and life satisfaction. A battery

of neurocognitive measures assessing executive functioning, working memory, and processing speed was administered.
**RESULTS:** A series of independent samples t-tests were conducted to examine differences between treatment completion groups in terms of clinical, social, and cognitive characteristics. No significant group differences were observed on negative symptoms ($p = .117$), nor positive symptoms ($p = .256$). Additionally, no significant group differences were observed on state, trait, and social anxiety ($p= .763 - .963$). When examining cognitive domains, no significant group differences were found on working memory ($p = .09$) and executive functioning ($p= .08$). However, a significant difference was observed in concentration performance as measured by the d2 test of attention: individuals who discontinued from the intervention ($M = 58.68$) exhibited significantly lower concentration performance at baseline compared to those who completed the intervention ($M = 108.38$), $t (47) = -4.49$, $p < .001$ - this comparison maintained significance when adjusted for multiple comparisons (Bonferroni corrected alpha level at 0.005).
**DISCUSSION:** This study revealed no significant differences in clinical presentation between individuals who discontinue and completed CET. In contrast to findings from prior studies, there were no significant differences in negative or positive symptoms between the two groups. Life satisfaction did not differ between the two groups, which may be attributable to the recruitment methods and participants' overall engagement in treatment. Notably, concentration performance differed significantly between the two groups. Individuals who discontinued from the intervention had significantly lower baseline concentration performance compared to those who completed the intervention. These findings suggest that attentional demands associated with the intervention may contribute to treatment discontinuation. Further research is needed to investigate the role of concentration performance and attentional factors in decisions to disengage from cognitive remediation interventions.

## M131. Longitudinal Convergence of Dispersed Clinical Ratings and Ecological Momentary Assessment (EMA) Burst Assessments of Negative Symptoms in Schizophrenia

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**BACKGROUND:** Traditional clinical trials for negative symptom (NS) rely on dispersed in-person assessments, and longer trials have greater dispersion. This study examined convergence between dispersed clinical ratings and daily remote ecological momentary assessment (EMAs) of behaviors and moods associated with experiential NS in a 12-month open-label safety and efficacy trial of xanomeline/trospium chloride (X/T). Participants completed EMA surveys 3 times per day, 7 days per week, one week per month to assess time spent at home, alone, and engaged in passive and unproductive activities. These were compared to Negative Symptoms Assessment (NSA) ratings at two key time points: Month 4 (post-baseline assessment) and each participant’s final NSA assessment.
**METHODS:** Participants completed monthly EMA burst assessments and up to four post-baseline NSA evaluations over the 12-month study. A total of 12,636 EMA surveys were linked to NSA ratings by Month 4, and 25,548 surveys by each participant’s final NSA assessment. Hierarchical linear modeling (HLM) predicted total NSA experiential NS subscale scores and its

five individual items (interest in intimacy, everyday activities, hobbies, social drive, and sense of purpose). EMA predictors included the proportions of surveys completed at home (vs. away), while alone (vs. with others), and during productive, passive or unproductive activities, as well as concurrent levels of momentary positive affect (PA). Time since baseline served as the repeated-measures factor, while baseline NSA score was a covariate.
**RESULTS:** There were 350 participants who answered at least 33% of their EMA surveys during the first month, 337 who had NSA scores at month 4, and 202 study completers had NSA scores at month 12. There were significant effects for treatment duration, with both NSA scores and EMA variables improving across the study period. HLM of EMA growth curves as predictors of NSA scores found significant effects for all NSA total and item scores at month 4 and at the final NSA assessment (all $X2 > 142$, all $p < .001$). At month 4, total NSA scores were significantly predicted by the following EMA variables: fewer surveys answered alone [$p=.004$], more productive activities [$p < .001$], fewer passive activities [$p=.009$], and higher PA [$p < .001$]. Final NSA scores were similarly predicted by the same variables, along with: reduced time spent at home [$p < .001$] and increased away from home activities [$p < .001$]. EMA and NSA variables shared 15% and 12% variance [$p < .001$] at the two time points, with baseline scores accounting for 28% and 29% variance [$p < .001$].
**DISCUSSION:** Treatment with X/T was associated with improvements in NSA experiential NS at both 4 months and the end of treatment. EMA behavioral indicators of experiential NS also improved, with changes in EMA variables preceding and predicting NSA ratings. These findings suggest that EMA captures behavioral changes that meaningfully align with clinician-rated NS improvements. Both NSA and EMA were sensitive to changes in NS throughout the course of treatment with X/T.

## M132. Exploring the Efficacy of the Ketogenic Diet in Severe Mental Illness (SMI) and Neurocognitive Disorders: A Systematic Review and Meta-Analysis

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**BACKGROUND:** The established safety and efficacy of the ketogenic diet in the treatment of epilepsy and other neurological disorders supports its potential as a treatment option for individuals with psychiatric and neurocognitive disorders. The purpose of this review was to identify and analyze results from all primary research investigating the impact of the ketogenic diet on clinical outcomes for individuals with severe and persistent mental illness and/or neurocognitive disorders.
**METHODS:** We searched English-language articles in OVID Medline, Embase, PsycINFO, CENTRAL, Web of Science, CAB Abstracts, and Cochrane Database of Systematic Reviews from database inception to April 19, 2024. Studies were included that reported on psychopathology, cognitive, and metabolic outcomes in individuals with a major mood disorder, schizophrenia spectrum, or neurocognitive disorder, who were treated with a ketogenic diet, ketone supplement, or medium-chain triglycerides. Evidence was qualitatively synthesized and

organized by the population and outcome of interest, and supplemented by a quantitative meta-analysis.
**RESULTS:** A total of 6,424 records were identified through the comprehensive search, of which 52 independent studies were included in the systematic review reported among 69 records. Of the included studies, 29 were either prospective randomized controlled or single-arm trials (56%), 20 were case reports (38%), and three were other study designs (6%). A large majority, 39, were conducted in patients with mild cognitive impairment and/or major neurocognitive disorder (75%). Seven were conducted in individuals with either major depressive disorder or bipolar disorder (13%); four in schizophrenia spectrum disorders including schizoaffective disorder (8%); and two in a mixed severe mental illness population (4%). The studies captured treatment durations ranging from single-dose interventions to 12 years. Remission of symptoms, improved mood, and decreased positive and negative symptoms were seen among patients with severe mental illness. Furthermore, improvements in cognitive performance were observed in individuals with neurocognitive disorders (SMD 0.24, 95% CI [0.06, 0.43], p = 0.01, n = 587, k = 14, I^2 = 61%), with subanalyses highlighting significant effects in patients with mild cognitive impairment, and not Alzheimer's disease, emphasizing the importance of early intervention. Metabolic benefits, such as weight loss, were also noted in this patient population (MD -3.13 kg, 95% CI [-5.91, -0.35], p = 0.03, n = 80, k = 3, I^2 = 6%). Gastrointestinal symptoms were the most frequently reported adverse events while on the ketogenic diet.
**DISCUSSION:** This systematic review and meta-analysis highlights promising findings from studies of the ketogenic diet in improving symptom severity and metabolic outcomes in populations with severe mental illness and neurocognitive disorders. High-quality primary research (e.g. randomized controlled trials) is needed to replicate these effects in controlled settings to better establish the clinical efficacy of the ketogenic diet in these populations.

## M133. Personalized TDCS Targeting Visual Motion Area V5 to Modulate Smooth Pursuit Performance, a Biomarker for Psychosis

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**BACKGROUND:** Visual area V5 represents a core visual motion processing region in the cortical network driving smooth pursuit eye movements (SP). SP deficits are considered a robust biomarker for psychosis and are associated with subtle alterations of V5 activity during SP in patients. Yet, the exact mechanisms connecting SP deficits with functional modulation of V5 remain elusive.
**METHODS:** To assess SP deficits due to a subtle neuromodulation of V5, healthy participants (N=30) completed a SP test battery while transcranial direct current stimulation (tDCS) was applied. We hypothesized a cathodal inhibition and an anodal facilitation of SP performance. To control inter-individual anatomical differences and functional variability of the stimulation target, individual right V5 was functionally localized using structural and functional magnet-resonance imaging, electroencephalography and magnet-encephalography. tDCS montages were personalized based on finite-element simulations of transcranial electric fields and algorithmic optimization.

**RESULTS:** Personalized cathodal/inhibitory tDCS targeting right V5 induced a specific delay of SP initiation towards the right in healthy participants in line with findings from human and monkey lesion studies. These tDCS effects were only observed during tasks sensitive to study SP initiation, but neither during continuous SP maintenance, nor during anodal or sham tDCS. Also, no tDCS effect on SP initiation was observed by application of conventional tDCS over V5 or personalized tDCS targeting the right frontal eye field as a spatial control condition. Results of simulated transcranial electric fields confirmed the significant improvement by personalized tDCS with respect to electric field intensity and precision, compared to conventional normative tDCS.
Preliminary results from four patients with a schizophrenia spectrum disorder using the same extensive experimental procedure indicate a modulation of visually guided continuous SP maintenance by 20 minutes tDCS application. In detail, personalized anodal tDCS over right V5 resulted in reduced leftward SP maintenance eye velocity compared to cathodal and sham tDCS. Additionally, results from continuous SP with transiently blanked visual targets suggest a modulation of cognitive, i.e. predictive, input to SP in patients by personalized tDCS.

**DISCUSSION:** Inhibitory personalized tDCS targeting V5 specifically modulates ipsiversive SP initiation in healthy participants and thereby provides a model for specific and subtle SP impairment on behavioral level, but no facilitation by tDCS. Preliminary results in patients indicate differential effects by personalized tDCS compared to healthy controls. In the light of a growing interest in tDCS for clinical settings, a personalized approach yields huge potential to increase the efficacy of tDCS.

### M134. Beyond Evidence-Based Medicine: The Schizophrenia Information Center Illuminatum.com

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**BACKGROUND:** There are narrow limits to evidence-based medicine. With randomized trials, one can only provide a certain corridor. The more detailed the question, the less evidence there will be.
**METHODS:** To counter these problems, we have set up an information platform, called Illuminatum.com, at the center of which is an evidence-based schizophrenia guideline that is “living”. Living means that we can update it at any time when new evidence is available. In contrast, conventional guidelines are rapidly out of date. At the same time, clinicians and experts have the opportunity to comment on the recommendations. We will collect these comments regularly and update the guideline accordingly. At the same time, we ask colleagues to share their experiences and tips on how to treat people with schizophrenia.
**RESULTS:** We, thus, aim to integrate the experiences of practitioners beyond the evidence. In addition, various tools are presented on the website, for example a conversion of dosages between medications, an application that supports the selection of antipsychotics, a PowerPoint slide deck with which colleagues can immediately start psychoeducational groups. There is a news corner where we will share news and we provide links to other relevant guidelines and information systems for schizophrenia treatment.

**DISCUSSION:** Busy clinicians do not have the time to read scientific papers. We hope that Illuminatum.com will bridge this evidence-practice gap.

## M135. Dietary Interventions for Schizophrenia and Psychosis: A Review

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**BACKGROUND:** Schizophrenia spectrum disorders (SSD) are substantially disruptive to patients' lives; however, they can be difficult to treat due to heterogeneity between patients and insufficient treatment options to address negative symptoms and poor cognition. Emerging evidence suggests that modulating diet may improve symptoms and quality of life for patients with SSD. This review poster explores evidence for dietary interventions and discusses challenges with treatment implementation.
**METHODS:** We searched PubMed.gov with combinations of the keywords "schizophrenia" and "psychosis" with "nutrition," "metabolic psychiatry," "ketogenic diet," "gluten-free diet," "Mediterranean diet," "gut-brain axis," "supplementation," "dietary intervention," "omega-3," "vitamins," and "probiotics." We then summarized these papers into five broader categories: gluten-free diet, ketogenic diet, Mediterranean diet, probiotic supplementation, and nutritional supplementation, which was further categorized into vitamin D, B vitamins, and omega-3s.
**RESULTS:** Dietary interventions showed clinical benefits including reduction of positive and negative symptoms, improvements in metabolic and gastrointestinal comorbidities, improvements in cognition, and reduced depression and anxiety. Poor adherence to a Mediterranean diet was associated with more severe negative symptoms and greater risk of developing metabolic comorbidities. Potential mechanisms underlying improvements associated with other interventions included reduction of oxidative stress and compensation for impaired cerebral glucose metabolism (ketogenic diet), decreased inflammation (gluten-free diet, probiotic supplementation, and omega-3 fatty acids), supporting proper neurodevelopment and neural function (omega-3 fatty acids and B vitamins), maintaining proper calcium homeostasis (vitamin D), and maintaining neurotransmitter balance and formation (vitamin D and B vitamins).
**DISCUSSION:** Collectively, this review indicates that dietary modulation could be beneficial in improving symptoms of SSD and psychosis. Dietary interventions offer a promising and modifiable target with minimal side effects; however, adherence presents a hurdle. Furthermore, the broader field of nutritional psychiatry has not reached a consensus regarding which interventions are the "best" for clinical use, and more studies need to be performed in inpatient settings where diet can be tightly controlled. Additionally, implementing these interventions in the clinical setting and ensuring SSD patients can access and afford foods included in these treatments remain challenging.

## M136. Exploring the Intricacies of Linguistic Abilities in Spontaneous Speech Production Across Schizophrenia Spectrum, Bipolar and Major Depressive Disorders: A Network Analysis Approach

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**BACKGROUND:** Language impairments are frequently observed in affective and psychotic disorders, but their specific patterns and underlying mechanisms are not yet fully understood. A transdiagnostic perspective offers an opportunity to identify shared and unique language-related alterations across diagnostic boundaries. To investigate this, natural language processing provides a cutting-edge, objective, and sensitive approach for analyzing language impairments on various linguistic levels. A network analysis approach is particularly well-suited for this purpose, as it captures complex interactions between linguistic, cognitive, and psychopathological variables, enabling deeper understanding of their interrelationships.
**METHODS:** For the present study, we included N=372 participants (n=119 MDD, n=27 bipolar disorder, n=48 SSD and n=178 HC). Three dimensions were examined: (1) latent linguistic features (LLP), (2) psychopathology, and (3) language-related cognitive functions. Spontaneous speech was assessed using four pictures of the Thematic Apperception Test. Each participant provided approximately 12 minutes of spontaneous speech, from which various linguistic features (LLPs) were extracted using large natural language processing (NLP) models. These LLPs encompassed a wide range of linguistic markers across various linguistic levels. A variety of features were used to evaluate lexical diversity, syntactic complexity, semantic coherence, and speech disfluencies, including among others, type-token ratio (TTR), mean length of utterance (MLU), open-closed ratio (OCR), and syntactic complexity (SynC) and diversity (SynD). Advanced network analysis was used to investigate transdiagnostic networks of different linguistic features and psychopathology and cognition.
**RESULTS:** Network analyses indicated varying degrees of domain-specific and cross-domain network connections. LLPs, such as TTR, OCR, and MLU, played a central role in the network structure, with TTR
bridging linguistic and cognitive domains, linking lexical diversity, verbal fluency, and executive functioning. Psychopathological measures (SAPS and SANS) formed a cohesive cluster, while TLI Impoverished bridged cognitive and linguistic domains. Executive functioning exhibited a central role, connecting linguistic and psychopathological variables. Syntax measures, such as MLU and syntactic diversity (SynD), emerged as key integrators, underscoring the interconnected nature of linguistic, cognitive, and clinical features in a transdiagnostic framework.

**DISCUSSION:** Our study enhances the overall understanding of how cognition, LLP, and psychopathology interact in the production of spontaneous speech across affective and psychotic disorders.

## M137. Negative Symptoms in Schizophrenia and Outcomes of Weight Gain and Level of Functioning: A Real-World Data Study in the United States

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**BACKGROUND:** Negative symptoms in schizophrenia (NSS) are associated with poor clinical outcomes. Reduced motivation, social withdrawal, and diminished emotional expression inherent to NSS are all linked to worse overall functioning and quality of life. In addition to these symptoms, people with schizophrenia experience weight gain, often induced or exacerbated by antipsychotic treatment. Excessive weight gain contributes to increased morbidity and lower adherence to treatment, further impairing functioning. Understanding the impact of NSS on weight gain and functioning in real-world setting is essential to developing targeted interventions. This study utilizes real-world data (RWD) to identify patients with schizophrenia with and without NSS and to assess the impact of NSS on weight and functioning.

**METHODS:** This is a retrospective cohort study using de-identified electronic health records (EHRs) in the NeuroBlu database (Version 24R5) collected across US mental healthcare providers (1999–2024). Patients aged ≥18 years diagnosed with schizophrenia and ≥1 record of Mental Status Examination (MSE), Brief Negative Symptom Assessment (BNSA), or Natural Language Processing (NLP) label linked to schizophrenia were included. Patients were stratified based on NSS presence.

The index date was the first MSE/NLP/BNSA record indicating NSS (exposure) or without NSS (control) within ±14 days of a schizophrenia diagnosis. Weight and functioning were assessed between baseline (±14 days from index date) and a 12-month follow-up period. An event of significant weight gain was assigned if weight increased by ≥7%; an event of worsened functioning was assigned if the global assessment of functioning (GAF) scale decreased by ≥10 points during follow-up. First, the proportion of patients who were recorded for each outcome during follow-up were estimated in the exposure and control group.

To follow, Cox-proportional hazards regression employing propensity score methods to minimize confounding are currently being conducted, for which the effect estimates between NSS and changes in weight (≥7% in weight gain) and functioning (≥10 points decrease on the global assessment of functioning (GAF) scale) following baseline will be presented.

**RESULTS:** A total of 60,020 patients with schizophrenia were included, of whom 40,024 (66.7%) had NSS features. Among these patients, weight measurements were available for 9,553 patients (6,876 with NSS, 2,677 without NSS). Events of weight gain were recorded in 2,179 (31.7%) patients within the NSS cohort, and 669 events (25.0%) among patients without NSS. Within the total population, GAF measurements were available for 5,524 patients (3,513 with NSS, 2,011 without NSS). Events of worsened functioning were recorded in 675 (19.2%) patients within the NSS cohort, and 341 events (17.0%) in patients without NSS.

**DISCUSSION:** Using RWD from routine mental healthcare, we identified a large cohort of patients with schizophrenia and stratified them based on the presence or absence of negative symptoms features. A larger proportion of patients with negative symptoms were recorded with weight gain and worsened functioning during a 12-month follow-up. Regression analyses will be conducted to assess whether there is an independent effect of NSS on these outcomes.

**M138. Understanding the Daily Dynamics of Positive Symptoms, Emotions, and Cognition in Schizophrenia: Bridging Brain Imaging and Ecological Momentary Assessment**

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**BACKGROUND:** Schizophrenia is characterized by significant symptomatic and functional variability over time. Longitudinal studies have provided essential information about symptomatic and functional changes in patients occurring over relatively long periods of time. However, few studies have explored short-term variability, that is, fluctuations that express themselves over periods ranging from minutes to hours. Therefore, little information is available concerning the short-term variability of symptoms and their associated phenomena (cognitive functioning, emotional experiences, perception of time), and despite their importance for providing precise descriptions of this complex disorder. Traditional methods of evaluation conducted in the laboratory or clinical settings are confronted with a number of methodological limitations that make it impossible to assess such variability. This research work therefore aims to provide the missing information regarding the short-term temporal links between cognitive functioning, emotional experience, and time perception in relation to the manifestation of schizophrenia symptoms and examines the brain correlates of these associations. To address this issue, an innovative approach was applied that combined Ecological Momentary Assessment (EMA) using mobile technologies with Magnetic Resonance Imaging (MRI) of the brain.
**METHODS:** 33 individuals with schizophrenia completed five EMA assessments per day for a one-week period including real-time assessments of positive symptoms, cognitive performance, emotional experience and time perception. A subsample of patients (N=13) also completed an anatomical and a functional MRI examination. Hierarchical linear regression models were used to identify cognitive, emotional, and time perception predictors of positive symptoms. Volumetric gray matter analyses and resting state functional connectivity analyses based on graph theory were performed on the MRI data. Multilevel analyses were finally also used to identify brain correlates of prospective links between cognitive performance, emotional experiences, time perception and positive symptoms.

**RESULTS:** The EMA methodology employed provides specific evidence of cognitive, emotional, and time-perception predictors of positive symptoms over brief periods of time in patients' daily lives. In particular, for the first time, these explorations made it possible to identify that a decrease in cognitive performance and a momentary alteration in the processing of durations would influence the subsequent manifestation of positive symptoms. Multilevel analyses linking EMA and MRI data revealed the anatomical and functional correlates of these relationships, confirming the central role of fronto-temporo-cerebellar regions in this disorder.
**DISCUSSION:** Overall, this dual approach provides a better understanding of the relationships between major processes underlying schizophrenia phenotypes and promote a better understand the factors that place patients at high risk for experiencing symptoms in daily life. This research has shown that cognitive, emotional, and time-perception variables assessed at several points in the day predict the expression of positive symptoms in the following hours. Because effective treatment of schizophrenia focuses on reducing and controlling these symptoms, the present findings provide highly novel information regarding their potential precursors in everyday life. These results therefore provide important suggestions for treatment research that could focus on cognitive and emotional functioning at the same time as a target for reducing psychotic symptoms.

## M139. On Autonomy and the Experience of Hearing Voices: An Interpretative Phenomenological Analysis

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**BACKGROUND:** Hearing voices are often experienced as controlling, powerful, threatening and critical. This study aimed to examine how autonomy is experienced among people who hear voices.
Employing a qualitative design, this study sought to examine the lived experiences, personal narratives, and meaning-making processes of voice hearers to gain deeper insights into nuanced ways autonomy is experienced, diminished, attempted, reestablished and constructed by those who hear voices.

**METHODS:** In-depth semi-structured phenomenological interviews with voice hearers were analysed using Interpretative Phenomenological Analysis to capture the ways participants interpret and respond to their experiences.
**RESULTS:** Two superordinate themes were identified in the data. First, participants reflected how hearing voices challenged their sense of self, individuality, and the space available for self-authorship. Developing a personally meaningful narrative became crucial for re-establishing autonomy. They portrayed a coexisting dynamic where autonomy and power were shared and negotiated with the voices. Second, participants described how hearing voices interfered with their perceived efficacy, competence, and decision-making, introducing limitations in their ability to navigate life on their own terms. Participants' capacity for integration, perceptions of their ability to influence and cause change affected the extent to which they felt having autonomy.

**DISCUSSION:** The study suggests the importance of supporting voice hearers in constructing self-oriented, meaningful narratives to strengthen their sense of autonomy. Future research may further investigate strategies that empower voice hearers to integrate their experiences constructively, facilitating resilience and autonomy.

## M140. Pharmacological Interventions to Manage Cardiometabolic Outcomes in Adults With Severe Mental Illness: An Umbrella Review

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**BACKGROUND:** People living with severe mental illness (SMI) experience a shorter life expectancy and poorer physical health than those without SMI. Cardiometabolic illness accounts for a significant proportion of this health inequality. Pharmacological management of this could reduce the noted inequalities. This umbrella review aimed to synthesise the evidence from systematic reviews for pharmacological interventions to manage cardiometabolic outcomes in adults with SMI.

**METHODS:** Databases (Embase, Medline and Cochrane Database of Systematic Reviews) were searched from inception for systematic reviews of pharmacological interventions for all cardiometabolic outcomes in adults. Titles, abstracts and full texts were independently screened by two reviewers. Corrected cover area was calculated, and quality was assessed using AMSTAR 2.

**RESULTS:** Twenty-nine systematic reviews were included following screening of 1719 titles. Metformin, the most commonly studied intervention (n=16), was effective at preventing and treating weight gain, treating dylipidaemia (total cholesterol and triglycerides) and dysglycaemia.

Topiramate and glucagon-like peptide-1 agonists demonstrated efficacy for treating weight gain but the effect across other cardiometabolic parameters was less consistent. Licensed treatments such as statins for dyslipidaemia were reviewed in low numbers (n=2). Nicotine replacement, bupropion and varenicline were effective for smoking cessation, an outcome that can significantly lower cardiometabolic risk.

The corrected cover area was 5.5% indicating slight overlap across reviews. Most reviews (n=14, 48%) were rated critically low-quality using AMSTAR 2, and the remaining rated low (n=6, 21%), moderate (n=2, 7%) or high quality (n=7, 24%).

**DISCUSSION:** Pharmacological interventions can improve cardiometabolic health in adults with SMI. The results of this review will be important in shaping future guidance.

## M141. Psychological and Psychosocial Interventions for People With Schizophrenia and Co-Occurring Substance use Disorders: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Substance use disorder is frequently observed among patients with schizophrenia, contributing to the complexity of treatment and leading to poor clinical outcomes. The high prevalence of comorbid substance use disorder and schizophrenia poses significant challenges in managing these patients effectively. Previous research has demonstrated that psychological and psychosocial interventions can be beneficial when their effects are evaluated independently. Therefore, we conducted a pairwise meta-analysis to examine the efficacy of these interventions specifically within this population – schizophrenia and comorbid substance use disorders.

**METHODS:** We included randomized controlled trials (RCTs) comparing psychological or psychosocial interventions in adults with schizophrenia and co-occuring substance use disorders. The main outcome were overall symptoms and reduction measured with validated and published rating scales. To investigate the eligible studies from the inclusion criteria, we searched for all RCTs by performing a systematic database search on BIOSIS, CINAHL, Cochrane CENTRAL, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PsycINFO, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform up to 31.01.2020, the Study registry of Cochrane Schizophrenia Group up to 31.03.2022 and PubMed and Cochrane CENTRAL up to 31.07.2023. Random effects pairwise meta-analysis has been performed to calculate standardized mean differences (SMDs) or risk ratios (RRs) with 95% confidence intervals (CIs). The study protocol was registered in PROSPERO with the number CRD42024517885.

**RESULTS:** We included 22 RCTs (1796 participants) that were eligible for qualitative synthesis after excluding 24505 records by title and abstract screening and 6394 records at full-text screening. When compared to control groups, psychological and psychosocial interventions demonstrated no statistically significant effects across key outcomes. Specifically, no significant differences were observed in the treatment of overall symptoms (11 trials; 1,035 participants; SMD = 0.04, 95% CI: [-0.11, 0.19]), reduction in alcohol use (6 trials; 251 participants; SMD = -0.12, 95% CI: [-0.43, 0.19]), or reduction in cannabis use (5 trials; 297 participants; SMD = -0.11, 95% CI: [-0.42, 0.20]).

**DISCUSSION:** Further RCTs or higher-quality evidence are warranted to more comprehensively evaluate the efficacy of psychological and psychosocial interventions in this specific population.

## M142. Examining the Cognitive Pathways to Negative Symptoms in Schizophrenia Spectrum Disorders: The Role of Neurocognition and Social Stress

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**BACKGROUND:** The cognitive model is a widely used psychological framework for conceptualizing negative symptoms in schizophrenia spectrum disorders (SSDs). Accordingly,

the development and maintenance of negative symptoms are hypothesized to be related to dysfunctional belief systems that emerge in the face of recurrent failures and setbacks in life. While the model highlights the role of neurocognitive impairments in fostering dysfunctional beliefs, there is only limited evidence to support this supposition. Further, the role of other factors, such as social determinants, has yet to be explored. In order to advance our understanding of the cognitive model of negative symptoms, the current study aimed to examine psychological pathways to negative symptoms by comparing different predictors of dysfunctional beliefs.
**METHODS:** After excluding invalid responders, the sample consisted of 103 patients with SSDs. Participants completed a battery of assessments, including the SANS for negative symptoms, the BACS for neurocognition, and the Everyday Discrimination Scale (EDS) for social stress. Measures of dysfunctional beliefs included the Dysfunctional Attitudes Scale for defeatist performance beliefs and the Revised Self-Efficacy Scale (RSES) for low expectancies for success. For each dysfunctional belief, two hypothesized models were tested with path analysis. The first model tested the paths from neurocognition to dysfunctional beliefs to negative symptoms, while the second model replaced neurocognition with social stress.
**RESULTS:** For defeatist performance beliefs, the first path model fit the data moderately well, $\chi2 = 1.3$, $p = 0.26$, RMSEA = 0.06, 90% CI [0, 0.29], TLI = 0.6, AIC = 996.8, BIC = 1006.9. According to this model, the path from BACS cognition to defeatist performance beliefs was not significant, $\beta = -0.09$, $Z = -0.98$, $p = 0.33$, nor was the path from defeatist beliefs to SANS, $\beta = 1.9$, $Z = 1.8$, $p = 0.07$. In contrast, the second path model fit the data well, $\chi2 = 0.2$, $p = 0.68$, RMSEA = 0.00, 90% CI [0, 0.21], TLI = 1.2, AIC = 979.6, BIC = 989.7 and all paths in this model were significant, with the EDS predicting defeatist beliefs, $\beta = -0.1$, $Z = -3.8$, $p < 0.001$ and defeatist beliefs predicting SANS, $\beta = 2.4$, $Z = 2.3$, $p = 0.02$, and with the EDS indirectly predicting the SANS through defeatist performance beliefs, $\beta = -0.2$, $Z = -1.9$, $p = 0.049$. For low expectancies for success, the first path model fit the data well, $\chi2 = 0.8$, $p = 0.36$, RMSEA = 0.00, 90% CI [0, 0.26], TLI = 1.04, AIC = 938.9, BIC = 949.05. In this model, the path from BACS cognition to expectancies for success was not significant, $\beta = 0.09$, $Z = 1.25$, $p = 0.21$, while was the path from expectancies for success to SANS was significant, $\beta = -4.8$, $Z = -3.8$, $p < 0.001$. The second path model fit the data better, $\chi2 = 0.4$, $p = 0.52$, RMSEA = 0.00, 90% CI [0, 0.24], TLI = 1.1, AIC = 926.1, BIC = 936.6, with the EDS significantly predicting expectancies for success, $\beta = 0.5$, $Z = 3.04$, $p = 0.002$, expectancies for success significantly predicting SANS, $\beta = -4.8$, $Z = -3.6$, $p < 0.001$, and with the EDS indirectly predicting the SANS through expectancies for success, $\beta = -0.2$, $Z = -2.3$, $p = 0.02$.
**DISCUSSION:** The current study suggests that social stressors, specifically experiences of discrimination, rather than neurocognitive impairments, may play a central role in engendering dysfunctional beliefs and contributing to negative symptoms in SSDs. To this end, our findings add to a growing body of research highlighting the detrimental impact of social adversity on symptom presentation in SSDs. Identifying the socio-environmental factors that render individuals vulnerable to developing dysfunctional belief systems may be critical for effective and timely interventions for negative symptoms.

**M143. Self-Stigma in Intimate Relationships of Persons Living With Serious Mental Illness: Scale Development and Validation**

Meryl Caiada*[1], Antoinette Prouteau[2], Luc Vigneault[3], Simon Felix[2], Sarah Guionnet[4], Justin Lamontagne[1], Emma Tison[4], Valery Kevin-Marc[4], Tania Lecomte[1]

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**BACKGROUND:** Background: Young people with psychosis as well as people with Serious Mental Illness (SMI) often encounter significant challenges in developing Intimate Relationships (IR, Cloutier et al., 2020). They frequently experience discrimination in this domain and face specific stereotypes regarding their IR, constituting a major barrier to relationship development (Caiada et al., 2024; Thornicroft et al., 2009). Moreover, these stereotypes are sometimes internalized, particularly by youth with psychotic disorders, leading to self-stigmatization and reluctance to engage in IR (Elkington et al., 2012). However, no validated tool exists to assess self-stigma in this context. This study aims to develop and validate a scale to assess self-stigma in IR among individuals with SMI (major depression, schizophrenia, bipolar disorder).
**METHODS:** Method: The scale's items (n = 40) were collaboratively developed through focus groups with peer workers. Seven themes emerged, including feeling of incompetence in IR ("I am not able to keep my commitments in my relationship"), hopelessness ("It is impossible for me to find love"), concerns about mental health ("A romantic partner could harm my recovery"), poor self-esteem ("I am not desirable"), divulgation ("My partner will leave me if I disclose my condition to them"), fear of losing control ("I am emotionally dependent on my partner"), investment in intimate relationships ("It is not normal for my intimate relationships to be one of my priorities").
**RESULTS:** Results: Preliminary analyses indicate excellent internal consistency ($\Omega = .94$) and good convergent validity. Analyses of structural validity and test-retest reliability are ongoing and will be presented at SIRS 2025.
**DISCUSSION:** This study will provide mental health providers with a novel, validated scale, developed in collaboration with individuals living with SMI, to help identify those who self-stigmatize in their IR. Such tools could also encourage professionals and researchers to explore this central, yet under-investigated, area of life.

## M144. Co-Developing a Satisfaction Survey for Mental Health Care: A Participatory and Democratic Approach With Users, Families, and Professionals

Sarah Guionnet*[1], Camille Aragnou[2], Julien Bonilla-Guerrero[2], Benoit Hillairet[2], Romain Lagarde[2], Meryl Caiada[1], Simon Felix[1], Kevin-Marc Valery[1], Emma Tison[1], Adrien Seguela[1], Jean-Marc Destaillats[2], Antoinette Prouteau[2]

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**BACKGROUND:** Proving high-quality care for mental health service users is a key priority within the healthcare system (Le Guludec et al., 2018), with care quality evaluation serving as a critical tool to achieve this objective. Indeed, this evaluation is essential for identifying necessary actions to improve care quality. While traditionally conducted by healthcare professionals, it has more recently incorporated the perspective of users through quality-of-care indicators perceived by the users themselves. Therefore, the involvement of both users and professionals is crucial to benefit from these indicators and leverage them to enhance care quality (French National Authority for Health, HAS, 2021). Although psychiatry is moving towards greater participation

of users and partnership between users and professionals, users participation is still insufficient (Greacen and Jouet, 2019 ; Greacen, 2020 ; Coldefy, 2022 ; National Health Conference, NHC, 2022 ; World Health Organization, 2022). Mental health services should further develop democratic partnerships between users and professionals to improve care, focusing more on the needs, concerns, and complaints of users (Coldefy, 2022 ; NHC, 2022).
The objectives of the study were: i) to co-develop a satisfaction survey regarding care for users of the adult psychiatry department at Jonzac Hospital Center, and ii) to collaboratively identify areas for improvement in care based on the survey results, in partnership with users, families, and mental health professionals.

**METHODS:** A group composed of users (N = 6), family members (N = 6), and professionals (N =8) met during working sessions to co-develop the survey. Researchers from the University of Bordeaux were consulted regarding the methodological aspects of the tool =. To ensure the comprehensibility of the questionnaire, a clarity survey was conducted with members of the Clubhouse of Bordeaux (individuals who have experienced psychiatric care). The group will meet again to co-analyze the results and collaboratively identify areas for improvement in care.
**RESULTS:** The survey includes 46 items grouped into seven dimensions evaluating satisfaction with : care (e.g., do you feel you were involved in decisions regarding your care?) ; medication treatment (e.g., do you feel you were sedated in an aggressive or excessive manner?) ; relationship with professionals (e.g., did you receive attentive listening from the professionals ?) ; information received during the care process (e.g., was the information you received upon your admission to the facility clear?) ; the position of close ones or family in the care process (e.g., was the way your family was involved in your care satisfactory?). Additionally, respondents were asked for suggestions for improvement and to provide socio-demographic data. The survey will be disseminated among users and results will be presented at the Schizophrenia International Research Society in 2025.
**DISCUSSION:** These initial findings demonstrate that it is feasible to implement a participatory and democratic approach within a mental health service, thereby involving all stakeholders in the process of evaluating and enhancing the quality of care. Furthermore, this method could be applied to other services to improve care and foster partnerships within mental health systems. To this end, the effectiveness of this approach in enhancing care will be evaluated.

## M145. Psychometric Testing of the French Adaptation of the Recovery Self-Assessment (RSA-R) Services' Recovery-Orientation Measure

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**BACKGROUND:** Orienting professional practices and service delivery toward recovery-centered care is now globally recommended (WHO, 2021). There is a need for valid patient-reported experience measures (PREMs) of services fidelity to the principles and values of the recovery approach (Slade and Hayward, 2007). The Recovery Self-Assessment scale (RSA-R, O'Connell et al., 2005) is the most internationally utilized measure of services' recovery-orientation (Leamy et al., 2023). The recovery model is slowly gaining momentum in France (Coldefy and Maugiron, 2022), and yet there are no validated measures of recovery orientation.

This study objectives were therefore to translate and culturally adapt the RSA-R to the French context, and provide preliminary data on its psychometric properties.
**METHODS:** One hundred and sixty-nine participants with self-reported severe mental illnesses participated to an online survey. The following psychometric properties of the RSA-R were tested: structural validity was assessed via an exploratory factor analysis; internal consistency parameters were computed; convergent validity was assessed through regressing the RSA-R scores with proxy measures of the CHIME (Leamy et al., 2011) model of personal recovery; and an additional analysis of content validity was realized through matching the RSA-R items with dimensions of LeBoutillier et al. (2011) recover-orientation conceptual framework.
**RESULTS:** Participants were mostly females (72.8%), with an average age of 42.5 (sd=11.6) and self-reported diagnosis of bipolar disorders (60.9%). Exploratory factor analyses supported a 3-factor structure of the RSA-R, with satisfactory fit parameters and internal consistency statistics. The three dimensions identified were i) promoting person-centered care, ii) promoting social inclusion and iii) promoting citizenship. Convergent validity analyses showed that recovery-orientation was mainly associated with users' satisfaction towards received social support.
**DISCUSSION:** This study provides sound data to support the use of the French RSA-R, and addresses several issues identified in previous validation studies of the scale. This PREM will prove useful to the required transformations of the French mental healthcare system towards a recovery-centered approach (Slade et al., 2014).

## M146. Results From a 4-Year Research Program Investigating Peer Support and Recovery in the North Denmark Region

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**BACKGROUND:** Peer support is a collaborative practice, where individuals are employed to make use of their personal experiences as mental health service users to provide support to others with similar experiences. Of note, employment of peer support workers is described as the fastest-growing segment of the workforce in mental health services. However, implementation of peer support faces several challenges, including issues related to organisational culture, ambiguity surrounding the peer support worker role, and the attitudes of mental health professionals towards collaborating with peer support workers.
The Flexible Assertive Community model (FACT) integrates recovery-oriented care, evidence-based medicine and best practices delivered by multidisciplinary teams with a peer support worker working alongside mental health professionals.

In September 2020 peer support workers were employed in eight new FACT teams in mental health services in the North Denmark Region to support persons with psychotic disorders in their recovery journey. Shortly hereafter, a 4-year research program "Peer Support and Recovery 2021

- 2024" was initiated with the overall purpose to investigate peer support and recovery in four work packages from the perspectives of the peer support workers, mental health professionals, FACT managers and patients.

**METHODS:** The overall design for the research program was exploratory using qualitative and quantitative methods. The data collection was completed November 2023 and analysis within and between the four work packages is ongoing.

**RESULTS:** The presentation will give an overview of the research program and present results and preliminary results from all perspectives, peer support workers, patients, health care professionals and FACT managers. The findings indicated that while mental health professionals perceived recovery-oriented practices as complex and characterized by conflicting values, and expressed concerns about the integration of peer support workers into their teams, and peer support workers reported challenges in establishing their roles within the team, patients consistently reported that peer support positively contributed to their personal recovery process. Additionally, examining the results from multiple perspectives provided valuable insights into the organizational complexities and challenges encountered during the implementation of the research program.

**DISCUSSION:** Despite existing literature highlighting numerous challenges associated with implementing peer support in mental health services, the findings of our research program align with these observations. This suggests that either decision-makers and healthcare professionals tasked with implementing new practices fail to incorporate this knowledge into their strategies, or perhaps that mental health services remain deeply rooted in a biomedical paradigm, limiting the integration of experiential knowledge contributed by individuals with lived experience.

## M147. Early-Stage Trajectories of Psychosocial Functioning and Prospective Functional Outcome Prediction in Early Psychosis: A 12 Follow-Up of the Randomized Controlled Trial on Extended Early Intervention

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**BACKGROUND:** Psychotic disorders are associated with significant functional disability. To facilitate early intervention and functional recovery, better clarification of longitudinal course of functional impairment is warranted, which is nonetheless understudied. We aimed to identify patterns and baseline predictors of early-stage psychosocial functioning in early psychosis patients, and investigated the prospective relationship between these functional trajectories and functional outcomes at 12-year follow-up.

**METHODS:** One-hundred-sixty Chinese patients were recruited from specialized EI program (EASY) for FEP in Hong Kong after they had completed this 2-year EI service, and underwent 1-year randomized-controlled trial (RCT; i.e., Extended EI RCT) as well as 2-year post-RCT follow-up (i.e., 3-year follow-up). Clinical interviewed reassessment was conducted 12 years after the RCT commencement. Assessments on premorbid adjustment, onset profile, psychopathology, functioning and treatment characteristics were conducted. Individual class membership of early-stage functional trajectory derived from growth-mixing-modeling (GMM) analysis was based on SOFAS scores measured at four different time-points (baseline, 1, 2 and 3

years of follow-up) for 148 patients. Long-term functional outcomes measured at 12 years of follow-up included SOFAS scores, Role Functioning Scale (RFS), and sustained employment in the last 12 months of the 12-year follow-up period.
**RESULTS:** Four distinct functional trajectories were identified including persistently-poor (27.7% [n=41]), suboptimal-stable (48.6% [n=72]), gradually-improved (10.8% [n=16]), and persistently-good (12.8% [n=19]). Multinomial regression analysis revealed that poor baseline functioning ($P < .001$) significantly predicted membership in the persistently-poor trajectory, while a longer duration of untreated psychosis (DUP) ($P=.059$) approached significance in predicting membership in the persistently-poor trajectory. Compared to the persistently-good group, participants in the persistently-poor, suboptimal-stable, and gradually-improved classes had significantly worse SOFAS scores at 12-year follow-up. For role functioning, the total RFS score and all subscales (Work, Immediate Social, and Extended Social) showed significant differences across groups ($p < .001$), with the persistently-good group consistently achieving the best outcomes. Trajectory membership also predicted significant differences in sustained employment ($p = 0.02$).
**DISCUSSION:** Our findings indicate a heterogeneous course of psychosocial functioning in young people with early psychosis. Early-stage functional trajectory patterns represent a major determinant of long-term functional outcomes, underscoring the need for promotion of early functional recovery. Our results that prolonged DUP predicted poor functional trajectories, further highlighting the necessity of early detection to reduce treatment delay. Overall, our results emphasize the importance of incorporating comprehensive and individualized treatments for functional enhancement as a critical component of early psychosis intervention to optimize long-term outcomes.

## M148. Prevalence and Predictors of Healthcare use for Psychiatric Disorders at Nine Years After a First Episode of Psychosis: A Swedish National Cohort Study

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**BACKGROUND:** Psychotic disorders are known to exhibit heterogeneity with regards to illness course and prognosis, yet few studies have examined long-term healthcare use. The aim of the present study was to determine the prevalence and predictors of healthcare use for psychiatric disorders at nine years after the first episode of psychosis (FEP).
**METHODS:** National registers were used to identify all Swedish residents aged 18-35 years with FEP between 2006-2013. The 12-month period-prevalence of secondary healthcare use was determined at each year of the nine-year follow-up, categorised according to main diagnosis (psychotic disorder vs. other psychiatric disorder vs. none). Multinomial logistic regression models examined associations between baseline characteristics and healthcare use at nine years and derive predicted probabilities and 95% confidence intervals (CIs) for each predictor variable.

**RESULTS:** Among 7733 individuals with FEP, 31.7% were treated in secondary healthcare for psychotic disorders at the nine-year follow-up, 24.1% were treated for other psychiatric disorders, 35.7% did not use healthcare services for psychiatric disorders, and 8.5% died or emigrated. Having an initial diagnosis of schizophrenia was associated with the highest probability of secondary healthcare use for psychotic disorder at nine years [0.53, 95% CI (0.49-0.58)] followed by inpatient treatment at first diagnosis [0.41, 95% CI (0.39-0.42)]. In contrast, the factors associated with highest probabilities for healthcare use for other psychiatric disorders were receipt of disability pension [0.33, 95% CI (0.30-0.37)] and having > 90 days of sickness absence [0.31, 95% CI (0.26-0.37)] in the year prior to illness onset.
**DISCUSSION:** Although 56% of individuals with FEP were treated for psychiatric disorders in secondary healthcare nine years later, a substantial proportion were treated for non-psychotic disorders. The factors which we have shown to be associated with healthcare use for psychotic disorders specifically have important implications for patients and their families, clinicians, and those responsible for planning healthcare provision. Individuals with an initial diagnosis of schizophrenia, who received their first diagnosis in inpatient settings, may need more intensive treatment to facilitate remission and recovery.

## M149. The Added Value of Group CBT Combined With Supported Employment Programs: Findings From a Quasi-Experimental Study in France

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**BACKGROUND:** In 2023, group interventions inspired by Cognitive Behavioral Therapy (CBT) were implemented in seven supported employment programs in France. The CBT-SE approach consists of eight weekly sessions offered to a group of individuals (from 4 to 6 individuals) with severe mental disorders (e.g., schizophrenia) undergoing a work integration process. These individuals also receive services from employment specialists working within the supported employment programs. The objective of this study was to demonstrate the added value of this type of intervention in improving work integration outcomes for individuals with severe mental disorders.
**METHODS:** This study was conducted using a mixed-methods approach, combining a longitudinal quasi-experimental evaluation (a 6-month comparison between an experimental group (N=48) and a control group (n=48)) and a qualitative evaluation (semi-structured interviews and focus groups).
**RESULTS:** The results showed a post-intervention employment rate of 42% in the experimental group compared to 33% in the control group, while the pre-intervention employment rate was 37% in both groups. Participants highlighted the benefits of the group intervention in enhancing self-confidence, stress management, and awareness of their own skills.
**DISCUSSION:** CBT-SE has previously been validated in Canada. It now appears promising in France as well. Future studies are warranted in order to improve its wider-scale implementation.

## M150. A Study of the Digital Divide and its Factors in Patients With Schizophrenia in Hong Kong

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**BACKGROUND:** In the past two decades, digital technology has developed rapidly, with numerous breakthroughs, from reliable and quick access to the internet to smartphones and artificial intelligence. As our lives become increasingly dependent on digital technologies, the digital divide has emerged, referring to the disparity in digital access, usage, and outcomes. Individuals lacking access or the skills and opportunities to use digital technologies are at risk of digital exclusion, restricting their access to resources and opportunities offered by the digital world. This study is part of a 20-year follow-up study on a territory-wide early intervention program for first-episode psychosis patients aged 15-25 years at onset in Hong Kong. The current sample was diagnosed with schizophrenia-spectrum disorder and treated during a period of significant digital technology advancement. Hence, the study investigated whether this sample experienced a digital divide compared to the general population and examined factors associated with their digital skills.

**METHODS:** 69 patients and 35 healthy controls aged 31-51, in Hong Kong participated in the study. All participants completed face-to-face (and phone) interviews, providing sociodemographic information, employment status, digital access, digital usage, digital skills based on the Essential Digital Skills (EDS) framework, and general cognitive functions were assessed using MoCA. Symptom severity in patients was also assessed using PANSS.

**RESULTS:** 94.2% of patients own a smartphone which did not significantly differ from healthy control (100%). Only 10.3% of patients experienced insufficient data in the past year, similar to healthy controls (11.1%; $p > 0.05$). However, significantly fewer patients (46.3%) own computers compared to healthy control (77.8%; $p = 0.002$) and fewer patients (86.6%) ($p = 0.017$) had Wi-Fi at home compared to healthy controls (100%). Patients also have significantly lower digital usage levels, digital confidence, foundation skills, and skills for life (SFL) ($p < 0.001$). Among those employed (patient = 26; HC = 31), lower skills for work (SFW) were observed ($p < 0.001$). Hierarchical regression models were adopted to examine the predictors of digital skills. After controlling for age, gender and years of education, lower foundation skills were significantly associated with a higher likelihood of unemployment ($p = 0.002$). More severe negative symptoms were associated with lower foundation skills but the significance did not remain after controlling for other variables. Lower SFL was associated with weaker general cognitive functions ($p = 0.005$) and a higher likelihood of unemployment ($p < 0.001$) after controlling for demographic variables. No significant predictors were associated with SFW.

**DISCUSSION:** Although patients with schizophrenia had a similar level of basic digital access compared to healthy controls, a digital divide exists in digital use, confidence and skills. Patients lacked foundation skills, SFL, and SFW, raising concerns about their risk for digital exclusion. Lower foundation skills and SFL are significantly associated with unemployment, suggesting that opportunities for using digital technologies may be crucial for developing digital skills. This may also reflect the difficulty for patients lacking digital skills to integrate into society. There is a need to develop the digital skills of patients with schizophrenia to prevent the widening of the digital divide and ensure they remain relevant in both society and the workforce. Policymakers

must be cautious when promoting digitalization to ensure that patients can retain access to and benefit from essential public services.

## M151. Urbanicity, Social Fragmentation, Social Isolation and Psychosis Risk: Case-Control Study From a Large-Scale Data Linkage of Person-Level English Census to Health Records, from an Urban Area

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**BACKGROUND:** The association between urbanicity and increased psychosis risk has been well established within western Europe and North America, and there are many theories relating to the underlying causes. It has been hypothesised that isolation and social fragmentation within cities are associated with a higher risk of psychosis. Using a large-scale first-of-its-kind data linkage between mental health records and the English census, we assessed the association between urbanicity , neighbourhood social fragmentation, and individual-level social isolation with the onset of psychosis.

**METHODS:** The SocioEconomic Predictors of Mental Disorders (SEP-MD) study dataset links data extracted from electronic health records from the South London and Maudsley National Health Service Foundation Trust (SLaM) to the 2011 English census at the individual level. SLaM is the principal provider of secondary mental health care services to an area of southeast London with 1.3 million residents. This project was conceived in collaboration with SLaM, the UK Office for National Statistics, and King's College London.

We developed a case-control design using the data linkage with a multilevel modelling approach to assess the associations between onset of psychosis with individual- and neighbourhood-level experiences. Cases with clinically determined diagnoses of psychotic disorders living in the SLaM locality were identified alongside population controls from the area. Neighbourhoods were defined as census "lower super output areas" (equivalent to the small census tracts) comprising of 1000-3000 residents. Neighbourhood urbanicity was determined by population-per-hectare. Neighbourhood social fragmentation was calculated as an index based on a prior methodological approach, derived from proportions of households of single occupancy, unmarried people and residential instability. Individual social isolation was defined as individuals reporting living alone or being unmarried.

Multilevel logistic regression models were used to determine the associations between neighbourhood urbanicity, neighbourhood social fragmentation, and individual-level social isolation indicators with psychosis. Effect modification was assessed using cross-level interaction terms and likelihood ratio tests. We included age, sex and neighbourhood deprivation as a priori confounders, and calculated adjusted odds ratios (aOR).

**RESULTS:** 577,200 observations were included in the analysis, with 12,091 cases of psychosis. There were substantial associations evident at the individual-level, between being unmarried (aOR 3.11 (2.95-3.27)) and living alone (aOR 2.60 (2.49-2.71)) with psychosis risk. There was evidence that the association between living alone, and psychosis risk was modified by urbanicity ($p < 0.001$) and social fragmentation ($p < 0.001$). There was an increase in the

association between living alone and psychosis at higher levels of urbanicity compared to lower. However, when modelling the association between social fragmentation, living alone and psychosis, the interaction effect was largest in the middle quintiles. There was weaker, but significant, evidence of modification of the association between psychosis and being unmarried by population density (p=0.04) and social fragmentation (p=0 .001) in separate models. Any association observed between urbanicity or social fragmentation with psychosis was attenuated by neighbourhood deprivation.
**DISCUSSION:** The findings suggest a synergistic effect between isolation, neighbourhood social fragmentation and urbanicity within an urbanized environment. These observations will help create targeted preventative policies.

## M152. Disparities in Subclinical Schizophrenia-Related Symptoms in Sexual and Gender Minority Adults

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**BACKGROUND:** Sexual and gender minority (SGM) groups are at higher risk for mental health conditions, yet our understanding of disparities in schizophrenia-related symptoms and their subclinical manifestations is sparse. While some research indicates that similar disparities may exist in the realm of positive symptoms (e.g., paranoia), no research has yet assessed for differences in other subclinical experiences that may correspond to negative or disorganized symptoms, such as alexithymia and schizotypy. Further, research has predominately been conducted outside of the United States, where minority stress experiences, thought to be a major contributor to mental health disparities, may be unique and linked to a highly charged political climate. Therefore, this study aimed to assess whether SGM adults in the United States experience worse paranoia, schizotypy, and alexithymia than non-SGM adults. We further examined associations between minority stress exposure and symptoms among SGM participants.
**METHODS:** Participants (N = 456) were recruited via Prolific to complete an online survey (~30 minutes for completion), which included attention checks to ensure high-quality data. All participants completed self-report measures of alexithymia, schizotypy, and paranoia; participants who identified as SGM (n = 100) reported on exposure to minority stressors. T-tests were run to assess for differences in symptoms between SGM and non-SGM groups. Pearson's correlations were run to evaluate associations between minority stress and symptoms.
**RESULTS:** Results indicated that SGM participants had significantly higher levels of alexithymia, schizotypy, and paranoia than non-SGM participants [$t(432) = -3.31$, $p = .001$; $t(421) = -3.86$, $p < .001$; $t(452) = -4.21$, $p < .001$]. Further, within the SGM group, more exposure to minority stress was significantly correlated with higher alexithymia ($r = .41$, $p < .001$), schizotypy ($r = .28$, $p < .001$), and paranoia ($r = .56$, $p < .001$).
**DISCUSSION:** Our findings suggest that SGM groups experience more severe subclinical schizophrenia-related symptoms than non-SGM groups. This extends past SGM mental health disparities research to a variety of subclinical schizophrenia symptoms, including those related to negative and disorganized symptoms. Additionally, within the SGM group, greater reports of

minority stress were associated with more severe symptoms, highlighting that minority stressors contribute to heightened schizophrenia-like experiences in SGM adults. Future work should assess these experiences using clinical interviews, in which adaptive cultural mistrust related to SGM identity may be disentangled from clinically relevant symptoms. Researchers should also aim to assess for disparities in symptom severity between SGM and non-SGM groups diagnosed with schizophrenia-spectrum disorders in the United States.

## M153. The Relationships Between Minority Stress, Schizotypy, and Social Cognition in Sexual and Gender Minority Participants

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**BACKGROUND:** People who identify with one or more marginalized groups often experience discrimination, stigma, and prejudice related to their minority group membership, called minority stress. While minority stress is inherently social in nature, little work has explored its impact on social cognition. Evidence of social cognitive differences between marginalized and non-marginalized groups is mixed and typically does not explicitly measure minority stress or schizotypy symptoms. Schizotypy symptoms impact social cognition and may be increased in marginalized groups, suggesting the importance of these symptoms in the relationship between minority stress and social cognition. Few studies have explored these connections in the context of sexual and gender minority (SGM) adults. This study aimed to fill this gap by examining whether SGM-related minority stress is associated with social cognition, and whether schizotypy moderates this relationship.
**METHODS:** Prolific participants (n = 90) who identified as SGM completed several online measures related to social cognition and minority stress experiences. To control inattentive responding, five attention check items were included. Participants with incorrect responses to two or more of these items were excluded from data analysis.
**RESULTS:** There was a significant negative relationship between minority stress and theory of mind scores ($r = -0.33$, $p = 0.002$). A similar relationship was observed with minority stress and empathic perspective taking ($r = -0.27$, $p = 0.043$), but not empathic concern. Schizotypy significantly moderated the relationship between minority stress and theory of mind ($p = 0.036$), such that this association was significant for participants with lower schizotypy scores. Associations between minority stress and theory of mind were nonsignificant for those with total schizotypy scores above 112.86 (21% of the sample). Schizotypy did not significantly moderate the relationship between minority stress and empathy measures.
**DISCUSSION:** Our results indicate that minority stress and social cognition are significantly related in SGM populations. This relationship was not evident for all measures of social cognition but appeared particularly relevant for empathic perspective taking and theory of mind, where relationships demonstrated a negative association, such that greater minority stress was associated with worse social cognition. The relative dearth of relationships with empathic concern may suggest that minority stress has a stronger relationship with the cognitive aspects of social cognition than the affective aspects, although more research is needed in this area. Our findings suggest that for those with high levels of schizotypy, minority stress was not associated with theory of mind. This could be a result of the impact of schizotypy traits on social cognition,

which would be more impactful at higher levels. Another potential explanation for this finding could be that those with higher schizotypy levels are less aware of or impacted by the negative effects of minority stress. Future work should extend to include relationships between minority stress and other domains of social cognition, such as emotion recognition and attribution biases.

## M154. Exploring Psychosocial Interventions for Individuals Experiencing Involuntary Care in Adult Mental Health Inpatient Units: A Scoping Review

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**BACKGROUND:** Individuals admitted involuntarily to acute psychiatric inpatient units often experience significant challenges, including heightened distress, feelings of coercion, and limited engagement in their care. Psychosocial interventions offer potential for improving these experiences and outcomes, yet a comprehensive synthesis of their components, delivery methods, and effectiveness is lacking. This scoping review addresses this gap, mapping existing evidence on psychosocial interventions for individuals undergoing involuntary care to inform future research and clinical practice.

**METHODS:** This review follows the Joanna Briggs Institute (JBI) methodology for scoping reviews. Searches were conducted across PsycINFO, MEDLINE, EMBASE, CINAHL, ASSIA, Web of Science, and grey literature sources. No restrictions were placed on publication date. Inclusion criteria targeted studies on psychosocial interventions aimed at improving patient experiences or recovery for adults in acute inpatient psychiatric settings, with at least 50% of participants undergoing involuntary care. Studies focusing solely on pharmacological treatments, substance use, or eating disorders were excluded. Data extraction captured study design, intervention characteristics, delivery methods, and reported outcomes.

**RESULTS:** A total of 19 studies met the inclusion criteria, encompassing 16 psychosocial interventions categorised as staff-focused (n=3), patient-focused (n=11), and mixed-focus interventions (n=2). Sub-categories included psychoeducation (n=4), skills-based interventions (n=2), therapeutic interventions (n=5), engagement and advocacy programmes (n=2), and staff/system-level interventions (n=3). Seven interventions were in forensic units and 9 in general inpatient settings. Delivery methods included group-based (n=8), one-on-one (n=5), and combined approaches (n=3), with durations ranging from one-off sessions (n=2) to short-term ( < 12 weeks, n=7) and long-term ( > 12 weeks, n=7). Peer involvement was evident in four interventions, where peers acted as advisory panel members, session facilitators, or co-researchers. The remaining 12 interventions had no peer involvement, underscoring a gap in integrating lived experience. Cultural considerations were rarely addressed, with only one study explicitly highlighting the need for inclusive practices to better engage foreign nationals. Preliminary findings indicate that interventions empowering participants, addressing individual needs, and incorporating staff training were associated with improved outcomes. Feasibility,

cost-effectiveness, and gender-sensitive approaches, such as tailored post-coercion reviews, emerged as critical factors for scalable and inclusive intervention design.
**DISCUSSION:** This scoping review highlights the diverse range of psychosocial interventions implemented for individuals involuntarily admitted to acute psychiatric inpatient settings and their potential to improve care experiences. The breadth of approaches, including therapy-focused interventions, psychoeducation, and creative activities like music and equine therapy reflects innovative and varied ways to support recovery. However, the limited standardisation, peer involvement, and cultural inclusivity highlight important gaps in intervention design and evaluation to date. These findings underscore the need for co-designed, evidence-based strategies that balance diversity with consistency, prioritise patient autonomy, and ensure inclusivity and provide a basis for future research to develop more effective and feasible interventions to improve the experience of involuntary care.

## M155. Effectiveness of Culturally Adapted Psychosocial Interventions for Psychotic Spectrum Disorders: A Systematic Review

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**BACKGROUND:** Psychotic spectrum disorders are severe mental conditions associated with significant distress and functional impairment. Psychosocial interventions (PSIs) are effective and internationally endorsed for the treatment of psychotic disorders, however, guidance is based on literature from high-income countries. Culturally adapted PSIs incorporating regional cultural beliefs and practices show promise in improving outcomes for individuals with psychosis. This systematic review aims to evaluate the effectiveness of culturally adapted PSIs for psychotic disorders.
**METHODS:** A systematic review was conducted following the PRISMA guidelines. Databases such as Embase, PsycINFO, MEDLINE, Web of Science, Scopus, Anthropology Plus, and Africa Index Medicus were searched for studies published up to 2023. Inclusion criteria were randomized controlled trials (RCTs) that evaluated culturally adapted PSIs for individuals with schizophrenia or related psychotic disorders. Data extraction focused on study characteristics, intervention details, cultural adaptations, and outcomes. Quality assessment was performed using the Cochrane Risk of Bias tool. Results were synthesized using a narrative synthesis approach due to the heterogeneity of the interventions and outcomes. The review protocol was registered with PROSPERO (CRD: 42023395909).
**RESULTS:** Fifty RCTs with a total of 4214 participants met the inclusion criteria, encompassing diverse cultural settings such as the United States, China, Pakistan, and Egypt. PSIs included family interventions (n=10), cognitive-behavioral therapy (n=5), psychoeducation (n=4), and metacognitive training (n=4), and skills training (n=3). Common cultural adaptations involved using culturally relevant language, embedding cultural values and beliefs, and supporting adaptive cultural practices. Most studies (n=42) reported significant improvements in

primary outcomes such as symptom severity (measured by PANSS or BPRS), quality of life, and functioning. Very few RCTs demonstrated a high risk of bias in key domains (n=4), although most studies had an unclear risk of bias in specific areas (n=37).
**DISCUSSION:** The findings suggest that culturally adapted PSIs are effective in improving clinical outcomes for individuals with psychotic disorders. These interventions are particularly beneficial in enhancing symptom management, quality of life, and social functioning. The incorporation of cultural elements such as language, family involvement, and culturally relevant examples appears to enhance the acceptability and effectiveness of these interventions. However, limitations include the variability in intervention types and the degree of cultural adaptations, which may affect the generalizability of the results. Future research should focus on long-term outcomes and the cost-effectiveness of culturally adapted interventions.

## M156. Feeding the Mind: The Impact of Diet on Schizophrenia

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**BACKGROUND:** Background: Nutrition plays a critical yet often overlooked role in mental health, particularly in schizophrenia. Traditional treatments heavily focus on dopamine pathways but fail to address the nutrient deficiencies that contribute to symptom severity. Recent evidence underscores the transformative potential of dietary interventions. Animal-derived nutrients, uniquely bioavailable and effective, are foundational for enhancing brain function and mitigating symptoms. This research advocates integrating these nutritional strategies into psychiatric care to improve outcomes.
**METHODS:** Methods: Findings from diverse studies examining nutrient deficiencies, supplementation, and inflammatory triggers like gluten were synthesized. Criteria such as sample sizes, study designs, and clinical outcomes were analyzed to develop practical dietary strategies that complement existing treatments.
**RESULTS:**
• Vitamin D3: Up to 97% of schizophrenia patients show deficiency, correlating with hippocampal atrophy and cognitive impairment. Supplementation improves memory, emotional regulation, and overall function.

• Vitamin B12 and B6: Elevated homocysteine levels, particularly in individuals with MTHFR mutations, worsen symptoms. Supplementation reduces severity, enhances mental clarity, and alleviates overall cognitive impairment.

• DHA and EPA: These omega-3 fatty acids reduce neuroinflammation, improve negative symptoms, and enhance antipsychotic efficacy. They also mitigate metabolic side effects associated with long-term medication use.

• Zinc: Low zinc levels, often observed in drug-naïve patients, correlate with more severe symptoms. Supplementation improves positive and negative symptoms, making zinc a valuable adjunct therapy.

• Gluten: Sensitivity worsens inflammation, disrupts the blood-brain barrier, and exacerbates cognitive and behavioral symptoms. Gluten-free diets have shown significant reductions in symptom severity, especially cognitive and negative symptoms.

• Sarcosine: This NMDA receptor co-agonist enhances glutamatergic signaling. Clinical trials report a 40% reduction in negative symptoms when used alongside antipsychotics.

• Taurine: Known for its neuroprotective properties, taurine reduces psychotic symptoms and improves brain function.

• Glycine: This amino acid modulates NMDA receptors, reducing negative symptoms by 30% and improving quality of life.

• L-Carnosine: A potent antioxidant, L-carnosine enhances cognitive performance, especially attention and memory.

**DISCUSSION:** Discussion: Nutritional strategies represent an underutilized opportunity to transform schizophrenia care. Essential nutrients discussed are available only in sufficient and bioavailable amounts in animal-based foods. Plant-based diets lack these nutrients and may include inflammatory compounds like gluten, which exacerbate neuroinflammation. Prioritizing animal-based diets while eliminating inflammatory triggers provides a practical, scientifically supported strategy for improving mental health outcomes. Future research should refine these interventions to maximize their accessibility, safety, and therapeutic potential.

Sources:

1. Pub Med: Vitamin D and Hippocampal Volume in Cognitive Impairment

2. Cambridge University: Vitamin D Schizophrenia and Depression

3. Pub Med: Low Maternal Retinol as a Risk Factor for Schizophrenia

4. Pub Med: Beneficial effects of omega-3 fatty acid supplementation in schizophrenia

5. NIH: Homocysteine levels in schizophrenia and affective disorders—focus on cognition

6. Journal of Family Medicine: Effects of zinc sulfate on schizophrenia symptoms in patients

7. Sarcosine or D-Serine Add-on Treatment for Acute Exacerbation of Schizophrenia

8. University of Melbourne: What is taurine and how can it improve psychosis?

9. Efficacy of High-Dose Glycine in the Treatment of Enduring Negative Symptoms of Schizophrenia

10. Pub Med: Cognitive and negative symptoms in schizophrenia with L-Carnosine adjuvant therapy

11. Lectin-Positive Spherical Deposits (SPD) Detected in the Molecular Layer of Hippocampal Dentate Gurus of Schizophrenia

12. Markers of Gluten Sensitivity and Celiac Disease in Recent-Onset Psychosis and Multi-Episode Schizophrenia

13. International Journal of Celiac Disease: Gluten and Schizophrenia: What's Next?

14. Interaction between food antigens and the immune system: Association with autoimmune disorders

**M157. The Effect of Multisession Bi-Parietal TDCS on Visuospatial Attention in Patients With Schizophrenia**

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**BACKGROUND:** Line bisection test (LBT), which involves bisecting the midpoint of horizontal lines, is theorized to reflect visuospatial function, which is predominantly attributed to the posterior parietal areas (PPA). Impaired illness awareness (IIA) in schizophrenia may be associated with hemispheric asymmetry, resulting from either right PPA dysfunction or left PPA overactivity. Transcranial direct current stimulation (tDCS), a non-invasive form of brain stimulation, may have the potential to improve IIA in schizophrenia by restoring the interhemispheric balance of the PPA (i.e., P3 anodal stimulation to increase the excitability of the right PPA and P4 cathodal stimulation to decrease the excitability of the left PPA). It was hypothesized that post-stimulation changes in LBT scores may be an indicator of the modulatory effects of tDCS on the functions of the PPA.
**METHODS:** A total of 34 participants with schizophrenia with IIA were randomized to receive either biparietal active (n=18) or sham (n=16) 2mA tDCS for 20 sessions. IIA was measured using the VAGUS, Self-report (VAGUS-SR). LBT was collected pre- and post-tDCS, and scored according to the degree of deviation from the midpoint of the lines. Bivariate correlation of absolute LBT and VAGUS-SR scores was conducted. Paired-sample t-tests of the absolute LBT scores were conducted separately for the active and sham groups.
**RESULTS:** The mean age was 42.2 (SD=13.7) and 23.5% were female. The baseline mean VAGUS-SR score was 5.9/10 (SD=1.5). The baseline mean LBT score was +0.73 mm (SD=2.28). Baseline absolute LBT and VAGUS-SR scores were not correlated. Absolute LBT scores were decreased (i.e. less deviation from the midpoint) after multisession tDCS compared to baseline in the active group ($t(17)=2.89$, $p=0.010$), with a less rightward bias (LBT score (pre vs. post)=+1.18mm vs. +0.86mm), but not the sham group ($t(15) = -0.48$, $p=0.639$, LBT score (pre vs. post)=+0.21mm vs. +0.94mm).
**DISCUSSION:** The results indicate that biparietal tDCS may be effective in modulating PPA area function in patients with schizophrenia, as reflected by improvement in the LBT. Further investigation with functional neuroimaging may more comprehensively assess the effect of tDCS on PPA function in relation to changes in LBT scores and IIA.

## M158. Behavior and Cytokines Level Evaluation in Mam Model Male/Female Rats Under Pubertal Antioxidants Treatment

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**BACKGROUND:** The hypothesis of impaired neurodevelopment in schizophrenia (EZ) has led to the use of animal models based on interventions in the perinatal phase. Among them, MAM consists of the injection of the antimitotic methylazoxymethanol acetate (MAM) on the seventeenth day of gestation in Wistar rats, whose offspring present behavioral and

neurochemical impairments in adulthood, such as increased locomotion in the arena, sensitivity to psychostimulants, reduced social interaction (SI) and deficit in the pre-attentional pre-pulse inhibition (PPI) test. Several of this evidence resembles alterations observed in patients with EZ. Recent studies point to an increase in inflammatory cytokines and a reduction in the endogenous antioxidant glutathione (GSH) in schizophrenic patients, raising the hypothesis about the role of oxidative stress and inflammation in the pathophysiology of this disorder. Our recent results demonstrated that acute or chronic treatment in adulthood with the GSH precursor, N-Acetyl-L-Cysteine (NAC), reversed the behavioral deficits of the MAM model. Purinergic receptors appear to play an important role in neurodegeneration, especially P2X7R, whose activation increases the production of reactive oxygen species and cytokines. Thus, the use of P2X7R antagonists, such as Brilliant Blue G (BBG), may be effective in investigating EZ. In addition, it is necessary to evaluate whether pharmacological treatments in the prepubertal phase can promote behavioral and neurochemical changes.
Objective: the aim of this study is to evaluate whether acute or chronic treatment with NAC or BBG in the pubertal phase can reduce behavioral deficits and inflammatory cytokines in male and female rats of the MAM model.

**METHODS:** Methodology: All procedures were approved by CEUA nº 1121171221. Wistar rats approximately 90 days old were used for mating. Initially, the rats received treatment with MAM (25 mg/kg, ip) or saline from the 17th day of gestation. After weaning, the females were separated from the males and divided into six groups (Sal/Sal, MAM/Sal, Sal/NAC, MAM/NAC, Sal/BBG, MAM/BBG), N=12. At PN45, the offspring received an injection of NAC (250 mg/kg, ip), BBG (50 mg/kg) or saline and one hour later were subjected to behavioral tests (acute evaluation), locomotion in the arena, SI and PPI. They were treated with daily doses of respective treatment for 15 days and 24h after the last treatment (Chronic), the rats were again subjected to the same tests. Blood and ventral hippocampus (vHipp) were collected for the cytokine evaluation. The statistical analysis was developed using two-way ANOVA and Tuckey's post hoc test. Considered statistically significant differences at $p < 0.05$.
**RESULTS:** Results: MAM-treated male rats exhibited higher acoustic startle responses (ASR) than females across acute and chronic evaluations. NAC and BBG treatments significantly reduced ASR deficits during chronic evaluation in male rats. In the Open Field test, female rats exhibited higher locomotion than males, with MAM-treated males showing increased locomotion on the acute evaluation only. In SI tests, females displayed more active interaction than males. MAM-treated rats showed reduced proximity and active interaction and increased self-grooming behavior in both sexes. NAC and BBG treatments ameliorated these deficits, particularly during chronic evaluation and in females this was specific during pro/est phases. Rats in pro/est showed less active interaction compared to those in di/meta phases. MAM treatment caused in pups a reduction of IL-6 level at vHipp and in serum, an increase in IFN-γ and IL-2 levels. Females had lower IL-4, IL-2 and TNF-α vHipp levels and IL-2 on serum than male rats. MAM females showed lower IL-4, IL-2 and TNF-α level than controls. NAC treatment increased the anti-inflammatory IL-10 in MAM rats.
**DISCUSSION:** Discussion: Taken together, this data indicates the MAM model presents inflammatory alterations and NAC or BBG treatment during puberty can reduce some of the behavioral deficits of the MAM model. Additionally, this data indicate a sex difference in cytokine expression between male and female rats and also that sex and estrous cycle influenced on treatment outcomes and behaviors.
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## M159. Environmental Adversity Predicts Attenuated Positive Symptoms and Complex Cognition in Females in a Long-Term Follow Up of the Philadelphia Neurodevelopmental Cohort

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**BACKGROUND:** Environmental adversity has been robustly associated with poor mental health outcomes, including psychosis spectrum (PS) symptoms, and associated challenges such as cognitive deficits. However, environment may differentially impact males and females due to known differences in stress reactivity. We hypothesized that environmental adversity would predict PS symptoms in early adulthood, and this relationship would be more pronounced in females following greater exposure to adversity.

**METHODS:** Individuals (n=343) from the Philadelphia Neurodevelopmental Cohort, enriched for high and low adversity and psychosis-risk at baseline, were assessed 10+ years later. A baseline environment risk score (ERS) was calculated using methods described previously (Moore et al., 2022). The Structured Interview for Psychosis-risk Syndromes assessed PS symptoms at follow-up, and the Penn Computerized Neurocognitive Battery (CNB) assessed cognitive performance. Linear regressions and interactions were conducted for the whole sample and stratified by sex assigned at birth.

**RESULTS:** Higher ERS at baseline predicted greater total PS symptoms (β=.11, p=.005) and specifically perceptual abnormalities (β=.11, p=.005) at follow-up in the full sample. While there was no significant interaction of adversity x sex, after stratifying, ERS was predictive of total PS symptoms (β=.14, p=.007) and perceptual abnormalities (β=.19, p=.004) in females, but not males. Evidence supported impact of ERS on complex cognition in the full sample (β=-.05, p=.03), and exploratory analysis of complex cognition tasks revealed significant impact of ERS on language reasoning in the full sample (β=-.11, p=.008) and in females (β=-.12, p=.02), but not males.

**DISCUSSION:** These findings suggest that individuals and particularly females are at risk following early adversity for PS symptoms (perceptual abnormalities) and cognitive deficits related to complex cognition.

## M160. Treatment Outcomes for Asian Americans Diagnosed With Schizophrenia Spectrum Disorder

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**BACKGROUND:** Considerable progress has been made in understanding Asian Americans' use of mental health services, but knowledge about users' responses to these services remains poor. Notably, there is a significant gap in our understanding of the treatment outcome of Asian Americans diagnosed with schizophrenia, a less common but among the most debilitating and costly psychiatric disorders. We implemented a pilot study to investigate symptoms and functional outcomes of Asian Americans treated in urban community mental health centers for a diagnosis of schizophrenia spectrum disorder. Furthermore, we investigated whether these outcomes differed between East and Southeast Asians.
**METHODS:** We collected quantitative data from 75 participants recruited using a nonprobability sampling strategy from six urban community mental health centers. We used the Positive and Negative Syndrome Scale (Kay et al., 1987) and the Strauss and Carpenter Outcome Scale (Strauss and Carpenter, 1972) to measure their symptoms and functional outcomes. To compare the outcomes between East and Southeast Asians, we used a multivariable logistic regression model, which adjusted for the estimated effects of age, sex assigned at birth, and age at onset of illness for each outcome examined.
**RESULTS:** The data shows that the treatment outcomes for this group are poor. Only a small number of participants experienced symptomatic remission (30.67%), role restoration (34.67%), and clinical recovery (21.33%). The majority of those who did not experience clinical recovery had difficulties sustaining symptomatic remission and restoring role functioning (54.67%). However, more participants achieved social restoration (68.00%). The results did not vary by national origin groups and sex assigned at birth. However, the participant's age, the age at which the illness began, or both determined whether the treatment outcomes were favorable.
**DISCUSSION:** Findings underscore the need for interventions that improve symptom control to increase the likelihood of other favorable outcomes.

## M161. Computational Mechanisms of Multimodal Hallucinations

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**BACKGROUND:** Hallucinations can occur across various sensory modalities, including auditory, visual, and tactile experiences (Montagnese, Marcella, et al., 2021). Research has shown that an overreliance on prior knowledge, as opposed to sensory evidence, increases the likelihood of auditory hallucinations (Powers, Mathys, and Corlett, 2017). However, it remains unclear whether an over-reliance on priors is modality-specific, driving expression of different modality hallucinations, or if this tendency is uniform across sensory modalities regardless of the modality of hallucinations exhibited. Modality-specificity may point to upstream disruptions in sensory systems driving hallucination emergence, whereas modality-general findings may speak to supramodal disruptions driving that emergence.

Exploring how an over-reliance on prior beliefs interacts with sensory information could help clarify the shared and distinct features of hallucinations, leading to more targeted prevention strategies. In this study, we investigate how auditory and visual hallucination symptoms influence multimodal conditioned hallucinations (CH) and examine the sensory computations that may explain these phenomena.

**METHODS:** Participants (n = 727), aged 18-65, were recruited via Amazon Mechanical Turk (MTurk) and the Yale Control Over Perceptual Experiences (COPE) Project. After screening for cognitive, neurological, or substance-related disorders, they provided informed consent and completed demographic and clinical assessments (e.g., COPE Scale, Peters Delusion Inventory, Launay-Slade Hallucination Scale). Participants were grouped by hallucination symptoms into four categories: A-V-, A+V+, A-V+, and A+V-. Data were collected via Yale's HIPAA-secure platform, REDCap, and approved by the Institutional Review Board.
Two conditioned hallucination (CH) tasks, Auditory Conditioned Hallucinations (ACH) and Visual Conditioned Hallucinations (VCH), were used to assess hallucination susceptibility. Participants completed practice trials, followed by QUEST-thresholding to determine individual detection thresholds. In the ACH task, participants detected a 1kHz tone in white noise with a visual cue, while in the VCH task, they detected a Gabor patch with an auditory cue. Each task consisted of 12 blocks of 30 trials, and responses were analyzed using Hierarchical Gaussian Filter (HGF) modeling to assess beliefs about target presence, cue prediction power, and belief volatility.

**RESULTS:** Auditory and visual detection thresholds were similar regardless of group classification (CIs for detection thresholds: A+V+ [-0.58, -0.56], A+V- [-0.60, -0.57], A-V+ [-0.64, -0.58], and A-V- [-0.60, -0.57]). Intriguingly, we found that auditory symptoms increased CH rates for both ACH and VCH tasks (ACH: $t=3.30$, $p=0.001$; VCH: $t=2.55$, $p=.011$) while visual symptoms selectively increased VCH rates ($t=3.87$, $p < 0.000$), leaving ACH rates intact ($t=0.47$, $p=0.637$). Diving deeper, we saw that the severity of visual hallucinations, as measured by simple frequency, reliably modulated this effect in a dose-dependent manner ($beta=0.018$, $p < 0.000$).
Assessing the computations driving these effects, we likewise saw a steady increase in prior precision as a function of visual symptom severity ($beta=0.008$, $p < 0.000$), suggesting that more severe visual symptoms lead to stronger reliance on priors during sensory processing.

**DISCUSSION:** The findings suggest that auditory and visual hallucinations may share some sensory-processing dynamics, but the relationship between modality-specific symptoms and hallucination susceptibility is complex. Auditory symptoms increased hallucination rates in both auditory and visual tasks, while visual symptoms selectively heightened visual hallucination susceptibility. This cross-modal influence implies that disruptions in sensory processing, driven by an over-reliance on prior expectations, could contribute to hallucinations across domains. However, the effects were not uniform. Visual symptoms appeared to be more modality-specific, indicating that visual hallucinations (VHs) might be more stable or persistent over time compared to auditory hallucinations (AHs). If VHs are indeed more enduring, they could create a stronger prior for visual experiences, making individuals more susceptible to visual hallucinations, while leaving auditory hallucination rates unaffected. Also, a relatively high proportion of those with VH also experience AH. This could imply that individuals with VH are more likely to experience broader sensory disruptions than those with AH, which might influence conditioned hallucination likelihoods across modalities.

These findings highlight the complexity of hallucination dynamics and the need for further research into the computational mechanisms behind these effects. While auditory and visual hallucinations may share some underlying processes, the nuances of how they interact across modalities remain unclear. Understanding these mechanisms will be crucial for developing targeted interventions and improving therapeutic strategies for individuals with psychosis.

## M162. Modality-Specific Disruptions in Bistable Perception Among Multimodal Hallucination

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**BACKGROUND:** Bistable perception occurs when the same external stimulus evokes alternating percepts that are driven by top-down perceptual factors. Visual and auditory verbal hallucinations have been linked to an over-reliance on top-down expectations, although no studies have demonstrated these effects in bistable perception. Understanding how these symptoms affect perception in bistable tasks across sensory modalities might inform if these disruptions are modality- and symptom-specific.
**METHODS:** Methods: Data were analyzed from 310 participants in the Yale Control Over Perceptual Experiences (COPE) study. Participants were categorized into four groups: auditory and visual hallucinations (AH+VH+, n = 114 ), auditory hallucinations only (AH+, n = 99 ), visual hallucinations only (VH+, n = 35), and healthy controls (HC, n = 66 ). They completed two bistable perception tasks: an auditory "Yanny/Laurel" task involving ambiguous auditory stimuli and a visual Dots Task requiring direction detection in an ambiguous dot motion paradigm. Self-report assessments included the White Bear Suppression Inventory (WBSI), Peters et al. Delusions Inventory (PDI), and the Launay-Slade Hallucination Scale (LSHS) questionnaire.
**RESULTS:** Results: Self-report measures indicate that those with AH+ have higher delusion and hallucination propensity, as well as more intrusive thoughts than AH+VH+, and those higher than VH+, and all of them higher than HC. For both visual and auditory tasks, no significant group differences were found in the number of natural switches and when instructed not to switch. However, when they were instructed to switch voluntarily, the mean switching times in the Dots Task were shorter in those with auditory hallucinations ($F(3,310) = 3.279$, $p = 0.021$), AH+VH+ ($p = 0.0179$) and AH+ ($p = 0.0431$) in contrast with HC. In the Yanny/Laurel Task, participants with visual hallucinations AH+VH+ and VH+ and VH+ switched more than HC (ps $< 0.05$).
**DISCUSSION:** Discussion: These findings indicate that perceptual disruptions in hallucination-prone individuals are linked to a particular sensory modality. For the visual task, participants with AH demonstrated shorter switching times when voluntarily instructed to switch, potentially indicating less precise visual priors for individuals experiencing auditory hallucinations. Conversely, in the auditory task, participants with VH switched more frequently compared to HC, suggesting heightened auditory perceptual flexibility or less precise auditory priors in those with visual hallucinations. This dissociation in performance aligns with the notion that hallucination modality influences perceptual processing in the opposite sensory domain.

## M163. Functioning Trajectories in First-Episode Psychosis: A Five-Year Follow-Up of Early Intervention Services With and Without Extended Care

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**BACKGROUND:** Early intervention services (EIS) operate on the premise that first episode of psychosis (FEP) occurs during a "critical period" of neuronal and psychosocial plasticity—a window of opportunity where timely treatment may yield long-term benefits. Systematic reviews and meta-analyses consistently demonstrated the short-term superiority of EIS over regular care. However, its long-term benefits remain uncertain, as gains may not persist after patients transition to regular care. Extending EIS beyond the typical two-year follow-up, to cover the entire five-year critical period has shown promise, yet considerable heterogeneity remains in outcomes trajectories. It remains unclear who maintain these benefits and who may require prolonged specialized EIS care. This study investigates the maintenance of functioning trajectories during the critical period, comparing three-year extension EIS to regular care following two-years EIS in FEP.

**METHODS:** The Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) is a high-fidelity, catchment area-based, 2-year EIS for FEP. Between 2006 and 2016, 220 individuals (aged 14–35) with a first episode of non-affective or affective psychosis received specialized EIS care. At the two-year mark, participants were randomized into either a 3-year EIS extension or transitioned to regular care. Participants underwent comprehensive assessments every six months over the 5 years, evaluating sociodemographic, psychopathology, and functioning as measured with the global assessment of functioning (GAF) scale. Piecewise, longitudinal latent growth modelling was used to identify distinct trajectories of functioning. Covariates were investigated following the manual three-step approach. Multinomial logistic regressions were performed to identify baseline predictors of latent class membership.

**RESULTS:** Three distinct global functioning trajectories were identified over the 5-year follow-up. During the first two years of EIS, all trajectories showed significant improvement, reaching a plateau after the first year corresponding to slight, moderate or serious impairment. Over the following three years, 25% of participants maintained high functioning, 50% remained stable at a moderate level, and 25% experienced a decline. Membership to the declining trajectory was associated with greater symptom severity and lower symptom remission by the end of the 2-year EIS follow-up, particularly negative symptoms (OR=0.15; $p < 0.005$). Trajectory membership was not significantly predicted by allocation to either regular care or extended EIS, nor by any of the sociodemographic variables examined.

**DISCUSSION:** While functioning trajectories varied greatly across individuals, our findings suggest that most patients maintain the benefits gained during the initial two years of EIS. Encouragingly, some individuals may achieve sufficient stability within the first year, potentially reducing the need for prolonged intervention. However, a substantial subgroup of individuals experiences functional decline. The identification of individuals at risk for deterioration is critical for informing treatment planning. Ultimately, the identification of individuals who may benefit from extended EIS with more intensive and targeted care becomes crucial in optimizing EIS efficacy.

## M164. Adapting a Large Language Model (LLM) to Assess Clinical Ratings of Thought Disorder in Psychosis

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**BACKGROUND:** The present study investigates the capability of large language models (LLMs) to analyze transcripts from participants responding to language tasks and assign them ratings on the Scale for Assessment of Thought, Language, and Cognition (TLC). We explore the capabilities of LLMs to detect linguistic signals of thought disorder through elicited speech and to discern the types of linguistic tasks for which LLMs make the best symptom assessments.
**METHODS:** Clinical and healthy control language samples were taken from four studies with a combined total of 592 participants. Among the four studies, interviews include 24 unique stimuli including picture descriptions, open-ended responses, and fluency tasks. Each transcript was associated with clinical rating labels for TLC items given by the expert trained assessor who evaluated the participant and administered the tasks. The resulting dataset of 7,585 transcripts was randomly divided into 90% training and 10% evaluation sets. The training set was used to fine-tune GPT-4o via low-rank adaptation with the goal of predicting the TLC ratings. The evaluation set was used to test the accuracy and mean absolute error of the resulting model. Performance was benchmarked against a zero-shot approach utilizing the native GPT-4o model with no fine-tuning.
**RESULTS:** The fine-tuning process improved task-independent accuracy from 8.0% to 61.5% versus purely prompt-based approaches. It achieved high agreement with human annotators and low distance from correct judgements, on average achieving a distance of 0.5 points from the correct judgement, compared to the average 1.6 points of the prompting-based approach. The fine-tuned LLM performed best when evaluating responses to open-ended stimuli, attaining 70.4% accuracy when assessing subject responses to the question “How are you?”.
**DISCUSSION:** The model demonstrates promising performance in recognizing and assessing thought disorder across all tasks, even for highly domain-specific axes and best performance assessing unstructured responses. Notably, even for interviews on which the fine-tuned model makes mistakes, the mistakes are smaller in magnitude than that of the generic model. This research has significant implications for the development of AI-assisted psychiatric diagnostic tools.

## M165. Interindividual Variability in Memory Performance is Related to Cortico-Thalamic Networks During Memory Encoding and Retrieval

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**BACKGROUND:** Emerging evidence suggests that abnormal activity of the thalamus and deficits in thalamocortical connectivity are implicated in cognitive impairments commonly seen in schizophrenia, including deficits in episodic memory. Understanding the role of the thalamus in memory processes is crucial, as the encoding and retrieval of new memories rely on functional connections between the medial temporal lobe (MTL) and frontoparietal cortices, possibly modulated by the thalamus. The thalamus consists of many nuclei involved in distinct cognitive functions and brain circuits. Our previous research found changes in thalamic functional

connectivity (FC) with the fronto-parietal network (FPN) across two resting-state fMRI sessions that precede and follow an episodic memory task. In this study, we aimed to establish a baseline for the physiological brain function in healthy individuals, relevant for investigating cognitive deficits in clinical conditions. We hypothesized that individual variations in cortico-thalamic recruitment may impact individual memory performance.
**METHODS:** We used a multi-scan fMRI protocol in two independent samples of healthy adults (N1=29, mean age=26; N2=108, mean age=28), consisting of a baseline resting-state scan, followed by an associative memory task including encoding and retrieval phases. We analyzed FC and task-related activity in the individual native space to minimize registration biases. Thalamic nuclei were segmented on the individual T1 and grouped into four subdivisions (anterior, medial, ventral, posterior). To explore the interplay between baseline FC, task-related activity, and memory performance, we conducted path analyses within a structural equation modeling (SEM) framework. Additionally, we applied k-means clustering to identify distinct subgroups of individuals with corticothalamic recruitment patterns.
**RESULTS:** By modeling the direct and indirect effects of cortico-thalamic recruitment on memory performance using SEM, we showed a positive association between baseline resting-state FC of the medial thalamic subdivision within the FPN and memory performance across samples (effect size R2: 0.27-0.36; pFDR: 0.01-4e-05). This direct relationship was mediated by a decreased activation of the anterior thalamus during encoding (R2: 0.04-0.2; pFDR: 0.05-0.006) and by increased activation of the medial thalamus during retrieval (R2: 0.04-0.2; pFDR: 0.05-0.004). Moreover, clustering analyses revealed three distinct groups of individuals characterized by unique corticothalamic recruitment patterns across conditions, each associated with different memory performance profiles.
**DISCUSSION:** These results suggest the role of the flexible recruitment of distinct cortico-thalamic pathways involving the medial subdivision within the FPNs while suppressing the anterior subdivision during encoding to support effective memory formation. Our findings suggest that disruptions in thalamic engagement may underlie the memory consolidation and retrieval deficits associated with various psychiatric conditions. Schizophrenia, in particular, includes difficulties in forming stable associations and accessing stored information. Our findings lay the groundwork for testing cognitive enhancement strategies in patients with schizophrenia and risk for psychosis using-circuit specific connectivity information.

## M166. Paranoia and High Schizotypy are Associated With Significant Differences in Functional Connectivity in Social Brain Regions During Threatening Social Interaction

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**BACKGROUND:** High schizotypes and patients with schizophrenia commonly experience a range of aberrant socio-cognitive experiences or impairments including heightened threat perception and paranoia, impairments in theory of mind, intention, eye-gazing, and reduced social engagement, social learning and motivation. These form, or contribute, to (sub)-clinical symptoms and, in turn, challenges in daily social interaction and functioning. To understand this more, we aimed to examine differences functional connectivity in brain regions processing negative social interaction or threat. Studies have revealed brain activation (BOLD) changes

during social-processing tasks or during social interaction, or FC in other tasks or resting state, but what is lacking is understanding of the role of FC during 'in vivo' social interaction particularly in comparison of threatening and non-threatening social agents. Following our previous work, we hypothesised that high (vs low) schizotypes would show impairments in FC between brain regions involved in social processing, fear and reward – and specifically when engaged in an interactive game with malevolent (socially threatening), not benevolent players.
**METHODS:** We administered a multi-trial prisoner's dilemma (PDG) task with benevolent (B) and malevolent (M) conditions ('other players') to 43 healthy participants split into low (LSZ) and high (HSZ) schizotypy groups. On each trial, participants provide social decisions (cooperate/compete) followed by trust ratings (indexing paranoia) after being shown the other players action towards them. PDG paranoia ratings have previously been shown to be sensitive to drug effects (MDMA; Gabay et al., 2017). The CONN Toolbox was used to calculate FC differences between amygdala, TPJ, ventral striatum in HSZ and LSZ participants for each player condition and phase of the trial (decision-making, outcome, trust rating). A secondary sensitivity analysis was conducted for high and low paranoia groups (from an ad hoc paranoia score derived from SPQ items).
**RESULTS:** HSZ and high paranoia groups showed significantly lower overall trust, and significantly lower ratings for M vs B players, than the low SZ and paranoia groups. As predicted, there were significant group x condition x phase differences in FC. The HSZ and high paranoia participants showed significantly lower bilateral amygdala/ventral-striatum (VS) FC ($p < 0.05$, pFDR-c $< 0.05$) and right amygdala/right orbitofrontal cortex FC ($p < 0.023$, pFDR-c $< 0.05$) during social interaction. However, more importantly, greater right-amygdala/VS FC was observed in both HSZ (vs LSZ) and high (vs low) paranoia groups only when rating the trustworthiness of the malevolent player ($p < 0.035$, pFDR-c $< 0.05$) – not for the benevolent player.
**DISCUSSION:** These findings provide evidence that paranoia and schizotypy are associated with significant impairments in functional connectivity between social, fear and reward-related brain regions during 'in vivo' interaction with other social agents –specifically those which represent a threat to the self. Further research should aim to examine these effects in patients with psychosis, particularly those with paranoid delusions. These findings extend what is known about the neural basis of social threat perception, and provides a potential biomarker and treatment target to reduce paranoia.

## M168. Dopamine-Dependent Changes in Cortical Sensory Prediction Errors Drive Speech Hallucinations in Schizophrenia

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**BACKGROUND:** Patients with hallucinations show both behavioral and neural alterations in statistical learning in simple sensory tasks, but the upstream drivers of this change are unclear. Neuroimaging and pharmacological evidence have implicated both excess striatal dopamine and cortical glutamate dysfunction in psychotic symptoms. As a result, prominent theories have

emerged positing causal relationships with both upstream mechanisms and sensory learning. However, arbitrating between these mechanisms has been difficult since multimodal studies with measures of dopamine function (e.g., positron emission tomography (PET)), cortical glutamate (e.g., magnetic resonance spectroscopy (MRS)), and sensory learning (e.g., task-based fMRI) collected in the same subjects are exceptionally rare. Here, we present such a dataset and show evidence specifically linking excess striatal dopamine function to changes in cortical sensory learning and auditory verbal hallucinations.
**METHODS:** We used fMRI to record neural activity while patients with schizophrenia (N=53) and healthy controls (N=45) were presented with a dynamic auditory environment. Participants were presented with speech, non-speech (e.g., rainfall), or silence at varying probabilities in a blocked structure and reported whether they heard voices. Building on neural models of predictive coding, we then constructed a computational learning model that updates trial-by-trial stimulus expectations via sensory prediction errors (sPEs). To evaluate individual differences in learning, we fit the model to neural responses of each participant. In a subset of participants (N=30), we also collected PET and MRS scans to measure differences in dopamine function and cortical glutamate+glutamine (glx), respectively.
**RESULTS:** Patients experience auditory verbal hallucinations (AVHs) intermittently in the scanner (i.e., report hearing voices in objective silence), and the rate was specifically correlated with hallucination severity but not negative symptoms or general psychopathology (Spearman $\boldsymbol{\rho}$=0.41; p=2.8x10-3). If patients learn the statistics of the sensory environment and incorporate their expectations into their perception, the probability of an AVH should vary with expectations of speech. Consistently, the rate of AVHs varied as a function of block speech probability (mixed effects regression p=3.1 x10-6). To measure neural signatures of sensory learning, we analyzed activity in speech-specific auditory cortex (defined as temporal lobe voxels where speech activation was > non-speech at the group level) using our computational learning model. We find that in patients, sPE scaling is negatively correlated with both clinical hallucination severity (Spearman $\boldsymbol{\rho}$=-0.35; p=0.011) and task AVH rate (Spearman $\boldsymbol{\rho}$=-0.33; p=0.022). To assess candidate upstream alterations that could disrupt sPEs, we measured dopamine function and glutamate concentration in the auditory cortex using PET and MRS, respectively. We find that sPE scaling was related to dopamine function in the associative striatum but not dopamine in other brain regions or auditory cortical glx (mixed effects regression p=0.0089).
**DISCUSSION:** Our results are consistent with a model of hallucinations whereby excess nigrostriatal dopamine disrupts cortical signals of sensory learning and alters the probability of experiencing false percepts.

## M169. A Meta-Analysis of Cognitive Impairments on Cantab Computerized Assessment of Matrics Domains

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**BACKGROUND:** Cognitive impairment in Schizophrenia (CIAS) is a core symptom associated with functional impairments in work and social activities, substantially impacting quality of life. Patients with schizophrenia perform significantly worse than controls across a range of cognitive

tests. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus process identified seven cognitive domains particularly relevant to CIAS. Although recommendations were made for pencil and paper assessments corresponding to these domains, computerized cognitive tests offer operational advantages for clinical trials. Understanding the magnitude of case-control differences can help to 1) demonstrate the sensitivity and potential utility of computerized tasks to measuring the core cognitive domains affected by schizophrenia, 2) provide context for interpreting the magnitude of treatment effects in placebo-controlled trials, and 3) target assessments to those which are most pronounced in this patient group, reducing burden of testing. Here, we focus on data from the CANTAB cognitive battery, which has been used for more than 30 years, generating a substantial volume of data spanning the MATRICS domains.
**METHODS:** Seven CANTAB tasks were analyzed, corresponding to MATRICS cognitive domains: Speed of processing – Choice Reaction Time (RT), Attention/vigilance - Rapid Visual Processing (RVP), Working memory - Spatial Span (SSP), Visual learning – Paired Associates Learning (PAL), Verbal learning - Verbal Recognition Memory (VRM), Social cognition - Emotion Recognition, and Reasoning and problem solving - Stockings of Cambridge (SOC). Using PRISMA guidelines, publications were identified through PubMed and Google Scholar databases. Inclusion criteria were: 1) DSM or ICD for diagnosis, 2) Included a healthy comparison group, 3) Used CANTAB to assess cognition, 4) Reported sufficient descriptive data to conduct meta-analysis, and 5) Published in a peer-reviewed journal. Studies were evaluated for eligibility and quality by two independent raters. Descriptive statistics and relevant covariates (e.g. age, sex, medication, duration of illness) were extracted. Meta-analyses were conducted using the 'meta' package in R, using a random effects model, accounting for expected heterogeneity in effect sizes across studies. The systematic review is registered on PROSPERO.
**RESULTS:** 54 eligible publications were identified, with between 10 and 277 participants with schizophrenia per study and between 12 and 207 healthy controls. Coverage varied by task, with participants with schizophrenia ranging from n = 1,383 for working memory (SSP) to n = 83 for verbal memory (VRM). Significant case-control differences were observed across all cognitive tasks. The highest levels of impairment were seen in attention and vigilance (RVP) with a Hedges' g of 1.10, followed by working memory (SSP: 0.94) and visual learning (PAL: 0.8). The task with lowest effect size was VRM at 0.42.
**DISCUSSION:** Consistent with prior research, deficits were moderate to large. The low estimates for VRM may be driven by the small number of studies which have used this measure relative to other tasks and represents a gap in the literature. Overall, the results demonstrate that computerized cognitive testing is sensitive to CIAS and may therefore have utility in the assessment of this core symptom of schizophrenia. Further work will focus on narrowing down the range of tasks to those with greatest sensitivity to functional impairments to prioritize assessments associated with the greatest patient benefit

## M170. Childhood Neglect, Inflammation, and Negative Symptoms in People With Schizophrenia

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**BACKGROUND:** Experiences of childhood trauma have been linked to an increased risk of schizophrenia and increased inflammation. Inflammation has been associated with deficits in motivation and pleasure across psychiatric illnesses, and specifically related to negative symptoms in schizophrenia. Childhood neglect has also been found to be associated with negative symptoms. Herein, we investigate whether inflammation is associated with the relationship between childhood neglect and negative symptoms specific to motivation and pleasure.
**METHODS:** Data was collected from a sample of 56 patients with schizophrenia or schizoaffective disorder who were recruited from a community behavioral health clinic in Atlanta, Georgia. Subjects underwent blood sampling for inflammatory markers including hsCRP and were administered the Childhood Trauma Questionnaire (CTQ) and the Brief Negative Symptoms Scale (BNSS). Two linear regression analyses were conducted to examine predictors of the motivation and pleasure domain (MAP) of the BNSS. The first model included the combined CTQ scores of emotional and physical neglect along with covariates including age, biological sex, race, education level, smoking status, BMI, and chlorpromazine equivalent dose. The second model included the same variables with the addition of log-transformed CRP to assess its impact on the model. Subsequently, to determine a potentially moderating effect of CRP on the model, CRP was divided into high ( > 3), moderate (1-3), and low ( < 1) levels and a multiple regression analysis was conducted to examine the effects of CRP level, combined emotional and physical neglect CTQ subscales, and their interaction with the BNSS motivation and pleasure (MAP) domain using robust standard errors (HC3) while controlling for age, biological sex, race, smoking status, BMI, chlorpromazine equivalent dose, and education level.
**RESULTS:** In the first linear regression model, which included CTQ combined neglect scores and covariates, the model reached statistical significance (Adjusted $R^2$=.151, p=.047), however none of the individual predictors were statistically significant. In the second model, which included the same variables with the addition of CRP, the model reached significance (Adjusted $R^2$=.297, p=.003) and significant predictors were found to include CRP ($\beta = 0.473$, $p = .002$), CTQ combined neglect scores ($\beta = 0.327$, $p = .009$), and race ($\beta = -0.315$, $p = .030$). In the multiple regression analysis with the varying CRP levels, we found that the interaction between combined neglect and BNSS MAP domain was statistically significant when CRP was high (B=0.52, p=0.01), but was not found to be statistically significant when CRP was moderate (B=0.069, p=0.668) or low (B=0.388, p=0.374).
**DISCUSSION:** These findings suggest that at higher levels of inflammation, greater childhood neglect is associated with more severe negative symptoms in the motivation and pleasure domain, which could indicate that inflammation moderates the relationship between childhood neglect and negative symptom severity. This highlights the potential for inflammation to be a key biological pathway linking early trauma to negative symptoms in schizophrenia. Understanding this pathway could inform targeted treatment strategies, such as anti-inflammatory pharmacology, for individuals with a history of childhood neglect who present with prominent negative symptoms.

**M171. Positive Allosteric Modulator of MGLUR2, JNJ-46356479, Ameliorates Cognitive and Schizophrenia-Like Behaviours in Adolescent Mice Following Postnatal Ketamine Exposure**

Patricia Gassó*[1], Albert Martínez-Pinteño[2], David Olivares Berjaga[2], Natalia Rodríguez[2], Juan Ignacio Mena[3], Alex.G. Segura[4], Gisela Mezquida[1], Constanza Morén[1], Eduard Parellada[5]

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**BACKGROUND:** Schizophrenia (SZ) is a chronic mental disorder characterised by its severity and complexity. Symptoms of this disease are divided into positive, negative and cognitive deficits. SZ affects approximately 1% of the population and mainly appears during early adulthood. Glutamatergic dysregulation is one of the main pathophysiological hypotheses of SZ. Given the lack of efficacy of antipsychotics (AP) on treating negative and cognitive deficits, glutamate (GLU)-based interventions could be a good pharmacological strategy to improve these symptoms. Positive allosteric modulators (PAM) of metabotropic GLU receptor 2 (mGluR2), such as JNJ-46356479 (JNJ), inhibit the presynaptic release of GLU. At animal level, we have previously reported that both, adolescent and adult JNJ treatment, partially improves neuropathological deficits and SZ-like behaviour in adult mice in a postnatal ketamine (KET) mouse model (Martínez-Pinteño et al., 2020; 2023, Olivares-Berjaga et al., 2025). Additionally, we previously demonstrate early treatment with clozapine (CLZ) during animal adolescence also prevent the behavioural deficits during animal adulthood (Martínez-Pinteño et al., 2023). Dealing with GLU storm during early stages of SZ may be particularly effective to prevent the disease appearance or slow the psychosis progression and the clinical deterioration of patients. We aimed to evaluate if the effects of adolescent JNJ or CLZ reported in adulthood could be also detected in young animals.

**METHODS:** A total of 120 C57BL/6J pups were exposed to KET (30mg/kg) or saline on postnatal days (PND) 7,9, and 11 to transiently disrupt NMDAR function. Then, mice were daily treated subcutaneously with 10 mg/kg of JNJ or CLZ, as a clinical AP of reference, during adolescence period (PND 35-60). Behavioural tests were performed in adolescent mice, once they reached PND 55, to evaluate cognitive and negative behaviours related to prodromal SZ symptoms. All mice in each experimental group (VEH +VEH, VEH+JNJ, VEH+CLZ, KET+VEH, KET+JNJ, KET+CLZ) underwent: (1) Y-maze, (2) Open Field Test (OFT), (3) Five-trial social memory test (5T-SMT). Data normality was assessed by Shapiro-Wilk. Sex effect was studied by Man-Witney test. Group differences were assessed using Kruskal-Wallis.

**RESULTS:** In OFT, significant differences were found in the distance travelled and the rearing activity, with reductions following JNJ or CLZ treatment. However, no significant differences were observed between groups in the time spent in the centre or the periphery of the field. In 5T-SMT, after four trials of exposure to the same mouse, the VEH+VEH and VEH+JNJ groups showed increased interaction times when presented with the novel mouse in the fifth trial. This expected dishabituation was not observed in the KET+VEH group. Interestingly, mice exposed to KET and treated with JNJ, regained interest in the novel animal. No significant differences were observed in Y-Maze test.

**DISCUSSION:** Our results support the efficacy of JNJ treatment for counteracting the deleterious behavioural effects induced by postnatal NMDA receptor blockade during early phases in the adolescence of the animal. These results reinforce previous data regarding the effects of adult and adolescent treatment with JNJ in the adult animal (Martinez-Pinteño et al. 2020; 2023). Moreover, our results support enhanced effectiveness of JNJ compared to CLZ in ameliorating negative and cognitive deficits.

## M172. Effects of Early MGLU2 Receptor Modulation With JNJ-46356479 on Brain Apoptotic Proteins Levels in the Prefrontal Cortex in a Postnatal Ketamine Mouse Model

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**BACKGROUND:** The glutamatergic dysfunction hypothesis of schizophrenia (SZ) suggests that excessive glutamate (Glu) leads to excitotoxicity during disease progression. Early excitotoxic events may cause excessive synaptic pruning via increased apoptosis of dendritic spines in key brain regions (Parellada and Gassó, 2021). Dysregulated apoptotic protein levels have been reported in SZ patients and animal models.

Different Glu-targeting therapies have emerged. Positive allosteric modulators (PAMs) of the mGlu2 receptor, like JNJ-46356479 (JNJ), inhibit presynaptic Glu release. Previous studies have shown the capacity of JNJ to ameliorate apoptosis, particularly Caspase-3 activation, in human neuroblastoma cell cultures (Gassó et al., 2023). In animal models, adult JNJ treatment improves cognitive and negative symptoms in a postnatal ketamine (KET) mouse model of SZ (Martínez-Pinteño et al., 2020) and partially normalizes KET-induced apoptotic protein dysregulation in the prefrontal cortex (PFC) and hippocampus (HPC) (Olivares-Berjaga et al., 2024). Early JNJ treatment during adolescence also improve cognitive and negative SZ-like symptoms in the adult animal (Martínez-Pinteño et al., 2023).

This study evaluates the effects of early treatment with JNJ or CLZ (as a current antipsychotic drug) on apoptosis-related proteins p53, Caspase-3, Bax, and Bcl-2 in the PFC of a SZ-like mouse model postnatally exposed to KET.

**METHODS:** An SZ-like mouse model was generated by exposing KET (30 mg/kg) on postnatal days (PND) 7, 9, and 11. From PND 35 to 60, animals received JNJ (10 mg/kg), CLZ (10 mg/kg), or vehicle (VEH), forming six treatment groups (VEH+VEH, VEH+JNJ, VEH+CLZ, KET+VEH, KET+JNJ, KET+CLZ). At adulthood (PND 120), mice were euthanized and perfused with PBS 1X and 4% paraformaldehyde. Coronal PFC sections (30 µm) were immunolabeled for p53, Caspase-3, Bax, and Bcl-2. Confocal images (Zeiss LSM880, 40×) were analysed via ImageJ to quantify fluorescence intensity. Group differences were assessed using Two-Way ANOVA (factors: group, sex). Additionally, correlation between the protein levels of the studied proteins were analysed via partial correlation, adjusting for treatment and sex.

**RESULTS:** Caspase-3, Bax, Bcl-2 protein levels and Bax/Bcl-2 ratio showed significant differences between the treatment groups in PFC. However, only Caspase-3 and Bcl-2 levels presented differences after Bonferroni posthoc comparisons. Early CLZ treatment increased Caspase-3 levels. Postnatal KET exposure reduced Bcl-2 levels and JNJ and CLZ partially restored Bcl-2 levels, with JNJ having a stronger effect.

A significant positive correlation between p53 and Caspase-3 protein levels was observed. This positive correlation persisted across the different treatment groups and remained statistically significant in VEH + JNJ, VEH + CLZ and KET + VEH groups. Similarly, a significant positive correlation was found between Caspase-3 and Bcl-2 protein levels, which was maintained in the

VEH + CLZ, KET + JNJ, and KET + CLZ groups. Interestingly, the KET + VEH group exhibited a negative correlation between Caspase-3 and Bcl-2 protein levels.

**DISCUSSION:** Our results evidenced early pharmacological treatment with JNJ could be able to attenuate brain apoptosis in the adult animal, as previously described in cell cultures (Gassó et al., 2023) and after treating the animals during adulthood (Olivares-Berjaga et al., 2024). Modulation of the glutamatergic system during the early stage of the disorder could be a target to alleviate SZ deleterious progression alleviating the exacerbated apoptotic brain state that could be present in SZ patients.

## M173. The Symptom Structure of Treatment-Resistant Schizophrenia and its Relationship With Social Functioning: A Cross-Sectional Network Analysis

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**BACKGROUND:** Although Kane defined treatment-resistant schizophrenia (TRS) on the basis of persistent positive symptoms and functional deterioration, the latest TRRIP criteria and current empirical evidence both supported the role of negative symptoms in TRS. Recent network analysis studies consistently suggested that the Motivation and Pleasure (MAP) domain of negative symptoms affected schizophrenia patients' social functioning more than other clinical symptom, such as the Expressivity (EXP) domain. However, the symptom structure, in particular the negative symptom domains, of TRS patients and its relationship with social functioning has seldom been studied.

**METHODS:** This study pooled the data of 150 TRS patients and 131 non-TRS patients from our earlier studies. We used the Clinical Assessment Interview for Negative Symptoms (CAINS) and the Positive and Negative Syndrome Scale (PANSS) to measure clinical symptoms. The Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess social functioning. We constructed regularized partial correlation networks for the combined, the TRS and non-TRS samples. The CAINS-MAP, CAINS-EXP, PANSS positive, disorganized, excited and depressive symptoms, SOFAS, and illness duration were entered as nodes. Centrality indices and Correlation Stability (CS) coefficients were estimated. The network structure in TRS patients was compared with that in non-TRS patients using the network comparison test (NCT).

**RESULTS:** The network of the combined sample (N = 281) showed that SOFAS was strongly connected with CAINS-MAP (regularized edge = -0.53). Among the four centrality indices, only the CS coefficients for strength (0.751) and expected influence (EI) (0.751) passed the recommended threshold, with CAINS-MAP having the highest strength and CAINS-MAP and EXP having the highest EI. In the subgroup analysis, the network of TRS patients also showed a strong link between SOFAS and CAIN-MAP (regularized edge = -0.68). Likewise, only the CS coefficients for strength (0.747) and EI (0.747) could reach the recommended threshold, with SOFAS and CAINS-MAP having the highest strength, and CAINS-EXP and PANSS positive symptoms having the highest EI. On the other hand, the network of non-TRS patients showed a modest connection between SOFAS and CAINS-MAP (regularized edge = -0.38). The CS coefficient for strength (0.672) and EI (0.672) both fell below the recommended threshold. The

NCT suggested that the in symptom network structure for TRS patients and non-TRS patients differed ($p = 0.01$).
**DISCUSSION:** Our findings suggested that negative symptoms in TRS patients are closely associated with social functioning, largely consistent with prior observations in schizophrenia patients in general. However, positive symptoms appear to play a more important role in influencing the network structure of TRS patients than non-TRS patients. Clinicians should intervene both negative and positive symptoms in TRS to improve patients' social functioning. Future research should recruit a larger sample of TRS patients to verify our preliminary findings.

## M176. Moderate to Severe Childhood Abuse Impairs Functional Scores Through Defeat and Entrapment in Early Psychosis

Luis Felipe Scarabelot*[1], Livio Rodrigues Leal[1], Gabriel Elias Correa-Oliviera[1], Jessica Muller Faria[1], Germaine Ingabire[1], Danielle Karina Martins Peruchi[1], Fabiana Corsi-Zuelli[1], Rosana Shuhama[1], Camila Marcelino Loureiro[1], Cristina Marta Del-Ben[1]

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**BACKGROUND:** Psychotic disorders are marked by a complex interplay of various risk factors. Childhood trauma is one of the most prominent risk factors, contributing to a population attributable fraction of 37.8%. However, the interaction between various risk factors and characteristics of psychotic disorders needs to be further investigated. It has been proposed that the concept of social defeat (later updated to low status and humiliation) may mediate the impact of environmental risk factors, such as childhood trauma, on psychotic disorders. Therefore, the present study aims to investigate the pathways through which childhood trauma may impair functional scores in early psychosis.
**METHODS:** We performed a cross-sectional analysis of individuals with early psychosis admitted to the Ribeirão Preto Early Intervention Program for Psychosis (Ribeirão Preto-EIP). At enrollment, we assessed trauma history with the Childhood Trauma Questionnaire (CTQ), functionality with the World Health Organization Disability Assessment Schedule 2.0 (WHODAS), psychopathology with the Positive and Negative Syndrome Scale (PANSS), and feelings of defeat and entrapment with the Short Defeat and Entrapment Scale (SDES). We performed mediation analysis using the PROCESS macro (model 4) for SPSS version 26. The mediation analysis included moderate to severe trauma as assessed by the CTQ (X), SDES score (mediator), WHODAS score at baseline (Y), and adjustments for the covariates: sex at birth, age, and total PANSS score.
**RESULTS:** Among 81 individuals with early psychosis, 54.3% were women (n=44). The median age was 31 years (IQR: 22–42), the median duration of untreated psychosis was 7.8 weeks (IQR: 1.9–23.1), and the median treatment duration before enrollment was 1.6 weeks (IQR: 0.8–3.0). Moderate to severe physical abuse (PA) was reported by 18 (22.2%) individuals, moderate to severe emotional abuse (EA) by 21 (25.9%), moderate to severe sexual abuse (SA) by 14 (17.3%), moderate to severe physical neglect (PN) by 18 (22.2%), and moderate to severe emotional neglect (EN) by 13 (16.0%). The median WHODAS score was 23 (IQR: 17.25–32), and median SDES score was 10 (IQR: 3.25–17.75). Mediation analysis revealed that no type of trauma assessed by the CTQ directly influenced the WHODAS score. The SDES score also did not directly affect the WHODAS score. However, moderate to severe emotional abuse and

sexual abuse affected the WHODAS score when mediated by the SDES score (EA: 2.53 [95%CI 0.34-5.15]; SA: 3.90 [95%CI 0.93-8.18]). We found no association between physical abuse, physical neglect or emotional neglect and the WHODAS score in the mediation analysis (PA: 1.55 [95%CI -0.47-4.30]; PN: 2.21 [95%CI -0.31-5.56]; EN: 1.83 [95%CI -0.99-5.32).
**DISCUSSION:** We demonstrated a full mediation pathway in which moderate to severe emotional abuse and sexual abuse affected functional scores in early psychosis through the SDES score. Unlike previous research, we found no association between physical or emotional neglect and functional outcomes. Our results suggest a psychodevelopmental pathway for functional impairment in FEP: early life abuse would lead to low status and humiliation, represented by feelings of defeat and entrapment, which ultimately results in poorer functionality.

**Lunch and Poster Session III**

## T1. Temporal Dynamics of Real-Time Paranoia-Like Thoughts and Their Social Correlates: Complex Temporal Network Approach

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**BACKGROUND:** Paranoia-like thoughts, characterized by extreme distrust and unfounded beliefs that others intend harm, are increasingly observed even in non-clinical populations. Research suggests that an increased vulnerability, particularly in relation to heightened social rejection sensitivity, is the foundation upon which paranoia develops. Although recent studies, primarily employing the Experience Sampling Method (ESM), have shed light on the daily dynamics of paranoia, they often focus on isolated factors, limiting our understanding of their interplay. To address this gap, the present study employs a temporal network approach to explore the complex interactions among factors contributing to paranoia-like thoughts and to identify the underlying mechanisms driving their development.
**METHODS:** A total of 175 individuals (58.3% of females) recruited from a non-clinical community sample, including 103 participants with low levels of paranoia-like thoughts (LP) and 72 participants with high levels of paranoia-like (HP) took part in a 7-day ESM study assessing momentary levels of paranoia, social functioning, feeling of social rejection, negative affect, body image, and misophonia symptoms. Multivariate vector autoregression (mlVAR) analysis was performed to estimate the temporal, contemporaneous, and between-subject network models and to explore the complex dynamic interrelationships between paranoia and its correlates.
**RESULTS:** All network models were well-connected, with no isolated nodes. The temporal model revealed that paranoia was significantly predicted by prior feelings of social rejection and a perceived lack of safety in the current environment. Paranoia, in turn, predicted social rejection, negative emotions, social stress, and negative body image, acting more as a precursor than a result of the measured outcomes. The contemporaneous model confirmed that, beyond temporal dynamics, paranoia was directly linked to momentary feelings of social rejection, negative affect, lack of social safety, and increased misophonia symptoms within the same time frame. The between-subjects model, in line with previous models, showed that social rejection, negative affect, and lack of social safety were directly associated with paranoia-like thoughts. Negative affect and feelings of rejection appeared to mediate the relationships between paranoia and other nodes in the networks. In the LP group, there was no direct temporal connection between paranoia-like thoughts and feelings of social rejection. This contrasts with the HP group, where this bidirectional link constituted a key effect of the temporal network model. The feeling of social rejection was characterized by having the strongest 'In-Expected influence' (In-EI), while paranoia-like thoughts were characterized by having the strongest 'Out-Expected influence' (Out-EI).
**DISCUSSION:** The network models presented consistently emphasize the critical role of social rejection and negative affect in shaping paranoia-like thoughts. While paranoia was a significant predictor of several variables, it itself was primarily driven by a perceived lack of social safety and feelings of social rejection. Importantly, social rejection emerged as the most central factor (In-EI) in the temporal model. Theoretical perspectives hypothesize that social rejection forms

the foundation upon which paranoia develops. This suggests a potentially more complex interplay among the variables included in the model, where their influence on paranoia-like thoughts may not be direct but mediated through their impact on feelings of rejection. Future research should integrate ESM data with experimental designs to test this hypothesis further.

## T2. Racial Differences in Rates of Psychotic and Trauma Disorders at Outpatient Mental Health Facilities in the United States

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**BACKGROUND:** Racial differences in rates of mental health disorders have been explored in the literature for many years. This research has focused primarily on identifying differences in rates of psychotic and mood disorders in Black and White individuals. Findings have consistently shown that Black individuals are more likely to be diagnosed with psychotic disorders and less likely to be diagnosed with affective disorders when compared to White individuals. Researchers have hypothesized that these disparities may be related to misidentification and overdiagnosis. It is essential to better understand this phenomenon across all racial groups and all mental health disorders. To date, few studies have considered rates of psychotic and trauma disorders together, despite frequent comorbidity, overlap of symptoms, cultural differences in symptom presentation, and foundational evidence that the disorders may be mistaken for each other in certain cultural groups. Furthermore, Asian clients have often been left out of studies that look at differential rates of mental health diagnoses. This quantitative study addresses gaps in the literature by identifying racial differences in rates of psychotic and trauma disorders in Asian, Black, and White clients at outpatient mental health facilities in the US.

**METHODS:** This study is an examination of data retrieved from the Substance Abuse and Mental Health Services Administration Mental Health Client-Level Data, which presents data for individuals receiving mental health services from state mental health systems in 2020. White, Black, and Asian clients who were 18 years or older and receiving outpatient treatment at a SAMHSA funded/operated community-based program were selected. This resulted in a final analytic data set of 3,399,268 clients. Chi-square tests were used to determine whether 1) certain racial groups were more likely to have a psychotic disorder diagnosis than others 2) certain racial groups were more likely to have a trauma disorder diagnosis than others 3) certain racial groups were more likely to have a primary diagnosis of psychosis when diagnosed with both psychosis and trauma.

**RESULTS:** Chi-square test for independence revealed a significant relationship of medium effect between psychotic disorder diagnosis and race. Black participants were most likely to be diagnosed with psychosis as their primary, secondary, or tertiary diagnosis, followed by Asian clients and then White clients. The second chi-square test revealed a significant relationship of small effect between trauma disorder diagnosis and race. White participants were most likely to be diagnosed with trauma, followed by Black clients and then Asian clients. The third chi-square test revealed a significant relationship between primary diagnosis of psychosis and race among

those diagnosed with both psychosis and trauma, however the effect size was small. Asian clients with both psychosis and trauma were most likely to have a primary diagnosis of psychosis, followed by Black clients and then White clients.
**DISCUSSION:** In support of hypotheses, Black clients exhibited the highest rates of psychotic disorder diagnoses, followed by Asian clients and then White clients. While we do not have symptom or assessment measures to consider, literature suggests the high rates seen in Black clients may be related to provider bias, the historical underdiagnosis of affective disorders, or difficulty in differentiating between psychosis and trauma. The finding that Asian individuals were significantly more likely than White individuals to be diagnosed with psychosis was expected based on early evidence that Asians may present with higher rates of psychosis than other racial groups. Due to a lack of research on this population, it is difficult to determine reasons for this finding. However, literature suggests this may be related to provider bias, cultural differences in symptom presentation, acculturation stress, or differences in help-seeking behaviors.
In partial support of hypotheses, Asian clients were indeed the least likely to be diagnosed with a trauma disorder. However, White clients exhibited higher rates of trauma than Black clients. It is important to consider the difference between rates of diagnosis and rates of experiencing trauma; it is highly possible that Black clients are facing higher rates of trauma but are exhibiting lower rates of PTSD diagnosis. This finding could also be related to help-seeking behavior, historical mistrust in the medical system, differences in symptom presentation, and provider bias. Asian individuals have consistently demonstrated low rates of trauma disorder diagnoses in the literature. In similar vein, this may be related to cultural differences between assessor and client, reluctance to seek help, or differences in symptom presentation.

In regards to the third aim, resultsdid not support author's hypothesis. Analyses revealed that, among individuals diagnosed with psychosis and trauma, most individuals received a primary diagnosis of psychosis regardless of race. This finding may reflect clinicians tendency to prioritize psychotic symptoms, as seen in previous literature. This is further supported by evidence that clinicians may be reluctant to address trauma in clients with SMI.

## T3. Increased Attenuated Psychosis-Risk Symptoms in Transgender and Non-Binary Individuals via Perceived Stress

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**BACKGROUND:** Previous studies have observed increased attenuated psychotic symptoms in transgender and non-binary individuals. Increased perceived stress has also been found to be associated with increased attenuated psychotic symptoms and may be particularly relevant among transgender and non-binary individuals who, according to minority stress theory, experience increased perceived stress. However, the potential mediating role of perceived stress

in the association between gender identity and attenuated psychotic symptoms has been under-examined in transgender and non-binary populations. We sought to investigate differences in total and individual attenuated positive symptoms between cisgender and transgender/non-binary gender groups. We hypothesized that transgender/nonbinary individuals would endorse greater attenuated positive symptoms through the indirect effect of increased perceived stress.
**METHODS:** Adolescents and young adults aged 16-30 were recruited through a multi-site community-based study. Individuals were grouped into transgender/nonbinary (n=46), cisgender male (n=106), and cisgender female (n=302) groups. Symptom ratings from the Structured Interview for Psychosis-risk Syndromes (SIPS) were used to assess total attenuated psychotic symptoms and sub-domains of unusual thought content, persecutory ideation, grandiosity, perceptual abnormalities, and disorganized communication. The Perceived Stress Scale was administered to assess self-reported global stress and coping abilities. Gender differences in total and individual attenuated psychotic symptoms were analyzed using ANCOVAs (controlling for age) and post-hoc comparisons. Indirect effects analyses examined the relationship of gender on attenuated psychotic symptoms through perceived stress.
**RESULTS:** Transgender/nonbinary and cisgender female groups endorsed significantly more attenuated positive symptoms in all domains except grandiosity compared to the cisgender male group. Significant indirect effects of perceived stress were found to account for the associations between transgender/nonbinary and cisgender females and these attenuated positive symptoms domains.
**DISCUSSION:** Results suggest that transgender/nonbinary and cisgender female individuals experience higher rates of attenuated positive symptoms compared to cisgender males. Results also point to the influence of perceived stress on increasing psychosis risk, which is especially relevant as minority stress has been shown to be associated with increased mental health risk for marginalized individuals. Additional research should test the effects of minority stress among transgender/nonbinary individuals using longitudinal designs to clarify our understanding of the directionality among variables.

## T4. Validation of Vista (Visual Stimuli for Thought and Articulation) for Eliciting Speech in the General Population and Assessing Sub-Clinical Psychotic-Like Experiences

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**BACKGROUND:** Psychotic disorders are characterised by disordered thought processes, sometimes presenting as disorganised and incoherent speech, known as Formal Thought Disorder (FTD). Recent work suggests that Natural Language Processing (NLP) markers of speech may be able to capture FTD. The results may, however, depend on the method of eliciting speech, likely due to different cognitive demands being involved.

A common and successful method for eliciting speech in psychosis research is asking participants to describe images from the Thematic Apperception Test (TAT). However, created in the 1940s, these images feature outdated stereotypes and lack diversity, limiting their applicability to modern research and ultimately clinical settings. We therefore commissioned an artist to generate a set of more diverse images showing ambiguous scenes (in line with those included in the TAT) called VISTA (Visual Stimuli for Thought and Articulation).

The aims of this study were to:

1) Compare NLP markers generated using the VISTA and the TAT, to assess whether VISTA produces a similar quantity of speech, with a similar range of NLP markers such as semantic coherence and SpeechGraph measures.

2) Test correlations between psychotic-like experiences (i.e., psychometric schizotypy and delusional ideation) with these NLP markers in the general population.

**METHODS:** Participants were recruited online via the platform Prolific with inclusion criteria of ages 18-40, fluency in English, and no head injuries or mental health diagnoses. The sample was balanced for sex.
Participants viewed eight VISTA and eight TAT images in random order and were asked, "Please describe what you see in this image," and after 30 seconds, "How does this image make you feel?". Speech was recorded for one minute per image. After being shown the first eight images, they completed the Peters Delusions Inventory (PDI) and Schizotypal Personality Questionnaire (SPQ).

Two TAT and two VISTA speech samples were randomly selected for each participant and manually transcribed.

The following NLP measures were calculated: total number of words, total number of sentences, mean number of words per sentence, semantic coherence, tangentiality, on-topic score (comparing speech to summary picture descriptions created by ChatGPT version 4) and SpeechGraph measures; largest connected component (LCC), largest strongly connected component (LSC) and randomised versions of these using moving windows to account for verbosity (rLCC and rLSC).

**RESULTS:** The final sample consisted of 303 participants, the majority of whom spoke English as a first language (86%) and had attended higher education (94%). Two participants were excluded from relevant analyses as they had recorded only one sentence.
Participants spoke significantly more words in response to VISTA than TAT, with speech being more on-topic, less tangential, and more coherent ($n= 301$, $d= 0.25$, $p= < 0.001$). All other measures were not significantly different.

Following Bonferroni corrections, the total number of words and sentences for the VISTA images were weakly negatively correlated with PDI and SPQ scores. For TAT, total number of words and sentences were weakly negatively correlated with PDI and very weakly correlated with SPQ scores. For both VISTA and TAT, rLCC was weakly negatively correlated and the rLSC was weakly positively correlated with PDI scores.

**DISCUSSION:** This study shows a weak correlation between both verbosity and SpeechGraph measures (rLCC and rLSC) generated from VISTA and sub-clinical psychotic-like experiences as measured by the PDI and SPQ. These results were comparable to TAT-generated NLP measures. Whilst there were some differences between NPL measures in VISTA and TAT, the effect sizes were small, suggesting that VISTA could be alternative stimuli for speech-eliciting tasks in populations with sub-clinical psychotic-like symptoms.

## T5. Comparative Impact of Mediterranean Diet and Standard American Diet on Psychosis, Psychiatric Symptomatology, and Cognition

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**BACKGROUND:** Emerging research highlights a connection between dietary factors and mental health, suggesting the foods we consume may influence psychiatric disease states. These findings are compelling, yet require further examination. The Mediterranean Diet is recognized for its multitude of health benefits, including its anti-inflammatory properties. Fruits, vegetables, fish, omega-3, and both supplemental and dietary multivitamins in the Mediterranean diet aid in the down regulation of inflammatory markers and inhibit the production of pro-inflammatory cytokines seen in the neurobiological manifestations of various psychiatric disorders (Lopez-Garcia et al., 2004). Similarly, fish is abundant in long chain omega-3 polyunsaturated fatty acids (PUFA) and are seen to inhibit the production of pro-inflammatory cytokines such as interleukin-1beta and tumor necrosis factor (Wu, D. et al., 2004). Vitamins, B, D, selenium, and iron aid in preventing oxidative stress-related DNA damage and controlling inflammation (Wimalawansa 2019)

Lopez-Garcia, E, Schulze, MB, Fung, TT, Meigs, JB, Rifai, N, Manson, JE, and Hu, FB. (2004). Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. The American journal of clinical nutrition, 80(4), 1029–1035.

Wimalawansa SJ. (2019). Vitamin D Deficiency: Effects on Oxidative Stress, Epigenetics, Gene Regulation, and Aging. Biology, 8(2), 30.

**METHODS:** We conducted a multi-level study exploring adherence to components of the Mediterranean Diet, an anti-inflammatory diet, the Standard American Diet (SAD), and their roles in psychiatric symptomatology and cognitive function among persons with chronic psychosis, non-psychotic mood disorders, and healthy controls. We included dietary information from a self-report Gut-Brain Axis Questionnaire (GBAQ) which was administered to persons with psychotic and affective disorders and comparison subjects without psychiatric disorders (Fendrich et al., 2022). All participants had research diagnostic interviews using the Diagnostic Interview for Genetic Studies (DIGS), research ratings of symptoms (PANSS), and cognitive

assessments with NIMH MATRICS. Participant responses to the GBAQ questions that relate to the Mediterranean Diet or supplement intake were scored. The GBAQ self report questionnaire asked about medical history, diet, and other life and health choices. Most GBAQ items had responses of Never, Rarely (a few times/month), Occasionally (1-2 times/week), Regularly (3-5 times/week), or Daily

Fendrich, SJ, Koralnik, LR, Bonner, M, Goetz, D, Joe, P, Lee, J. Mueller, B, Robinson-Papp, J, Gonen, O, Clemente, JC, and Malaspina, D. (2022). Patient-reported exposures and outcomes link the gut-brain axis and inflammatory pathways to specific symptoms of severe mental illness. Psychiatry Research, 312. 10.1016/j.psychres.2022.114526

**RESULTS:** Overall, Mediterranean Diet adherence (MDA) was significantly associated with decreased general psychopathology scores on the PANSS and lower PANSS-5 factor model scores for positive, negative, activation, dysphoric mood, and autistic preoccupation. MDA was inversely correlated with PANSS Positive (r=-.247, p=0.006), Negative (r=-.223, p= 0.014) and General Psychopathology (r=-.253, , p=0.005) scales. Similarly, lower adherence to the Mediterranean Diet was associated with higher PANSS-5 factor, Positive (r=-.255, p= 0.005), Negative (r=-.262, p=0.004), Activation (r=-.221, p=0.015), Dysphoric Mood (r=-.199, p= 0.029), and Autistic Preoccupation (r=-.261, p=0.004) scores. Adherence to SAD was associated with higher PANSS Positive (r=.234, p=0.010) scores, higher positive (r=.206, p=0.024), Activation (r=.241, p=0.008), and Autistic Preoccupation (r=.209, p=0.022) scores. The psychosis group had less MDA when compared with the non-psychosis group (p=0.046) and healthy controls (p= 0.023). Conversely, the psychosis group was more likely to adhere to SAD than compared to the healthy control group (p= 0.007). MDA was also positively associated with the Wechsler Memory Scale in the psychosis group [T-score (r=.461, $p < 0.001$)] and inversely correlated to the speed of processing T-score (r=-.376, p=.049) in the non-psychosis group. Across the entire sample, SAD was inversely correlated with verbal learning (r=-.208, p= 0.029), social cognition (r=-.202 p= 0.033), and MATRICS total cognition score (r=-.200, p= 0.046)
**DISCUSSION:** This study is the first of its kind to support the benefits of adhering to the Mediterranean Diet in the context of psychiatric symptoms and cognitive functioning. This study highlights the link between anti and pro-inflammatory diets along with activation symptom severity, shedding light on the benefits of full dietary interventions. Conversely, it has also shown the implications of poor dietary choices on chronic psychosis and the potential for an anti-inflammatory diet to improve general psychopathology and cognition. We propose that symptoms among those with psychosis may be more developmentally determined rather than having inflammatory origins

## T6. Neighborhood Characteristics and Their Relation to Computational Task Performance in Youth at Clinical High Risk for Psychosis

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**BACKGROUND:** Individuals at clinical high risk for psychosis come from widely different contexts. Some characteristics of these environments can provide individuals with increased risk for psychosis while others can provide resilience or protective factors. While some environmental factors have been consistently connected to an increased risk of developing a psychosis spectrum disorder, less is known about how environmental risk factors operate mechanistically. Computational cognitive functions have been related to environmental risk factors in the general and youth population, and as such can provide an underexplored avenue of possible mechanisms connecting environmental features to the presentation of psychosis and psychosis risk. The present project aims to investigate the connection between environmental risk and protective factors and cognitive functioning in youth at clinical high risk for psychosis as measured by computational tasks.
**METHODS:** Zip code data from the neighborhoods participants grew up in was collected and used to determine their neighborhoods' levels of social fragmentation, socioeconomic characteristics, pollutant levels, ethnic density, and access to cultural capital resources. Participants were also asked to complete a battery of computational tasks that aim to capture reward sensitivity, working memory aberrances, and prediction errors. These aberrances are hypothesized to play a role in the production and maintenance of hallucinations, delusions, disorganization, or negative symptoms. Group differences and differential correlations between healthy and psychiatric controls (N = 400) and youth with elevated positive symptoms (N = 632) were calculated.
**RESULTS:** On average youth with elevated positive psychotic symptoms grew up in neighborhoods that were more socially fragmented than healthy and psychiatric controls; however, this difference was not significant ($t(532) = -1.01$, $p = .31$). Youth with elevated psychotic symptoms also grew up in neighborhoods of lower average socioeconomic status than the comparison group, this difference was present at the trend level ($t(531) = 1.91$, $p = .057$). When looking at how these neighborhood characteristics related to task performance for youth with elevated psychotic symptoms there were associations between a tendency to persist in an ineffective strategy for a reward sensitivity task if the previous use of that strategy had been successful and their neighborhood rate of unemployment ($r = 0.11$, $p = 0.037$). There was also a relation in how arousing participants rated positive and negative stimuli to be and their neighborhood rates of social fragmentation ($r = 0.11$ , $p = 0.040$) and percentage of POC residents ($r = -0.14$, $p = 0.010$) respectively. Participants from neighborhoods with more libraries tended to rate neutral stimuli as more pleasant ($r = 0.12$ , $p = 0.016$) but also as more unpleasant ($r = 0.15$, $p = 0.0037$), and rated negative stimuli as more unpleasant ($r = 0.11$, $p = 0.030$). Participants' verbal working memory also related to the level of social fragmentation ($r = -0.15$, $p = 0.0054$) and socioeconomic status ($r = 0.13$, $p = 0.016$) in their neighborhoods growing up.
**DISCUSSION:** The findings from this study indicate that environmental factors, such as socioeconomic status, social fragmentation, and access to cultural resources, may impact cognitive functioning and emotional processing in youth at clinical high risk for psychosis.

Notably, youth with elevated psychotic symptoms grew up in neighborhoods that were more socially fragmented and had lower socioeconomic status. Even though these differences were not significant they modestly relate to their performance on tasks. For example, the relation between neighborhood unemployment and the persistence in ineffective strategies during a reward sensitivity task suggests that economic factors may foster cognitive rigidity, or difficulty balancing prior evidence when faced with recent disconfirming evidence which could influence symptom persistence and risk. Youth from fragmented neighborhoods showed reduced verbal working memory and heightened emotional responses to stimuli, suggesting that an unstable environment might affect executive function and emotional reactivity. Access to cultural resources was linked to complex emotional appraisals of neutral and negative stimuli, possibly indicating an increased sensitivity in emotional processing. This nuanced affective response might offer either resilience or added sensitivity depending on context, highlighting the varied role of cultural capital in emotional development. In summary, this study suggests that environmental characteristics may influence cognitive and emotional processes linked to psychosis risk. Further research is needed to clarify these relationships and inform interventions that address specific environmental risk factors and foster resilience in at-risk youth.

## T7. Social Support From Adult Educational Staff in Childhood And Hedonic Reactivity in Individuals at Clinical High-Risk for Psychosis

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**BACKGROUND:** Adult social support during childhood is crucial in the proper development of social skills, emotional regulation, and other behavioral outcomes. Individuals lacking adult social support during childhood are at a higher risk for many psychological disorders, including psychosis. Although adult social support is known to influence psychosis risk later in life, the specific role of support from teachers and other educational support staff has not been well established. The primary objective of this study was to determine the relationship between adult social support from teachers, school counselors, and school psychologists in childhood and subthreshold positive symptoms in individuals at clinical high-risk for psychosis (CHR) using hedonic response as a mechanism of interest.
**METHODS:** Data were drawn from the Computerized Assessment for Psychosis Risk (CAPR), a multi-site, longitudinal study examining associations between computerized task performance and psychosis risk. Subthreshold positive symptoms were assessed using the SIPS-P, and hedonic reactivity was measured using responses to pleasant, unpleasant, and neutral image

stimuli. Social support during childhood was quantified by staff-to-student ratios (teachers, counselors, psychologists) in participants' hometown school districts, calculated using zip code-based data from the National Center for Education Statistics. Linear regression was used to analyze the relationship between staff-to-student ratios and hedonic reactivity.
**RESULTS:** Analyses included 252 participants. No significant relationships were found between staff-to-student ratios and hedonic reactivity to neutral or pleasant stimuli (all $p > 0.05$). Positive responses to neutral stimuli showed a slight positive relationship with teacher-to-student ratio ($R^2 = 0.03$) and slight negative relationships with guidance counselor-to-student ($R^2 = -0.10$) and psychologist-to-student ratios ($R^2 = -0.05$). Positive responses to pleasant stimuli had weak positive relationships with teacher-to-student ($R^2 = 0.10$), guidance counselor-to-student ($R^2 = 0.03$), and psychologist-to-student ratios ($R^2 = 0.06$). Analyses regarding responses to negative stimuli are ongoing.
**DISCUSSION:** Preliminary analyses indicated that adult social support from teachers, guidance counselors, and school psychologists did not show a significant relationship with hedonic reactivity. Future studies should focus on adult social support within the specific schools attended by participants during childhood to clarify its impact on psychosis risk.

## T8. Functional Correlates of Atypical Visual Perception in a Multisite Clinical High Risk Sample

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**BACKGROUND:** Individuals at clinical high risk (CHR) for developing psychotic disorders are thought to
exhibit atypical perceptual organization. Furthermore, CHR is associated with reduced cognitive, social and role functioning. We hypothesize that atypical perceptual organization may lead to downstream impairments in cognitive, social and role functioning. However, the degree to which perceptual organization can predict and explain functioning is unclear.

**METHODS:** Our sample consisted of four groups: a CHR group (n = 339), a mild psychotic-like
experiences group (n = 161), a non-psychotic clinical group (n =109) and a healthy control group (n = 201). We measured perceptual organization via Ebbinghaus and

Mooney Faces tasks. In the Ebbinghaus task, participants judged the size of target circles in the presence of surrounding circles. In the Mooney Faces task, participants reported whether they detected faces in two-tone images.

**RESULTS:** Ebbinghaus context sensitivity related to measures of cognition such as symbol coding (r(572)=0.13, pfdr=0.007, 95% CI [0.05,0.21]), verbal learning (r(608)=0.1, pfdr=0.016, 95% CI [0.02,0.18]), and reading ability (r(550)=0.09, pfdr=.038, 95% CI [0.01,0.17]). In contrast, Mooney inverted face detection related to social functioning (r(636)=-0.09, pfdr= .025, 95% CI [-0.17,-0.01]), role functioning (r(638)=-0.16, pfdr < .001, 95% CI [-0.23,-0.08]), and social phobia severity (r(616)=0.14, pfdr=0.001, 95% CI [0.06,0.22]).

**DISCUSSION:** Increased inverted face detection may reflect overweighting of perceptual priors which have downstream effects on functioning in school and workplace settings. In contrast, the relationship between Ebbinghaus context sensitivity and cognition may be driven by propensity toward attentional lapses in CHR.

## T9. Exploring Clinician Narratives in Electronic Health Records of Adverse Childhood Events in a Norwegian Clinical High-Risk for Psychosis (CHR-P) Population

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**BACKGROUND:** The Prevention of Psychosis (POP2) study, Stavanger, Norway, seeks to deepen the understanding of the relationship between adverse childhood events (ACEs) and individuals at clinical high-risk for psychosis (CHR-P). ACEs is a risk factor for developing psychosis. Investigation of how childhood adversity impacts the in early stages of psychosis have therefore been a target in previous research. However, methodological challenges in how ACEs is investigated in across studies limits our understanding of this complex and multidimensional phenomenon. Most of the evidence relies on quantitative analyses of cross-sectional data derived from self-reported measures that may not fully capture the complexity and context of individual trauma events. These instruments tend to prioritize a restricted array of experiences and fail to encapsulate the multifaceted nature and contextual nuances of exposure.

A key challenge in understanding the link between ACEs and the risk of psychosis is the need for in-depth analytical approaches in clinical samples. Clinicians frequently provide detailed narratives on early ACEs in free-text Electronic Health Records (EHR), often documented across multiple time points complementing structured instruments and enhancing our understanding of these experiences. These narratives though typically underutilized in traditional research, hold

potential for a more nuanced and comprehensive exploration of trauma. They may be of paramount importance in understanding the association between childhood adversity and risk for psychosis and further trajectories into even more severe states, such as psychosis.

This study will explore novel, qualitative approaches to extract insights from these EHRs, with the goal of identifying patterns and nuances that may be missed by structured instruments. This study aims to describe the EHR characteristics of severe adverse childhood experiences and psychological traumas experienced by a population with CHR-P states in Norway.

**METHODS:** Study Sample
The sample for the POP2 study consists of individuals fulfilling CHR-P criteria from a population-based cohort of 350,000 inhabitants in Rogaland, Norway. Participants were recruited between 2019 and 2023 as part of an ongoing naturalistic longitudinal study. A total of 52 CHR-P individuals were included.

Data Collection

The primary data source for this study will be the free-text entries in the EHRs of the CHR-P patients. These records contain clinicians' detailed descriptions of patients' significant ACEs.

Data Analysis

We will conduct a qualitative thematic analysis of free text in the EHR notes on significant adverse life events among CHR-P patients (autumn 2024) employing a data-driven inductive methodology (Boyatzis, 1998). We aim to delve into narratives, reflections, and contextual nuances surrounding these adverse life events. Systematic text analysis techniques (Malterud, 2021) will be employed to methodically organize the textual data into a structured format.

**RESULTS:** The presentation will provide an overview of the search strategy, analysis, descriptive data (N=52), and the main themes identified.
**DISCUSSION:** The expected outcome and potential implications of the study will be discussed. The qualitative approach, grounded in inductive analysis and systematic text organization, is expected to yield a more comprehensive understanding of the nature and context of severe childhood adversities in CHR-P individuals. Information captured within free text could potentially be leveraged to improve patient care and decision-making support and to enrich structured adverse life event instruments.

## T10. Autistic Trait Severity in Early Schizophrenia: Role in Subjective Quality of Life and Social Functioning

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**BACKGROUND:** Cognitive impairment has been associated with poor social functioning in patients with schizophrenia. Recently, its treatment has evolved to include the goal of improving subjective quality of life (QoL). However, most of the factors influencing subjective QoL are unknown. Autistic traits have been shown to co-occur with various psychiatric conditions, including schizophrenia. Hence, the present study aimed to investigate whether cognitive function and autistic trait severity are associated with social functioning and subjective QoL in patients with early schizophrenia.

**METHODS:** Data were analyzed from 165 Japanese outpatients diagnosed with early schizophrenia. Autistic trait severity was assessed using the Autism Spectrum Quotient, while neurocognition was assessed using the Brief Assessment of Cognition in Schizophrenia. Social functioning and subjective QoL were measured with the Specific Levels of Functioning Scale and the Subjective Well-being under Neuroleptic drug treatment short form, respectively. A multivariable linear regression analysis was used to examined associations.

**RESULTS:** In an analysis adjusted for demographic characteristics (age, sex and education), both autistic trait severity and neurocognitive function were significantly associated with poorer social functioning. On the other hand, only autistic trait severity made a significant contribution to the prediction of worse subjective QoL.

**DISCUSSION:** The results of this study suggest that efforts to detect comorbid autistic traits in schizophrenia may be important for improving social functioning and subjective QoL in patients with early schizophrenia. In particular, interventions that target autistic trait severity may be key to facilitating personal recovery in this population.

## T11. Syntax and Schizophrenia: A Meta-Analysis of Comprehension and Production

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**BACKGROUND:** People with schizophrenia exhibit notable difficulties in the use of everyday language. This directly impacts one's ability to complete education and secure employment. An

impairment in the ability to understand and generate the correct grammatical structures (syntax) has been suggested as a key contributor; but studies have been underpowered, often with conflicting findings. It is also unclear if syntactic deficits are restricted to a subgroup of patients, or generalized across the broad spectrum of patients irrespective of symptom profiles, age, sex, and illness severity.
**METHODS:** We conducted a systematic review and meta-analysis, registered on OSF, adhering to PRISMA guidelines, searching multiple databases up to May 1, 2024. We extracted effect sizes (Cohen's d) and variance differences (log coefficient of variation ratio) across 6 domains: 2 in comprehension (understanding complex syntax, detection of syntactic errors) and 4 in production (global complexity, phrasal/clausal complexity, utterance length, and integrity) in patient-control comparisons. Study quality/bias was assessed using a modified Newcastle–Ottawa Scale. Bayesian meta-analysis was used to estimate domain-specific effects and variance differences. We tested for potential moderators with sufficient data (age, sex, study quality, language spoken) using conventional meta-regression to estimate the sources of heterogeneity between studies.
**RESULTS:** Overall, 45 studies (n=2960 unique participants, 64·4% English, 79 case-control contrasts, weighted mean age(sd)=32·3(5·6)) were included. Of the patient samples, only 29·2% were women. Bayesian meta-analysis revealed extreme evidence for all syntactic domains to be affected in schizophrenia with a large-sized effect (model-averaged d=0·65 to 1·01, with overall random effects d=0·86, 95% CrI [0·67-1·03]). Syntactic comprehension was the most affected domain. There was notable heterogeneity between studies in global complexity (moderated by the age ), production integrity (moderated by study quality), and production length. Robust BMA revealed weak evidence for publication bias. Patients had a small-to-medium-sized excess of inter-individual variability than healthy controls in understanding complex syntax, and in producing long utterances and complex phrases (overall random effects lnCVR=0·21, 95% CrI [0·07-0·36]), hinting at the possible presence of subgroups with diverging syntactic performance.
**DISCUSSION:** There is robust evidence for the presence of grammatical impairment in comprehension and production in schizophrenia. This knowledge will improve the measurement of communication disturbances in schizophrenia and aid in developing distinct interventions focused on syntax - a rule-based feature that is potentially amenable to cognitive, educational, and linguistic interventions.

## T12. Perceptions of the World in Psychosis: Stability and Impact on Mental Health Over Time

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**BACKGROUND:** 'Primals' are fundamental beliefs or schemas people hold about the world (Clifton et al, 2019). These are measured through self-report and organised hierarchically, with a primary belief the world is "Good" (vs. bad), and secondary beliefs regarding the world as "Safe" (vs. dangerous), "Enticing" (vs. dull), and "Alive" (has purpose and meaning vs. mechanistic). In healthy adults, primals are associated with personality traits, wellbeing, and markers of mental

health. Primals are generally stable over time, and relatively unchanged by the objective state of the world (Ludwig et al., 2023).
We previously demonstrated that people experiencing a psychosis-spectrum disorder (PSD) tend to perceive the world more negatively, viewing it as less "Good," "Safe," and "Enticing" compared to controls (Palmer- Cooper and Clifton). In PSD, increased paranoia and hallucinations, along with symptom-related distress and preoccupation with delusions were associated with perceiving the world as unsafe. Viewing the world as more "Alive", meaningful was linked to more delusional ideation, and greater conviction in delusions.

Our study sought to understand whether primals are stable in PSD and predict symptoms over 2-months. We hypothesised that primals at baseline would predict PSD experiences, depression, anxiety, psychological distress, and quality of life 2 months later.

**METHODS:** Our longitudinal repeated measures questionnaire study recruited 41 participants with self-reported PSD via an online recruitment platform (mean age =37.41 years, SD = 12.45, 43.9% female) and 37 completed follow-up measures. Participants completed clinical measures; the Prodromal Questionnaire-16 (PQ-16; Ising et al., 2012), the Peters Delusion Inventory (PDI-21; Peters et al., 2004), the Multi-Modality Unusual Sensory Experiences Questionnaire (MUSEQ; Mitchell et al., 2017), Patient Health Questionnaire-9 (PHQ-9; Kroenke and Spitzer, 2002), Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006), wellbeing measures; the Multicultural Quality of Life Index (MQLI; Mezzich, 2011), Kessler Psychological Distress Scale (K10; Kessler et al., 2002), and the Primals Inventory (PI-18; Clifton and Yaden, 2021) at both timepoints.
**RESULTS:** There were no significant changes in symptoms over time on MUSEQ, GAD-7, PHQ-9, K-10 or MQLI. Small but significant decreases were seen in PQ-16 (Mean change -1.6, $t(1, 37) = 3.78$, $p < .01$) and PDI-21 (Mean change 0.8, $t(1, 37) = 2.03$, $p = .05$).
There were no significant changes in Primals over the 2-month study period.

Safe belief predicted PQ16 ($R2 = .18$, $F(1, 36) = 7.97$, $p = .008$), MUSEQ ($R2 = .29$, $F(1, 36) = 14.9$, $p < .001$), PDI ($R2 = .13$, $F(1, 36) = 5.6$, $p = .024$), PHQ9 ($R2 = .18$, $F(1, 36) = 7.84$, $p = .008$), GAD ($R2 = .24$, $F(1, 36) = 11.42$, $p = .002$), K10 ($R2 = .35$, $F(1, 36) = 19.11$, $p < .001$) and MQLI ($R2 = .28$, $F(1, 36) = 14.13$, $p < .001$) total scores at follow up.

Good belief also predicted GAD ($R2 = .18$, $F(1, 36) = 7.69$, $p = .009$), K10 ($R2 = .18$, $F(1, 36) = 7.79$, $p = .008$) and MQLI ($R2 = .22$, $F(1, 36) = 10.36$, $p = .003$) total scores at follow up.

**DISCUSSION:** Our findings align with research in general population samples, confirming that primals are linked to mood and wellbeing. In individuals with PSD, our study has further demonstrated that beliefs in an unsafe world predict mood, psychosis symptoms, psychological distress, and quality of life over a two-month period when symptoms were stable. These results enhance theoretical understanding and further support integrating primals into psychological therapies for serious mental health conditions. By addressing primals and cognitive schemas, interventions may help individuals develop a more positive worldview, potentially reducing distressing symptoms.

**T13. The Impact of Sleep on Psychosis Symptoms: A Comparison of Self-Report vs Sleep Actigraphy**

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**BACKGROUND:** Previous literature notes that sleep disturbances, including sleep duration, efficiency, and continuity, may be associated with increased symptom severity in psychosis (Blanchard et al., 2020; Lunsford-Avery et al., 2015). In examining the association between sleep and symptoms it is increasingly apparent that the method of sleep assessment is relevant. Research has found that objective (e.g., sleep actigraphy) and self-report methods to measure sleep can show little agreements (Hughes et al., 2017). Similarly, in a transdiagnostic sample of psychosis spectrum disorders metrics from sleep actigraphy were unrelated to self-reported sleep problems (Savage et al., 2021). The current study aims to evaluate the relationship between self-reported sleep disturbances, and sleep actigraphy, and both positive and affective symptom severity in a transdiagnostic sample of including individuals with psychotic disorders. We hypothesize: 1) greater self-reported sleep-related impairment and disturbances will relate to greater Actigraph Wake After Sleep Onset (WASO) and lower Total Sleep Time (TST); 2) worse subjective and objective sleep will be related to greater positive symptoms; and 3) worse subjective and objective sleep will be related to greater affective symptoms.
**METHODS:** Data was collected from an ongoing NIMH-supported grant, including a transdiagnostic sample (N = 80) of clinical participants with psychotic disorders and nonclinical control participants living in the DC and Baltimore area. Paranoid ideation and negative affective symptoms (i.e., depression and anxiety) were assessed using the Brief Psychiatric Rating Scale (BPRS, Kopelowicz et al., 2007). Additionally, paranoid ideation was measured using the Revised Green Paranoid Thoughts Scale (R-GPTS; Green et al., 2008). The PROMIS Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) short-form scales were used to assess sleep-related impairments and disturbances (Yu et al., 2012). Actigraphy was collected using Actigraph wristwatches (Phillips Respironics, USA) to calculate objective sleep parameters. For this study, WASO and TST (Smith et al., 2018) are being used to assess objective sleep.
**RESULTS:** Greater self-report sleep disturbance was related to more severe paranoid ideation ($r = 0.33$; $p < 0.001$), other positive symptoms ($r = 0.41$; $p < 0.001$) and anxiety-depression ($r = 0.44$; $p < 0.001$) symptoms. Greater self-report sleep-related impairment was related to more severe paranoid ideation ($r = 0.52$; $p < 0.001$), other positive symptoms ($r = 0.59$; $p < 0.001$) and anxiety-depression ($r = 0.53$; $p < 0.001$) symptoms. The results indicated that both self-report sleep disturbance and sleep-related impairment were unrelated with WASO and TST actigraphy metrics. Lastly, WASO and TST actigraphy metrics were unrelated with both positive and affective symptoms.
**DISCUSSION:** The current findings demonstrate a relationship between self-reported sleep disturbances and impairment with both positive and affective symptoms, but sleep measured by actigraphy was unrelated to symptoms. This may mean subjective perceptions of sleep play a more vital role in symptom severity and overall functioning compared to more objective measures. Future studies should assess changes in symptom severity for this population in a

longitudinal study to better evaluate sleep outcomes and symptomatology utilizing both subjective and objective measures over time.

## T14. Schizophrenia and Cognitive Flexibility: A Comparative Study With two Other Populations—Bipolar Disorders and Neurodevelopmental Disorders

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**BACKGROUND:** Cognitive flexibility (CF) refers to the ability to adapt behavior and thinking in response to changing environments or task demands, a function often impaired in psychiatric and neurodevelopmental disorders. To our knowledge, no study has compared CF deficits across three distinct populations. This retrospective study aimed to assess CF deficits in individuals diagnosed with schizophrenia (SCZ), bipolar disorder (BD), and neurodevelopmental disorders (NDD). Additionally, we examined the influence of associated variables such as educational level and clinical factors, hypothesizing that cognitive profile differences exist across these diagnostic groups
**METHODS:** A total of 135 medical records were retrospectively analyzed. Data on sociodemographic variables, clinical history, neurodevelopmental status, and substance use were collected. Cognitive flexibility (CF) impairments were defined by the results in the Trail Making Test (TMT)-B. CF results were compared across individuals with schizophrenia (SCZ), bipolar disorder (BD), and neurodevelopmental disorders (NDD).
**RESULTS:** Individuals with NDD or SCZ exhibited significantly more CF impairments compared to individuals with BD. Additionally, the intensity of CF impairment was observed to be highest in the NDD group, followed by the SCZ and BD groups. After adjusting for potential confounding factors in the model, only educational level remained a significant predictor of the CF impairments between the three groups.
**DISCUSSION:** Although invalidating our main hypothesis, our results corroborate the fact that CF impairments are transdiagnostic, and that environmental factors such as educational level play a key role in the efficient development of this cognitive function. Our results suggest that a dimensional approach to cognitive disorders would help us to better understand individual variability and offer early and personalized care.

## T15. Emotion Regulation in Individuals With Mental Illness – A Target for Intervention to Cope With Psychological Distress, Loneliness and Boredom?

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**BACKGROUND:** Successful emotion regulation is important for coping with stressful life events such as the COVID-19 pandemic. While the mental health of the general population appears to have changed little during the initial phase of the pandemic, increased levels of stress and anxiety, difficulties coping with isolation, and worsening symptoms have been reported in those with pre-existing mental health disorders (MHD).
**METHODS:** Two hundred and nine individuals who had been admitted to a psychiatric ward in 2019, and four hundred and eighty-one control subjects, were assessed in a longitudinal online survey at the start of the pandemic and five months later. Scores on the Brief Symptom Checklist, the Three-Item Loneliness Scale, the Multidimensional State Boredom Scale-Short Form, and the Emotion Regulation Questionnaire were collected to examine a potential mediating role of emotion regulation on group differences in psychological distress, loneliness, and boredom.
**RESULTS:** Compared to control subjects, patients showed significantly higher levels of psychological distress, loneliness and boredom at both time points, and used reappraisal significantly less often and suppression significantly more often to regulate emotions. At both time points, the between-group differences in levels of psychological distress, loneliness, and boredom were partially attributable to the emotion regulation strategy used at T1, with suppression having a greater effect than reappraisal.
**DISCUSSION:** According to the present study's results, emotion regulation contributed to outcomes in terms of psychological distress, loneliness, and boredom in individuals with MHD as well as in members of the general population. This effect was more pronounced in patients and was mainly attributable to suppression, not to reappraisal. Tailored therapeutic interventions to reduce negative health outcomes should therefore address emotion regulation with a particular focus on the reduction of the suppression strategy.

## T16. Was That Me or You? Interoception and Self-Other Distinction in Felt Presence and Psychosis Risk

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**BACKGROUND:** Felt presence (FP)—the sensation of someone nearby when no one is present—is common in healthy adults. While it is related to psychosis risk, the overlap is inconsistent, suggesting potentially distinct mechanisms. FP may arise from a misattribution of internal signals to an external source. Indeed, interoception - the ability to perceive one's own bodily signals - may help to distinguish oneself from others. However, FP could relate to interoception in two ways: through reduced signal perception (interoceptive accuracy; IA), as

observed in schizophrenia, or altered awareness of that ability (interoceptive awareness; IAW). For instance, without trust in their own perception, individuals may experience physiological changes but fail to recognize these as their own. Thus, the current study aims to investigate the relationship between perceived self-other distinction and interoception in individuals experiencing FP and those at high risk for psychosis.
**METHODS:** In a community sample, we collected self-report data in 100 participants using the Prodromal Questionnaire-16 (PQ-16; Ising et al., 2012), a visual scale of perceived self-other overlap, the Multidimensional Assessment of Interoceptive Awareness (MAIA), and the occurrence of felt presence (Y/N). 55 healthy adults also completed the heartbeat counting task (HBCT) to assess interoceptive awareness (IAW; correspondence between accuracy and confidence in accuracy) and accuracy (IA) under three conditions: normal HBCT, self-view (observing oneself on a screen), and other-view (observing/being observed by the experimenter on a screen).
**RESULTS:** In the self-report data 34 reported FP. Those with FP had significantly lower scores on the MAIA trusting subscale and higher psychosis risk, with no differences on other MAIA subscales or perceived self-other overlap. In the HBCT data, 17 reported FP and 35 were at high psychosis risk (PQ-16 > 6). Linear mixed models examined how HBCT condition, perceived self-other overlap, FP, and psychosis risk interacted with IA and IAW. Overall, other-view reduced both IA and IAW, while higher perceived self-other overlap improved both measures. Distinct patterns emerged for IAW and IAW. For IA, FP had no effect. However, those with high psychosis risk had lower IA, particularly when the perceived self-other overlap was low. For IAW, psychosis risk had no effect. However, a significant FP*perceived self-other overlap interaction showed that individuals with FP had higher IAW when they perceived greater overlap between themselves and others.
**DISCUSSION:** FP and psychosis risk are related, but seem to have different interoceptive profiles. Individuals with FP perceived their bodily signals accurately, but lacked trust in these perceptions, providing the first evidence that their experience might stem from an internal misattribution of bodily sensations. In contrast, we replicated that individuals at high risk for psychosis detected less bodily signals, without a changed awareness of that. In both cases a lower perceived overlap of oneself and others exacerbated the effects, potentially reinforcing symptoms.

## T17. A Review and Meta-Analysis of Fmri Studies of Proactive and Reactive Cognitive Control

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**BACKGROUND:** The dual mechanisms of control (DMC) theory postulates that cognitive control is not a unitary construct, but has two modes, proactive control and reactive control. Proactive control refers to the process of selecting and maintaining goal-relevant information prior to the onset of cognitively demanding events such as conflict or interference. In contrast, reactive control is the process whereby control processes are transiently activated after onset of a cognitively demanding event. Proactive control is thought to involve sustained and preparatory

activation of the lateral prefrontal cortex (lPFC), enabled by midbrain dopaminergic inputs. In contrast, reactive control has been associated with transient activation of the lPFC along with activations in a larger network of regions including the anterior cingulate cortex, medial frontal cortex, and posterior parietal cortex. Here, we conducted a review and meta-analysis of functional magnetic resonance imaging (fMRI) studies of proactive and reactive control in healthy humans to test the assumptions of the DMC theory. As psychiatric disorders such as schizophrenia have been consistently associated with deficits in cognitive control and some studies suggest dysfunction in proactive control, in particular, in people with schizophrenia, understanding the neural mechanisms of proactive and reactive control might aid in the understanding of cognitive control deficits in people with schizophrenia.
**METHODS:** We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for this review and meta-analysis. The activation coordinates from the studies were analyzed using activation likelihood estimation (ALE), implemented using the GingerALE software.
**RESULTS:** lPFC regions were found to be consistently activated across the studies during proactive and reactive control. Clusters within the cingulate gyrus and inferior parietal lobule were also found to be consistently activated across the studies during proactive control. Clusters within the insula, cingulate gyrus, medial frontal gyrus, and inferior parietal lobule were found to be consistently activated across the studies during reactive control.
**DISCUSSION:** We found support for the DMC theory in that proactive and reactive control were associated with activity in the lPFC and reactive control was also associated with activations in a broad set of brain regions. However, proactive control was found to be associated with activations in a wider set of brain regions than suggested by the DMC theory. This indicates that the conceptualization of the neural correlates of proactive control might need to be revised to include a wider network of brain regions. Future studies will be conducted in our laboratory to examine the activity of the networks involved in proactive and reactive control in people with schizophrenia compared to healthy individuals.

## T18. Interactions Among Long-Term Trajectories of Positive and Negative Symptoms, Cognition, and Functioning in Psychotic Disorders

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**BACKGROUND:** Cognitive deficits and decline are consistently associated with the severity of symptoms and poor functional outcomes in psychotic disorders. While most longitudinal studies frequently focused on the static relationship between cognition and symptoms/functioning, few examined the dynamic relationship between functioning/symptoms and cognition over time.
**METHODS:** Data are drawn from the Suffolk County Mental Health Project, an epidemiological first-admission psychosis cohort. Symptom trajectories are based on data from 6-month, 24-month, 48-month, 10-year, 20-year, and 25-year follow-ups. Functional trajectories are based on data from the same follow-up points, as well as premorbid functioning data retrospectively collected at the 6-month follow-up. Cognitive trajectories are based on premorbid

cognitive testing data collected retrospectively at the 6-month follow-up and a comprehensive neuropsychological battery collected at 6-month, 24-month, 20-year, and 25-year follow-ups. The analysis sample included all individuals with at least two observations on model phenotypes. Trajectories were estimated using bivariate multilevel models with random intercepts and slopes. These models estimate an individual intercept and slope for each of a pair of phenotypes, as well as the correlations between these parameters.
**RESULTS:** The study revealed that changes in domains except positive symptoms were associated with changes in others, highlighting the complex, interrelated nature of these trajectories in psychotic disorders. A poor cognitive trajectory was especially strongly associated with functional decline ($r=0.69$, $p <= 0.025$), and inexpressivity symptoms ($r=-0.61$, $p <= 0.025$) in the cohort. The cognitive decline also correlated with a worsening course of avolition ($r=-0.58$, $p <= 0.025$), antipsychotic medication ($r=-0.52$, $p <= 0.025$), current cannabis use ($r=-0.62$, $p <= 0.025$). Severe baseline positive symptoms were linked to lower IQ intercepts ($r = -0.26$ for hallucinations and $r = -0.35$ for disorganization).
**DISCUSSION:** Symptom, cognitive, and functional trajectory slopes in psychotic disorders are interrelated over 25 years. Addressing cognitive deficits and disorganization may help mitigate functional decline.

## T19. Adolescent Cannabinoid Exposure: Insights Into Schizophrenia-Related Behaviours Using Rodent Models

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**BACKGROUND:** Cannabis use has been increasingly linked to cognitive deficits and schizophrenia susceptibility, especially among adolescent-onset users. Our recent meta-analysis found that THC and other cannabinoid receptor 1 agonists led to significant and wide-spectrum behavioural changes indicative of schizophrenia-resembling cognitive impairments. The meta-analysis also highlighted a need for further research to elucidate the effects of CBD in the context of schizophrenia.

Nevertheless, not all adolescents who use cannabis experience its harmful effects. Animal models offer a valuable approach for exploring this relationship, allowing us to investigate the mechanisms underlying the neurobehavioural impacts of cannabinoids and possible genetic moderating factors.

Aim of the current study: 1) Examine the effect of chronic adolescent THC, CBD, and THC+CBD exposure in wildtype and ErBB4 conditional knockout animals to separate the effect on behavioural tasks of the two cannabinoids as well as their combined one 2) and investigate the moderating effect of the ErBB4 conditional knockout (KO) genotype.

**METHODS:** WT and ErBB4 KO C57/BL6 mice of both sexes received daily i.p. injections of either THC (5mg/kg), CBD(20mg/kg), THC(5mg/kg)+CBD(20mg/kg) or vehicle during postnatal day (PND) 35-44. The animals were tested in the open field, Y-maze, and novel object recognition tests during adolescence (PND46) and adulthood (PND60).
**RESULTS:** Our findings showed ErBB4 KO mice exhibited behavioural deficits in open field and Y maze tests. However, although body weight gain was affected by drug treatment, behavioural outcomes did not show significant group-wise cannabinoid effects, with large within-group variances observed. Preliminary cluster analysis identified distinct subgroups among animals of the same treatment and genotype. Additional regression analyses identified significant moderating effects of sex and anxiety levels on behavioural outcomes. These findings suggest that individual animals may respond differently to cannabinoid exposure, highlighting the complexity of interpreting group-wide behavioural effects.
**DISCUSSION:** Findings from the meta-analysis and my experiment revealed clear limitations in behavioural tests, which are subject to uncontrolled covariates and may lack sensitivity in capturing obscure drug effects in the context of schizophrenia. For future directions of my project, I will provide an overview of plans to perform additional analyses to better address the within-group variability and potential covariates, and to examine DNA methylation patterns in tissue and blood samples to further explore potential neurobiological associations between drug treatment, epigenetic changes, and behaviour.

## T20. Differential Relationship Between Experimental and Expressive Negative Symptoms, Empathy and Social Functioning in Schizophrenia in a Residential Program: A Pilot Study

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[1]Cental Connecticut State University, [2]Yale School of Medicine, **BACKGROUND:** Experiential (avolition, anhedonia, asociality) and expressive (affect flattening, alogia) negative symptoms associated with schizophrenia (SZ) differentially impact social functioning ( Blanchard and Cohen, 2006; Jang et al., 2016). Recent research suggests that experiential symptoms may be more predictive of poorer social functioning compared to expressive symptoms (Cuñat et al., 2023). Several social cognitive constructs have been investigated as potential predictors of social functioning; however, none have been investigated as a moderator on the relationship between the specific experiential and expressive symptoms and functioning (Couture et al., 2006; Fett et al., 2011). Empathy is one such construct, though research on its impact on functional outcomes has yielded mixed findings (Corbera et al., 2014; Michaels et al., 2014). This present study aims to address this gap by: 1) Examining the relationship between these two categories of negative symptoms, empathy, and social functioning in individuals with SZ in a residential program; 2) Examining the predictive power of experiential and expressive negative symptoms and empathy on social functioning and quality of life; 3) Examining the moderating role of empathy in the relationship between negative symptoms and social functioning.
**METHODS:** Design: This is a pre-posttest design pilot study, approved by the Central Connecticut State University IRB (IRB Protocol #10556), conducted at the Neuropsychiatric Transitional Residential Program at Silver Hill Hospital in New Canaan, CT. Assessments are conducted at two time points: baseline assessments (T1) are completed within a week of admission, and post-test assessments (T2) after 6-weeks post-admission.

Participants: Participants must have a SZ diagnosis to participate in this study. Enrollment and testing are currently ongoing with a target of 30 participants anticipated by study completion.

Measures: Baseline assessments (T1): Demographic, clinical and medical questionnaire based on chart information; Positive and Negative Syndrome Scale (PANSS); the Motivation and Pleasure – Self-Report (MAP-SR) for experiential negative symptoms; Scale for the Assessment of Negative Symptoms (SANS subscales for alogia and affective blunting); the Questionnaire of Cognitive and Affective Empathy (QCAE); the Social Functioning Scale (SFS); and Heinrich's Quality of Life (QLS). Post-test assessments (T2) include the MAP-SR, SANS subscales for alogia and affective blunting, QCAE, and SFS.

**RESULTS:** Data collection is currently ongoing. We plan to present pilot findings at the conference. We expect that: 1) Individuals with SZ displaying higher experiential and empathy deficits will show lower functioning outcomes; 2) Both empathy and experiential deficits will be the stronger predictors of social functioning; 3) The relationship between experiential symptoms and functioning will be significant in those with low empathy; but this relationship may be weak or absent in individuals with high empathy. We expect a similar but weaker effect with expressive symptoms.
**DISCUSSION:** This study will contribute to understanding the moderating role of empathy in the relationship between experiential and expressive negative symptoms and social functioning in a transitional residential program for SZ. Results will differentiate the specific contribution of experiential vs expressive symptoms and the potential role of empathy to buffer the detrimental impact in social functioning.

## T21. Core Beliefs in Psychosis: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Increasing interest is growing for the identification of psychological mechanisms to account for the influence of trauma on psychosis, with core beliefs being proposed as a putative mediator to account for this relationship.
**METHODS:** Methods: A systematic review was conducted to summarise the existing evidence base regarding the role of core beliefs/schemas in psychosis, Clinical High-Risk (CHR), and non-clinical samples with psychotic-like experiences (PLEs). A random effects meta-analysis was conducted to examine the relationship between core beliefs and psychotic experiences across different clinical populations.
**RESULTS:** Seventy-nine studies were eligible for inclusion. Compared to Healthy Controls (HCs), patients with schizophrenia (SZ) or First Episode Psychosis (FEP) experiencing Auditory Hallucinations (AH) had significantly higher scores for negative self and other-beliefs and lower scores for positive other-beliefs. Persecutory delusions where characterised by high negative self and other-beliefs and low positive self and other-beliefs, while grandiose delusions were characterised by higher positive self and other-beliefs and lower negative self-beliefs. Compared

to HCs, CHR scored significantly higher on negative self and other-beliefs andsignificantly lower on positive self and other-beliefs. In non-clinical samples, several factors mediated the relationship between Traumatic Life Events (TLEs) and PLEs, such as greater perceived stress, dissociation, external locus of control, and negative self and other-beliefs. A meta-analysis (k = 62) showed that core beliefs had a significant large effect in the psychosis group (Hedges g = 0.68, 95% CI [0.54, 0.82], p < .0001), indicating a robust relationship between core beliefs and psychotic experiences.
**DISCUSSION:** Core beliefs/schemas were found to play a significant role in the development and maintenanceof positive symptoms of psychosis. The development of psychosocial interventions that explicitly targetnegative self and other-beliefs whilst also enhancing positive self and other-beliefs are warranted and wouldinnovate CBTp practices.

## T22. Bodily Sensations of Emotions and Interpersonal Distance Regulation in Relation to Paranoia

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**BACKGROUND:** Paranoia is a common feature of schizophrenia and is typically studied within the framework of abnormal social cognition or faulty thought processes. However, irrationally intense anxiety or fearful feelings also play a significant role in paranoia by presenting affective input signals that need to be integrated with top-down mechanisms to make sense of the world. Furthermore, awareness of emotions contributes to adaptive social behavior, especially under threat (Eslinger et al., 2021). Therefore, it is important to elucidate the affective components of paranoia to understand their interpersonal consequences. Self-awareness of anxiety and fear depends on bodily sensations associated with these emotions (i.e., interoception). In turn, embodied emotions may influence interpersonal interactions by regulating preferred social distance. Thus, we aimed to elucidate the roles of bodily self-awareness and interpersonal distance in relation to paranoia using self-report measures and experimental tasks.
**METHODS:** Participants from the general population (N=1181) completed a web-based survey. Paranoia levels were assessed by the Revised Green et al. Paranoid Thoughts Scale (R-GPTS). High-paranoia (HP; n=145) and low-paranoia groups (LP; n=1036) were designated based on the established R-GPTS cutoff score. Established self-report measures of loneliness, anxiety, well-being, and social functioning were also administered. Embodiment was assessed with the EMBODY tool that required subjects to localize sensations associated with specific emotions by shading body regions for activation and deactivation. Then bodily maps of emotions were generated and quantified (Nummenmaa et al., 2014). Lastly, the preferred personal space was estimated with the interpersonal distance (IPD) task for strangers, acquaintances, and close persons, as a proxy measure for the social self-boundary.
**RESULTS:** HP (Mage = 34.6) was younger than LP (Mage = 39.2; p < 0.001) but the two groups were matched for gender. HP reported increased loneliness, anxiety, and reduced well-being than LP (p < 0.001). HP also reported poorer social functioning and reduced social engagement than LP (p < 0.001). On EMBODY, HP and LP groups showed distinct maps of bodily sensations. Greater activation in the head region for anxiety and stress were observed in

the HP than LP. HP also showed less activation in the head and chest area for happiness, love, and pride compared to LP. There were no group differences in total areas shaded (e.g. pixel counts) but we found significantly more overlap between activation and deactivation (i.e., mixed pixels) in HP than in LP ($p < 0.05$). With respect to self-other boundary, there were no group differences in IPD but overall IPD was negatively correlated with paranoia level, anxiety, and loneliness ($p < 0.05$).
**DISCUSSION:** There were significant differences between HP and LP regarding emotional experience and bodily awareness. There was a stronger embodiment of anxiety and stress and weaker embodiment of positive emotions in HP. Interestingly, increased mixed pixels (co-localization of activation and deactivation of bodily sensations) in HP suggests that bodily awareness may be challenging for this group, which may affect their capacity for adaptive social interactions. Together, our findings highlight the importance of examining anomalous bodily self-experiences in relation to paranoia to better understand their interpersonal consequences. Understanding these dynamics is essential for developing targeted interventions to improve the emotional well-being of individuals affected by paranoia, ultimately fostering better social connections.

## T23. A Network Comparison Among Self-Awareness Constructs in Schizotypy

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**BACKGROUND:** Interoception is a facet of self-awareness concerning the awareness of bodily sensations. Alexithymia, cognitive insight, and introspective accuracy (IA) are also components of self-awareness. Despite conceptual similarities, no studies have explored the relationships between these constructs. In addition, people with high levels of schizotypy demonstrate difficulties with interoception, cognitive insight, alexithymia, and IA. Increased understanding in the associations between these constructs and how associations may vary between high and low schizotypy groups could inform future use of these measures. This study aims to examine relationships between interoception and other self-awareness measures in high and low schizotypy groups. We hypothesized that 1) higher interoceptive sensibility will be correlated with lower schizotypal traits, better cognitive insight, lower alexithymia, and better IA; and 2) high and low schizotypy groups will have different global strengths and structures in a network comparison.
**METHODS:** Participants ($n = 728$; 60.4% female; mean age= 33.1) recruited through SONA and Prolific completed self-report questionnaires assessing interoceptive sensibility (Multidimensional Assessment of Interoceptive Accuracy- 2), cognitive insight (Beck Cognitive Insight Scale), alexithymia (Toronto Alexithymia Scale), IA, and schizotypy (Schizotypal Personality Questionnaire- Brief Revised). Partial correlations, controlling for age, informed bivariate relationships among subscales. Network comparison was used to investigate differences between networks in high and low schizotypy groups among the subscales of the self-awareness variables. Expected influence and strength of the 13 subscale nodes were assessed.

**RESULTS:** Results indicated that the MAIA-2 Not Distracting, Not Worrying, Attention Regulation, Self-Regulation, Body Listening, and Trusting subscales were negatively associated with TAS subscales, BCIS Self-Reflectiveness, and SPQ-BR ($r = -.08$ to $-.36$; $p < .05$), and positively associated with BCIS Self Certainty ($r = .2$ to $.31$; $p < .01$). IA was negatively associated with the MAIA-2 Trusting ($r = -.07$; $p < .05$). The MAIA-2 Noticing and Emotional Awareness subscales were positively associated with BCIS subscales ($r = .1$ to $.22$; $p < .01$). High and low schizotypy networks were stable (strength and expected influence > .5) and showed no significant differences between global edge ($M = .18$, $p = .53$) and strength ($S = .29$, $p = .63$). MAIA-2 Emotional Awareness and Self-Regulation subscales showed the greatest expected influence on both models (ei > .93).
**DISCUSSION:** Our findings indicate that interoception, cognitive insight, alexithymia, IA, and schizotypy are interrelated, and that the interconnections among these variables are similar for those with high and low schizotypy. Identifying MAIA-2 subscales as the greatest influence on the network suggests that Emotional Awareness and Self-Regulation may be useful in the identification of self-awareness abilities. This investigation contributes to our understanding of interoception and its relation to other facets of self-awareness in schizotypy. Future work should explore the relationship between these facets of self-awareness in people with schizophrenia-spectrum disorders.

## T24. Association Between Time Perspective and Anxiety in Patients With Schizophrenia

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**BACKGROUND:** Anxiety is frequently observed among patients with schizophrenia. It has been suggested that this anxiety may be a component of schizophrenia, either as an acute psychotic episode, as a side effect of medications, or as a comorbid condition. However, it is still unclear which psychological factors are involved in patients' anxiety. Previous studies have reported that individual's level of anxiety is related to the individual's time perspectives (tendency to look at past, present, and future events), impulsivity, or emotion regulation strategies. Therefore, based on the results of previous studies, we investigated what psychological factors mentioned above were related to anxiety in patients with schizophrenia.
**METHODS:** Nineteen patients with schizophrenia were recruited from an outpatient clinic. We also recruited 33 healthy controls matched for age and education levels. To achieve the purpose of this study, all participants completed the following self-report questionnaires; The State-Trait Anxiety Inventory (STAI) to measure trait and state anxiety; Zimbardo Time Perspective Inventory (ZTPI) to measure five subtypes of time perspective (future, past-negative, past-positive, present-hedonistic, and present-fatalistic); Barratt Impulsiveness Scale (BIS-II) to measure of three facets of trait impulsivity (attentional, motor, non-planning impulsiveness); and Emotion Regulation Questionnaire (ERQ) to measure two emotion regulation strategies (cognitive reappraisal and expressive suppression). Willcoxon rank sum tests were conducted to determine whether there were significant group differences in the above-mentioned questionnaire data. Then, we performed Spearman's rank correlation analysis for each group to determine whether there was a significant relationship between variates that differed significantly between

groups. Bonferroni correction was applied to the correlation analysis results ($p < 0.05/10 = 0.005$).
**RESULTS:** When comparing the two groups, the trait and state anxiety subscores of the STAI were increased in patients compared to controls, indicating that patients' s anxiety levels were increased. We also observed that the past-negative subscore of the ZTPI was increased in patients compared to controls, indicating that patients had more negative attitudes toward their past experiences. Additionally, patients showed increased attentional impulsiveness subscore of the BIS-II and expressive suppression subscore of the ERQ, indicating that patients had difficulty concentrating their attention and suppressing the expression of emotions, respectively. As a result of conducting a correlation analysis among the variables that showed group differences, both patients and controls showed a significant positive correlation between the trait anxiety subscore of the STAI and past-negative subscore of the ZTPI. In other words, the higher the tendency to view past experiences negatively, the higher the anxiety.
**DISCUSSION:** These results suggest that anxiety in patient with schizophrenia is related to their time perspective. In particular, the higher the tendency to view the past negatively, the higher the level of anxiety. Therefore, improved cognitive processing in recognizing past experiences may help reduce anxiety.

## T26. A Novel Somato-Visual Functional Connectivity Biomarker Can be Conjoined to Cortical Thickness Values and Working Memory Performance to Identify Early Psychosis Patients With High Accuracy

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**BACKGROUND:** Psychosis patients functionally exhibit thalamo-cortical hyperconnectivity and cortico-cortical hypoconnectivity in somatomotor and secondary visual (visual2) networks. These dysconnectivity patterns can be combined to form a "somato-visual" biomarker that is highly robust, reliable, and generalizable across samples (Keane et al., 2024, Mol. Psych.). Can other biomarkers be conjoined to this FC biomarker to better discriminate patients? If so, such variables might be useful for predicting a conversion to psychosis in clinical high risk (CHR) studies. As an exploratory analysis, we also considered how the foregoing variables might relate to psychotic symptoms.
**METHODS:** To address these questions, we leveraged resting-state MRI data from the Human Connectome Project for Early Psychosis (HCP-EP), which included 54 healthy controls and 105 early psychosis patients (including 23 with "affective psychosis"). Data from the four functional scans (5.5 min/scan) were minimally preprocessed with fMRIPrep and underwent further nuisance regression (36 parameters, motion scrubbing). Data were analyzed in the Glasser atlas space and partitioned into twelve networks (Ji et al., 2019). Functional connectivity was derived using regularized partial correlation (see Keane et al., 2024). To calculate the somato-visual biomarker, we i) averaged the thalamo-cortical connectivity values for the somatomotor and visual2 networks, ii) averaged the cortico-cortical values for the same two networks, and then iii) normalized and subtracted the two averaged values (thalamo-cortical – cortico-cortical). Using

the same HCP-EP data set, we also derived cortical thickness values using Freesurfer and cognitive performance using the hit rate of the auditory continuous performance working memory task (Seidman et al., 2016). Leave-one-site-out cross-validation (4 testing sites) and weighted binary logistic regression were used to determine the efficacy of the model for discriminating patients and controls.
**RESULTS:** Patients and controls could be discriminated with progressively better accuracy using the cortical thickness values alone, the cognitive values alone, the thickness plus cognitive values combined, and then all three variables (AUC=.59- > AUC=.72- > AUC=.76- > AUC=.84). Adding the last variable (somato-visual biomarker) significantly improved the model (LRT=6.35, p=1e-10). Results were particularly impressive when the affective patients were excluded from the analysis (AUC=.87, sensitivity=.76, specificity=.84). Similar RESULTS: would emerge even if we were to use only the very first 5-minute resting-state scan (AUC=.87). Depending on the model, higher risk scores were correlated with higher PANSS 5-factor positive symptoms (cortical thickness only, r=.27, p=.013), disorganization (cognition only, r=.37, p=.001; thickness+cognition, r=.36, p=.001), and negative symptoms (thickness+cognition; r= 0.24, p=0.032).
**DISCUSSION:** A simple 3 variable model using cognition, cortical thickness, and a somato-visual biomarker can discriminate patients and controls with high accuracy. Risk scores in simpler versions of these models could also predict symptom severity. These results highlight the potential utility of these variables in predicting a transition to psychosis.

## T27. Neutrophil to Lymphocyte Ratio is a Reliable Measure of Peripheral Inflammation and Reduced Grey Matter Volume in Schizophrenia and Related Psychoses

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**BACKGROUND:** Schizophrenia and related psychoses are serious mental illnesses with no known cause or cure. An increasing body of recent evidence from postmortem brain, large scale genetic, clinical high-risk, first episode patient, and chronically ill patient studies provide support for the role of inflammatory processes in schizophrenia. However, reliable peripheral inflammation measures are needed for use as prognostic and theragnostic biomarkers of the illness.
**METHODS:** We compared neutrophil to lymphocyte ratio (NLR) as a measure of peripheral inflammation among three independent samples of acutely ill patients with psychosis and chronically ill patients with schizophrenia and related psychoses (totaling 568 patients) to establish reliability, patient proportions, and the biological, cognitive, and clinical factors related to inflammation in schizophrenia. Peripheral blood assayed for complete blood count was

obtained from a sample of 174 acutely ill inpatients with psychosis from Sydney, Australia, an independent replication sample of 297 acutely or chronically ill inpatients with schizophrenia and related psychoses from Syracuse, NY, USA, and an independent sample of 93 chronically ill outpatients with schizophrenia or schizoaffective disorder from Sydney, Australia who also had in depth assessments of cognition, structural MRI, and clinical factors. Patients in each cohort were classified based on NLR as having elevated ( > 2.2) or normal ( < 2.2) peripheral inflammation.
**RESULTS:** There were 111/174 (63.8%) acutely ill patients from Sydney, 119/297 (40.1%) acutely or chronically ill patients from Syracuse, and 52/93 (55.9 %) chronically ill patients from Sydney classified as having elevated peripheral inflammation. Elevated inflammation patients had significant reductions in right rostral anterior cingulate, left transverse temporal, and left pars triangularis volumes (p's < .02). There were no significant differences in cognitive abilities between elevated and normal inflammation groups among chronically ill patients.
**DISCUSSION:** Based on independent samples of over 500 patients with psychosis, NLR was a standardized, easily collected, inexpensive, and reliable measure of peripheral inflammation in substantial proportions of patients with schizophrenia and related psychoses that may be useful as a prognostic marker of illness in conjunction with early symptoms and may also direct early novel treatment with anti-inflammatory drugs in patients with schizophrenia and related psychoses who also display elevated peripheral inflammation.

## T28. Conceptualization of Psychosis Spectrum Disorders Using Individual-Level Brain Structural Abnormalities

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**BACKGROUND:** Psychotic and affective disorders have traditionally been characterized categorically following Kraepelin's original dichotomy. However, recent clinical, genetic, and neuroanatomical evidence suggests that schizophrenia (SZ), schizoaffective disorder (SZA), and bipolar disorder with psychotic features (BP) may be dimensionally characterized as a psychotic disorders continuum with increasing severity. Previous studies investigating these conceptualizations at the neurobiological level have largely been performed on raw structural variables, leaving significant influence of age and sex. Normative modeling can better contextualize these structural variables and help parse the significant heterogeneity seen in these disorders. With many initiatives currently focused on studying psychiatric disorders based on their underlying neurobiological measures, investigating brain structure of these disorders using normative modeling of cortical thickness will allow us to better understand the relationship between these disorders and how they are characterized.
**METHODS:** Structural neuroimaging data was collected at the University of Alabama at Birmingham (n=126) and obtained from the Psychosis Human Connectome Project (n=155). Data were processed in FreeSurfer 7.1.1 to quantify region-level cortical thickness measures

using the Destrieux parcellation. We used the Predictive Clinical Neuroscience braincharts toolkit to compute individual-level deviations from the reference norm for cortical thickness in individuals diagnosed with either SZ, SZA, or BP. A z-value cutoff of ±2 was used to define extreme positive and negative deviation. ANOVA and KS tests were run to compare the total number and distribution of positive and negative deviations between the three diagnoses. Inter-individual overlap was mapped to visualize spatial distribution of deviations in each group and across the entire patient sample. Finally, individuals were grouped by structural similarity and a chi-squared test was run to analyze the overlap between the structural groups and the diagnostic groups.
**RESULTS:** An omnibus ANOVA only showed a significant difference in total number of positive deviations (p=.03). Post-hoc testing revealed a significant difference in the number of positive deviations between the SZA and BP (p=.04). KS testing showed no significant difference in the distribution of positive and negative deviations between the groups. Inter-individual overlap showed no highly consistent regions of deviation nor evidence of a continuum of severity. Chi-squared tests comparing the patient composition of structural and diagnostic groups showed no significant relationship (p=.16).
**DISCUSSION:** Our results demonstrate that, at a large-scale neurobiological level, there is no significant evidence for either the discrete disorders or continuum conceptualization of the three disorders. All three disorders show similar rates of both positive and negative deviation load and similar spatial distribution of deviation while not increasing in severity in a linear fashion. There is also no over-representation of any diagnosis in any of the structural similarity groups, indicating that there is no one neurobiological phenotype representative of any of these disorders. These results highlight the significant heterogeneity seen in psychotic disorders and emphasize the importance of understanding these disorders at the biological, and not just clinical, level. Future directions will include expansion of the dataset and analysis of the relationship between clinical variables and structural abnormalities between the diagnostic groups.

## T29. P300 Event-Related Potential Responses to Auditory and Visual Oddball Stimuli in Individuals at Clinical High Risk for Psychosis: Further Evidence From NAPLS-3

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**BACKGROUND:** Improvements in the ability to predict the development of schizophrenia (SZ) are crucial for preventative treatment efforts. To this end, biomarkers are needed to help predict which individuals at clinical high risk for psychosis (CHR-P) will develop psychosis. Among electroencephalography (EEG)-based biomarkers sensitive to SZ, reduced amplitude of the P300 event-related potential (ERP) component elicited by infrequent target stimuli during auditory, and to a lesser degree, visual, oddball tasks is well-established and is thought to reflect deficient allocation of attentional resources to infrequent task-relevant events. Several prior studies have shown deficient target P300 amplitude to predict conversion to psychosis in CHR-P individuals, primarily using auditory paradigms. Here, we present data examining both auditory and visual P300 amplitudes as predictors of clinical outcomes in CHR-P individuals from the nine-site case-control North American Psychosis-risk Longitudinal Study (NAPLS-3).
**METHODS:** Analyses were performed on EEG data from the NAPLS-3 study recorded during auditory and visual oddball tasks from 78 healthy controls (HC) and 236 individuals meeting CHR-P criteria. Auditory and visual P300 amplitudes were measured from ERPs to infrequent (20%) target tone or large blue circle stimuli, respectively, and transformed to z-scores adjusted for normal age and collection site effects. These auditory and visual P300 z-scores were then compared across three groups – HC, CHR-P participants who converted to psychosis during the study (CHR-C), and CHR-P participants who did not convert to psychosis but completed the 24-month follow-up (CHR-NC) – using a three-way ANOVA that included Modality (auditory, visual) and Electrode (P1, Pz, P2) as within-subject factors. In a follow-up Group x Modality x Electrode ANOVA, CHR-NC participants were further categorized into those who remitted by the end of the study (CHR-R) and those who remained symptomatic (CHR-S).
**RESULTS:** There was a significant main effect of Group on P300 amplitude z-scores ($F = 14.89$, $p < 0.001$). Post-hoc Tukey tests showed that this was driven by CHR-C participants demonstrating significantly smaller P300 amplitude compared with both HC ($p < 0.001$) and CHR-NC ($p < 0.001$) participants. Group effects did not interact with electrode ($F = 0.10$, $p = 0.98$) or modality ($F = 0.32$, $p = 0.71$). Similar group effects were found when the CHR-NC group was split into CHR-R and CHR-S ($F = 10.32$, $p < 0.001$). Post-hoc Tukey tests suggested that this difference was driven by lower P300 amplitude in the CHR-C group as compared to HC ($p < 0.001$), CHR-R ($p < 0.001$), and CHR-S ($p < 0.001$). Tukey tests comparing CHR-S, CHR-R, and HC participants were not significant, indicating no group differences among these three groups.
**DISCUSSION:** These results replicate prior findings of reduced auditory target P300 amplitude in CHR-P individuals who subsequently convert to psychosis and extend them by showing a similar effect for visual P300. However, unlike our prior NAPLS-2 study, where the conversion effect was shown to be driven by intact auditory target P300 amplitude predicting remission from the CHR-P syndrome, the current NAPLS-3 data suggest that differences in P300 reflect a conversion effect; that is, CHR-P participants who had persistent CHR-P symptoms at 24-months without converting to psychosis did not show the P300 deficit observed in NAPLS-2. Both auditory and visual P300 show promise as biomarkers for prediction of clinical outcomes in CHR-P individuals and are poised to contribute to multivariate prediction algorithms incorporating biomarkers from multiple measurement domains.

**T30. Investigating the Underlying Mechanism of Psychosis Proneness in Relation to Environmental Factors, Cognitive Appraisals, and Structural Connectome Using Elastic Net Modeling**

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Seda Arslan

**BACKGROUND:** Psychosis-proneness (PP) is identified as the subclinical aspect of the psychosis continuum. Previous research suggests that PP has multimodal substrates. However, no studies have explored these factors together in a comprehensive manner. In this study, we present the first model that simultaneously examines environmental influences on psychosis, cognitive appraisals, and the structural network properties related to PP using a large youth sample. Additionally, we directly assess the model's ability to explain psychosis in an external validation cohort that is enriched with individuals experiencing psychosis.

**METHODS:** A strict variable selection was applied to 741 variables consisting of environmental factors, cognitive appraisals, cognitive functioning, and structural brain connectome. The latter included both number of streamlines- and fractional anisotropy-weighted connectivity matrices to observe both physical density and microstructural integrity of the underlying connectome. Obtained significant predictors were included in the elastic net model for predicting high/low PP in 396 healthy young participants aged 14-24 (Mean age= 19.81 ± 2.5). PP was assessed through two models: total frequency symptoms and associated distress with these experiences. Additionally, these PP-related indicators were applied to an external sample consisting of FEP patients (n=19), their siblings (n=20), and demographically matched healthy controls (n=19) for validation.

**RESULTS:** 14 environmental and cognitive appraisal variables and 20 structural network properties spanning frontal, temporal, occipital, and parietal regions, were significant predictors of frequency-based PP. The model demonstrated a good performance in predicting low vs. high PP in the healthy sample with a 75.2% and 0.750 AUC score. In the external validation cohort, specificity was high (84.2%) in distinguishing siblings from patients. The model performed poorly in distinguishing patients from healthy controls, with an accuracy of 41.18%. Physical abuse, semantic verbal fluency, and 21 structural network properties spanning primarily frontal, temporal, occipital, and parietal regions were critical factors of associated distress-based

PP. The model showed relatively lower performance in predicting high/low PP groups and poor performance in distinguishing patients from their siblings and healthy controls. While regional network metrics were associated with PP, global network metrics were not, and betweennness centrality, an index of integration that reflects a node's importance in facilitating communication between network regions, had the highest contribution to both models.

**DISCUSSION:** Some underlying substrates of PP are shared across the psychosis continuum, and specific predictors of PP may indicate resilience in reducing the expression of psychosis in siblings. Underlying predictors for frequency-based PP and associated distress PP differ, albeit neurobiological mechanisms play a significant role in both.

## T31. P2 Visual Event-Related Potential Response Predicts Clinical Outcomes in Patients at Clinical High Risk for Psychosis

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**BACKGROUND:** The P2 component of the visual event-related potential (ERP) response occurs approximately 200-300 ms after stimulus onset. Some but not all studies have found it to be smaller (less positive) than normal in patients with schizophrenia. It has been found to be reduced in patients at clinical high risk (CHR) for schizophrenia using a visual paradigm of facial expression recognition and target among standard stimuli. In the present study, we aimed to examine whether P2 amplitude is abnormal in CHR patients, and whether it predicts their symptomatic and functional outcomes at baseline and two-year follow-up.
**METHODS:** We measured mean P2 amplitudes from 175-300 ms in antipsychotic-naive CHR patients (n= 47) and healthy control participants (n = 25), in response to target words in a semantic priming paradigm, in which participants viewed prime words each followed by a target that was a related or unrelated word, or a non-word, at stimulus-onset asynchronies (SOAs) of 300 or 750 ms. We measured patients' psychosis-like symptoms with the Scale of Prodromal Symptoms (SOPS) Positive subscale, and academic/occupational and social functioning with the Global Functioning (GF):Role and Social scales, at baseline and two-year follow-up.
**RESULTS:** We found that CHR patients had significantly smaller (less positive) P2s for related targets than controls at the 300 ms SOA (p=0.031). P2 amplitude differences between related and unrelated targets (related minus unrelated) were smaller (less positive) in the CHR group than the control group, at the 300-ms prime-target SOA (p=0.04). Moreover, within the CHR group, larger P2 amplitude differences between related and unrelated targets (related minus unrelated) predicted lower SOPS P2 scores of suspiciousness (p=0.016) at baseline and SOPS Positive subscale scores (p=0.03) after two years. Differences also correlated with higher GF:Role scores (p=0.006) after two years.
**DISCUSSION:** In CHR patients, the presence of P2 enhancement for contextually related versus unrelated stimuli (which has previously been found in normal individuals in some studies using rapid stimulus presentation) may predict better outcomes. Deficiency in this early visual processing may also contribute to paranoid ideation and a decline in functioning over time. This

P2 priming may also reflect an early onset of the effect of contextual relatedness on the N400 ERP, which normally occurs in the subsequent time window, and which we previously found to be attenuated in CHR patients. Further study of the prognostic value of P2 amplitude with regard to psychotic symptoms and functional outcomes in CHR patients is warranted.

## T32. Pragmatic Production Deficits in Mood And Psychotic Disorders: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Pragmatics in linguistics is the production and comprehension of non-literal language and language in context. Those abilities might be compromised by serious mental illnesses such as mood and psychotic disorders. The impact of these deficits can be far-reaching. For example, among the various language impairments experienced by those with psychosis, productive pragmatic ones are the most likely to impact their socio-occupational functioning. Despite multiple studies investigating these impairments, we lack a systematic synthesis of the magnitude of deficits. Knowing this will help us determine the potential utility of pragmatic remediation approaches when treating SMI. These results are part of a more comprehensive study that investigates pragmatic impairments in mood and psychotic disorders.
**METHODS:** We conducted a systematic review and meta-analysis adhering to the PRISMA standards. Original articles have been extracted from PubMed and Scopus up until June 28th. Only patient-control comparison studies were included. Effect size (Hedge's g) has been calculated across three subdomains of pragmatic production: Cooperativity, Coherence, and Anaphoras. The bias and quality of studies are currently being assessed using a modified version of the Newcastle-Ottawa Scale. Bayesian meta-analysis was used to estimate domain-specific effects and variance differences.
**RESULTS:** In total, 46 studies have been included. Bayesian meta-analysis revealed a moderate to large impact of psychosis on all three domains of pragmatics with cooperativity being the most impacted: Anaphoras: averaged-effect d=-0.32, 95% Crl [-0.600- -0.049], Coherence: averaged-effect d=-0.36, 95% Crl [-0.52- -0.23], and Cooperativity: averaged effect d=-1.25, 95% Crl [-1.64- -0.77].
**DISCUSSION:** This study revealed strong evidence of productive pragmatic impairments in psychosis. This new knowledge will allow for better measurement of communication impairments in those with psychosis. Thus, our findings will pave the way for targeted speech-related pragmatic interventions. This is especially relevant given the proximity of pragmatic abilities to social functioning.

## T33. Blood Levels of Transcription Factors Involved in B-Lymphocyte Maturation Distinguish Schizophrenia From Major Depressive Disorder

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**BACKGROUND:** The current lack of biomarkers for schizophrenia (SZ) represents a challenge for distinguishing patients with SZ from other related psychiatric disorders. Genome-wide association studies, along with epidemiological and clinical research, suggest the involvement of molecular factors regulating B-lymphocyte lineage in SZ. MEF2C is an established risk gene for SZ that functions as a transcription factor critically involved in regulating B-cell germinal center maturation. E2A is an additional transcription factor involved in the same process and has not been implicated in schizophrenia. We tested the hypothesis that transcription factors involved in B-cell maturation can distinguish patients with SZ from patients with major depressive disorder (MDD) as a psychiatric control group. By investigating their correlation with clinical measures, we aim to gain insights into the biological mechanisms underlying SZ and develop quantitative diagnostic tools for psychosis research and clinical care.
**METHODS:** Whole blood samples were collected from 8 patients with SZ and 6 patients with MDD. Clinical and demographic characteristics were recorded. ELISA assays were conducted blinded to diagnostic groups. Statistical analysis was performed using ANCOVA to assess group differences, accounting for potential confounders.
**RESULTS:** There was no difference between SZ and MDD groups in sex (37.5% vs. 50% female), age (42.4 vs. 40.8), body mass index (33.9 vs. 29.4), duration of illness (17.8 vs. 15.2 years), or number of lifetime psychiatric hospitalizations (5.5 vs. 2.3); significantly more patients with SZ were African American (50% vs. 0%; p=0.02). Patients with SZ demonstrated significantly lower levels of MEF2C (p=0.01) and E2A (p=0.05) compared to patients with MDD. These differences were significant after adjusting for race, antipsychotic, and antidepressant exposure. No significant difference in CD20 expression was observed between the two groups.
**DISCUSSION:** Our findings suggest that peripheral measures of MEF2C and E2A protein levels distinguish patients with SZ from patients with MDD. The combination of normal CD20 expression with decreased MEF2C and E2A provides insight into molecular pathways involved in B-cell maturation in SZ and highlights the need for further investigation. Ongoing studies will examine molecular pathways downstream from MEF2C and E2A in patients with SZ.

## T34. A Longitudinal Network of Psychotic-Like Experiences, Depressive and Anxiety Symptoms, and Adverse Life Events: A Cohort Study of 3,358 College Students

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**BACKGROUND:** Psychotic-like experiences (PLEs), especially for persistent PLEs, are highly predictive of subsequent mental health problems. Hence, it is crucial to explore the psychopathological associations underlying the occurrence and persistence of PLEs. This study

aimed to explore the above issues through a longitudinal dynamic network approach among PLEs and psychological and psychosocial factors.
**METHODS:** A total of 3,358 college students completed two waves of online survey (from Oct 2021 to Oct 2022). Socio-demographic information was collected at baseline, and PLEs, depressive and anxiety symptoms, and adverse life events were assessed in both waves. Cross-lagged panel network analyses were used to establish networks among individuals with baseline PLEs as well as those without.
**RESULTS:** At baseline, 455(13.5%) students were screened positive for PLEs. Distinct dynamic network structures were revealed among participants with baseline PLEs and those without. While "psychomotor disturbance" had the strongest connection with PLEs in participants with baseline PLEs, "suicide/self-harm" was most associated with PLEs in those without. Among all three subtypes of PLEs, BEs and PI were the most affected nodes by other constructs in participants with baseline PLEs and those without, respectively. Additionally, wide interconnections within the PLEs construct existed only among participants without baseline PLEs.
**DISCUSSION:** The study provides time-variant associations between PLEs and depressive symptoms, anxiety symptoms, and adverse life events using network structures. These findings help to reveal the crucial markers of the occurrence and persistence of PLEs, and shed high light on future intervention aimed to prevent and relieve PLEs.

## T35. Attenuated Symptoms of Mania or Depression Compared With Those of Psychosis in Children at Familial Risk of Psychosis and Bipolar Affective Disorder Suggest two Different Pathways of Risk

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**BACKGROUND:** Investigation of children and adolescents at familial risk (FHR) for psychosis or mood disorders, and their risk trajectory for transition to major psychiatric illness, is typically conducted using risk indicators in different modalities (Faedda et al., 2019, Bipolar Disord). Risk studies of FHRs have examined attenuated childhood symptoms of psychosis (psychotic-like experiences; PLE) as risk indicators (Gregersen et al., 2022, Am J Psychiatry). Little is known about attenuated symptoms of mania or depression in FHRs. This study aims to address a gap in the literature by examining subclinical mood and psychotic symptoms in FHRs together.

Our aims were twofold: 1) to develop and test the reliability of a measure of subclinical mania, depression (mood) and psychotic symptoms, 2) to assess the prevalence, specificity and independence of mood and psychotic symptoms in our longitudinal sample of FHRs and to explore their relationships with other clinical and cognitive risk indicators.

**METHODS:** We used several sources of longitudinal data to define attenuated symptoms of mania, depression and psychosis: medical records and semi-structured interviews conducted with both the offspring and their parents. The sample consisted of 218 FHRs aged 6-27 years born to a

parent with schizophrenia, bipolar disorder or major depressive disorder (mean age = 19 years; 49% male) (Maziade et al., 2008, Acta Psychiat Scand, Paccalet et al., 2016, Schiz Res). A comparison sample of 143 unrelated adolescent controls was assessed (mean age =16; 36% male). All symptoms were scored as 0 (absent), 1 (once/twice), 2 (sometimes) and 3 (often). For each subclinical symptom scale, a total score was calculated for each FHR and the mean among FHRs with a score of at least 1. Then, using these means as a threshold for each scale, the FHRs on the mania, depression and psychotic scale were divided into two groups, i.e. FHRs with a relatively higher value versus those with a lower value. Logistic regression with generalised estimating equations was used to estimate odds ratios (OR). Analyses were adjusted for sex and age.

**RESULTS:** The attenuated symptoms of the mania, depression and psychosis scales were weakly correlated (r=0.3, 0.3, 0.37; minimum p=6x10-6) in FHRs. Consistently, FHRs from the same sibling rarely scored high on both scales. Logistic regressions showed that either FHRs with vs without psychotic symptoms or those with vs without mood attenuated symptoms were not significantly different with respect to gender, parental psychosis, SES and IQ (OR not different from 0). In particular, childhood trauma increased the risk of a higher score on the manic scale by a mean of 5.1 times (95%CI=[1.2;20.8], p=0.02) and the risk of a higher score on the depression scale by a mean of 3.0 times (95%CI=[1.2;7.8], p=0.02). Trauma had no effect on the psychosis scale (p = 0.28). According to our definitions, only 2 control subjects presented PLE and none presented mood attenuated symptoms.

**DISCUSSION:** The weak correlation observed between mood and psychotic symptoms suggests that each may represent different pathways in the FHR risk trajectory. It also suggests that mood symptoms could add substantial information to the PLE. In particular, trauma exposure would be a factor promoting the emergence of attenuated manic and depressive symptom scales. New studies should address i) the extent to which the FHRs risk trajectory and the risk of future transition might be differentially influenced by the attenuated psychotic or the attenuated mood pathway, and ii) the mechanisms underlying the mediating role of trauma in promoting the accumulation of risk indicators that have been shown to be highly predictive of transition (Berthelot et al. 2022 Schiz Bull Open).

## T36. Enhancing Attachment Security Through Open Dialogue: A Putative Pathway to Reducing Psychotic and Affective Symptoms

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**BACKGROUND:** Attachment insecurity is characterised by difficulties in trust, emotional regulation, and interpersonal relationships, and is in general associated with vulnerability to psychopathology (1). Recent reviews have highlighted its association with paranoia (2,3) as well as depressive symptoms (4). Paranoia is one of the most prevalent symptoms of psychosis, identified in over 70% of first episodes (5). It can raise the risk for psychosis and predict transition to it over time (6).

Increasing research advocates for interventions that promote attachment security as a pathway to improving mental health outcomes in both affective and psychotic conditions (7).

The Open Dialogue (OD) approach, developed in Northern Finland for treating psychotic crises, emphasises dialogue-based interventions, involvement of social networks, and fostering reciprocal understanding (8). These characteristics align closely with mechanisms central to promoting attachment security (9).

This work explores the hypothesis that OD may enhance attachment security by fostering trust, mutual understanding, and relational coherence, thereby reducing the risk of developing psychotic and affective symptoms.

**METHODS:** This poster integrates theoretical frameworks and evidence from attachment theory to examine the alignment between OD principles—such as psychological continuity, tolerance of uncertainty, and a social network perspective—and processes necessary for secure attachment (10,11). Specific attention is given to how OD's emphasis on reciprocal dialogue, reflective practice, and a supportive network can address attachment-related vulnerabilities

**RESULTS:** OD appears apt to facilitate key processes associated with attachment security, including:

1. Enhancing trust and emotional safety: Transparent and inclusive dialogues promote a greater sense of security in relationships (12,13).
2. Promoting emotional regulation: Shared experiences and reflective practice support improved regulation of emotional states (14)
3. Strengthening relational coherence: OD's integration of multiple perspectives fosters coherent narratives, reducing fragmented or distrustful thinking (15)

**DISCUSSION:** OD holds the potential to address attachment insecurity, and thereby act as a preventive and therapeutic intervention for individuals at risk of or experiencing psychosis and affective symptoms. Future research should empirically evaluate changes in attachment security among individuals undergoing OD and investigate how these changes mediate clinical outcomes, particularly in paranoia and mood regulation.

References:

1. Bakermans-Kranenburg, M. and van IJzendoorn, M. H. The first 10,000 Adult Attachment Interviews: Distributions of adult attachment representations in clinical and non-clinical groups. Attach. Hum. Dev. 11, 223–263 (2009).
2. Lavin, R., Bucci, S., Varese, F. and Berry, K. The relationship between insecure attachment and paranoia in psychosis: A systematic literature review. Br. J. Clin. Psychol. 59, 39–65 (2020).
3. Murphy, R., Goodall, K. and Woodrow, A. The relationship between attachment insecurity and experiences on the paranoia continuum: A meta-analysis. Br. J. Clin. Psychol. 59, 290–318 (2020).

4. Dagan, O., Facompré, C. R. and Bernard, K. Adult attachment representations and depressive symptoms: A meta-analysis. J. Affect. Disord. 236, 274–290 (2018).

5. Coid, J. W. et al. The Relationship Between Delusions and Violence. JAMA Psychiatry 70, 465 (2013).

6. Wilcox, J., Briones, D., Quadri, S. and Tsuang, M. Prognostic implications of paranoia and thought disorder in new onset psychosis. Compr. Psychiatry 55, 813–817 (2014).

7. de With, J., Korver-Nieberg, N., de Haan, L. and Schirmbeck, F. The association between attachment style and social functioning in patients with non-affective psychotic disorders, unaffected siblings and healthy controls. Schizophr. Res. 252, 96–102 (2023).

8. Seikkula, J. and Olson, M. E. The open dialogue approach to acute psychosis: Its poetics and micropolitics. Fam. Process 42, 403–418 (2003).

9. Diamond, G., Russon, J. and Levy, S. Attachment-Based Family Therapy: A Review of the Empirical Support. Fam. Process 55, 595–610 (2016).

10. Bowlby, J. A SECURE BASE Parent-Child Attachment and Healthy Human Development A Member of the Perseus Books Group. (1988).

11. Sidis, A. E., Moore, A. R., Pickard, J. and Deane, F. P. 'Always opening and never closing': How dialogical therapists understand and create reflective conversations in network meetings. Front. Psychol. 13, 992785 (2022).

12. Seikkula, J., Alakare, B. and Aaltonen, J. The Comprehensive Open-Dialogue Approach in Western Lapland: II. Long-term stability of acute psychosis outcomes in advanced community care. Psychosis 3, 192–204 (2011).

13. Bergström, T. et al. The family-oriented open dialogue approach in the treatment of first-episode psychosis: Nineteen–year outcomes. Psychiatry Res. 270, 168–175 (2018).

14. Seikkula, J. Dialogi parantaa–mutta miksi. perhejapariterapialehti.journal.fi (2023).

15. Marlowe, N. I., Nicholson Perry, K. and Lee, J. Ontological insecurity II: Relationship to attachment, childhood trauma, and subclinical psychotic-like experiences. J. Clin. Psychol. 76, 440–460 (2020).

## T37. Differential Neural Activation in Resilient vs Maladaptive Adolescents Following Early Life Adversity: An FMRI Study

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**BACKGROUND:** Exposure to Early Life Adversity (ELA) is an important risk factor for poor health outcomes later in life. Specifically, threat-based ELA as opposed to other adversity subtypes is associated with the development of psychopathology, including psychotic-like symptoms, during adolescence and adulthood. However, some individuals demonstrate resilience and remain asymptomatic despite exposure to significant adversity. The function of multiple brain regions has been implicated in the development of resilience, such as reduced limbic system activation and increased inhibitory action of prefrontal regions, reflecting improved emotional regulation. In this study, we investigated the neurobiological underpinnings of adolescent resilience to threat-based ELA using a working memory functional Magnetic Resonance Imaging (fMRI) task with emotional face stimuli. We hypothesized that maladaptive participants would exhibit increased limbic system activation compared to resilient participants, reflecting hyperactivation of threat detection mechanisms. This hyperactivation could be a potential mechanism linking early life adversity (ELA) to the development of psychopathology.
**METHODS:** We included 168 adolescents aged 11-14 who participated in the eBRAIN study in London. We assessed experiences of threat-based ELA using the Adolescent Appropriate Life Events Questionnaires (AALE) and current psychopathology using the Strengths and Difficulties Questionnaire (SDQ) and the Adolescent Psychotic Screening Scale (APSS). Participants were classified as ‘resilient’, ‘maladaptive, ‘vulnerable’ or ‘control’ based on pre-defined thresholds of presence or absence of ELA exposure and psychopathology. Neural activity was evaluated using a delayed match to sample fMRI task including emotional faces and shapes. Full Factorial design in SPM was used to investigate differences between ‘maladaptive’ and ‘resilient’ participants, covarying for age. A whole-brain was conducted at a voxel-wise threshold of $p < 0.05$ with small volume correction ($p < 0.05$ FWE corrected).
**RESULTS:** A total of 64 participants were classified as ‘control', 16 as ‘vulnerable’, 50 as ‘maladaptive’, and 38 as ‘resilient’. Male participants were more likely to be in the ‘resilient’ group ($X2$ (3, $N = 168$) = 8.35, $p < 0.05$) but there were no associations with resilience group membership and other demographic factors including age and ethnicity. Region of interest (ROI) neuroimaging analysis on the interaction between ELA exposure and psychopathology revealed reduced neural activation in the anterior cingulate cortex (ACC) and lingual gyrus in ‘resilient’ adolescents during face stimulus encoding contrasted with inter-trial interval ($p < 0.05$, FWE corrected). This finding suggests that participants resilient to threat-based ELA demonstrate more efficient emotional regulation when viewing emotional face stimuli.
**DISCUSSION:** Our findings demonstrate a reduced activation of the ACC and lingual gyrus during visual and facial information processing in resilient participants. These results support previous literature suggesting that poor emotional regulation is one of the key mechanisms linking the association between early life adversity and the development of mental health

problems. The observed reduced activation in the ACC and lingual gyrus among resilient participants indicates more efficient emotion regulation, supporting the idea that resilience involves adaptive neural responses to stress. Future research will aim to investigate the stability of these neural correlates over time, providing deeper insights into the substrates of susceptibility and resilience to adversity across adolescence.

## T38. Olanzapine for Extended-Release Injectable Suspension (TV-44749) for Subcutaneous Use is Designed for Sustained Efficacy and to Eliminate Causes of Post-Injection Delirium/Sedation Syndrome: In Vitro and Clinical Data

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**BACKGROUND:** Suboptimal treatment adherence is a modifiable risk factor for relapse in patients with schizophrenia. Long-acting injectable (LAI) antipsychotics are associated with improved clinical outcomes and lower discontinuation rates compared with corresponding oral antipsychotic formulations, which may be facilitated by improved treatment adherence. Olanzapine is a highly effective antipsychotic currently available in oral and intramuscular (IM) LAI formulations; however, due to the risk for post-injection delirium/sedation syndrome (PDSS) and the associated Risk Evaluation and Mitigation Strategy, the clinical use of IM olanzapine LAI is limited. PDSS may arise from vessel injury during IM injection, resulting in rapid olanzapine solubilization and subsequent substantial increase in plasma olanzapine concentration, leading to overdose. TV-44749 is a once-monthly, subcutaneous (SC), extended-release injectable olanzapine that utilizes an innovative copolymer drug delivery technology to ensure controlled olanzapine release over a 1-month period. The combination of TV-44749's SC route of administration and formulation was designed to provide sustained efficacy and eliminate causes of PDSS. Specific to route of administration, SC tissue is less vascular than muscle tissue; therefore, inadvertent intravascular injury is less likely. Moreover, if intravascular injury occurs, TV-44749 copolymers precipitate instantly in contact with plasma, forming a depot that entraps olanzapine particles, which prevents rapid dissolution.

Here, we report solubility and in vitro release (IVR) data demonstrating the markedly reduced risk of PDSS associated with the administration and formulation of TV-44749 versus IM olanzapine LAI. Moreover, so far, clinical data from phase 1 and 3 studies have confirmed the absence of PDSS risk with TV-44749 in patients with schizophrenia.

**METHODS:** Solubility and IVR studies of olanzapine in human plasma explored the risk of PDSS following TV-44749 injection versus IM olanzapine LAI. Solubilities of olanzapine base (active pharmaceutical ingredient [API] in TV-44749) and olanzapine pamoate monohydrate

(API in IM olanzapine LAI) in commercially available human plasma at 37°C were determined by the shake-flask method. The IVR analysis of TV-44749 and IM olanzapine LAI was performed using a dose of 30 mg to mimic a portion of olanzapine dose accidentally injected into a blood vessel, while depots of TV-44749 were characterized by environmental scanning electron microscope (ESEM) analysis at 0- and 72-hour time points of the IVR study.

Clinical evidence of minimized PDSS risk was collected from phase 1 and phase 3 studies. The phase 1 study was an open-label, single- and multiple-ascending dose study in healthy volunteers and patients with schizophrenia or schizoaffective disorder. Serial blood samples were collected at time points pre- and post-injection to evaluate TV-44749's pharmacokinetic characteristics, and safety was monitored throughout the study. The Subcutaneous OLAnzapine extended-Release Injection Study (SOLARIS; NCT05693935) was a randomized, double-blind, placebo-controlled, phase 3 study designed to assess the efficacy, safety, and tolerability of TV-44749 versus placebo in adults with acute exacerbation of schizophrenia.

**RESULTS:** The solubility study showed that the olanzapine base of TV-44749 demonstrated 1.8-times lower solubility in human plasma than olanzapine pamoate monohydrate of IM olanzapine (0.371 mg/mL vs 0.630 mg/mL). In the IVR study, TV-44749 maintained its controlled-release properties in plasma (14% in 72 hours) while IM olanzapine exhibited a rapid and uncontrolled release of olanzapine (100% in 72 hours). This large difference cannot be solely attributed to the differing API solubilities and reflects the novel slow-release technology of the TV-44749 formulation, whereby a solid depot is immediately formed upon contact of TV-44749 with human plasma. ESEM analysis of the surface and cross-sections of the depots confirmed the formation of a porous polymeric matrix in which olanzapine particles are entrapped, thereby preventing rapid release. The integrity of the depots was preserved after 72 hours in human plasma.

In the phase 1 study, TV-44749 maintained controlled-release properties without any burst or unexpected rise in olanzapine plasma concentrations following administration. The benefits of TV-44749's administration and formulation were seen in phase 1 and 3 studies, where there have been no suspected or confirmed PDSS events ( > 3485 active TV-44749 injections, December 2024). Through the phase 1 study and period 1 of SOLARIS (8-week acute treatment period; N=675), TV-44749 was well tolerated, with a systemic safety profile consistent with approved olanzapine formulations. TV-44749 also demonstrated significantly greater efficacy versus placebo in period 1 of SOLARIS.

**DISCUSSION:** The results of the solubility and IVR studies comparing TV-44749 with IM olanzapine LAI confirm that the combination of TV-44749's SC route of administration and formulation properties markedly reduces the risk of PDSS, with a targeted absent clinical risk of PDSS. Phase 1 and phase 3 study results provide robust clinical evidence for the absence of PDSS.

**T39. Evenamide, A Glutamate Release Modulator, as add-on to "Standard of Care" in TRS: Design of a Phase 3, Potentially Pivotal, International, Randomized, Double-Blind, Placebo-Controlled Trial**

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**BACKGROUND:** The proportion of patients who develop treatment-resistant schizophrenia (TRS) is almost 25% among first-episode patients, and it is even increased to 30% when considering also patients at later stages of illness who relapse after an initial response to treatment with antipsychotics (APs) (Siskind et al., 2022). Clozapine is the only drug that demonstrated superiority over other APs in TRS; differently to all other APs that modulate 5HT/DA transmission, clozapine seems to exert its effects through a combined action on multiple receptor systems (Brunello et al, 1995). The need to modulate non-monoaminergic targets is supported by increasing evidence that TRS is characterized by excessive glutamatergic activity, rather than increased dopamine synthesis (Mouchlianitis et al., 2023).
Evenamide, a new chemical entity, is a voltage-gated sodium channel blocker devoid of biological activity at > 150 CNS targets, that normalizes excessive glutamate release without affecting its basal levels. Preclinical experiments in various animal models of psychosis, mania, aggressiveness, and impulsivity have demonstrated benefits associated with evenamide, both when used as monotherapy and when combined with first- or second-generation APs. Clinical benefits of evenamide as add-on to an AP in TRS patients were demonstrated in a pilot, phase 2, open-label, rater-blinded, 1-year trial (Anand et al, 2023); in addition, a phase 2/3, international, randomized, double-blind, placebo-controlled trial in patients with schizophrenia not adequately benefitting from a SGA showed statistically significant and clinically meaningful improvements associated with evenamide add-on treatment for 4 weeks.

**METHODS:** This is a prospective, potentially pivotal, phase 3, international, 1-year, randomized, double-blind, placebo-controlled, study, with a primary efficacy endpoint at 12 weeks and long-term efficacy endpoints at 26 and 52 weeks that will evaluate the efficacy, safety, and tolerability of fixed doses of 15 mg bid and 30 mg bid of evenamide as add-on treatment in patients with documented TRS receiving AP treatment but not adequately benefitting from a stable therapeutic dose of an SGA. Eligible patients must have a diagnosis of TRS according to the TRRIP consensus guidelines (Howes et al, 2017). During the 6-week screening period and throughout the study, adherence to background AP(s) and evenamide will be confirmed through measurements of plasma levels. Psychiatric selection criteria include CGI-S of mildly to severely ill (3-6); BPRS total score ≥45, with a score ≥18 on core symptoms of psychosis, and PANSS total score ≥70. An Independent Eligibility Committee will determine patients' eligibility. Patients improving ≥20% on the BPRS or ≥1 category on the CGI-S during the screening period will be excluded. Efficacy (PANSS, CGI-S/C, Q-LES-Q-SF, GAF, PSP scales) and safety (vital signs, ECG, lab tests, physical/neurological/eye exams, ESRS-A, CDSS, C-SSRS) will be evaluated at regular intervals.
**RESULTS:** The study will be initiated by the time of the congress. Results from this study will determine whether addition of evenamide to AP treatment is associated with statistically significant and clinically important benefits in patients with TRS.

**DISCUSSION:** Positive results would support the need for glutamate modulation as add-on for the optimal treatment of patients not benefitting from SGAs.

## T40. A Randomized Controlled Trial of a Tele-Mentoring Program, Project Echo, to Increase Clozapine Prescribing

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**BACKGROUND:** Clozapine is the most effective antipsychotic, yet the number of people with schizophrenia who are prescribed clozapine nationally is < 5%, despite its recommended use in about 30-50% of people with treatment-resistant schizophrenia. Many barriers contribute to clozapine underutilization; however, research has shown that lack of prescriber competence to manage clozapine and challenging logistics including patient resistance to hematologic monitoring are some of the greatest barriers to clozapine use. In the last 15 years, a unique, structured and empirically validated tele-mentoring model has emerged called Project ECHO (Extension for Community Healthcare Outcomes). ECHO is a “hub” and “spoke” sharing network led by an expert academic team (the “hub”) that uses videoconferencing to conduct virtual clinics with non-expert prescribers (the “spokes”) located in areas outside the academic hub site.
**METHODS:** In a randomized controlled design, we tested the effectiveness of a 12-month intervention for improving the use of clozapine. The intervention, Clozapine CHAMPION-ECHO (Center for Help and Assistance for Maryland Prescribers- Improving Outcomes Network using ECHO, consisted of 26 biweekly tele-mentoring sessions with continuing education (CE) credits that included didactic sessions and case presentations and vignettes. This was compared to an enhanced treatment as usual (eTAU) group with all sites receiving FDA-cleared ANC point of care (POC) monitoring devices and a Statewide CHAMPION consultation line to all study sites. Prescribers completed baseline and endpoint assessments for knowledge, self-reported competence and prescription records were obtained from Maryland Medicaid files/state psychiatric hospital information systems and evaluated during 3 periods before, during and after the intervention. Knowledge was assessed by multiple-choice questions and competence was assessed by a visual Analog Scale (VAS) (0-100 mm). We evaluated whether there were differences in prescribing and persistence in time to clozapine discontinuation.
**RESULTS:** 277 prescribers from 53 sites were randomized. Among the 132/277 (48%) prescribers randomized to ECHO, n=84/132 (64%) attended at least one of the 26 ECHO

sessions. On average, prescribers attended 12.7 (+ 8.6) sessions (median (IQR):12 (4-21)). The mean (+ S.D) proportion of questions answered correctly at baseline was 63% (+11%) and at follow-up was 71% (+17%) in the ECHO condition and was 66% (+11%) at baseline and 77% (+12%) at follow up in the eTAU condition. When adjusting for baseline, the ECHO group demonstrated a significant increase in knowledge following the intervention compared to eTAU (p=0.0003). Within the CHAMPION- ECHO group, prescribers who attended between 1-13 ECHO sessions (p=0.012) and 14-26 ECHO sessions (p < 0.0001) had significant improvements in knowledge versus eTAU whereas in those who attended no sessions the change was not significant (p=0.478). Mean (+ S.D) perceived competence at baseline was 55.4 (+21.7) and at follow-up was 68.6 (+22.3) in the ECHO condition versus 58.9 (+20.3) at baseline and 71.4 (+19.3) at follow up in the eTAU condition. When adjusting for baseline, the change in perceived competence did not differ between the groups (p=0.819). Within the CHAMPION-ECHO group, only prescribers who attended 14-26 ECHO sessions reported significant improvements in perceived competence versus eTAU (p=0.014), whereas those who attended no sessions (p=0.253) or attended 1-13 sessions (p=0.264) did not report significant improvements versus eTAU. A total of180/277 (65%) prescribers (N=91 ECHO; n=89 eTAU) were included in the prescribing analysis (1,317 schizophrenia patients of ECHO prescribers and 1,219 patients of eTAU prescribers). The prevalence of clozapine prescribing among patients of prescribers randomized to ECHO was 7.4% in the pre-intervention baseline period (versus 5.4% in eTAU) and 11.9% in the post-intervention follow-up period (versus 9.3% in eTAU). We found that ECHO did not increase the likelihood of a patient being prescribed clozapine during the post-intervention period (aOR= 1.03, p=0.93). Also, the proportion of patients who discontinued clozapine among prescribers randomized to ECHO (n=37) was 3.9% in the follow-up period (versus 5.6% in eTAU (n=34)). Results of a cox survival model examining whether prescription times on clozapine before the first 45-day gap differed between ECHO and eTAU indicated a reduced hazard probability of discontinuation favoring the ECHO intervention; however, the result was not statistically significant (aHR = 0.56, p = 0.25).
**DISCUSSION:** We successfully implemented and conducted a 26-week clozapine ECHO intervention program with participation by over 275 prescribers in the state of Maryland. Education is effective at improving knowledge and self-reported competence; however, additional support and work is needed to motivate clozapine prescribing beyond providing education and increasing confidence in clozapine use.

## T41. Efficacy and Safety of Xanomeline and Trospium Chloride in Adults 55 and Older With Schizophrenia: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled Emergent Trials

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**BACKGROUND:** Xanomeline and trospium chloride combines the dual M1/M4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride and was recently approved in the U.S. for the treatment of adults

with schizophrenia. Xanomeline/trospium was studied in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. In pooled analyses of the acute EMERGENT trials, xanomeline/trospium demonstrated statistically significant improvements across efficacy measures and was generally well tolerated. Schizophrenia is a chronic illness, and older adults may have a reduced response to therapy due to decades of antipsychotic use. Here we report pooled efficacy and safety results from the EMERGENT trials in participants ≥55 years of age.
**METHODS:** The EMERGENT trials randomized people aged 18 to 60 years (EMERGENT-1) or 18 to 65 years (EMERGENT-2 and EMERGENT-3) with a recent worsening of positive symptoms warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score 80-120, and Clinical Global Impression–Severity (CGI-S) score ≥4. Xanomeline/trospium dosing started at 50 mg/20 mg BID and increased to a maximum 125 mg/30 mg BID. In each trial, the primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Other efficacy measures included change from baseline to week 5 in PANSS Marder 5-factor scores. Data from participants ≥55 years of age in the acute EMERGENT trials were pooled. Efficacy analyses were conducted in the modified intent-to-treat (mITT) population, defined as all randomized participants who received ≥1 trial medication dose and had 1 baseline and ≥1 postbaseline PANSS assessment. The safety analysis population was defined as all randomized participants who received ≥1 trial medication dose.
**RESULTS:** Safety analysis included 146 participants (xanomeline/trospium, n=69; placebo, n=77) and the mITT population included 136 participants (xanomeline/trospium, n=63; placebo, n=73). Across trials, xanomeline/trospium significantly reduced PANSS total score compared with placebo in participants ≥55 years of age (-21.0 vs -10.9, P=0.0004; Cohen's d effect size: 0.69). At week 5, xanomeline/trospium was also associated with a significantly greater reduction than placebo in PANSS Marder disorganized thoughts (-4.1 vs -2.0 [LSM difference, -2.1; 95% CI, -3.5 to -0.6; P=0.005]), uncontrolled hostility/excitement (-2.1 vs -0.5 [LSM difference, -1.5; 95% CI, -2.8 to -0.3; P=0.012]), negative (-4.9 vs -2.3 [LSM difference, -2.6; 95% CI, -4.3 to -0.9; P=0.0025]), and positive factor scores (-6.2 vs -2.8 [LSM difference, -3.4; 95% CI, -5.3 to -1.6; P=0.0004]). Difference in PANSS Marder depression/anxiety factor between treatment groups at week 5 was not statistically significant. TEAEs related to treatment were reported in 46 (66.7%) and 37 (48.1%) of participants in the xanomeline/trospium and placebo groups, respectively. The most common treatment-related TEAEs in the xanomeline trospium group were constipation (23.2%), nausea (21.7%), vomiting (17.4%), and dyspepsia (14.5%). Treatment-related extrapyramidal symptoms were reported in 3 patients, all in the xanomeline/trospium group. Measures of weight gain, sedation, and somnolence were similar between groups.
**DISCUSSION:** In participants ≥55 years of age, xanomeline/trospium demonstrated statistically significant improvements across certain efficacy measures with consistent and robust effect sizes. Xanomeline/trospium was generally well tolerated with a safety profile similar to the overall trial population.

**T42. Preliminary Results of the Oxymind-Study – A Mindfulness-Based Group Psychotherapy in Combination With Oxytocin for Negative Symptoms in Patients With Schizophrenia Spectrum Disorders**

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**BACKGROUND:** Current treatments for negative symptoms (NS) in schizophrenia spectrum disorders (SSD) are insufficient, and new approaches are urgently needed. NS may result from disruptions between the mesocorticolimbic dopamine system for social reward expectancy and the socioemotional process network. Oxytocin (OXT) has been found to enhance functional connectivity between these neuronal networks. Lower plasma OXT levels are associated with NS severity and deficits in social cognition in SSD. While intranasal OXT improves social cognition in healthy individuals, findings in SSD have been inconsistent. According to the social salience hypothesis, OXT's effects depend on social context and individual factors, with genetic variants of OXT receptors (OXTR) potentially influencing outcomes. In a pilot study, we observed lower NS in patients with SSD receiving OXT in a positive social setting compared to placebo. We also found improvements in NS and other symptoms after mindfulness-based group psychotherapy (MBGT). This study aims to assess the synergistic effect of OXT and MBGT on the five NS domains, as well as affect, and stress in individuals with SSD. The main hypothesis is that OXT combined with MBGT (OXT+MBGT) will result in a greater reduction in NS compared to placebo (PLC+MBGT).

**METHODS:** This is an experimental, triple-blinded, randomized, PLC-controlled trial. The MBGT is manual-based, delivered by two experienced psychotherapists over four weeks, with one session per week for groups of up to six patients. As OXT's effects peak 30–80 minutes after intranasal administration, participants will receive either OXT (24 I.U.) or placebo 30 minutes before each session for optimal social behavior reinforcement. Recruitment takes place at the Department of Psychiatry and Neuroscience, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany. Mixed-gender groups are used to avoid gender bias. Hormonal factors like contraceptives and menstrual cycle phase are controlled for. The primary outcome is the change in NS, measured by validated interviews such as the Brief Negative Symptom Scale (BNSS) and Positive and Negative Syndrome Scale (PANSS), and psychometric questionnaires like the Self-Evaluation of Negative Symptoms (SNS). Secondary outcomes include changes in stress and affect. Data will be collected at baseline, post-session, and post-intervention, with results analyzed using ANCOVA, controlling for baseline severity and treatment condition. Based on prior research, a conservative effect size of $f = 0.25$ was assumed for sample size calculation. With 1:1 randomization, 80% power, and a two-sided significance level of 5%, we plan to recruit 120 participants. The role of OXTR gene variants will be looked at exploratively.

**RESULTS:** The study aims to determine to what extent the positive effects of MBGT on NS can be improved by augmentation with OXT. Preliminary results indicate a significant reduction in NS for the OXT group, particularly in Blunted affect ($p < .05$, $\eta 2p = 0.24$) and social withdrawal ($p < .05$, $\eta 2p = 0.20$) compared to PLC, based on PANSS scores. No severe adverse events or side effects were reported.

**DISCUSSION:** Current pharmacological and psychotherapeutic treatments for NS in SSD remain inadequate, highlighting the need for new approaches. Evidence is growing that augmented psychotherapy may offer benefits. The combined effect of MBGT and OXT has not been fully studied yet. This project could pave the way for more personalized and complementary psychiatric treatments for individuals with SSD.

## T43. Empowering Families of Relatives With Early Psychosis and Substance Use Problems With Craft-EP

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**BACKGROUND:** Treatment engagement and retention are significant concerns in early psychosis. Co-occurring substance use disorder is a primary predictor of treatment dropout, and over 50% of people with early psychosis have a lifetime history of substance use problems. Although treatments are available for substance use and early psychosis, they result in limited reductions in substance use; novel strategies are needed to increase engagement in substance use treatment. Community Reinforcement Approach and Family Training (CRAFT) is an evidence-based approach that increases treatment engagement for problematic substance use. CRAFT recognizes that people with a substance use problem may not be ready to change their substance use, and it capitalizes on the motivation of family members as agents of change. We recently adapted CRAFT for families of clients with early psychosis and substance use in a pilot telehealth feasibility study. Since elevated family distress is associated with both substance use and psychosis, reducing such distress may be a potential mechanism by which CRAFT improves treatment engagement in addition to reinforcement of non-substance use behavior and allowing for natural consequences of substance use. The current study is a randomized controlled trial of CRAFT for Early Psychosis and substance use (CRAFT-EP). We hypothesized that the CRAFT-EP + treatment as usual (TAU) group would have greater improvements in readiness to change substance use, treatment engagement, and family well-being compared with TAU alone.
**METHODS:** Participants were family members of relatives with early psychosis (onset within the past 6 years) who used alcohol and/or cannabis in the past 30 days. Family members participated in 8 weekly sessions of 1-on-1 CRAFT-EP coaching via telehealth video conferencing + TAU or TAU alone. Participants completed assessments at baseline, mid-, post-intervention, and 12-week follow-up. The primary outcome was the relative's readiness to change substance use per family report. Secondary outcomes included relative's past 30-day substance use and treatment engagement (% of psychiatric treatment sessions attended) per family report, and family distress and wellbeing (Beck Depression Inventory-II, State-Trait Anxiety Index–6, Relationship Happiness Scale) outcomes.
**RESULTS:** As of December 2024, 43 family members were randomized and will complete the study by the end of 2024. Participants were primarily mothers (88%) with at least mild depressive symptoms (40%) and high anxiety (70%). They lived with (65%) clients who were male (74%), young (mean age = 24 years) with affective psychosis (56%) or non-affective psychosis (44%) who attended mental health appointments in the past month (72%). Most participants reported that the client's most problematic substance was cannabis (86%), and that the client used the substance an average of 14 of the past 30 days. Most participants expressed concern about substances exacerbating psychosis (56%) and wanted to be more involved in the client's treatment (58%). At baseline, participants reported that the client was ready to cutdown/quit using their most problematic substance on average 2 on a scale of 0 = not at all to 10 = extremely. We will report group differences in pre-post outcomes for family member-

reported client readiness to change substance use, past 30-day substance use, treatment engagement, and personal depression, anxiety, and relationship happiness.
**DISCUSSION:** This study builds on our feasibility pilot and to test whether CRAFT-EP yields added benefit to substance use, treatment engagement, and family well-being outcomes beyond TAU. Our results will inform the viability of CRAFT-EP for larger trials.

## T44. Cardiovascular Safety and Tolerability of Xanomeline and Trospium Chloride in People With Schizophrenia: Pooled Results From the 5-Week, Randomized, Double-Blind, Placebo-Controlled Emergent Trials

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**BACKGROUND:** Currently approved antipsychotics are associated with a range of problematic adverse events (AEs). A significant need remains for more effective, better-tolerated treatments with novel mechanisms of action for people with schizophrenia. Xanomeline and trospium combines the dual M1/M4 preferring muscarinic receptor agonist xanomeline and peripherally restricted muscarinic receptor antagonist trospium. In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium improved symptoms with a safety profile that is differentiated from current standard of care. Overall, xanomeline/trospium was generally well tolerated in people with schizophrenia experiencing acute psychosis. The most common AEs associated with xanomeline/trospium were gastrointestinal in nature, but also included AEs associated with increases in heart rate and blood pressure.
**METHODS:** Data from the acute EMERGENT trials were pooled to further characterize the cardiovascular safety and tolerability of xanomeline/trospium. The acute EMERGENT trials enrolled adults with a DSM-5 diagnosis of schizophrenia, a Positive and Negative Syndrome Scale total score 80-120, a Clinical Global Impression-Severity score > /=4, and recent worsening of psychosis warranting hospitalization. Eligible participants were randomized 1:1 to twice-daily oral xanomeline/trospium or matched placebo for 5 weeks. Dosing started at xanomeline 50 mg/trospium 20 mg and was titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg. Safety analyses included the incidence of treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to discontinuation. Orthostatic hypotension was evaluated as an AE of special interest (AESI). Vital signs were recorded 2 hours after the morning dose at each postbaseline visit to correspond with maximum concentration (Cmax) and included both seated and standing (after 2 minutes) measurements to assess orthostatic change. A 12-lead electrocardiogram (ECG) was obtained on day 1 and at weeks 4 and 5. Analyses were performed in the safety population, defined as all participants who received > /=1 dose of trial medication.
**RESULTS:** A total of 683 participants (xanomeline/trospium, n=340; placebo, n=343) were included in the safety population for analysis. The most common cardiovascular TEAEs in the xanomeline/trospium vs placebo group were systemic hypertension (including hypertension, blood pressure increased, labile hypertension, and orthostatic hypertension; 8.5% vs 1.7%) and

tachycardia (5.0% vs 2.3%). Hypertension and tachycardia TEAEs were all mild or moderate in intensity; the majority resolved with continued dosing, and none led to treatment discontinuation. One TEAE each of increased heart rate (0.3%), palpitations (0.3%), and abnormal ECG (0.3%) led to treatment discontinuation in the xanomeline/trospium group compared with none in the placebo group. There were no cases of orthostatic hypotension meeting the criteria for AESI in either treatment group. Xanomeline/trospium was associated with small increases in observed blood pressure (BP); placebo-adjusted mean systolic BP increased 0.7 mmHg and mean diastolic BP increased 1.5 mmHg at week 5 vs baseline. Xanomeline/trospium was also associated with a placebo-adjusted mean increase from baseline to week 5 in observed heart rate (HR) of 6 bpm. Except for HR, which was higher in the xanomeline/trospium vs placebo group, there was no difference in ECG parameters between groups.
**DISCUSSION:** In the acute EMERGENT trials, xanomeline/trospium was associated with a low risk for cardiovascular TEAEs and small, generally transient increases in BP and HR.

## T45. Yoga-Based Group Intervention for Inpatients With Schizophrenia Spectrum Disorders—Feasibility, Acceptability, and Preliminary Outcomes of a Rater-Blinded Randomized Controlled Trial

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**BACKGROUND:** The efficacy of yoga as an adjunctive treatment for schizophrenia spectrum disorders (SSD) has garnered interest, however, meta-analytic findings exhibit heterogeneity. While yoga may positively influence various symptom domains, further investigation is needed due to the limited number, quality, and generalizability of studies. Yoga-based Group Intervention (YoGI) was specifically developed together with persons with SSD through a participatory approach and its mechanisms and processes were explored within qualitative studies.
This pre-registered randomized controlled trial (RCT) assessed the acceptability and feasibility as well as preliminary outcomes of YoGI compared to a commprehensive treatment as usual (TAU) in an inpatient setting.

**METHODS:** Fifty inpatients with SSD received either treatment as usual (TAU, n = 25) or YoGI+TAU (n = 25) for four weeks. Preliminary analyses examined rater-blinded positive and negative symptoms, self-rated depressive and anxiety symptoms, body mindfulness, mindfulness, psychological flexibility, subjective cognition, social functioning, quality of life, and medication regime at baseline and post-intervention.
**RESULTS:** Outcomes showed a 95% protocol adherence, feasibility and retention rates of 91% and 94%, respectively, and a dropout rate of 6%. ANCOVA revealed significant between-group post-intervention improvements for YoGI+TAU in positive symptoms, depression, cognitive fusion, and a mindfulness subscale. Medium-to-large pre-to-post intervention effects were found for body-mindfulness, positive, negative, and general symptomatology, depression, anxiety,

stress, cognitive fusion, attention, and quality of life in YoGI+TAU, while within-group changes were consistently smaller in TAU. No severe adverse events were reported.
**DISCUSSION:** This trial contributes to the growing evidence supporting the feasibility and acceptability of yoga for persons with SSD in an inpatient setting. Furthermore, preliminary evidence suggests that YoGI may provide additional benefits beyond TAU alone, across various self- and rater-based outcomes. These outcomes include improvements in body mindfulness, mindfulness, and psychiatric symptomatology, including positive and negative symptoms, subjective cognition, depression, anxiety, stress, social functioning, and quality of life. Additional fully powered RCTs are warranted to further elucidate the efficacy and potential mechanisms of action of YoGI for SSD, which should also assess the cost-efficiency of YoGI and explore longitudinal changes associated with the intervention. Such comprehensive research endeavours will not only enhance our understanding of the therapeutic potential of YoGI but also inform clinical practice and intervention strategies for persons with SSD.

## T46. Results of the Clozapine Consultation Center Associated With the State of Maryland Project ECHO Telementoring Program

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**BACKGROUND:** Clozapine is the gold standard medication for treatment resistant schizophrenia and schizoaffective disorder and the only drug with FDA approval for reducing the risk of recurrent suicidal behavior in these illnesses. It is severely underutilized in the US when compared to much of the world, in part due to cumbersome monitoring and needed expertise to safely implement this lifesaving medication. Breaking barriers through education and consultation could serve to improve patient outcomes and increase clozapine utilization ( < 5% in Maryland). Our research team is completing a randomized education program for prescribers in the State of Maryland to improve prescriber knowledge, competence and use of clozapine. Prescribers were assigned to the educational program or the enhanced treatment as usual condition. The project known as the Center for Help and Assistance for Maryland Prescribers-Improving Outcomes Network (CHAMPION) using Extension for Community Healthcare Outcomes (ECHO) or CHAMPION-ECHO included an enhanced treatment as usual platform for all sites. Among the benefits included to registered sites, they each received the Athelas Onepoint of care (POC) device free of charge to reduce logistical issues with Absolute Neutrophil Count (ANC) monitoring. Additionally, they had access to the Clozapine

Consultation Center (CCC) which was created. Here we present an analysis of the 3 years of the CCC

**METHODS:** Over 400 prescribers and clinicians enrolled in the CHAMPION program. We developed a team of 12 clozapine experts that could provide consultation on various topics regarding clozapine treatment including initiating clozapine treatment, managing common side effects, registering in the Clozapine Risk Evaluation and Mitigation Strategies (REMS) system, etc. These experts included psychiatrists, psychiatric pharmacists, nurses, physician assistant, cardiologist and a hematologist. The CCC provided consultations through a referral system using email or phone. Prior to triage, the clinicians provided a summary of their issue and preferred contact method. The CCC was advertised through the email network repeatedly and specific mention during all 26 of the educational sessions for those assigned to the educational program. Though not extensively advertised outside of the CHAMPION-ECHO participant group, the CCC was open to any prescriber or clinician in Maryland. All requests for consultation were captured and categorized based on the primary topic of the consultation. Time from initial contact to expert referral and from referral to the actual consultation was tracked, and experts were asked to make note of the recommendations made during the consultation. Follow-up consultations were provided if necessary or requested.

**RESULTS:** The CCC received a total of 54 requests for consultation from 41 different providers (34 prescribers, 7 non-prescribers). Fifty-one were from CHAMPION-ECHO participating sites and three were from providers outside the CHAMPION-ECHO project. Most requests were received via email

(90%). Fifty of the 54 requests resulted in recommendations directly from the CHAMPION team (six) or were triaged for consultation from an expert (44). Most consultation requests received responses from the CHAMPION team within 24 hours (90%). Clozapine experts were highly responsive to requests for consultation with time from referral to consultant contact typically occurring within 24 hours (72%). Consultations were completed evenly via email (46%) and via phone (54%). Of the 216 prescribers, 21 (9.7%) reported using the line and 20/21 (95%) of those who did found it always helpful. Two of 48 nonprescribers (4.1%) used the CCC, both reporting satisfaction. However, 24/216 (11.1%) of prescribers and 6/48 (12.5%) nonprescribers noted they were not aware of the CCC despite signing up with this it listed as a benefit, over 12 emails detailing the service and reminders at every biweekly ECHO session.

**DISCUSSION:** Reducing barriers to clozapine underuse is vitally important. The CHAMPION ECHO aimed to improve mastery and address gaps in education while helping to ease logistical hurdles surrounding blood draws and continuity of care are the focus of study in the CHAMPION ECHO project. This data suggests that a consultation line may be a useful tool to assist with clozapine initiatives but was not widely used and despite our best efforts as 1/10 of both prescribers and nonprescribers were unaware of this service. Nonetheless for those who used the CCC they were highly satisfied and found it helpful. Future initiatives with phone consultation lines should consider ways to increase awareness and use.

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**T47. Use of Point of Care Absolute Neutrophil Count Monitoring During a Randomized Controlled Trial of a Tele-Mentoring Program, Project Echo, to Increase Clozapine Prescribing**

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**BACKGROUND:** Clozapine has been repeatedly shown to have superior efficacy and effectiveness in treatment-resistant schizophrenia and is the only antipsychotic with a Food and Drug Administration (FDA) indication for reducing suicidality in schizophrenia. Despite superior efficacy and outcomes for many patients, clozapine is prescribed infrequently in the United States (US). While there are many barriers to prescribing clozapine, two primary ones are the logistics related to performing the required absolute neutrophil count (ANC) monitoring and the lack of prescriber knowledge and self-reported competence about how to use clozapine.
**METHODS:** In a randomized controlled design, we tested the effectiveness of a 12-month educational based clozapine intervention, Clozapine CHAMPION-ECHO (Center for Help and Assistance for Maryland Prescribers- Improving Outcomes Network using Extension for Community Healthcare Outcomes, which consisted of 26 biweekly tele-mentoring sessions. This was compared to an enhanced treatment as usual (eTAU) condition with all sites offered FDA-cleared ANC point of care (POC) monitoring devices and access provided to a State-wide CHAMPION consultation line. We provided the Athelas One device to provide easy and immediate ANC results needed for the mandatory FDA monitoring requirements associated with clozapine prescribing. All study sites were also offered a laptop and materials for the Athelas. At baseline and endpoint, prescribers were assessed for self-rated clozapine knowledge and competence and use of, and results of ANC tests were recorded from the devices. Competencies were measured by a 100 mm visual analog scale (100 representing most competent). Here we report prescriber competence and attitudes about blood draw-related barriers to clozapine prescribing and use of the POC devices. We examined 3 periods for analysis: an introductory period of 11 months during which the POC devices were offered and implemented prior to the intervention period, 12 months during the intervention period, and the 12-month period after the intervention concluded.
**RESULTS:** Of the 277 prescribers at study entry (N=132 ECHO; N=145 eTAU), 65% reported that patients' unwillingness to complete blood draws was a barrier to clozapine prescribing. A total of 53% reported that logistical challenges for patients to complete blood draws and 26% reported a lack of on-site staff to complete blood draws were also significant barriers to prescribing clozapine. At baseline, however, among the 27 competencies rated, the ability of prescribers to monitor ANC was one of the highest rated with a mean score of 72.6 ± 25.6. On the other hand, one of the lowest-rated competencies by prescribers was their ability to recognize

benign ethnic neutropenia (mean 48.3 ± 27.8) and to understand how to develop a plan of treatment when severe neutropenia occurs (mean 45.8 ± 27.5). With regard to the POC devices, 72% of sites participating in the CHAMPION study (38/53) accepted the Athelas One device and 36 (95%) used it at least once during the introductory period. During the ECHO intervention period, 6/18 (33%) sites in the ECHO condition used the device a mean of 221.3 (+ 274.6) times on an average of 30.2 (+39.0) patients. This was compared to 10/20 (50%) sites in the eTAU condition that used the device a mean of 67.3 (+ 91.2) times on an average of 9.0 (+8.9) patients. During the 1-year follow-up period, N=6/18 (33%) sites in the ECHO condition used the device a mean of 374.8 (+394.4) times on an average of 42.2 (+46.9) patients. This was compared to N=9/20 (45%) sites in the control condition that used the device a mean of 110.7 (+78.4) times on an average of 13.9 (+9.8) patients. At endpoint, 71/225 (31.6%) prescribers self-reported they were using the POC device, which did not differ by group (p=0.81). A total of 76% (54/71) of prescribers rated the Athelas One device as moderately to extremely important in their decision to prescribe clozapine, and 29% (66/225) reported the device was used to initiate new patients, which did not differ by group (p=0.14 and p=0.85, respectively). Among prescribers who reported using the device, a total of 97% reported satisfaction with it which also did not differ by group (p=0.89). With regard to the use of the POC device across the study periods and conditions, 94.8- 98.8% of ANC's monitored were in the normal range; 1.2-4.3% showed mild neutropenia, 0.6-0.7% showed moderate neutropenia, and there was only one instance of severe neutropenia detected.

**DISCUSSION:** The most commonly reported barriers to the use of clozapine are around the issues of blood draw logistics. About three-quarters of prescribers think the POC device aided in their decision to use clozapine and about one-third stated it was used to initiate new patients. Sites assigned to the ECHO condition used the Athelas One device on more patients than did the eTAU sites. We will present data on the impact of the Athelas One device on clozapine prescribing across groups.

## T48. Interoceptive Predictive Coding in Psychosis: Psychometric Functioning and Bayesian Modeling of Heat-Based Behavior

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**BACKGROUND:** Internal body states (heartbeats, temperature) shape our experience of self and the world. For example, a racing heart can influence our judgment of a stranger as hostile. Thus, accurate detection, integration, and interpretation of internal body states, termed interoception, is essential. Interoception is hypothesized as disrupted in psychosis. For example, interoceptive accuracy tasks (e.g., heartbeat counting) have revealed poor detection of internal body states in psychosis-spectrum samples. However, manipulation of internal body states during predictive coding experiments is necessary to move beyond descriptive work, to elucidate subprocesses of disrupted interoception. Toward this goal, the current study employs a novel Interoceptive Conditioning (IC) task with non-painful heat stimuli, modeled after Powers and colleagues (2017) Conditioned Hallucination task.

**METHODS:** A community-based psychosis-spectrum sample (ages 18-40), with wide-ranging psychosis symptoms, is currently being recruited. In the IC task, first, a visual cue (CS) is repeatedly paired with a non-painful heat stimulus (US), establishing a 'prior belief' about their association. Second, in a testing phase, the strength of the 'prior belief' is examined by presenting the visual cue with an increasing number of subthreshold or no heat (unpaired) stimuli. Each trial, participants report if they perceived a heat stimulus and confidence of that judgement. Critically, this captures conditioned interoceptive responses (i.e., false detection of heat stimuli when none is delivered) as well as weighting and updating of the instantiated 'prior belief' in an unpredictable environment.
**RESULTS:** Current analyses examine psychometric properties of heat stimuli (Aim 1) and feasibility of a Bayesian hierarchical Gaussian filter (HGF) model for capturing task behavior (Aim 2). Toward aim 1, I will compare fit of a Weibull and logistic function on a range of stimuli (33-40°C), with a focus on reliability of slope and threshold estimates for identifying individualized heat intensities (e.g., 75%, 50%, and 25% likelihood of detection). These intensities are subsequently used in the experimental portion of the task. Toward aim 2, prior predictive checks will evaluate feasibility of the HGF model for the IC task, by sampling from prior distributions to examine whether a range of parameters produce plausible behavioral outcomes consistent with experimental expectations.
**DISCUSSION:** The application of predictive coding to interoception has been neglected, despite theoretical evidence linking strong interoceptive 'priors' to false perceptions (hallucinations) and formation of false beliefs (delusions) that fail to reflect the environment. This gap partly stems from a lack of experimental control over interoceptive stimuli, which is here addressed by the precise delivery of non-painful heat stimuli as a homeostasis-relevant perturbation. Thus, the IC task holds promise to yield mechanistic insights to disrupted interoception in psychosis-spectrum samples. Furthermore, the current analysis contributes to clinical science at large by presenting on the utility of non-painful heat stimuli as an interoceptive probe of predictive coding.

## T49. Digital Phenotyping and Serious Mental Disorders, Predicting Symptom Re-Emergence and Relapse Among Slum Residents in Dhaka, Bangladesh: A Machine Learning Study

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**BACKGROUND:** Digital phenotyping (DP) represents a promising avenue for monitoring psychotic disorders such as schizophrenia through passive data collection from smartphones. However, its implementation in low- and middle-income countries (LMICs), particularly in underserved slum communities, has not been fully explored. In Dhaka, Bangladesh, the Korail slum is home to a significant population that owns and uses smartphones with cellular data, and experiences high levels of mental health disorders, exacerbated by extreme poverty, overcrowded living conditions, and limited access to mental health services. This abstract pools findings from a qualitative study investigating the awareness and acceptance of DP in these

communities and outlines a prospective cohort study designed to leverage these findings to predict mental health relapse using smartphone-based DP.
**METHODS:** Eight focus group discussions (FGDs) with 38 participants were conducted to explore the awareness, acceptance, and perceived utility of DP for mental health monitoring among residents of the Korail slum in Dhaka, Bangladesh. Participants included individuals diagnosed with serious mental disorders (schizophrenia, bipolar disorder and major depressive disorder) and their caregivers.

The study design allowed us to design a six-month prospective cohort study to explore the feasibility and accuracy of using DP to predict relapse in individuals with SMDs. Passive data streams, such as sleep patterns, mobility, and social interactions, will be continuously monitored via smartphones, and machine learning algorithms will be used to identify early warning signs of relapse. Active data, including regular symptom assessments and quality-of-life surveys, will also be collected.

**RESULTS:** The qualitative study revealed that while smartphones are widely used, there was limited awareness of digital tools for mental health monitoring. Participants initially associated DP with government surveillance or privacy concerns. Once explained, DP was recognized as potentially beneficial for managing mental health and reducing hospital visits. However, barriers such as privacy concerns, the digital divide (technological literacy issues), and shared smartphone use (only 45% of participants owned smartphones; 92% relied on shared devices) were significant. Participants were more open to sharing non-intrusive data but wary of sharing personal communications. Caregivers saw value in DP for providing real-time alerts indicating possible relapse. Future interventions may need family-centered monitoring systems or technologies to differentiate between users on shared devices.
**DISCUSSION:** The qualitative findings from this study emphasize the cultural and practical challenges of introducing DP in low-resource settings. Despite initial concerns about privacy and data misuse, participants showed a willingness to engage with DP tools once they understood the potential benefits, such as reducing hospital visits and providing real-time monitoring of mental health conditions. Privacy and data security concerns were prevalent, with participants particularly wary of sharing personal communication data, although they were more comfortable sharing non-intrusive information like location and app usage. Additionally, the digital divide emerged as a significant barrier, with older adults struggling with the technological literacy needed to engage with DP tools. The normalization of shared smartphone use within families also presents a challenge, as DP often requires individual data for accurate monitoring. These findings underscore the need for tailored educational programs and transparent communication about data usage to build trust in DP systems in impoverished settings.

The primary objective of the prospective cohort study is to validate whether DP can reliably predict relapse among schizophrenia in a low-resource setting like Korail. By integrating both active and passive data types, predictive models will be developed to provide a comprehensive and accurate forecast of relapse risk. Secondary objectives include evaluating participants' engagement with DP tools and examining the practical challenges of implementing DP in slum communities. Broader implications for LMICs include the potential of DP to bridge the mental

health care gap in settings with a high prevalence of mental health disorders and inadequate health infrastructure. For successful DP implementation in LMICs, cultural context, privacy concerns, and user education must be carefully considered. Ultimately, this study aims to contribute to the growing body of evidence supporting DP as a cost-effective and scalable solution for mental health monitoring in low-resource settings, improving access to mental health care for vulnerable populations like those in Dhaka's Korail slum.

## T50. Machine Learning for Personalized Treatments in Schizophrenia

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**BACKGROUND:** The heterogeneity of schizophrenia-spectrum disorders (hereafter schizophrenia) means that treatment regimens need to be tailored to the clinical situations of these individuals and adds complexity when determining the effectiveness of different psychotropic medications. Observational data has a wealth of information on regimens commonly prescribed to individuals with schizophrenia and can inform more personalized treatments that are prohibitively complex to test via clinical trials. We used Medicaid claims data to identify a national cohort of Medicaid recipients diagnosed with schizophrenia. Within this cohort, we used machine-learning to identify data driven clusters of distinct psychiatric comorbidity phenotypes and unique medication clusters (pharmacophenotypes) used by the individuals within the phenotypes.
**METHODS:** We selected Medicaid claims national data because Medicaid is one of the largest providers of healthcare coverage for individuals with schizophrenia in the US. Over one year we identified 306,955 individuals who met established criteria for schizophrenia, that is ≥1 inpatient admission and/or ≥2 outpatient visits with the principal or secondary diagnoses of a schizophrenia spectrum disorder (ICD9 295.xx). We used unsupervised machine learning, a type of artificial intelligence, specifically Latent Dirichlet Allocation (LDA) or topic modeling, incorporating all behavioral health comorbidities (features) to identify phenotypes (clusters). Within each phenotype we then used topic modeling to identify distinct clusters (pharmocophenotypes) of psychotropic medications they used. The LDA models integrated a principal components analysis (PCA) to validate the topic modeling results. Demographic characteristics including mean age, sex at birth, and ethnoracial group were identified for all phenotypes and pharmacophenotypes.
**RESULTS:** The analysis classified individuals with schizophrenia into 5 clinically meaningful distinct phenotypes: depression, substance use, bipolar, anxiety, and conduct disorders/developmentally delayed. A sixth phenotype included individuals with only schizophrenia diagnoses. Construct validity was demonstrated when comparing the demographic characteristics between these groups, which were all significantly different. Within each of the 6 phenotypes the analysis identified 3 to 5 distinct pharmacophenotypes used by individuals that also had significantly different demographic characteristics. As an exploratory analysis we tested whether these different pharmacophenotypes had different odds of any psychiatric inpatient admission in the year after the baseline period within each phenotype. We found that all

pharmacophenotypes did have significantly different likelihoods of an inpatient admission when compared to taking no medications; the same was also found between the comorbidity phenotypes.
**DISCUSSION:** This study found that individuals with schizophrenia receiving coverage by Medicaid belong to 6 distinct comorbid profiles. This study demonstrates the feasibility of using machine learning with claims data to identify clinical phenotypes among individuals with schizophrenia and their associated pharmacophenotypes. The exploratory analysis revealed that some pharmacophenotypes may be associated with a lower likelihood of a psychiatric inpatient admission within the year following the baseline period. A subsequent pharmacoepidemiologic investigation will use the results of these analyses to compare the effectiveness of psychotropic regimens for the schizophrenia phenotypes, which will facilitate future efforts to tailor treatments for people with schizophrenia.

## T51. Subtyping First-Episode Psychosis Based on Longitudinal Symptom Trajectories Using Machine Learning

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**BACKGROUND:** Clinical course after first episode psychosis (FEP) is heterogeneous. In order to improve personalized treatment planning and the development of novel treatments targeting specific symptom trajectories, it would be of value to determine if trajectories of positive and negative symptoms after FEP could be parsed into coherent subgroups. Furthermore, it would be useful to determine if membership in one of these putative subgroups could be predicted based on data available near the start of treatment. This would enable clinicians to proactively allocate resources and modify treatment plans in a manner that is patient- or person-centered. While previous studies have looked at illness trajectory at a group level, or compared treatment-resistant schizophrenia with non-resistant groups, there is less research on symptom trajectory subgroups during treatment for a first episode psychosis. Here, we set out to determine if clear symptom trajectory subgroups exist after first episode psychosis, and if these can be predicted using baseline data.
**METHODS:** The dataset for this study comes from the Prevention and Early Intervention for Psychosis Program (PEPP) in Montreal, Canada, which serves individuals experiencing FEP. The dataset includes 695 individuals aged 14 to 35 years (mean age 23.64 ((4.77)); 69.9% are male. Of these, 411 patients had sufficient data across the two year follow-up to be included in the analysis. We utilized k-means clustering to identify distinct clusters of 411 FEP patients based on longitudinal positive and negative symptom patterns (SAPS and SANS scores). Ridge logistic regression and SHapley Additive exPlanations (SHAP) were then used to identify predictors of cluster membership using baseline data. Antipsychotics were standardized into chlorpromazine equivalents (CE). We employed the MissForest package for data imputation.
**RESULTS:** Three clusters were identified, demonstrating unique demographic, clinical and treatment response profiles. Cluster 1 exhibits lower positive and negative symptoms (LS), lower

antipsychotic dose, and relatively higher affective psychosis; Cluster 2 shows lower positive symptoms, persistent negative symptoms (LPPN), and intermediate antipsychotic doses; Cluster 3 presents persistently high levels of both positive and negative symptoms (PPNS), as well as higher antipsychotic doses. We effectively predicted patients' cluster membership (AUC of 0.74). The most important predictive features included contrasting trends of apathy, affective flattening, and anhedonia for the LS and LPPN clusters. Global hallucination severity, positive thought disorder and manic hostility predicted PPNS. Medication trajectories also differed between the clusters, with the LS group having low and reducing CE over time and the other groups demonstrating higher CE.
**DISCUSSION:** Using machine learning, we identified three clusters of psychotic symptom trajectories after a FEP, each characterized by unique demographics, illness histories, longitudinal symptom patterns and prescribed antipsychotic doses. Furthermore, we have demonstrated that it is possible to predict membership in a longitudinal symptom cluster using data available upon entry into a clinic. These findings may eventually allow clinicians to identify patients at risk for less favorable illness trajectories earlier in treatment, allowing for the modification of treatment plans and the assignment of clinical resources to better meet expected individual patient needs. In addition, the subgroups detailed here could serve as targets for the development of novel, personalized treatment approaches, based on further neurobiological and psychosocial research into the etiology of each subgroup. To our knowledge, ours is the first study to identify symptom trajectory clusters in a longitudinal first episode sample based on both positive and negative symptoms, and to predict membership in these clusters using symptom data available solely at baseline.

## T52. Simulating Thought Disorder: Fine-Tuning Llama-2 for Synthetic Speech in Schizophrenia

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**BACKGROUND:** Individuals with schizophrenia (SZ) frequently experience formal thought disorder (FTD), characterized by disturbances in thinking and speech. Clinically, FTD is measured through interactions between patients and clinicians or, more recently, with natural language processing (NLP) tools. However, data availability remains a significant challenge due to the privacy-sensitive nature of patient speech. Synthetic language generation provides a promising avenue to address this issue, enabling in silico experiments that can advance understanding, detection, and potential treatment of FTD
**METHODS:** To generate synthetic speech reflective of FTD, we fine-tuned two models derived from the open-source Llama-2-7B foundation model. The training utilized 150 transcripts from healthy controls (HC) and 325 from individuals with SZ, sourced from prior studies employing the DISCOURSE speech protocol and the thematic apperception task. Before training, transcripts were preprocessed into question-response pairs. A total of 1,200 synthetic transcripts (600 per model) were generated. The synthetic outputs were evaluated using variance of word-to-word distance and pseudo-perplexity derived from BeRT, two computational linguistic metrics

identified as clinically significant in prior literature. These metrics were compared across synthetic outputs (HC vs. SZ models) and against real-world clinical data.
**RESULTS:** Comparison of model outputs revealed distinct linguistic patterns consistent with FTD-related disruptions. The variance in word-to-word distance increased by 22.7% ($p < 0.001$) in synthetic transcripts generated by the SZ model compared to the HC model. In real-world data, a smaller increase of 8.3% was observed between SZ and HC interviews. For pseudo-perplexity, the SZ model exhibited a 46.4% increase ($p < 0.001$) relative to the HC model, compared to a 77.1% increase in real-world SZ data. These findings suggest that the synthetic SZ model effectively emulates linguistic disturbances associated with FTD while also reflecting unique, model-specific properties.
**DISCUSSION:** The observed similarities and differences between synthetic and real-world data highlight the potential of large language models for simulating disordered speech. While the synthetic SZ model approximates clinical features of FTD, deviations in specific metrics may stem from limitations in data representation or the fine-tuning process. Future refinements could enhance the models' ability to accurately replicate the linguistic phenomena of FTD. Potential applications include augmenting datasets for training diagnostic tools, generating controlled scenarios for in silico experiments, and creating educational materials for clinician training. These findings underscore the utility of NLP tools in advancing computational psychiatry and offer a novel avenue for studying thought disorders in schizophrenia.

## T53. The Effect Of Semaglutide On Antipsychotic-Induced Weight Gain And Other Metabolic Variables, Among A Cohort Of Inpatients At The Centre For Addiction And Mental Health: A Chart Review

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**BACKGROUND:** Individuals with severe mental illnesses including schizophrenia spectrum disorders (SSDs), major depressive disorder, and bipolar disorder, have a significantly reduced life expectancy of 15-20 years when compared to the general population due to cardiovascular disease. While antipsychotic (AP) drugs remain the cornerstone of treatment for SSDs, their use is associated with significant metabolic disruptions including weight gain, dyslipidemia and type 2 diabetes among others. At present, metformin is recommended as an appropriate first line pharmacological intervention in the context of AP-induced weight gain and dysmetabolism. However, close to 20% of individuals fail to respond to metformin, with limited evidence supporting alternative pharmacological interventions. Although evidence is still emerging, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown efficacy and tolerability in SSDs. The current evidence is based on older, daily injectable agents, while efficacy and safety of newer and more promising medications, such as once weekly semaglutide, is lacking. This study aimed to explore the effectiveness of semaglutide over time, to help draw evidence-based conclusions from a sample of patients located in a controlled, hospital setting.
**METHODS:** A retrospective chart review was conducted examining psychiatric inpatients taking APs who have been initiated on semaglutide injections between 2018, post semaglutide

approval in Canada and 2024 at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. All demographic, metabolic and anthropometric data were collected until they were discharged from the hospital, as long as they were within our protocol's approved timeframe. Given loss to follow-up post hospital discharge, only data from baseline, 3, 6, 9 and 12 months were analyzed. All demographic data have been shown either as a mean with standard deviation or as a percentage, while all model-specific data have been shown as a mean with their respective standard errors.
**RESULTS:** A total of 47 patients were included in our analysis, with a mean age of 42.96 years ±13.23 years. Among this cohort, 59.6% were male, 85.1% of the sample was diagnosed with either schizophrenia or schizoaffective disorder and 66% of the sample was noted to have Type 2 diabetes at baseline. The mean weight was 113.15 ± 30.71 kg with a BMI of 40.18 ± 10.31 kg/m2. and a mean HbA1c of 7.3± 2.1% at baseline. Patients were on a mean semaglutide dose of 0.25 ± 0.18 mg/week at initiation (N=47), 0.90 ± 0.34 mg/week at 3 months (N=47), 1.23 ± 0.49 mg/week at 6 months (N=24), 1.12 ± 0.45 mg/week at 9 months (N=15), and 1.36 ± 0.55 mg/week at 12 months of follow up (N=11). The maximum dose that individuals were titrated to was 2 mg/week. After initiation of semaglutide and following adjustment of age, sex and baseline weight, a significant weight change was noted over time ($p < 0.001$). There was a mean weight loss of 3.15 ± 0.74 kg at 3 months ($p < 0.001$), 7.66 ± 1.04 kg ($p < 0.001$) at 6 months, 9.45 ± 1.62 kg ($p < 0.001$) at 9 months, and 12.71 ± 2.52 kg ($p < 0.001$) at 12 months. Additionally, a significant change from baseline was seen in HbA1c levels at all timepoints ($p < 0.001$) with a mean reduction of 1.0± 0.2% at 3 months (N=23), 1.2± 0.3% at 6 months (N=16), 1.4 ± 0.3% at 9 months (N=11), and 1.3± 0.2% at 12 months (N=10). There were also improvements seen in lipid parameters in the cohort such as in triglycerides levels. While there were no major adverse events reported in this cohort, commonly occurring side effects included nausea and diarrhea, which however did not result in treatment discontinuation.
**DISCUSSION:** This retrospective chart review offers both clinical and research insights, in relation to the effectiveness of semaglutide among individuals with severe mental illnesses and metabolic comorbidity. The study findings showcase the potential of semaglutide in antipsychotic-induced weight gain, with minimal side effects. Given these findings, studies involving semaglutide with both a larger sample size and the higher approved dose of semaglutide for chronic weight management are warranted.

## T54. Effects of Independent Versus Dependent Stressful Life Events on Major Symptom Domains of Schizophrenia

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**BACKGROUND:** Stressful life events (SLEs) are associated with schizophrenia spectrum disorders (SSD) but the causal relationship between SLEs and SSD symptom domains remain unclear. We evaluated two models to link (SLEs) with the psychopathology of SSD.
**METHODS:** We separated SLEs into independent (iSLEs, unlikely influenced by one's behavior) and dependent (dSLEs, likely influenced by one's behavior). Stress-diathesis and stress generation models were evaluated for the relationship between total, i- and d- SLEs and the severity of positive, negative, and depressive symptoms in participants with SSD. Participants with SSD (n = 286; 196 males; age = 37.5 ± 13.5 years) and community controls (n = 121; 83 males; 35.4 ± 13.9 years) completed self-report of lifetime negative total, i- and d-SLEs.
**RESULTS:** Participants with SSD reported a significantly higher number of total SLEs compared to controls (B = 1.11, p = 6.4 × 10–6). Positive symptom severity was positively associated with the total number of SLEs (β = 0.20, p = 0.001). iSLEs (β = 0.11, p = 0.09) and dSLEs (β = 0.21, p = 0.0006) showed similar association with positive symptoms (p = 0.16) suggesting stress-diathesis effects. Negative symptom severity was negatively associated with the number of SLEs (β = –0.19, p = 0.003) and dSLEs (β = −0.20, p = 0.001) but not iSLEs (β = –0.04, p = 0.52), suggesting stress generation effects. Depressive symptom severity was positively associated with SLEs (β = 0.34, p = 1.0 × 10–8), and the association was not statistically stronger for dSLEs (β = 0.33, p = 2.7 × 10–8) than iSLEs (β = 0.21, p = 0.0006), p = 0.085, suggesting stress-diathesis effects.
**DISCUSSION:** The SLE – symptom relationships in SSD may be attributed to stress generation or stress-diathesis, depending on symptom domain. Findings call for a domain-specific approach to clinical intervention for SLEs in SSD.

## T55. Introducing the Mape: A New Tool for Measuring Real-Time Psychotic Symptoms

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**BACKGROUND:** Traditional assessments of psychotic symptoms often measure their presence over the lifetime or over extended timeframes (e.g., "in the past month/week"). Recent studies using ecological momentary assessment (EMA) have shown that psychotic symptoms can fluctuate not only daily but moment to moment.

Current methods, however, fail to capture real-time symptoms during clinical interactions or research tasks, limiting our ability to truly relate specific symptoms to patient outcomes and task performance.

To address this gap, we developed the Momentary Assessment of Psychotic Experiences (MAPE), a self-report questionnaire designed to measure in-the-moment psychotic symptoms across the psychosis continuum.

**METHODS:** The MAPE was developed following Rosellini and Brown's (2021) guidelines: identifying and defining target constructs, reviewing literature, developing items, and conducting exploratory and confirmatory validation, as well as validity evaluations.

Convergent validity in community samples was assessed using the Paranoia Scale, Magical Ideation Scale (MIS), Revised Hallucinations Scale (RHS), and Revised Social Anhedonia Scale. Concurrent validity in clinical samples was evaluated using the Scale for the Assessment of Positive (SAPS) and Negative Symptoms (SANS).

Validation was conducted in four community samples (N = 3,556) and is ongoing in a clinical sample of individuals with psychotic disorders (N = 33).

**RESULTS:** Exploratory analysis (N = 1,032) identified five symptom clusters: unusual thoughts/sensory experiences, amotivation/anhedonia, negative affect, paranoia, and social anhedonia. The model showed excellent fit (TLI = 0.92, RMSR = 0.02, RMSEA = 0.065, 90% CI [0.062, 0.068]).

Confirmatory Study 1 (N = 918) supported this structure, with excellent fit (CFI = .99, TLI = .98, RMSEA = .05, SRMR = .03) and strong internal consistency (omegas ≥ 0.89). Studies 2 (N = 857) and 3 (N = 796) confirmed these results with similarly strong fit indices (CFIs = .99, .92; TLIs = .99, .99; RMSEAs = .05, .04; SRMRs = .03, .03) and internal consistency (omegas ≥ 0.77).

The MAPE demonstrated good convergent validity in Studies 1 and 2:

- Paranoia and Paranoia Scale (rs = .50–.51, ps < .001)
- Unusual experiences and MIS (rs = .47, ps < .001)
- Unusual experiences and RHS (rs = .46–.50, ps < .001)
- Social anhedonia and Revised Social Anhedonia Scale (rs = .58–.53, ps < .001).

In the clinical validation study, current results are consistent with the community sample, showing excellent fit (CFI = .99, TLI = .99, RMSEA = .03, SRMR = .06) and internal consistency (omegas ≥ 0.87). Concurrent validity in the clinical sample is also strong:

- Unusual experiences and SAPS hallucinations (r = .55, p < .001) and delusions (r = .48, p = .01)
- Paranoia and SAPS delusions (r = .53, p < .001)
- Amotivation/anhedonia and SANS avolition/apathy (r = .41, p = .02) and anhedonia (r = .53, p < .001)
- Social anhedonia and SANS asociality (r = .35, p = .05).

**DISCUSSION:** The MAPE is a novel tool for assessing real-time psychotic symptoms, capturing momentary fluctuations across the psychosis continuum. This tool has significant utility: Clinically, it enables efficient symptom check-ins, potentially replacing lengthy interviews, and may serve as a quick screening tool in primary care settings to aid in early detection. For research, the MAPE provides a means to link current symptoms directly to experimental outcomes, such as MRI or task performance, offering greater accuracy than retrospective clinical interviews conducted days or weeks before testing. These applications underscore the MAPE's potential to enhance clinical care and research precision in psychosis.

## T56. Parental Mental Health Does not Explain the Relation Between Childhood Trauma and Psychosis

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**BACKGROUND:** Childhood trauma (CT) increases the risk for schizophrenia spectrum disorders (SSDs) and the severity of psychosis symptoms. CT includes physical abuse and neglect, emotional abuse and neglect, and sexual abuse. Mechanisms involved in the relation between CT and SSDs are to date unresolved, and it is imperative for the prevention of psychosis to examine the possible influence of parental mental health problems (MHP) on the relationship between CT and psychosis. Is there a direct relationship between CT and SSDs independent of parents' mental health problems, or is CT more of a marker of genetic vulnerability through parental mental health? The present study aimed to examine the moderating effect of parental mental health on CT and psychosis in SSDs. We hypothesized a dose-dependent positive association between CT severity and psychosis symptom severity not moderated by parental MHP.
**METHODS:** Patients with SSDs (ICD-10: F20-29) (N = 133) from the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) study were included and assessed for CT (Childhood Trauma Questionnaire - Short Form; CTQ-SF), psychosis symptoms (The Positive and Negative Syndrome Scale; PANSS) and parental MHP (focused patient interviews). Data was analyzed by means of linear regression analyses using the following dependent variables 1) PANSS total scale, 2) PANSS subscales (positive, negative, general psychopathology), 3) PANSS items P1(delusions) and P3 (hallucinations). P1 and P3 were used as outcomes to examine specific psychosis symptoms. Age, sex, parental mental health, CTQ-SF sum score, and the interaction between parental MHP and the CTQ-SF sum score were included as independent variables.
**RESULTS:** One-fourth of the patients (36 of 133 [27%]) reported mental health problems in their parents. More patients in the CT group were diagnosed with schizophrenia, and the CT

group showed higher PANSS total, positive and negative subscale scores, and more severe symptoms of depression. Regression analyses showed a dose-response relationship between CT and overall psychosis symptoms and negative symptom severity. Inclusion of the interaction parental mental health x CT showed that the association between CT and psychosis symptom severity was independent, and not moderated, by parental MHP.
**DISCUSSION:** Parental MHP was not found to moderate the association of CT and psychosis severity in our sample. We found a dose-dependent association between CT and psychosis symptom severity in SSDs, especially for the PANSS total and negative subscale scores. Our results are consistent with other studies showing dose-response relations between severity of CT and severity of psychosis symptoms, and studies controlling for shared genetic and environmental factors in the relation between CT and adult psychiatric disorders. The current results are further supported by previous studies emphasizing CT as a risk factor for SSDs, and research showing that a reverse association is unlikely. The present study has several limitations: The study is based on a sample from pragmatic cross-sectional data, which entails that we cannot ascertain neither causal direction nor the possibility of other confounding variables, but in return provides improved external validity. Further, the assessment of parental mental health was based on the assessment by the included patients, not diagnosis from the parents' medical records. In sum, the relationship between CT and psychosis was not explained by parental mental health, suggesting that CT has an independent and true effect on psychosis symptoms in a dose-dependent manner.

## T57. Risk Profiles Shortly Before Suicide Mortality in Patients With Schizophrenia Across the Life Span

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**BACKGROUND:** Patients with schizophrenia face a heightened risk of suicide mortality. However, research on suicide risk profiles across different age groups has been limited, likely due to small sample sizes. In this study, we examined both suicide mortality rates and risk profiles across various age subgroups ( < 25, 25-34, 35-44, 45-54, 55-64, ≥65 years) using data from an Asian cohort of individuals with schizophrenia.
**METHODS:** This study utilized data from Taiwan's National Health Insurance Research Database, covering the period from January 1, 2000, to December 31, 2019, and included a cohort of 195,787 patients with schizophrenia. Among them, 3,848 died by suicide during the study period. Using an age-stratified nested case-control design, each case was matched with four living controls from the cohort based on age, sex, and the year of first schizophrenia diagnosis, using risk set sampling. The standardized mortality ratio (SMR) was calculated as the ratio of observed deaths in the schizophrenia cohort to the expected deaths in the general population. Conditional logistic regression was employed to estimate age-stratified risks associated with demographics, psychiatric, and physical illnesses.
**RESULTS:** The SMR was found to be highest in individuals under 25 years old (52.8) and declined with age, with those over 65 having an SMR of 3.4. Suicide cases had a higher rate of

unemployment compared to controls in the 25-64 age group. Regarding psychiatric comorbidities, the case group exhibited significantly higher risks of depressive and sleep disorders shortly before suicide across all age groups. Additionally, drug- and alcohol-induced mental disorders were significantly associated with suicide, but only in those younger than 54. Several physical illnesses, such as other forms of heart disease, pneumonia, and moderate to severe renal disease, were identified as risk factors for suicide in individuals younger than 64.
**DISCUSSION:** Suicide risk was notably elevated in patients with schizophrenia, with the highest risk observed among younger individuals. However, specific risk factors for suicide varied across different age subgroups. These findings could inform the optimization of healthcare intervention strategies tailored to prevent suicide in schizophrenia patients at various stages of life.

## T58. Insight Paradox Revisited: A Longitudinal Study of Insight, Depression, and Suicidality in First-Episode Psychosis

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**BACKGROUND:** Understanding the relationship between insight, depression, and suicidality in first-episode psychosis (FEP) is crucial for improving clinical outcomes and preventing suicide during early treatment stages.
**METHODS:** This longitudinal cohort study examined 264 participants enrolled in coordinated specialty care (CSC) services for FEP to investigate how insight and depression at admission impact suicidality at 6 and 12 months, assess the mediating role of depression at admission between insight and suicidality, and evaluate the persistence of depression over time. Regression analyses assessed the relationships among these variables, while mediation analyses explored the mediating effect of depression at admission. Additional exploratory analyses were conducted to evaluate for effect modification by demographic variables.
**RESULTS:** After controlling for covariates (i.e., previous suicide attempts, positive symptoms, substance use, global functioning, DUP), significant predictors of suicidality at 6 months were insight (OR 0.71, 95% CI: 0.53 - 0.94), depression (OR 5.40, 95% CI: 2.45 - 12.61), and previous suicide attempts (OR 2.91, 95% CI: 1.21 - 7.00). At 12 months, insight (OR 0.70, 95% CI: 0.52 - 0.92) and depression (OR 2.82, 95% CI: 1.26 - 6.50) remained significant. Depression at admission mediated 27.32% of the effect of insight on suicidality at 6 months and 19.76% at 12 months. This effect was stronger for males than females. Despite a general decrease in depressive symptoms, a subset of participants remained persistently depressed.
**DISCUSSION:** The study highlights the significant mediating role of depression at admission in the relationship between insight and suicidality, identifying it as the strongest predictor of suicidality. Early detection and treatment of depression in FEP should be prioritized, and further research should focus on targeted interventions within CSC.

## T59. Feasibility and Acceptability of Group-Based Resiliency Training in an Early Psychosis Intervention Program Co-Led by Peer and Physician

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**BACKGROUND:** Multidisciplinary early psychosis intervention programs improve overall mental health outcomes and quality of life for affected individuals. In the U.S., NAVIGATE is an exemplary model of such services, as it has been shown to increase work and school participation, decrease symptoms, and enhance overall treatment engagement. A hallmark component of NAVIGATE is Individual Resiliency Training (IRT), which focuses on personal strengths, individualized goals, education and skills training around understanding illness, and building resiliency. Studies also show the importance of peer support and that group-based interventions may have a larger effect size compared to individual treatment in those with psychotic illness.
**METHODS:** To combine the strengths of IRT with those of group- and peer-based interventions, we developed a Group-based Resiliency Training (GRT) through adapting components of NAVIGATE's IRT 2014 manual into a group co-led by a physician and a peer with lived experience of psychosis. The intervention was delivered at the Recovery from Early Psychosis Program (REPP) at Northwestern Memorial Hospital, a multidisciplinary clinic serving 18–26-year-olds with new onset psychosis. Weekly topics were selected from the IRT manual to complement other REPP services. GRT was held virtually, and participants were urged to have cameras on for social connection. Engagement was further enhanced through socratic discussion and curriculum slides augmented with engagement tools tailored to the target audience (e.g. memes, gifs). Because robust discussion of session topics often delayed progression in planned content, an additional peer support hour was added. Feasibility and acceptability were examined through qualitative feedback surveys. Themes solicited through qualitative feedback were quantified. A Mann-Whitney U Test was used to compare mean attendance in GRT iterations.
**RESULTS:** Two iterations of GRT were held between 01/2021 and 07/2023, lasting 4-6 months each. Average group attendance increased between first (n=4.2) and second runs (n=7.0, p = 8e-5), as did total number of participants (from n=9 to n=20). Most participants surveyed (91.7%) found the group to be helpful. Social connection, discussion of shared experiences, and psychoeducation were themes most named to be benefits from the group. Most participants surveyed (67%) felt they could better pursue goals following participation in GRT. All participants surveyed provided positive feedback on the peer co-lead and the peer support hour.
**DISCUSSION:** A physician and peer co-led group intervention based on IRT were well-received by participants. Most participants felt better equipped to pursue goals after the intervention. Social connectedness, discussion of shared experiences, and psychoeducation were primary benefits. Well-received involvement of peers in the group format underscores the importance of social connection and peer support in the context of resiliency training.

## T60. Effects of Collective Physical Activities Among People With Psychotic Disorders: A Systematic Review of Randomized Controlled Trials

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**BACKGROUND:** Physical activity (PA) has demonstrated positive effects on schizophrenia spectrum and other psychotic disorders, addressing various aspects such as negative symptoms, social and cognitive functioning, comorbid anxiety and depression, and overall quality of life. While PA encompasses diverse modalities, most research has primarily focused on individual PA, leaving collective PA interventions underexplored. Notably, social participation has been identified as a key facilitator for engaging in PA. This study aims to specifically investigate the effects of collective PA compared to individual PA or no PA among individuals with schizophrenia spectrum and other psychotic disorders.
**METHODS:** This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Studies were included based on the following PICOS criteria: (1) Participants: adults diagnosed with schizophrenia spectrum or other psychotic disorders according to DSM (IV or V) or ICD criteria; (2) Interventions: collective PA interventions; (3) Comparators: a control group on a waiting list, receiving usual care, or participating in individual PA; (4) Outcomes: mental health measures (e.g., symptoms, depression, quality of life, cognitive functioning, global functioning); and (5) Study design: Randomized Controlled Trials (RCTs). Data were extracted from six databases (EBSCO, PsychNET, PubMed, Web of Science, Cochrane Trials, and EMBASE).
**RESULTS:** Thirteen RCTs involving a total of 1,251 participants were included. The findings revealed significant improvements in general symptoms in 60% of the total studies, cognitive symptoms in 80% of the total studies, and quality of life in 50% of the total studies. However, fewer than half of the studies reported significant improvements in other outcomes (positive and negative symptoms, depression, anxiety, and functioning), while some showed non-significant effects.
**DISCUSSION:** Although numerous studies have evaluated the effects of PA among individuals with schizophrenia spectrum and other psychotic disorders, limited research has focused on the specific benefits of collective PA. This review highlights the need for more robust evidence regarding collective PA's impact on mental health outcomes. Future research should prioritize collective PA interventions and examine the role of social interactions in PA to determine whether they contribute to the observed benefits. Identifying these mechanisms could provide valuable insights into designing more effective PA interventions for this population.

## T61. Provider Attitudes Towards Family Interventions for Early Psychosis: Implications for Competency-Based Training and Implementation

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**BACKGROUND:** Family interventions for psychosis (FIP; e.g., psychoeducation, single family, or multifamily group) is a defining element of first-episode psychosis (FEP) coordinated specialty care (CSC) programs, but have low adoption rates and are implemented with variable fidelity. Providers' lack of buy-in and confidence in providing evidence-based treatments compromise real-world implementation. We examined CSC provider attitudes towards providing FIP, and their associations with FIP fidelity and training.
**METHODS:** Providers from FEP CSC programs in Massachusetts completed an attitude survey comprising three subscales: 1) perceived effectiveness of FIP, 2) perceived impact of family involvement on client's treatment; and 3) stigma related to working with families. Total and subscale scores on attitude scales were correlated with program-level fidelity ratings on type and level of family involvement (i.e., provision and training in evidence-based FIP; majority of families involved in initial assessment; frequent family contact) (adapted FEP Services Fidelity Scale 2.0). We identified provider characteristics (years of experience, role, training received, type of interventions used in practice) associated with provider attitudes towards FIP. In open-ended responses, providers were also asked to identify perceived challenges in working with families in CSC and priority areas for training.
**RESULTS:** 52 providers from nine programs participated in this study (M= 39 years; 73% female; 56% white; 12% Hispanic/Latine; mean clinical experience: 4 years; 40% providing FIP). More positive FIP attitude was correlated with higher FIP fidelity (r=.29, p=.04). Provider perception of FIP effectiveness (r=.23, p=.10) and perceived positive impact of family involvement on client's treatment (r=.37, p=.01) was significantly correlated with FIP fidelity. Stigma related to working with families was not associated with FIP fidelity. Compared to other clinical team members, peer specialists had significantly less positive attitudes towards FIP (mean difference range: -0.55 to -0.77; ANOVA effect size: .39; $p < .001$) and perceived more negative impacts of family involvement on client care (mean difference: -0.96 to -1.1; effect size: .32; p=.007). Over a quarter of providers identified families' unrealistic expectations about treatment and recovery as well as balancing client autonomy and confidentiality with family involvement as the most challenging aspects of working with families in CSC. Providers requested additional training on evidence-based FIP and supervision on navigating these challenges.
**DISCUSSION:** Providers with more positive attitudes about FIP belonged to programs with higher FIP fidelity. Further work is needed to understand the finding that peer specialists had more negative attitudes towards family involvement than clinical team members. Ongoing training and supervision for the whole team could improve provider attitudes towards FIP and competency in navigating unique challenges of working with families in team-based FEP care.

## T62. Polygenic Risk Score of Glycemic Homeostasis, Type 2 Diabetes Mellitus and Clinical Components in First Episode Psychosis

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**BACKGROUND:** Patients with a first episode of psychosis (FEP) present glucose homeostasis abnormalities
even before the use of pharmacological agents. Genome-wide association studies yielded inconclusive results when assessing the relationship between the genetic risk of psychosis and that of type II diabetes mellitus (T2DM). We compared a group of FEP patients with matched healthy control participants regarding the genetic risk for glycemic homeostasis and its association with clinical variables.

**METHODS:** We examined the relationship between polygenic risk score (PRS) for Type II Diabetes Mellitus
PRST2DM, fasting glucose PRSfasting glucose, and glycated hemoglobin PRSglycated hemoglobin and two
glycemic clinical variables used in the diagnosis of T2DM: fasting glucose and glycated hemoglobin in a sample of 256 minimally treated FEP patients and 124 healthy control participants assessed at baseline and at 24-month follow up.

**RESULTS:** FEP patients and controls did not differ in terms of PRS while no significant association was

described with clinical values over the follow-up period. Marginal associations were described in FEP between PRSglycated hemoglobin fasting glucose at 24-month (p=0.069) and glycated hemoglobinover the follow-up period (p=0.075).

**DISCUSSION:** Despite the high prevalence of glucose disturbances in FEP described in the literature, only
non-significant statistical trends were observed between PRS and clinical values in the FEP group. Our negative results regarding genetic measures highlight the importance of environmental factors in the later development of glycemic abnormalities. Further research focusing on epigenetic markers might further clarify the mechanisms underlying glycemic abnormalities.

## T63. Early Detection in Coordinated Specialty Care: The Added Value of Reducing Dup to Functional Outcome

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**BACKGROUND:** Early intervention services can improve outcomes in first-episode psychosis (FEP). While Coordinated Specialty Care (CSC) models are effective, the additional impact of reducing access delays to these best-practice clinics is uncertain. This study examines the effect of reducing the Duration of Untreated Psychosis (DUP) on improved functional outcomes in CSC.

**METHODS:** We compared the functioning over one year of FEP patients admitted to one of two CSC programs from 2014 to 2019. The program for Specialized Treatment Early in Psychosis, STEP (n = 147), implemented a 4-year Early Detection (ED) campaign ('Mindmap'), while the clinic for Prevention and Recovery in Early Psychosis, PREP (n=75), continued usual detection. Linear regression was used to analyze the relationship between DUP and functional outcomes at 6- and 12 months post-admission. Mixed-effects analysis compared site differences, and mediation analysis evaluated DUP's role in these outcomes.

**RESULTS:** A shorter DUP was associated with improved Global Assessment of Functioning (GAF) and Quality of Life (QoL) scores at 6 and 12 months across both sites. STEP patients demonstrated greater improvements in GAF and QoL at 6 months compared to PREP. Shorter DUP accounted for 12% of the GAF improvement and 34% of the QoL improvement at 6 months at STEP compared to PREP. At 12 months, it accounted for 17% of GAF improvement. There was no statistically significant difference in QoL improvement between the two sites, hence no mediation effect was estimated.

**DISCUSSION:** Reducing DUP leads to additional short-term benefits beyond the effects of CSC, particularly in GAF and QoL improvements. However, this advantage was not evident after 12 months of CSC, when both groups showed similar functional improvements. While reducing DUP can hasten functional recovery in CSC, additional interventions may be required to maintain these improvements over time.

## T64. Reliability of the Nottingham Onset Schedule (NOS) in Nigerian and Bangladeshi Psychiatric Care Settings

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**BACKGROUND:** In low-and-middle-income countries (LMICs), most individuals with schizophrenia remain untreated due to scarce mental health services and medication. While significant strides have been made towards improving schizophrenia treatment, the prognosis is still poor.
The duration of untreated psychosis (DUP), the gap between the onset of psychotic symptoms and the commencement of treatment, has been associated with negative patient treatment outcomes. Reducing DUP is a priority in the treatment of schizophrenia and accurate assessment instruments are required. The Nottingham Onset Schedule (NOS) is a short, guided interview and rating schedule to capture the onset of psychosis. However, it is imperative to establish reliability in underserved populations given the subjective nature of symptoms and their cultural context. We investigate the reliability and clinical applicability of the NOS in assessing DUP in Nigerian and Bangladeshi patients with psychotic symptoms accessing psychiatric care.

**METHODS:** Participants were recruited from outpatient clinics at the University College Hospital in Ibadan, Nigeria, and the National Institute of Mental Health in Dhaka, Bangladesh. Participants were aged 18+, diagnosed with schizophrenia and living in slums without a primary substance use disorder.
The NOS was translated by two psychiatrists at each site and back-translated into English. Local and English language specialists rechecked the translation for accuracy.

Three raters at each site were trained to administer the NOS and then independently rated 20 patients at each site across prodromal (i.e., behaviour, thinking, perceptions) and psychotic symptoms (i.e., hallucinations, delusions, bizarre behaviour, positive formal thought disorder (pFTD)). The NOS was used to determine the date of definite diagnosis (DD) and the start of anti-psychotic medication (T) which were used to calculate the DUP (DD-T).

We calculated the average percentage agreement (observed) between the raters for psychotic and prodromal symptoms and inter-rater agreement using Gwets AC coefficient. For DUP, we calculated the intra-class correlation coefficient (ICC) and 95% confidence intervals. All tests were two-tailed, and the level of significance was set at 0.05.

**RESULTS:** The mean age of patients in Bangladesh was 29 (±10.3) and 41 (±13.9) in Nigeria. Ratings were high for prodromal symptoms in both Bangladesh (81%) and Nigeria (84%). For psychotic symptoms, the mean observed agreement between raters was lower than prodromal symptoms in both countries (Bangladesh 80%; Nigeria 70%). In Nigeria in particular, agreement was 'poor' for pFTD. The DUP in Bangladesh was 119 (±147) weeks with high agreement between raters (ICC= 0.81, 95% CI = 0.61 – 0.92, $p < 0.01$). The DUP in Nigeria was 283 (±268) weeks with high agreement between raters (ICC=0.97, 95% CI = 0.93 – 0.99, $p < 0.01$).

**DISCUSSION:** Results show that the translated versions of the NOS reliably measured DUP among first-episode psychosis patients. We found high agreement between raters when rating prodromal symptoms but lower for psychotic symptoms, particularly for pFTD, compared to previous literature. This indicates the difficulty in capturing certain symptoms based on patient history due to the subjectivity involved. The high inter-rater reliability across raters suggests that with comprehensive training it is possible to achieve acceptable reliability in multiple raters across multiple sites. Our findings highlight the crucial role of training and cultural adaption as they enable healthcare professionals to provide more accurate diagnosis, leading to timely interventions for patients and improved treatment outcomes. Future studies should aim to examine the reliability of the NOS in other cultural contexts.

## T65. Efficacy and Safety of Paliperidone Palmitate Long-Acting Injections in Chinese Patients With Early-, Mid-, and Late-Phase Schizophrenia

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**BACKGROUND:** Schizophrenia is a leading cause of psychiatric disability in China. Lack of adherence to antipsychotics is a major risk factor for relapse, and nonadherence is associated with increased risk of hospitalization and mortality. Long-acting injectable (LAI) antipsychotics have improved treatment adherence and continuity compared with oral antipsychotics. While some guidelines recommend the use of LAIs in early-phase patients, evidence gaps persist to support their endorsement in early-phase disease in China. This post hoc analysis evaluated efficacy and safety of once-monthly paliperidone palmitate (PP1M), an LAI antipsychotic, following early-, mid-, and late-phase use of PP1M in Chinese patients with schizophrenia.
**METHODS:** This analysis was based on data from 3 phase 4 studies (NCT01527305, NCT01947803, and NCT01685931). Chinese patients with schizophrenia (disease duration – early: ≤2 years, mid: > 2 and ≤5 years, late: > 5 years) who received at least one injection of PP1M treatment were included. The primary end point was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline (BL) to Week 13. PANSS responder rates, defined as a reduction of ≥50%, and the rate of treatment-emergent adverse events (TEAEs) were also assessed. Analysis of covariance was used to assess differences between groups with

study as a factor and BL as a covariate. The last observation carried forward (LOCF) method was used to impute missing data.
**RESULTS:** This study included 1053 patients (early: 383, mid: 290, late: 380). Mean (standard deviation [SD]) ages were 28.8 (10.1), 28.9 (9.7), and 36.6 (10.5) years, and 50.7%, 63.1%, and 51.8% were male for the early-, mid-, and late-phase groups, respectively. PANSS total scores at BL were consistent between groups (mean [SD], early: 89.6 [13.6], mid: 89.6 [13.0], late: 89.3 [13.1]).
Improvements across all groups were seen in PANSS total score from BL to Week 13 following PP1M treatment; improvements were greatest in early-phase patients (LS mean change [95% confidence interval] early: -31.6 [-34.1, -29.1], mid: -28.4 [-31.2, -25.5], late: -25.6 [-27.7, -23.4]). LS mean differences (p value) between the phases of disease were: mid versus early: 3.23 (0.2175), late versus mid: 2.78 (0.2783), and late versus early: 6.00 (0.0011).

Patient responder rates at Week 13 were 54.8% (early), 44.1% (mid), and 43.2% (late). For patients with a BL PANSS score ≤70, reductions of ≥30% and ≥50% were seen in 71.4% and 53.6% (early), 60.0% and 26.7% (mid), and 50.0% and 35.0% (late) of patients. For those with a PANSS score of 70-90, reductions of ≥30% and ≥50% were seen in 76.9% and 59.5% (early), 68.6% and 40.9% (mid), and 64.2% and 40.8% (late) of patients. For patients with a PANSS score ≥90, reductions of ≥30% and ≥50% were seen in 76.4% and 50.5% (early), 72.5% and 49.3% (mid), 69.6% and 46.4% (late) of patients. These results indicate that, regardless of BL disease severity, earlier use of PP1M appears to be advantageous.

Proportions of patients experiencing ≥1 TEAE (early: 44.3%, mid: 38.4%, late: 39.8%) and possibly related TEAEs (early: 37.1%, mid: 29.0%, late: 28.8%) were numerically higher in the early-phase group. The incidence of serious TEAEs was low (early: 2.8%, mid: 4.0%, late: 4.2%). TEAEs leading to death occurred in 1 (early), 0 (mid), and 6 (late) patients; 1 TEAE leading to death in the late-phase group was considered possibly related to the study drug.

**DISCUSSION:** The safety profile showed that PP1M was well tolerated, consistent with the previously established profile. These efficacy findings support the use of PP1M in Chinese patients with schizophrenia at all stages, but also show earlier use of PP1M is associated with greater improvements in outcomes.

## T66. The Connection of Family Communication to Psychiatric Symptoms and Beliefs of Self-Recovery Among Clients With Psychosis

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**BACKGROUND:** Conflictual family communication is a known predictor of psychosis symptom severity (Koutra et al., 2015; Koutra et al., 2016), but less is known about the interaction between service users' perceived family communication and how this may affect progress in treatment for psychosis. In particular, the impact of family communication on personal recovery – the development of hope and meaning in life – has yet to be explored. To address this, the present study investigated whether family communication moderates the effect of treatment on both psychiatric symptoms and beliefs of self-recovery.
**METHODS:** The study included 23 participants recruited from early psychosis clinics in California participating in the EPI-CAL program (9 female, Mage = 20.435, SDage = 3.97). The small sample was due to inclusion criteria that required completion of the measures at both baseline and during treatment at least 6 months after baseline. Participants completed the Systemic Clinical Outcome and Routine Evaluation (SCORE-15) to evaluate family communication, the Modified Colorado Symptom Index (MCSI) to assess psychiatric symptoms, and the Questionnaire about the Process of Recovery (QPR) to measure beliefs of self-recovery in Beehive, an eHealth application. The Beehive application was introduced to service users at their treatment intake and surveys were completed at two time-points with at least 6 months in between. A within-subjects moderation analysis using linear regression was run to test the hypothesis that treatment reduced symptom frequency and strengthened beliefs of self-recovery more strongly for service users with harmonious family communication than conflictual family communication.
**RESULTS:** No relationship was found for treatment effects on psychiatric symptoms ($R2 = .034$, $F(1, 16) = .557$, $p = .466$) and conflictual family communication ($R2 = .037$, $F(1, 19) = .724$, $p = .405$). The Johnson-Neyman procedure was utilized to determine the range of family communication scores that demonstrate a significant effect of treatment on psychiatric symptoms, but no statistically significant transition points were observed in the data ($p > .050$). However, contrary to our hypothesis, a positive relationship was observed for post-treatment effects on beliefs of self-recovery and a lack of family communication. Conflictual family communication was associated with greater improvement in self-recovery beliefs from time 1 to time 2. The effect of family communication on beliefs of self-recovery was significant only at a moderate range of reported conflictual family communication (SCORE-15 = 31.626 - 56.257) ($\beta = 3.127$ to 5.430, $p = < .050$).
**DISCUSSION:** These results suggest that while perceived family communication does not directly impact psychiatric symptoms, service users with reporting conflictual family communication may experience significant growth in self-recovery beliefs, highlighting the potential role of treatment in fostering resilience and self-efficacy in challenging relational contexts. However, these conclusions should be tempered by the small sample size.

## T67. Clinical, Cognitive, and Neuroanatomical Deficits Emerge at Different Stages of the Psychosis Spectrum

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**BACKGROUND:** The clinical, cognitive, and neural deficits seen in schizophrenia are thought to be present to a milder degree at earlier stages of the psychosis spectrum, including in familial high-risk, clinical high-risk, and first episode psychosis populations. However, it is unclear which markers show abnormalities at which stages of the psychosis spectrum, limiting our abilities to develop an integrated framework describing the sequence of deficits preceding a schizophrenia diagnosis.
**METHODS:** 198 participants aged 14-37 were recruited from the Prevention and Early Intervention for Psychosis clinic at the Douglas Mental Health University Institute. Participants were either diagnosed with first episode psychosis in the previous 3 months (FEP, n = 70), at clinical high-risk for psychosis defined by the SIPS (CHR, n = 42), siblings of FEP participants (FHR, n = 44), or healthy controls (HC, n = 42). Clinical symptoms, alongside cognition and functioning, were assessed using 11 instruments, including the PANSS-6 and the CogState Research Battery. For each scale, we used one-way ANOVAs and post-hoc Tukey's tests to evaluate group differences in summary scores. We also performed an exploratory factor analysis across 86 subjects with complete symptom data, choosing the solution which minimized both the number of factors and items with weak loadings. Finally, 180 T1-weighted images passing quality control were processed using FreeSurfer 7.1.0, giving cortical thickness estimates for the 68 Desikan-Killiany regions. For each group, we implemented region-wise linear models to quantify cortical thickness differences relative to HC while covarying for age, sex, and intracranial volume. The effect size maps for each group were spatially correlated with those from 8 psychiatric conditions provided by the ENIGMA toolbox. Significance was assessed using spatially informed spin tests. P-values were not corrected for multiple comparisons.
**RESULTS:** PANSS-6 summary scores differed between groups at the omnibus level ($p < 0.001$), though the effect was driven by FHR, with no significant differences between CHR and FEP ($p = 0.963$). We also saw group differences in CogState scores ($p < 0.001$), with the effect driven by FEP, and no significant differences between FHR and CHR ($p = 0.914$). To summarize variance across our 11 clinical instruments, we implemented an exploratory factor analysis, which revealed 3 underlying symptom dimensions. Analyzing factor scores, we saw that CHR were the most impaired on the depression/anxiety dimension ($p = 0.006$ relative to FEP), FEP trended towards being the most impaired on the negative/cognitive dimension ($p = 0.056$ relative to CHR), and CHR/FEP were equivalently impaired on the psychosis/functioning dimension ($p = 0.876$). Finally, our neuroimaging analysis revealed that the FEP cortical atrophy pattern was most correlated with those of bipolar disorder ($r = 0.552$, $p < 0.001$) and schizophrenia ($r = 0.512$, $p < 0.001$), while the CHR atrophy pattern was most associated with that of 22q11 deletion syndrome ($r = 0.275$, $p = 0.042$).
**DISCUSSION:** Together, we saw that multimodal markers of schizophrenia risk progressed at different stages of the psychosis spectrum. Cognitive impairments did not emerge until FEP, alongside neuroanatomical deficits characteristic of schizophrenia. Meanwhile, psychotic symptoms and functional deficits were present at CHR and did not worsen in the FEP group. Importantly, CHR were more symptomatic than FEP when considering depressive/anxious symptoms, and also showed an atrophy pattern most like that of 22q11 deletion syndrome, a

genetic condition associated with a range of cognitive and developmental deficits – suggesting that, in many cases, CHR patients are not necessarily pre-psychotic.

## T68. Life History of Aggression Accounts for Associations Between Schemas of the Self/ Others and Suspiciousness

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**BACKGROUND:** Negative schemas toward the self and others have been consistently linked with increased subthreshold positive psychotic symptoms, including suspiciousness. Additionally, these negative self/other schemas have been associated with increased aggression. However, research examining the relationship between aggression and suspiciousness is limited, though it may be relevant to our understanding of increased suspiciousness as threshold level persecutory delusions are among the strongest correlates to violence among individuals with psychotic disorders. To our knowledge, no studies have yet explored associations among negative schemas toward the self, negative schemas toward others, a history of aggression, and suspiciousness.
**METHODS:** College students (n=1773) aged 18-34 at a racially/ethnically and economically diverse urban university in the United States self-reported: lifetime history of aggression (Life History of Aggression Scale), negative and positive schemas concerning the self and others (Brief Core Schemas Scale), and suspiciousness (Prodromal Questionnaire). Analyses examined direct and indirect effects from negative schemas toward the self and negative schemas toward others to suspiciousness via life history of aggression. Supplementary analyses were conducted to examine indirect effects through positive self/other schemas.
**RESULTS:** Significant direct effects were found from negative schemas toward the self and negative schemas toward others to increase suspiciousness, as well as significant direct effects from positive schemas toward the self and positive schemas toward others on decreased suspiciousness (all $p < 0.0001$). Significant indirect effects were found through increased life history of aggression from negative-self schemas [95% CI: (0.0192, 0.0349)], negative-other schemas [95% CI: (0.0097, 0.0201)], and increased negative-self and other schemas [95% CI: (0.0104, 0.0185)] to increased suspiciousness. Significant indirect effects were found through decreased life history of aggression from positive-self schemas [95% CI: (-0.0205, -0.0106)] and, positive-other schemas [95% CI: (-0.0230, -0.0119)] to decreased suspiciousness.
**DISCUSSION:** Results suggest negative-self schemas and negative-other schemas are associated with increased suspiciousness, with increased life history of aggression statistically mediating this association. This association is specific to negative schemas toward the self and others, as positive self/other schemas were associated with decreased suspiciousness. Findings have potential clinical and policy implications for addressing aggression in those with subclinical persecutory delusions to ameliorate risk for psychosis.

## T69. Can Early Intervention Prevent Psychosis? A Meta-Analysis

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**BACKGROUND:** Early intervention has been a cornerstone in preventing the onset and improving outcomes of psychosis for decades. Various strategies, including cognitive-behavioral therapy (CBT), psychoeducation, family intervention, adjunctive nutrients, and low-dose antipsychotics, are employed for individuals at high risk of psychosis and those with recent-onset psychosis. This study aims to demonstrate the clinical benefits of early detection and intervention of psychosis, as part of a feasibility study for introducing a screening item in the National Health Examination of South Korea.
**METHODS:** Meta-analyses were conducted adhering to PRISMA guidelines. Randomized controlled trials comparing treatment-as-usual with early interventions (psychosocial or pharmacological) for Clinical High Risk for Psychosis or Recent-Onset Psychosis were retrieved from three international and four Korean databases (MEDLINE, Embase, Cochrane Library, KoreaMed, ScienceOn, RISS, KISS). Primary outcomes were transition-to-psychosis (TTP) and psychiatric admission rates. The Cochrane's Risk of Bias tool for randomized trials (RoB2) was used to assess the risk of bias in individual studies. Meta-analyses were conducted for different follow-up periods when data from more than 2 studies were available.
**RESULTS:** Sixteen studies (12 for TTP, 14 for admission) were included. Interventions comprised cognitive-behavioral therapy (CBT), multi-component early intervention services (EIS), and omega-3 fatty acids. The risk ratio (RR) for TTP at 6 months, 1 year, 1.5-2 years, and 3-4 years was 0.80 (95% CI: 0.50-1.28), 0.49 (95% CI: 0.30-0.79), 0.53 (95% CI: 0.36-0.76), and 0.83 (95% CI: 0.53-1.30), respectively. Significant overall effects were observed at 1-year ($Z=-2.94$, $P < 0.01$) and 1.5-2-year follow-up ($Z=-3.43$, $P < 0.01$). Heterogeneity was noted at 1-year follow-up ($Chi^2=19.62$, $df=9$, $P=0.02$; $I^2=54\%$). Post-hoc analyses by intervention type revealed significant benefits for CBT (RR=0.51, 95% CI: 0.30-0.87, $Z=-2.46$, $P=0.01$) and EIS (RR=0.23, 95% CI: 0.09-0.57, $Z=-3.15$, $P < 0.01$), while omega-3 effects were insignificant and heterogeneous. The risk ratio for admission at 0.5-1-year follow-up was 0.45 (95% CI: 0.23-0.86), with a significant overall effect ($Z=-2.40$, $P=0.02$) but significant heterogeneity ($Chi^2=12.55$, $df=3$, $P < 0.01$, $I^2=76\%$).
**DISCUSSION:** Early interventions offer significant benefits over standard care in preventing psychosis transition and psychiatric admission for individuals with early psychosis. Independent CBT or multi-component early intervention services are particularly effective up to 1-2 years post-early detection. Longer-term benefits remain unclear due to limited intervention periods and few long-term follow-up studies. Further research is needed to explore the long-term benefits of other outcomes, optimal intervention duration, and goals for sustained effects.

## T70. Preliminary Findings on the Association Between Psychotropic Medication and Symptom Profile Changes in Youth at Clinical High Risk for Psychosis

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**BACKGROUND:** For individuals at clinical high risk for psychosis (CHR-P), research suggests that baseline antipsychotic use is linked with higher psychosis conversion, but this may be due to confounding symptom severity with medication. This study examines associations between post-baseline psychotropic medication by CHR-P youth and changes in symptoms at 4-month follow-up.
**METHODS:** Utilizing data from the North American Prodrome Longitudinal Study 3 (NAPLS-3), we examined symptom severity reduction between baseline and 4-month follow-up among CHR-P youth not on baseline psychotropics. Positive, Negative, Disorganization, and General domains were evaluated using the Scale of Prodromal Symptoms (SOPS). We hypothesized that the initiation of antipsychotics post-baseline would be associated with reduced symptom severity at the follow-up compared to no psychotropic medication. Data analyses included MANOVA and non-parametric methods to explore symptom trajectories across 3 medication types (antipsychotics, antidepressants, and antipsychotics with other psychotropics).
**RESULTS:** The sample included 138 participants in four groups: those receiving antipsychotic medication only (AP, n = 9), antipsychotic with other psychotropic medications (n = 8), antidepressant medication only (n = 17), and a group with no psychotropic medications (n = 104). In the non-parametric test, significant medication group differences were found in positive ($\chi^2(3, 138) = 9.67$, $p = .022$) and general ($\chi^2(3, 138) = 9.3$, $p = .022$) symptoms. Post-hoc tests showed that antidepressants group had less positive symptom reduction compared to the antipsychotic group ($Z = 2.48$, $p = 0.039$) and the antipsychotic with another psychotropic medication group ($Z = 2.40$, $p = 0.041$. The antipsychotics ($Z = -2.23$, $p = 0.076$) and antidepressants group ($Z = -2.21$, $p = 0.068$) exhibited a greater decrease in general symptoms compared to no-medication control group.
**DISCUSSION:** New antipsychotic medication prescription was associated with reductions in symptom severity over time, with variations observed across different symptom domains, underscoring the potential benefits of tailored symptom-specific management strategies in psychiatric care.

## T71. Involuntary Treatment in First-Episode Mania and Psychosis: A Population-Based Study

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**BACKGROUND:** Involuntary treatment is commonly used during first-episode psychosis (FEP) or mania (FEM) to ensure patient and community safety, especially when insight is impaired. Despite its frequent use, the factors related to its application and its long-term outcomes remain poorly understood. This study examines the prevalence, characteristics, and outcomes associated with involuntary treatment during the first year of illness.
**METHODS:** This retrospective cohort study utilized data from the Rochester Epidemiology Project, a population-based database in Minnesota, USA. The study included 202 individuals experiencing FEP or FEM. Patients were categorized into involuntary (INV) and voluntary (VOL) treatment groups based on the presence or absence of involuntary interventions (e.g., hospitalization, antipsychotic treatment, electroconvulsive therapy, or civil commitment) within the first year. Demographic and clinical variables, including antecedent psychiatric diagnoses, illness severity (Clinical Global Impression-Severity [CGI-S]), and employment status, were analyzed. Functional outcomes over five years were assessed using the Social and Occupational Functioning Assessment Scale (SOFAS), and time to relapse—defined as hospitalization post-first episode—was evaluated using Kaplan-Meier survival analysis.
**RESULTS:** At least one involuntary treatment intervention was administered to 44.1% (89/202) of patients during the first year after the first episode making the INV group. At the time of first episode, patients in the INV group were older (21.9 ± 3.3 years vs. 19.9 ± 3.8 years, $p < 0.001$), had greater illness severity (CGI-S: 5.4 ± 0.7 vs. 5.0 ± 0.7, $p < 0.001$), and higher unemployment rates (40.4% vs. 16.8%, $p < 0.001$).

During the five-year period, we found no significant differences in the prevalence of most comorbid psychiatric diagnoses (excluding substance use disorders) between the two groups. However, the involuntary treatment (INV) group had a higher prevalence of substance use disorders compared to the voluntary treatment (VOL) group (78.7% vs. 65.5%, $p = 0.040$). Neither race nor diagnoses of schizophrenia or bipolar disorder were significantly associated with involuntary treatment ($p > 0.05$). A history of autism spectrum disorder was inversely associated with the likelihood of involuntary treatment, with no cases in the INV group compared to 5.3% in the VOL group ($p = 0.02$).

Relapse occurred in most patients (INV 75.3% vs. VOL 64.6%, $p = 0.085$), with no significant difference in time to re-hospitalization ($p = 0.38$). Police involvement during the first relapse was more frequent in the INV group (47.8% vs. 24.7%, $p = 0.006$)

The SOFAS scores during the first five years were approximately 5 points lower ($p < 0.05$) in the INV group compared to the VOL group following the first episode. This difference will be illustrated in a figure.

**DISCUSSION:** To our knowledge, this is the first study to compare involuntary versus voluntary treatment in patients with FEP and FEM in a U.S. population, examining prevalence, associated mental health events, and outcomes. Using a distinctive U.S. population-based cohort, this study highlights that involuntary interventions are commonly used (44.1% of our sample) during the first year following the first episode. This is comparable to the wide range of involuntary treatment frequency that has been described in first episode populations in other countries.

Key factors associated with involuntary treatment include older age at onset, greater illness severity, and co-occurring substance use disorders, while race and specific diagnoses were not significant factors.

Although the primary aim of involuntary treatment is to ensure immediate safety, the observed worse SOFAS scores over a five-year period for individuals in the INV group suggest that such interventions may not improve long-term functioning. Instead, the results may indicate a more severe illness trajectory in the INV group which might be driven by in drug use or insight.

Future research should explore the role of patient insight and develop strategies that optimize outcomes while minimizing reliance on involuntary care.

## T72. SYMPTOM DIMENSION PROFILES IN PATIENTS WITH SCHIZOPHRENIA ARE ASSOCIATED WITH GENETIC RISK

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**BACKGROUND:** Previous reports associated genetic risk for schizophrenia (SCZ) with inter-individual differences in symptom severity across patients. However, symptom severity varies

over time, hindering the association between genetic risk and psychopathological dimensions. We hypothesized that multivariate dimension evaluations could be more stable over time and characterize patient clusters based on symptom patterns. We then associated the identified clusters with genetic risk for different psychiatric disorders to address the role of genetic variation in patient clinical presentation.
**METHODS:** We assessed Positive And Negative Syndrome Scale (PANSS) in 2010 patients with SCZ of Caucasian ancestry from eight independent cohorts after at least 2 weeks of stable treatment with antipsychotics. We performed K-means clustering of patients based on five symptom factors identified with a factorization approach and obtained four psychopathological clusters. Longitudinal evaluations served to assess cluster membership stability over time. We computed individual polygenic risk scores (PGS) for SCZ and seven other psychiatric disorders as well as for SCZ resilience on a larger cohort of 3156 patients for which genotype data was available and performed K-means clustering based on the eight PGSs. Finally, we evaluated the overlap between the clinical and genetic clusters obtained using the Jaccard Index (JI = intersection/union of the groups considered) employing a 10,000 permutation approach to assess the statistical significance of the JI.
**RESULTS:** We identified 4 clinical-based clusters of patients with 1) overall severe, 2) predominantly negative, 3) overall mild, and 4) limited negative symptoms with cluster membership stable over time (empirical-p[T3,T6,T9] < .05). When compared to Positive or Negative symptoms quartiles, only the mildest and the most severe quartiles were confirmed after 6 and 9 months.
We identified 3 genetic-based clusters of patients with 1) high SCZ and bipolar disorder genetic risk, 2) high depression and neurodevelopmental disorders genetic risk, and 3) low genetic risk across all traits. These clusters showed no ancestry confounds. The overlap between the clinical and genetic clusters showed that patients with overall severe symptoms (clinical cluster 1) tended to have high SCZ and bipolar disorder genetic risk (genetic cluster 1; JI = .14; nominal p-value = .044). Instead, patients with limited negative symptoms and more severe positive and excitement symptoms (clinical cluster 4) had overall mild genetic liability, particularly for SCZ, and relatively high SCZ resilience (genetic cluster 3; JI = .18; nominal p-value = .004; Bonferroni-adjusted p-value = .048).
**DISCUSSION:** Multivariate clustering techniques applied to psychopathology described dimensional profiles that were relatively stable over 9 months and more consistent over time than PANSS dimension-based evaluations. Clustering patients based on their genetic risk showed that such clinical heterogeneity was associated with genetic heterogeneity within a multi-site cohort of European ancestry. Our findings suggest that the heterogeneous clinical presentation of patients with SCZ may reflect, in part, genetic heterogeneity.

## T73. Relationship Between Striatal Dopamine Synthesis, Anterior Cingulate Glutamine-Glutamate Levels, and Formal Thought Disorder in First-Episode Psychosis

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**BACKGROUND:** Formal thought disorder (FTD) is a core symptom of schizophrenia, often manifesting during the first episode of psychosis (FEP). Although dopaminergic dysregulation, particularly in the striatum, is linked to psychosis, the specific neurochemical underpinnings of FTD remain unclear. Emerging evidence suggests that glutamatergic dysfunction, particularly in the anterior cingulate cortex (ACC), may also contribute to FTD. This study investigates the interaction between striatal dopamine synthesis capacity and ACC glutamate levels and their relationship to FTD severity in individuals with FEP.
**METHODS:** mean age 40.9 ± 13.6 years). Positron emission tomography–magnetic resonance imaging was used to measure striatal dopamine synthesis capacity (Kocc(min-1)), while magnetic resonance spectroscopy (MRS) assessed ACC glutamine-glutamate levels. Based on the median cutoff levels of each measure, we categorized participants into four groups: (i) low levels in both measures, (ii) low dopamine but high ACC glutamine-glutamate, (iii) high dopamine but low ACC glutamine-glutamate, and (iv) high levels in both measures. We then compared FTD-related symptoms, as measured by items in the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), and Clinical Language Disorder Rating Scale (CLANG), using analysis of covariance (ANCOVA). The models were adjusted for duration of untreated psychosis, age, sex, years of education, and medication use at the time of scanning.
**RESULTS:** FEP patients exhibited significantly higher striatal dopamine synthesis capacity and elevated ACC glutamine-glutamate levels compared to controls (both $p = 0.02$). While no overall correlation was observed between dopamine and glutamate levels, a moderate positive correlation emerged in younger-onset patients ($rs = 0.47$, $p = 0.047$). Individually, neither dopamine nor glutamate levels were significantly associated with FTD symptoms. However, when both neurochemical systems were considered together, significant differences in FTD severity were found. Compared to other three groups, patients with low levels of both dopamine and glutamine-glutamate showed the most severe FTD symptoms, including higher SAPS FTD subscale scores, pressure of speech, distractible speech, clanging, and CLANG referential failures and subscale score of items 4 (semantic association deficits) and 5 (referential failures). These patients also displayed increased SAPS incoherence and CLANG subscale scores (items 1 to 6, and 4 to 6), compared to those with low dopamine but high glutamine-glutamate, or high levels of both measures. Furthermore, patients with low levels of both dopamine and glutamine-glutamate exhibited higher levels of tangentiality, compared to patients with high dopamine but low glutamine-glutamate, or high levels of both measures. These patients demonstrated significantly higher CLANG total scores and poverty of speech compared to those with high levels of both measures and high pressure of speech compared to those with low dopamine but elevated glutamine-glutamate levels.
**DISCUSSION:** The findings indicate that impairments in striatal dopamine synthesis capacity and anterior cingulate glutamate function are linked to more severe formal thought disorder in first-episode psychosis patients. This is particularly noteworthy, as positive symptoms in psychosis are typically associated with elevated striatal dopamine synthesis, which is often accompanied by decreased glutamate neurometabolic levels. Further research with larger sample sizes is needed to confirm these results and elucidate the specific biological mechanisms underlying the relationship between neurotransmitter dysregulation and disorganized cognition in the early stages of psychosis.

## T74. Characterizing Sleep Disturbances in Early Psychosis Within the Epinet Connection Learning Healthcare System

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**BACKGROUND:** Up to 80% of patients with psychosis-spectrum disorders experience challenges with sleep that negatively impact functioning and quality of life. Less is known about sleep disturbances in first-episode psychosis (FEP). By examining baseline intake data from a large cohort of FEP patients receiving care at one of 23 Coordinated Specialty Care programs within the EPINET Connection Learning Healthcare System (CLHS) hub, we seek to better characterize sleep disturbances in treatment-seeking individuals with FEP.
**METHODS:** Baseline data were extracted from the CLHS Core Assessment Battery (CAB) administered to 433 FEP patients (mean age=20 years, SD=4.29; 35% female) who experienced a first episode of psychosis within the past two years. Subjective sleep quality was self-reported using the Minimal Insomnia Symptom Scale (MISS). Psychiatric symptoms were clinician-rated using the COMPASS-10 and RAISE CP Negative Symptoms Scale. Constructs of interest were examined using bivariate correlations and regression-based analyses.
**RESULTS:** Preliminary results suggest that poor self-reported sleep quality in FEP is associated with increased general ($r=0.286$, $p < 0.001$) and positive ($r=0.108$, $p=0.039$) symptom expression and with decreased negative ($r=-0.228$, $p < 0.001$) symptom expression. Sex differences in MISS total score and subscale scores were detected such that females endorsed poorer subjective sleep quality overall, more frequent nighttime awakenings, and higher likelihood of non-restorative sleep (all $p$'s $< 0.01$).
**DISCUSSION:** Findings are consistent with prior research implicating sleep disturbance in psychosis spectrum disorders, and support conceptualizing sleep as an important treatment target in Coordinated Specialty Care programs for FEP. Future work implementing and examining the efficacy of tailored sleep-based interventions in this clinical population is warranted.

## T75. Stepdown Care: Goals and Needs of Services Users in the Transition out of Coordinated Specialty Care

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**BACKGROUND:** Long-term follow-up studies on coordinated specialty care (CSC) programs have indicated the positive outcomes acquired during CSC are not maintained after transitioning out of CSC programs. The CSC model is based on collaborative, shared decision-making to meet

the needs and goals of the individual experiencing psychosis. Even with this aim of CSC, there is currently limited literature examining the needs of individuals with first episode psychosis during and after CSC. To address this gap, the present qualitative study explored the goals of services users for their care and sought to understand service users and family members' perspectives on their needs and support in transitioning to stepdown care.
**METHODS:** From September 2021 to December 2022, service user and family member participants were recruited from ten of Washington's CSC programs. Eligibility criteria to participate in the qualitative study included age 18 or older, receiving or received services from one of the CSC programs or a family member of an individual who received services, ability to speak and understand English or Spanish, and consented to be audio recorded. All interviews were conducted using a semi-structured interview guide centered on experiences, expectations, and perspectives across the continuum of care. Interviews were conducted in English and Spanish then transcribed. Spanish interviews were translated to English. Qualitative data was then evaluated using grounded theory and a descriptive approach to conceptualize and capture the participants' perspectives. Transcripts were uploaded to Atlas.ti, coded, compared by two coders on the research team, and discussed until a consensus was reached.
**RESULTS:** Thirty-two individuals participated in the qualitative interviews, of which nine were service users (n=6; 67% male) and 23 were family members or support persons (n=13; 57% mothers). Of the entire sample, 50% self-identified as an ethnoracial minority and the mean age was 42.6 years (SD=15.4; range: 19 to 69). Four themes materialized: goals around education and employment to support independence, establishing relationships as part of wellbeing, perceived readiness to transition out of CSC, and continued mental health care and other support in their stepdown care. Goals related to education and employment often coincided with the desire for independence (e.g., obtaining a good job, housing stability, and self-sufficiency) while establishing platonic and romantic relationships were exclusively voiced by family members for their loved one to have a life reflective of normal societal milestones. There were some discrepancies around the limited timeframe of receiving CSC services (i.e., 2 years from enrollment) and perceived readiness to transition out of the program. Most family members noted concern around the timeframe and hesitancy in preparedness of their loved one to transition out of CSC. Service users' perspective varied on their feelings of preparedness to leave CSC services. Service users and family members concurred that continued support was necessary to support their wellbeing, including therapy at a less frequent time interval to CSC and medication management with service users additionally specifying the need for support and connection with their peers.
**DISCUSSION:** While individuals receive effective support, including attaining their goals around employment and education within CSC services, additional support is needed in transitioning out of CSC. Future research should examine and develop a standardized stepdown care guide to sustain improvements reached while receiving CSC services and improve long-term outcomes.

## T76. A Delphi Consensus Report on the Treatment of First Episode and Early-Phase Schizophrenia in Adolescents and Young Adults in Latin America

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**BACKGROUND:** Early-Onset Schizophrenia (EOS) – illness onset before 18 years of age – was reported to affect up to 0.5% of adolescents and account for 25% of adolescent psychiatric admissions. In clinical settings, the presentations are complex with many symptom proxies and high comorbidity, leading to diagnostic and nosologic difficulties and thereby affecting the overall clinical outcomes. It demonstrates that specialized multicomponent systems of care for first-episode psychosis produce significantly better, clinically important out- comes in the first 2 years compared with treatment as usual. Although early intervention was demonstrated to improve clinical and disease burden-related outcomes there is little guidance about the pharmacological treatment of EOS due to difficulties in translating conflicting randomised-controlled trials results into clinical guidelines recommendations.

Objetives: 1. To explore areas of uncertainty about the management of the earlyEOS in Latin America, 2. To develop evidence-based recommendations useful to mental health professionals

in our region, 3. To compare the results obtained in the Latin American Delphi Consensus on managing EOS with those obtained in the European Delphi Consensus

**METHODS:** he Delphi questionnaire on managing EOS was developed for a European expert. Approval has been obtained for the translation of the questionnaire into Spanish and Portuguese. Both, the Spanish and Portuguese versions were sent to a group of experts from ten Latin American countries. The group of experts was asked to read the questionnaire without modifying the original questions. They could only add some questions that they considered relevant for our region. The Latin-American questionnaire consisted in 98 items. Both, European an Latin-American version of the Delphi questionnaire comprises 18 statements grouped into six topics (1-timely detection of signs of psychosis/EOS and formal diagnosis, 2-Access to care of individuals with symptoms and signs of psychosis or EOS, 3-Treatments and outcomes, 4-Non-pharmacological interventions, 5-Strategic management, 6-Clinical Practice/Scientific Evidence). The Latin American expert group added only 8 questions. Respondents are required to indicate their level of agreement or disagreement with each statement using a 5-point Likert Scale. The first two items on the Likert Scale represent negative consensus, while the subsequent three represent positive consensus. The criterion for reliability with regard to consensus is 66%. Any percentage below this threshold is considered to indicate a lack of consensus. A total of 139 psychiatrists (both adult and child psychiatrists are included in this study), from 13 countries responded to the initial round of the Delphi questionnaire (Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Paraguay, Peru, Uruguay, Venezuela). Of these, 90 proceeded to the second round of the Delphi questionnaire.
**RESULTS:** Following round I, consensus was reached for 96/100 items (97%), while it was reached for 5/9 (71%) of the items sent out for rerating in round II. As in the European consensus, there was broad agreement on diagnostic standards, multimodal approaches and focus on adverse events. However, in our study, there was a divergence of opinion regarding the optimal duration of follow-up for early onset schizophrenia (EOS), including clozapine, for younger patients.
**DISCUSSION:** This study synthesizes the expert opinions and regional perspectives of Latin American healthcare providers to provide valuable guidance for those working with adolescent patients with schizophrenia. It aims to optimise outcomes and improve the quality of care across Latin America.

## T77. The Association of Anterior Cingulate Cortex Glutamate and Clozapine Eligibility in an Early Psychosis Sample

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**BACKGROUND:** The ability to identify patients who may benefit from clozapine at the earliest opportunity is important for maximizing long-term outcomes in schizophrenia and may facilitate stratification of treatment based on neurobiology. Approximately one third of individuals with schizophrenia do not respond appreciably to first-line pharmacological treatment options and meet criteria for treatment resistant schizophrenia (TRS), the majority of whom demonstrate

poor response from the first episode of psychosis (FEP). Given first line dopamine blocking medications are essentially ineffective in this subgroup, it has been hypothesized that alternative neural pathways may be implicated. Glutamate, an excitatory neurotransmitter, has been shown to be elevated in individuals with FEP who do not respond to dopamine blocking antipsychotic medications. Despite the considerable evidence of superiority for clozapine in TRS, its use is frequently delayed. There are currently no objective biomarkers available to support clinicians in identifying individuals who may benefit from a clozapine trial. Given the response to clozapine is more robust if used earlier in the illness, there is an urgent need to characterize the neurobiological underpinnings of clozapine eligibility. To date, no studies have investigated the association of elevated glutamate with clozapine-eligibility in a FEP sample, a group in which clozapine initiation may have the most profound effects on long-term outcomes. We hypothesized that elevated glutamate in the Anterior Cingulate Cortex (ACC) would be associated with clozapine-eligibility in an early psychosis sample.

**METHODS:** In this study, clozapine eligible (CE) individuals and treatment responders (TR) with non-affective psychotic disorders from the Nova Scotia Early Psychosis Program (within the first five years of illness onset) underwent magnetic resonance spectroscopy (1H-MRS) to measure glutamate in the bilateral dorsal ACC. 1H-MRS acquisitions were performed using Point RESsolved Spectroscopy (TE=40ms, TR=2000ms; 128 averages). Criteria for clozapine eligibility was according to modified treatment response and resistance in psychosis working group consensus criteria. CE individuals continued to have moderate psychotic symptoms on the PANSS, an illness severity of moderate on the CGI-S, and moderate functional impairment, and had undergone at least two trials of non-clozapine antipsychotic medications. The TR group had no more than mild symptoms on all PANSS items and were taking a single antipsychotic medication.

**RESULTS:** 46 individuals completed the study with 24 meeting criteria for clozapine eligibility, and 22 as treatment responders. 26 individuals (56.5%) were receiving treatment with a long acting injectable antipsychotic (LAI) medication. The TR group (16 male, 6 female) did not differ from the CE group (19 male, 5 female) in age, years of education, family history of psychosis, or regular nicotine and cannabis use. The CE group had higher PANSS total scores, a longer duration of untreated psychosis, worse social functioning, and were on a higher burden of antipsychotic treatment as per the chlorpromazine equivalencies. Glutamate was compared between the groups using an ANCOVA, accounting for the effects of covariates that differed significantly between the CE and TR groups. While ACC glutamate was not found to be significantly different between the groups, glutamine, a precursor for glutamate, showed a trend towards higher levels in the CE group (M=6.97) relative to the TR group (M=5.52), $F(1,40) = 3.46$, $P = .070$.

**DISCUSSION:** While elevated ACC glutamate has been associated with poor response to antipsychotic medications in early psychosis samples, this is the first study to examine the association with clozapine-eligibility. The ability to triage clozapine eligibility based on objective neurobiological findings could revolutionize early psychosis care in that some individuals may be offered clozapine after a single failed trial. Contrary to our hypothesis, ACC glutamate was not higher in the CE group. Overall however, our finding of a trend towards elevated glutamine supports the theory of disrupted glutamatergic metabolites in the pathophysiology of treatment resistant schizophrenia. Limitations include the fact that antipsychotic treatment was not standardized, serum levels of antipsychotic medications were not obtained to confirm adherence, and we did not obtain drug tests at the time of glutamate

measurement. Further studies are warranted to explore the association of elevated ACC glutamate at baseline and eventual CE in early psychosis samples.

## T78. Treatment-Resistant Schizophrenia and Genetic Risk Parsed for a Specific Dopaminergic Co-Expression Pathway

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**BACKGROUND:** Treatment-resistant schizophrenia (TRS) is hypothesized to involve distinct pathophysiological mechanisms compared with non-TRS. The study of the neurobiology of TRS can be instrumental in developing diagnostic biomarkers and guiding research toward specific treatments. Despite the importance of genetic risk, no genetic screening for schizophrenia (SCZ) or TRS exists due to the polygenic nature of SCZ and the limited explanatory power of genome-wide association studies (GWAS). SCZ polygenic risk scores (PRSs) are higher in TRS and may predict antipsychotic response, but they aggregate variants regardless of function, potentially obscuring specific biological pathways. An alternative approach involves using post-mortem brain transcriptomics to identify co-expressed gene sets linked to specific pathways, such as dopamine function. Computing PRSs based on these genes may help associate genetic risk with neurobiological and clinical outcomes. We investigated whether a dopamine-related gene set could differentiate TRS from non-TRS patients, offering insights into the mechanisms of treatment resistance.
**METHODS:** We recruited 86 individuals diagnosed with schizophrenia: 56 subjects on treatment with clozapine were classified as treatment-resistant (TRS) and 30 as non-TRS. Participants underwent blood tests for genotyping and comprehensive clinical assessments to evaluate resistance to treatment retrospectively. We utilized a schizophrenia-related gene component (C80), previously identified through Sparse Decomposition of Arrays of post-mortem brain RNA-sequencing data, which is associated with schizophrenia diagnosis and genetic risk and is enriched for dopamine function genes (Sportelli et al., 2024). Parsed Polygenic Risk Scores (parsed-PRSs) were calculated by computing PGC3-PRS stratified for genes within this gene set at multiple p-value thresholds (PRS1 to PRS10). As a negative control, complementary parsed-PRSs were calculated based on GWAS risk genes not included in the gene set. ANCOVAs were conducted with the parsed-PRS as the dependent variable, patient category (TRS/non-TRS) as the independent variable, and the top 10 genetic principal components as covariates.
**RESULTS:** The TRS group had significantly higher parsed-PRS6 compared to the non-TRS group ($p = 0.015$). This difference was also significant for parsed-PRS5 ($p = 0.007$), PRS7 ($p = 0.011$), PRS8 ($p = 0.036$), PRS9 ($p = 0.028$), and PRS10 ($p = 0.029$). No significant differences were observed in complementary parsed-PRSs between the groups.
**DISCUSSION:** The elevated dopamine-related PRS in TRS patients aligns with prior research indicating higher PRS levels in TRS, supporting specific genetic underpinnings in this subgroup. The lack of significant findings for SNPs outside the co-expression pathway would suggest that dopamine-related SNPs primarily drive the increased genetic risk. However, these findings do

not align with previous evidence of reduced dopamine function in patients with TRS. Further studies are needed to characterize TRS, considering that multiple neurobiological mechanisms may contribute to treatment resistance.

## T79. Serotonin Receptor HTR2A Single Nucleotide Polymorphisms and Cannabis use in First Episode Psychosis

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**BACKGROUND:** Epidemiological studies suggest that cannabis use may increase risk for first episode psychosis and subsequent schizophrenia (SCZ)(1,2) as well as genome-wide association studies (GWAS) have found significant genetic correlations between SCZ and cannabis ever-use (3). We have studied the possible interaction between cannabis use and single nucleotide polymorphisms (SNPs) on the long arm of chromosome 13 where the 5-HTR2A, which codes for the 5HT2a receptor is located. The 5HT2a receptor has already been linked with SCZ (4). Thus, a genetic mutation may be related to the disorder.

References:

1. Di Forti M et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. The Lancet Psychiatry 6, 427–436 (2019).

2. Marconi A, Di Forti M, Lewis CM, Murray RM and Vassos E Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr. Bull. 42, 1262–1269 (2016).

3. Pasman JA et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat. Neurosci. 21, 1161–1170 (2018).

4. Abdolmaleky HM, Faraone SV, Glatt SJ, Tsuang MT. Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. Schizophr Res. 2004;67:53–62

**METHODS:** Sixteen participating centers from the PEPs project in Spain recruited 310 first episode psychosis (FEP) patients [32.8% males/67.8%females; mean age (SD) 24.2 (6.1) years and 228 sex/age matched healthy controls. The Spanish translation of the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) was used to assess current and past psychopathology in children and adolescents according to DSM-IV criteria, and the Structured Clinical Interview for

DSM Disorders (SCID) parts I and II (SCID-I and II), with a Spanish translation available, was used for adults (5-8). We studied 17 HTR2A SNPs: rs4942577, rs9567733, rs7333412, rs9567736, rs9567737, rs2296972, rs7984966, rs2770298, rs731779, rs1002513, rs985934, rs927544, rs4942587, rs2296973, rs6313 (102T/C), rs6311 (-1438A/G), rs731245.
Blood samples were collected using BD Vacutainer® tubes, with K2 EDTA (Becton Dickinson, Franklin Lakes ,New Jersey). Genomic DNA was extracted with the MagNA Pure LC DNA isolation Kit using an LC MagNA Pure system (Roche Diagnostics GmbH, Mannheim, Germany).

Genotyping data were submitted to the Michigan Imputation Server employing the standard Minimac4 software pipeline and setting a European Population reference from build GRCh37/hg19 and Eagle v2.4 phasing. For the PRS-SZ calculation, we employed as reference GWAS summary results derived from 76,755 cases and 243,649 controls (9). Duplicated and unknown strand GWAS summary SNPs were excluded.

Quality control was performed with PLINKv1.07.32 Inclusion criteria for SNPs were minor allele frequency > 0.01, Hardy–Weinberg equilibrium p > 10-6, marker missingness < 0.01 and imputation INFO > 0.8. Pruning was done using a window/step size of 200/50 kb and r2 > 0.25. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate < 0.01, matching chromosomal and database-labelled sex and self-reported European ancestry.

PRS were constructed using the PRSice-2 v2.3.3 software.33 Clumping for the SNPs in the reference data was set at 250 kb andr2 > 0.1 and the effect values of the SNP's risk alleles were added to create the individual score.

For the analyses we employed 2 normalised PRS-SZ, constructed from SNPs with P < 5 x10 -8 (PRS-SZ 10 -8) and P < 1 x10 -6 (PRS-SZ 10 -6)(10)

Statistical analyses were performed using IBM SPSS Statistics 27 plus PROCESS v4.2 extension for the mediation model.

**RESULTS:** We performed logistic regression analyses including every SNP but only the rs7984966 SNP made it to the final model. We tested the rs7984966 SNP in a new regression model including cannabis use and other FEP risk factors such as sex, cocaine use, or childhood trauma and both, cannabis use and the HTR2A rs7984966 SNP, were associated with the risk of FEP (p=0.022) with a similar effect in reducing the risk of being a PEP case for the CC allele of the rs7984966 SNP (relative risk 0.291; p=0.006; CI 95% 0.120-0.707) and for cannabis non-users (relative risk 0.299; p < 0.001; CI 95% 0.186-0.482)
We explored the subsample of FEP vs. matched normal controls both with comorbid cannabis use and found a different allelic distibution of the the SNP rs7984966: the CC allele was present in 12.8% of the controls vs. 2.9% of the cases (p=0.030). These results suggested a possible interaction between cannabis use and the SNP rs7984966.

We checked the posible mediation of the SNP rs7984966 between cannabis use and FEP but the result was not statistically significant.

**DISCUSSION:** Both, cannabis use and the HTR2A SNP rs7984966 are associated with FEP risk independently with no interaction between both risk factors in mediation models, while HTR2A SNPs rs4942577, rs9567733, rs7333412, rs9567736, rs9567737, rs2296972, rs2770298, rs731779, rs1002513, rs985934, rs927544, rs4942587, rs2296973, rs6313 (102T/C), rs6311 (-1438A/G) and rs731245 were not associated with an increased risk of FEP.

## T80. Insights Into Schizophrenia Risk and Antipsychotic Response Using Transcriptome-Informed Polygenic Risk Scores

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**BACKGROUND:** When studying polygenic traits such as schizophrenia (SCZ) or response to antipsychotics (APs), a polygenic risk score (PRS) can be a valuable tool. A PRS is calculated as the weighted sum of all SNPs affecting the trait. SCZ, bipolar disorder (BPD) and major depressive disorder (MDD) PRSs have all been previously associated with SCZ symptoms/diagnosis and AP response. However, PRSs may be enhanced by including functional information such as gene expression. A gene expression risk score (GeRS) is a type of PRS that weights genes by their expression levels in the tissue of interest, as well as by their effect sizes on the trait, and therefore represents a functionally-informed PRS. Here, we investigated the association between GeRS and SCZ case/control status, as well as response to APs.
**METHODS:** Using GWAS summary statistics for SCZ, MDD, BPD and antidepressant response (ADR), a FUSION transcriptome-wide association study (TWAS) was done to establish gene expression-trait correlations. An ADR GWAS was selected due to the lack of a well-powered AP GWAS, and shared pathways between AD and AP action. FeaturePred was used to impute gene expression in target cohorts using GTEx reference data. Reference tissues included cortex, caudate nucleus, nucleus accumbens and putamen, the latter three being part of the basal ganglia which have a high density of dopamine neurons and are therefore relevant for SCZ.

Imputed expression and TWAS effect sizes were used with IFRisk to calculate the GeRS for individuals in the Individualized Medicine: Pharmacogenetic Assessment and Clinical Treatment (IMPACT) (n=3377) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (n=322) cohorts. IMPACT was used for SCZ diagnosis, while CATIE was used for ΔPANSS and ΔPANSS subscale scores after 6 months of AP treatment. Logistic and linear regression models assessed GeRS associations with each outcome, and model performance was compared using Nagelkerke R2 (logistic) or R2 (linear). Age, sex, first three PCAs, and baseline PANSS/PANSS subscale scores (for AP response) were used as covariates. FDR correction was applied with a significance threshold of $p \leq 0.05$. Additionally, GeRS was compared with PRS calculated using the p-value clumping and thresholding method to assess their relative performance.

**RESULTS:** Cortex-derived SCZ GeRS was significantly associated with SCZ diagnosis (Nagelkerke R2=0.0968, p=0.019). The same was observed with cortex-derived BPD, MDD and ADR GeRS. For basal ganglia (caudate nucleus, nucleus accumbens and putamen), SCZ and BPD GeRS, but not ADR or MDD GeRS, showed significant associations and had comparable Nagelkerke R2 values to cortex-derived GeRS.

In contrast, there were only nominal associations between GeRS and ΔPANSS. Cortex-derived ADR GeRS was nominally associated with ΔPANSS (R2=0.16, uncorrected p=0.02) and ΔPANSS psychopathology scores (R2=0.183, uncorrected p=0.011), and had a suggestive association with ΔPANSS positive (R2=0.206, uncorrected p=0.057). ΔPANSS negative was not nominally associated with any GeRS. The effect size of the GeRS in all models was negligible.

GeRS marginally outperformed PRS for modeling antipsychotic response; for example, ΔPANSS was nominally associated with ADR GeRS (R2 = 0.16), but not ADR PRS (R2 = 0.149). On the other hand, SCZ diagnosis was better modeled by PRS compared to GeRS; both SCZ GeRS and PRS were significantly associated with this outcome, but the former's Nagelkerke R2 was 0.0968, while the latter's was 0.159.

Combined PRS + GeRS models did not provide a meaningful increase in R2 compared to GeRS alone for AP response. The ADR combined model had a 0.002 increase in R2 over the ADR GeRS model (p=0.5). On the other hand, there was a statistically significant increase of 0.01 for the ADR combined model over the ADR PRS model (p=0.03). For SCZ diagnosis, combined models improved GeRS-only models (e.g., an increase of 0.06 in Nagelkerke $R^2$ for SCZ combined vs. SCZ GeRS, $p < 2e\text{-}16$) but not PRS-only models (e.g., an increase of 0.0003 for SCZ PRS + GeRS vs. SCZ PRS, p=0.3).

**DISCUSSION:** This study is consistent with a previous study showing an association between SCZ and SCZ GeRS. Basal ganglia derived SCZ and BPD GeRS, but not ADR/MDD GeRS, were associated with SCZ, which may point to the greater genetic overlap between the former two disorders. For ΔPANSS, the association with ADR and MDD cortex/putamen GeRS points to shared underlying pathways in AD and AP response. However, there was a difference in predictive value across subscales, with ΔPANSS negative in particular showing no nominal associations. This may reflect the lower efficacy of APs in treating negative symptoms.

In summary, we showed that GeRS was significantly associated with SCZ diagnosis, and nominally associated with AP response. GeRS derived from cortex and basal ganglia showed comparable results for both outcomes. In addition, GeRS had improved predictive power over PRS for AP response, but not SCZ diagnosis. However, all GeRS had very small effect sizes, indicating limited clinical utility. To our best knowledge, this is the first study evaluating the association between AP response and a functionally-informed PRS. Further studies with larger sample sizes may be needed to confirm the robustness of these findings.

**T81. Individual-Level Outcomes of Schizophrenia Patients Receiving a Community-Based Treatment and Management Program in China: A Retrospective Cohort Study**

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**BACKGROUND:** The Treatment and Management Program for Serious Mental Illnes is a national program to provide community-based mental health services, mainly follow-up visits, to individuals with serious mental illness (SMIs) in mainland China. The effectiveness of this Program' services on symptoms and functioning remained unclear after implemented for two decades. Our study aimed to estimate the associations between the Program's services and a set of outcomes among schizophrenia patients.

**METHODS:** This multi-centered, retrospective cohort study was conducted among schizophrenia patients discharged from psychiatric hospitals in three Chinese metropolitans. Exposed participants were service users of follow-up visits in the Treatment and Management Program. One unexposed patient was matched with two exposed patients according to city, sex, and age (±3 years). Baseline data were retrieved from medical records. Follow-up data were collected via face-to-face interview. Psychiatric symptoms and social function were primary outcomes. Secondary outcomes included relapse, readmission, employment duration, quality of life, number of outpatient clinic visits, medication adherence, violent behavior, and perceived stigma. Multivariate regressions were used to estimate associations between exposure and outcomes. Sensitivity analyses were used to examine the robustness of our findings.

**RESULTS:** A total of 249 eligible unexposed patients were identified and 105 of them (Mean (SD) age: 38.0 (13.4); female: 59%) agreed to participate (response rate: 42.2%). 181 matched exposed patients (39.0 (12.2); 58%) participated the interview. Multivariate regression showed no significant difference in psychiatric symptoms (adjusted mean difference [AMD]=3.171, 95%CI -1.216 to 7.558) between services users and nonusers, while services users had more social function deficits (AMD=1.611, 0.563 to 2.659), shorter employment duration (incidence rate ratio [IRR]: 0.486, 0.271 to 0.871) and more outpatient clinic visits (IRR:1.149,1.010 to 1.308). We found significant education × service interaction. Among patients with lower educational levels, the Program's services were associated with less psychiatric symptoms and fewer social function deficits. Regarding secondary outcomes,
there were no significant differences regarding relapse, readmission, quality of life, medication adherence, violent behavior, and internalized stigma between services users and non-users. Results of sensitivity analyses were similar with main results.

**DISCUSSION:** As a community-based program providing broad coverage with less intensive services, the Treatment and Management Program improved health care accessibility for patients with schizophrenia. However, the Program's services could not alleviate psychiatric symptoms

and social function deficits for all enrolled patients. Despite that, it could benefit individuals with socio-economic disadvantages. Our findings highlight a service priority of socially disadvantaged patients for efficient resources allocation, and the need for tailored, intensive, and evidence-based care to support the recovery of patients with serious mental disorders.

## T82. Interpersonal Distance Regulation and Paranoia in the General Population

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**BACKGROUND:** Paranoia, characterized by mistrust and heightened threat perception, has social consequences. For example, paranoid threat increases preferred interpersonal distance (IPD) in the schizophrenia-spectrum (Schoretsanitis et al., 2020). However, in the general population, the relationship between paranoia and IPD remains unclear. This study aimed to investigate the link between paranoia and IPD in a large general population sample, exploring how demographic factors such as gender and political affiliation modulate these relationships.
**METHODS:** An online survey (N=1814) was administered to the general public in the spring, summer and fall of 2024. Demographic data and Revised Green et al. Paranoid Thoughts Scale (rGPTS) scores were collected. IPD was obtained by asking participants to indicate comfortable social distances for close persons, acquaintances, and strangers on a diagram.
**RESULTS:** Democrat women consistently reported the lowest levels of paranoia, while Republican men had the highest levels regardless of time. Across all groups, paranoia levels increased from spring to the election period. In contrast to findings in schizophrenia populations, higher paranoia was associated with smaller IPD in the general population, particularly toward close individuals.
**DISCUSSION:** Sex and political differences highlight the socio-cultural impact on paranoia level. Paranoia in the general population may drive approach behaviors rather than withdrawal. This could reflect an attempt to monitor or control perceived threats in close interpersonal distance. Future studies should explore whether paranoia operates qualitatively differently in psychosis versus non-psychosis populations.

## T83. Homelessness and First-Episode Psychosis: An Integrative Review of Current Literature

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**BACKGROUND:** About 115,000 young people in the US experience a first episode of psychosis (FEP) annually. FEP is associated with functional decline and long-term executive functioning impairment. Schizophrenia is a risk factor for homelessness with as many as 20% of individuals diagnosed experiencing homelessness over their lifetime. Homelessness conveys many burdens including higher rates of victimization, incarceration, and substance use. The

intersection of homelessness and FEP represents a uniquely vulnerable population undergoing the compounding effects of two highly stigmatizing burdensome experiences which negatively impact health outcomes, treatment engagement, and life expectancy.
**METHODS:** An integrative review was conducted in April 2023 with APAPsychInfo, APAPsychArticle, Medline, and CINAHL using PRISMA guidelines and search terms of: homelessness or homeless youths or unhoused or housing youths AND first episode psychosis or first-episode psychosis or early psychosis or new episode psychosis or new psychosis.
**RESULTS:** Nine of eighteen publications were from Canada, five were from the US, and one each were from Denmark, England, Switzerland, and Ireland. Publication year ranged from 2001- 2023 with over 80% published in 2017 or later. All studies were quantitative aside from one qualitative study by Roy et al. (2013). Using Critical Appraisal Skills Programme (CASP) guidelines for critical appraisal all eighteen articles were determined to be trustworthy and relevant for inclusion in the review.
Rates of homelessness in FEP are not widely reported and may be under-estimated based on a lack of clear definition of homelessness. Rates have been reported as high as 40% in individuals making initial contact for services and persist at high rates over the first few years of CSC treatment (England et al., 2001). Black Americans and first-generation immigrants are more likely to be homeless than white individuals and non-immigrants, respectively (Nagendra et al., 2018; Abdel-Baki et al., 2018).

Homelessness in FEP leads to increased rates of involvement and interaction with the legal system, including coercive pathways to CSC treatment. Individuals experiencing homelessness in FEP are more likely to be Black and non-Hispanic, spend longer in inpatient hospitals with greater frequency of readmission, have higher rates of co-morbid diagnoses such as substance use, and consistently have the poorest illness trajectories. Homeless individuals have less family involvement in their care and poorer social support. Homelessness is associated with the persistence of substance use disorders, while living with family is associated with stopping substance use.

There is evidence that housing for homeless FEP individuals helps them engage in care, resume education or employment, and reduce substance use. FEP individuals identify homelessness and housing instability as contributors to social isolation and liken the experiencing of incarceration, frequently moving, overcrowding and sharing bedrooms in group living situations as equally disruptive as being homeless.

**DISCUSSION:** Little research is available examining homelessness in FEP, particularly in the US, although there are clear detrimental effects of experiencing both homelessness and psychosis.
Collective action is needed to address this global problem which contains multi-level challenges encountered by individuals experiencing FEP, healthcare providers providing care, the systems of care they operate in, as well as housing systems. Future work should be comprised of research, policy, as well as advocacy. One universal, consistent definition of homelessness needs to be established and utilized nationally and within all future research to ensure the scope of this problem is understood. All FEP programs publishing research should include rates of homelessness for their clients. Rates of homelessness in FEP programs can be used to better

understand variation across states and regions, as well as identify need for resource allocation. Future studies should examine the compounding effects and interactions between FEP and homelessness as well as variables such as substance use, legal involvement, and holding minoritized racial or ethnic identities. Given that Black Americans disproportionately experience schizophrenia, homelessness, and incarceration, among other vulnerabilities secondary to systemic racism, future research should strive to characterize these disparities to inform policy reform and advocacy to dismantle disadvantageous and oppressive systems. Priority should be given to a pilot of Housing First for FEP in the United States at several sites across the country, to evaluate its impact with the hope of presenting data in support of Housing First for all individuals with FEP. Research should also be done to better understand the impacts that long-term and even brief experiences with homelessness have on individuals with FEP, to better support their resilience as well as advocate for prevention. Advocacy work is needed to bring the issues of homelessness in FEP to lawmakers for action, with the goal of establishing FEP as a special population requiring priority housing opportunities.

## T84. Exposure to Discrimination is Associated With Greater Risk for Psychotic Symptoms: Data From the Tokyo Teen Cohort

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**BACKGROUND:** Epidemiological research in the United States and other Western nations has linked exposure to discrimination to a greater likelihood of psychotic symptoms and schizophrenia-spectrum disorders. As a highly salient, stressful, and marginalizing exposure, this is consistent with etiological theories of psychosis (e.g., diathesis-stress model, social defeat hypothesis, and others), but may also be dependent on social contexts characterized by widespread ethnoracial inequities. For the first time to our knowledge, this study collected data on everyday discrimination exposure in Japan to examine the broader generalizability of the association between discrimination and psychotic experiences.
**METHODS:** Data are drawn from the 5th wave of the Tokyo Teen Cohort, collected in 2023-2024 as the 20-year-old wave of a 10-year prospective cohort study of youth living in three municipalities of the Tokyo metropolitan area (N=1372). Discrimination was assessed using a newly translated Japanese version of the widely used and validated Everyday Discrimination Scale. The Everyday Discrimination Scale allows respondents to self-report the severity of discrimination experienced and, separately, the perceived cause of this discrimination (e.g., race/ethnicity, physical appearance, age, gender, etc.). Psychotic experiences were assessed using the Adolescent Psychotic-Like Symptom Screener (APSS). Logistic regression was used to test for associations between discrimination and psychotic experiences, adjusted for gender identity.
**RESULTS:** Exposure to everyday discrimination was reported 29.0% of study respondents, and psychosis-like experience were reported by 14.7% of respondents. Youth attributed their experiences of discrimination primarily to physical characteristics (9.7%), age (5.4%), or height

(4.3%). Race/ethnicity, the dominant driver of discriminatory experiences in the United States and many other Western nations, was only identified as the cause of discrimination by 1.2% of respondents. Adjusted for gender, discrimination exposure was significantly associated with psychotic experiences in logistic regression analyses. This association was significant whether it was coded as a binary variable: OR(95% CI)=2.59(1.90-3.52); or as a continuous variable in which odds ratios indicate the increased risk with each additional point on the discrimination scale: OR(95% CI)=1.14(1.09-1.20). The prevalence of psychotic experiences was 23.8% among those who reported any exposure to discrimination, compared to 10.8% among those who did not.
**DISCUSSION:** Discrimination was self-reported by a notable minority of youth in Tokyo, although at lower rates than typically found in western countries. Additionally, discrimination was attributed to distinct causes, particularly physical characteristics rather than race/ethnicity or gender. Despite lower overall rates of discrimination and variation in causal attributions, discrimination exposure was associated with a greater likelihood of self-reporting psychotic experiences. This is the first study to our knowledge examining discrimination and psychosis in an East Asian country, supporting the subjective experience of discrimination as a consistent risk factor for psychosis across cultural contexts. Potential limitations are the cross-sectional design due to the novel discrimination scale being administered at a single timepoint, as well as attrition over the 10-year period of the broader cohort study. Future studies should build upon our understanding of discrimination as a risk factor for psychosis, both in terms of its commonalities across cultures as well as its unique context-dependent characteristics.

## T85. Healthcare Resource Utilization 12 Months Following Initiation of Olanzapine/Samidorphan: Real-World Assessment of Patients With Schizophrenia

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**BACKGROUND:** The combination of olanzapine and samidorphan (OLZ/SAM) provides the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. OLZ/SAM treatment was associated with significant reductions in healthcare resource utilization (HCRU) in a previous 6-month pre/post study. This study examined HCRU among patients with schizophrenia in the 12 months after OLZ/SAM initiation.
**METHODS:** This retrospective analysis used administrative claims data from October 18, 2020, to December 31, 2023, from the Komodo Healthcare Map. Adults with schizophrenia and continuous enrollment ≥12 months before (baseline) and after (follow-up) OLZ/SAM initiation were eligible. Inpatient (IP) admissions, emergency department (ED) and outpatient (OP) visits, and average numbers of inpatient days/patient were compared between baseline and follow-up. A secondary analysis was conducted in patients who received OLZ/SAM treatment for the full 12 months of follow-up.
**RESULTS:** Patients (n=1287; mean age: 39 years; female: 46%) were on average persistent for 196.6 days. Proportions of patients with ≥1 all-cause, mental health (MH)-related, and

schizophrenia-related IP admissions and ED visits significantly decreased between baseline and follow-up (all P < 0.001). Mean numbers of all-cause, MH-related, and schizophrenia-related inpatient days/patient decreased significantly (all P < 0.001). Proportions of patients with OP visits were similar during baseline and follow-up. Larger reductions in IP admissions and ED visits were observed in the population receiving OLZ/SAM treatment for the entire 12-month follow-up period (both P < 0.001; n=481).
**DISCUSSION:** Among patients with schizophrenia, OLZ/SAM initiation may result in clinically meaningful reductions in real-world disease burden, as evidenced by reductions in hospital-based HCRU. Longer treatment retention was associated with improved effectiveness.

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## T86. CO-Morbid Substance Use Disorders in People With Schizophrenia in Lmics: A Scoping Review of Psychosocial Interventions

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**BACKGROUND:** This scoping review aimed to produce an overview of the current evidence on psychosocial interventions for people with co-morbid schizophrenia and substance use disorders (SUDs) in low- and middle-income countries (LMICs).
**METHODS:** The following databases were searched from inception to July 23, 2024: PubMed/MEDLINE, Global health, EMBASE, PsycINFO and Global Index Medicus. We also searched for grey literature using Google Scholar, ProQuest and Clinical trial.gov. We reported this scoping review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. Studies were eligible if they focused on any psychosocial intervention targeting substance use in people with schizophrenia from LMICs.

Review registration number Open Science Framework ID: https://osf.io/867rf

**RESULTS:** We screened 6,304 records for title/abstract, of which 138 full-text articles were assessed, and 13 articles were included for data extraction. Many of the studies (n=9) were quasi-experimental in design which were from Latin America South Asia, and four of the studies were RCTs. The primary outcomes examined were; substance use abstinence, treatment engagement and retention, reduction in psychiatric symptoms, functioning, and suicidal behaviors. The heterogeneity in outcomes, study designs, and target populations made it difficult to draw concrete conclusions regarding the optimal type, mode, dosage, and characteristics of psychosocial interventions.
**DISCUSSION:** Our review reveals that there have been few initiatives to design and test psychosocial interventions for individuals with co-morbid severe MHCs and SUDs in schizophrenia. We strongly advocate for the design and testing of feasible, acceptable, and

effective interventions, such as dual screening programs and integrated psychosocial interventions, to address both schizophrenia and substance use when they co-occur.

## T87. Integrate: Developing an Algorithmic Global Guideline for Schizophrenia

Toby Pillinger*[1], Rob McCutcheon[2], Olatunde Ayinde[3], Christoph Correll[4], Nicolas Crossley[5], Margaret Hahn[6], Heidi Taipale[7], John Kane[8], Sean Halstead[9], Oliver Howes[10], Christy Hui[11], Marco Solmi[12], Hiroyuki Uchida[13], Ioana Varvari[2], Ganesan Venkatasubramanian[14], Iris Sommer[15], Asa Konradsson-Geuken[16], Thomas Kabir[2], Nicola Warren[9], Belinda Lennox[2], Susan Rossell[17], Eric Chen[11], Dan Siskind[18]

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**BACKGROUND:** Schizophrenia affects approximately 0.7% of the global population during their lifetime and imposes a significant healthcare burden worldwide. Effective treatments exist; however, pharmacological treatments are often associated with significant side-effect burden and delays in providing optimal treatment are common. Numerous guidelines exist regarding the treatment of schizophrenia. However, existing guidelines are typically lengthy, country-specific, and often lack an evidence-based algorithmic approach, which limits their use in clinical settings. A recent review highlighted these shortcomings, and also noted inadequate guidance on maintenance treatment duration and management of negative symptoms.
**METHODS:** From May 2023, INTEGRATE (INTErnational Guidelines foR Algorithmic Treatment) authors from all United Nations regions collaborated to develop a consensus guideline for the pharmacological treatment of schizophrenia. Following an umbrella review of the literature, input from expert workshops, consensus survey, and lived experience focus groups, a consensus algorithmic guideline and associated digital tool were developed.
**RESULTS:** Key recommendations include a focus on metabolic health from treatment initiation, timely assessment and management of non-response, symptom domain-specific interventions, mitigation of side-effects, and the prompt use of clozapine in cases of treatment resistance.
**DISCUSSION:** The treatment of individuals with schizophrenia is a central component of general psychiatric practice. Effective treatments exist, but maximising therapeutic effects requires a dynamic and flexible approach involving patients in decision-making.

## T88. Addressing Barriers to COVID-19 Vaccination in People Living With Psychotic Disorders

Tammy Hall[1], Katie Atwell[1], Vera Morgan[1], Susie Hincks[2], Anna Waterreus*[1]

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**BACKGROUND:** International evidence indicates that people with psychotic disorders face increased risks from COVID-19, including higher hospitalisation and mortality rates compared to the general population. Despite calls during the pandemic to prioritise this group for vaccination, immunisation rates remained low. Vaccination uptake can be driven by access to vaccines and willingness to accept them. Understanding these dynamics is crucial for designing targeted interventions to improve vaccination rates. We explored barriers to COVID-19 vaccination for people with psychotic disorders to inform future pandemic planning.

**METHODS:** This mixed-methods cross-sectional study was conducted with 233 participants who had previously taken part in the Perth, Western Australia (WA) catchments of the National Survey of High Impact Psychosis (SHIP). A short survey was developed in conjunction with our research partner with lived experience, which comprised open- and closed-ended questions about vaccination status, COVID-19 concerns, perceived importance of vaccination, and other factors influencing vaccination decisions. Experienced mental health researchers contacted participants by phone from September 2022 to September 2023.

**RESULTS:** Reflecting WA's overall high vaccination coverage, 93.1% of respondents reported being fully vaccinated against COVID-19, 0.9% said they ceased vaccinating after their first dose, and 6% refused vaccination. While many cited barriers to accessing the vaccines, these had not prevented vaccination. Therefore, under- and non-vaccinated individuals were combined into a single 'refused vaccination' group. Over half (54.1%) of our respondents reported not being contacted about COVID-19 vaccination. All refusers denied receiving information on vaccine timing or safety while around half of vaccinated individuals had received this information (52.5% and 44.7%, respectively). Refusers reported lower trust in their general practitioner or psychiatrist compared to vaccinated individuals yet higher trust in other healthcare professionals. Participants doubting vaccination importance cited side-effect and efficacy concerns, while those valuing vaccination sought to prevent illness, provide peace of mind, and were motivated by mandate policies. Notably, 31.5% cited mandates as a reason for vaccination, with 24.7% stating it was the sole reason. However, only three participants said they felt coerced to vaccinate.

**DISCUSSION:** Although half of our participants were not approached for COVID-19 vaccination, all who were willing had overcome access barriers to complete at least a two-dose course. Mandates appear significant for this group. It is often debated whether mandates are reasonable, with many experts preferring voluntarism underpinned by strong programs delivering effective outreach. Our participants did not receive this outreach, indicating that mandates may be beneficial for cohorts facing vaccination barriers, and who may otherwise be at risk from severe illness or death. However, utilising other interventions, especially outside of emergency situations, is vital. To enhance uptake, services should train nurses and case managers to provide vaccination advice, including addressing concerns regarding side-effects. Establishing vaccination sites in hospitals or mental health services, run by staff experienced in working with people with psychotic disorders, and offering vaccinations during routine clinical appointments, could mitigate access barriers. This study emphasises the need for tailored vaccination programs and enhanced communication strategies to improve vaccination rates among people with psychotic disorders.

## T89. Non-Affective Psychosis in the Second Half of Life (NAP-2): Which Personal and Clinical Factors Influence Medication Adherence of Patients?

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**BACKGROUND:** Non-affective psychotic disorders such as schizophrenia (SCZ) are particularly debilitating in the second half of life. As a chronic condition with long-lasting symptoms, SCZ can severely impact quality of life in older age. Older SCZ patients face specific challenges that likely affect medication adherence, which is crucial for management of the illness. For instance, older adults with SCZ may face more severe cognitive impairments and social isolation, which can compromise daily functioning and access to care, in addition to experiencing negative side effects of long-term intake of antipsychotics. Non-adherence to antipsychotics can lead to symptom exacerbation, higher hospitalization rates, and increased mortality. Understanding sociodemographic, clinical, and personal factors influencing medication adherence is key to improving long-term treatment outcomes and quality of life in older SCZ patients. This study is the first of its kind to investigate adherence-related factors in this specific age group of SCZ patients. Our approach is unique and valuable since there is currently a lack of data on how adherence is influenced by both personal and clinical factors in older adults with SCZ. This research is filling a critical gap in the field and contributing to better-tailored treatments for this growing patient population.

**METHODS:** The study includes individuals with non-affective psychosis over the age of 40 with F2 diagnoses (ICD-10), which correspond to the DSM-5 diagnoses 295.90, 297.1, 298.8, and 298.9. Adherence is measured using the Medication Adherence Rating Scale (MARS), consisting of three factors: (1) intake behavior, (2) attitude towards medication, and (3) subjective negative side effects. Sociodemographic and clinical data is obtained through questionnaires and interviews, alongside symptom assessments with PANSS (Positive and Negative Syndrome Scale), SANS (Scale for the Assessment of Negative Symptoms) and SAPS (Scale for the Assessment of Positive Symptoms). Additional tests include the Mini-ICF-APP for functional impairment, the UCLA-L Scale for loneliness, and neurocognitive assessments such as the Montreal Cognitive Assessment (MoCA). The study includes n=80 patients and n=80 healthy controls. Logistic and ordinal regression models will be applied to identify predictors of adherence.

**RESULTS:** Pilot data from n=27 patients examined variables such as gender, age, relationship status, living situation, employment, education, outpatient treatment, illness duration, antipsychotic treatment duration and administration of depot antipsychotics. Significant results showed higher medication adherence for patients with longer treatment durations ($p=0.001$) and those taking somatic co-medication ($p=0.007$). Additionally, MARS factor 1 correlated positively with factor 2 ($r=0.471$) and factor 3 ($r=0.49$). Trends towards higher adherence were

observed in males, younger patients, those with higher education, and patients on depot antipsychotics.
**DISCUSSION:** These promising pilot results indicate factors that positively influence adherence in older SCZ patients. Significant associations with treatment duration, co-medication, attitude toward antipsychotics, and side effects were identified. The expanded study (n=80) will further explore these factors. Additional factors such as social contacts, relationship status, living situation, insight into the illness, and neurocognitive performance will also be analyzed. Comparisons with healthy controls will provide unique insights, enhancing the understanding of medication adherence in this population. These findings are crucial for improving treatment approaches and the quality of life for older individuals with SCZ.

## T90. Neurocognitive Performance of Elderly Patients With Non-Affective Psychosis – A Meta-Analysis

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**BACKGROUND:** Neurocognitive deficits are a core symptom of psychotic disorders and substantially impact prognosis and functioning. In elderly people with non-affective psychosis (NAP), neurocognitive decline is a factor of major societal and individual relevance, affecting treatment, prevention and burden of the disease. Despite its significance, there is a lack of consensus regarding the temporal course of cognitive impairments among patients with psychotic disorders over the lifespan, which may hinder targeted prevention and treatment for further neurocognitive decline with older age. While some studies have found an additional neurocognitive decline in old age in people with NAP compared with healthy controls, other studies have found neurocognitive deficits to remain stable over time. The latter, however, rarely included very old patients. Our study therefore aims to clarify the developmental trajectory of neurocognitive performance across the lifespan in people with NAP compared with healthy controls by conducting the most comprehensive and systematic review including meta-analysis on the topic to date. This research thus seeks to advance both scientific understanding and clinical interventions for preventing and treating cognitive impairments in the expanding population of older adults with NAP as well as to improve their health outcomes and psychosocial functioning while reducing burden of disease.
**METHODS:** We searched MedLine, PsycINFO, and Embase databases for relevant studies published until 01.09.2022 and will update the search by January 2025. We included controlled studies that have examined neurocognitive abilities in elderly patients (i.e., being 65 years old or older) with NAP compared to healthy controls, using quantitative, validated neuropsychological measures, and including specific age-related information. After study selection, summary data extraction, and risk of bias evaluation, data will be pooled in random-effects meta-analyses. Main outcome was defined as the difference between patients and healthy controls in global cognition and more specifically the difference in correlations of cognition with age. Secondary outcomes will analyze effects for cognitive subdomains. Several pre-specified sensitivity and subgroup analyses will assess the impact of possible confounders.
**RESULTS:** From 7,660 articles in the initial search, 21 studies were selected.

Preliminary results are available for verbal fluency (6 studies). The studies included data from 1,226 people: 615 patients with a confirmed NAP diagnosis and 611 healthy controls. The mean age of participants was 52.58 (±13.1), ranging from 18 to 85 years. The non-affective psychosis group demonstrated significantly worse results in verbal fluency than healthy controls in all age cohorts (SMD = -1.173; 95% CI = -1.430 – (-)0.915; p = 0.000; $I^2$ = 75.21%; tau2 = 0.142). In terms of the effect of age on cognitive decline, we found a higher rate of declining verbal fluency in the NAP group than in the healthy group (b = -0.0079; 95% CI = -0.0250 – 0.0091; p = 0.3606). Although this result was not statistically significant, the effect sizes tended to increase with increasing age.

**DISCUSSION:** Preliminary results show that people with NAP perform significantly worse in verbal fluency tests than healthy controls across all age groups. Results also indicate that people with NAP are affected by a higher rate of cognitive decline than healthy controls with age. Emerging data may therefore necessitate a paradigm shift away from the conventional model of fixed neurocognitive deficits in neuropsychiatric populations.
We anticipate presenting comprehensive results from our expanded meta-analyses at the SIRS Congress 2025. These analyses will encompass the complete dataset of included studies, examining both global cognitive function and specific cognitive domains.

## T91. Clozapine's Effect on Plasma Neuroactive Steroids and Symptoms in People With Schizophrenia Related Disorders as Compared to Other Antipsychotics

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**BACKGROUND:** Neuroactive steroids (NAS) encompass a range of cholesterol-derived molecules that are synthesized de novo by glial and neuronal cells. NAS have been implicated in mood, stress and traumatic disorders, but their role in psychotic disorders and modulation by antipsychotics is less developed. Clozapine has been shown to increase pregnenalone (a NAS and a progesterone-derived precursor of NAS), but clozapine's effect on the 5-α and β-reduced progestogens (allopregnanolone, isoallopregnanolone, pregnanolone, and epipregnanolone, respectively) is not known. Given the advantageous effect of the neuroactive steroids on mood and anxiety and their potential effects on aggression, we hypothesize that clozapine may improve mood and aggression in patients with schizophrenia related disorders (SCH) at least in part by its effect on NAS levels. Specifically, we hypothesize that clozapine increases NAS with positive allosteric modulation of GABAA receptors (allopregnanolone and pregnanolone) and decreases NAS that are negative allosteric modulators (epipregnanolone and isoallopregnanolone).
**METHODS:** Participants aged 18-64 were recruited for a 4 visit, 6-month prospective open label study that included N=26 with SCH on clozapine, N=20 with SCH on other antipsychotics (OAP) and N=15 healthy volunteers (HV). Diagnosis was confirmed using the DSM and structured clinical interview for diagnosis (SCID). Clinical assessments included the Brief

Psychiatric Rating Scale (BPRS) and the Modified Overt Aggression Scale (MOAS). At baseline, 1, 3 and 6 months, plasma was drawn, frozen at -80◦F, and assayed for NAS by the Pinna Lab at the University of Illinois Chicago (UIC) using HPLC/GC-MS.
**RESULTS:** The mean baseline plasma levels of pregnanolone were higher in the clozapine group compared to both the other antipsychotic group and HV (μ±SD: Clz 193 ±1866 vs OAP 1846 ±1820 vs HV 1031 ± 1368, p=0.03). Changes in pregnanolone over time did not differ by group (p=0.257, Cohen's d= -0.004); however, at 6 months, those on clozapine had a significant increase in pregnanolone relative to the OAP group when compared to baseline (Clz 191 ± 1540 vs OAP -966 ± 1195, F(1,29), p=0.050). Additionally, clozapine decreased epipregnanolone compared to the OAP group (p=0.047, Cohen's d= -0.387). The clozapine group showed a non-significant trend toward more improvement on Total BRPS than the OAP group (p=0.10, Cohen's d=1.20). Clozapine significantly improved the BPRS activation subscale in the clozapine relative to the OAP group (p=0.003, Cohen's d= -0.882), and a trend was noted for the anxiety and depression subscale (p=0.081, Cohen's d= -0.77). A non-significant trend towards improvement was noted for the total aggression score for clozapine vs the OAP group (MOAS total: p=0.249, Cohen's d= -0.917), and clozapine showed a significant positive effect for the violent aggression subscale score relative to the OAP group (MOAS violent aggression: p=0.052, Cohen's d= -0.982).
**DISCUSSION:** Our pilot study supports that clozapine increases a positive allosteric modulator (pregnanolone) and decreases a negative allosteric modulator (epipregnanolone) of the GABAA receptor, therefore, possibly inducing 3α-HSD at the expense of 3β-HSD and potentially contributing to the increased net effect of GABA. We also saw large effect sizes on clozapine's effects on aggression and symptoms. We will report the mediating effects of NAS on these outcomes and examine the role of childhood trauma and reproductive status on outcomes in a small sample.

## T92. Cellular Conversations With Implications for Schizophrenia: IL-6 and the 22Q11.2 Deletion Modulate Transcriptional and Cellular Responses of hiPSC-Derived Microglia-NPC Co-Cultures

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**BACKGROUND:** Both elevated interleukin-6 (IL-6) levels and genetic risk factors are associated with increased schizophrenia (SZ) risk, but the specific human mechanisms of how they interact are unclear (Perry et al., 2021). Human-induced pluripotent stem cells (hiPSCs) are valuable for studying the combined effects of genetics and IL-6 on psychosis risk. While hiPSC-derived neurons have helped clarify cytokine and genetic impacts on neurodevelopment separately, IL-6's effect on non-neuronal cells such as microglia, remain underexplored. We previously showed hiPSC-derived microglia-like cells (MGLs) respond to IL-6, unlike neural progenitor cells (NPCs) which lack IL-6 receptor expression (Couch et al., 2023). Since MGLs secrete soluble (s)IL-6Ra, the present study aimed to elicit an IL-6 response in hiPSC-derived

NPCs co-cultured with MGLs from both typical and 22q11.2 deletion genotypes, a polymorphism thought to increase SZ risk by ~40% (Schneider et al., 2014), to assess IL-6's effects on NPCs and its interaction with genetic SZ risk.
**METHODS:** To confirm trans-signaling, we exposed hiPSC-derived NPCs (N = 3 control donors) to 0.1µg/ml IL-6 for 15-180 mins with varying sIL-6Ra doses and measured STAT3-Y705 phosphorylation by immunoblotting and immunocytochemistry (ICC). NPCs and MGLs (N = 4 control donors, N = 2 with 22q11.2 deletion) were co-cultured, exposed to IL-6 for 24 hours, and analyzed by bulk RNAseq. The co-culture secretome was examined for secreted cytokines in response to IL-6. Finally, IL-6-exposed NPCs were differentiated into post-mitotic cultures and assess for changes in cell-fate acquisition and synaptic density by ICC.
**RESULTS:** NPCs responded to IL-6 by trans-signaling only, and pSTAT3 was dependent on sIL-6Ra concentration (2-way ANOVA interaction: $F(4,20) = 31.94$, $p < 0.0001$). Specifically, pSTAT3 peaked 30 mins after exposure in the nucleus (2-way ANOVA interaction $F(9,32) = 2.76$, $p = 0.016$). In co-cultures, the microglia-secreted sIL-6Ra concentration was insufficient to induce NPC trans-signaling (mean $0.32 \pm 0.009$ ng/ml), and was unchanged by IL-6 and genotype (2-way ANOVA: treatment $F(1,8) = 0.069$, $p = 0.80$; genotype $F(1,8) = 0.23$, $p = 0.65$). IL-6 significantly increased TNFα levels in co-culture media of control genotype (unpaired t-test: FC = 13.75, $t(6) = 2.63$, $p = 0.04$), and rose insignificantly in 22q11.2 genotype media (unpaired t-test: FC = 6.55, $t(2) = 0.996$, $p = 0.42$). VEGF was 3.63 times more concentrated in 22q11.2 co-cultures compared with controls. NPCs showed minimal transcriptional response to IL-6; only two differentially expressed genes (DEGs) were found in control co-cultures (TNFAIP3, PABPC1; FDR < 0.05) and none in 22q11.2 co-cultures. IL-6 robustly effected the MGL transcriptome (FDR < 0.05 DEGs; controls 43 up and 29 down in; 22q11.2 18 up and 9 down), with significant overlap between upregulated genes sets and a SZ post-mortem dataset. The 22q11.2 deletion had a greater impact on NPC transcriptomes than MGLs in vehicle-treated co-cultures (control vs. 22q11.2 DEGs: NPCs = 343, MGLs = 28; FDR < 0.05). NPC IL-6 treatment reduced vGlut1 neurite puncta density by half in subsequently differentiated 22q11.2 deletion neurons but not control neurons (Welch's t-test; control $t(3) = 0.48$, $p = 0.66$; 22q11.2 $t(1) = 15.03$, $p = 0.04$).
**DISCUSSION:** Our results highlight the need to characterize IL-6 cis- and trans-signaling in NPC and microglia development and their potential roles in SZ etiology. They emphasize the importance of including diverse neuronal and non-neuronal cell types in hiPSC-derived models to better understand IL-6's effects on neurodevelopment. Lastly, the findings suggest that the 22q11.2 deletion has cell-specific effects, impacting the NPC transcriptome more than the MGLs'.

## T93. Relationship Between Striatal Connectivity and Apathy During Phosphodiesterase 10 Inhibition in Schizophrenia: A Randomized Clinical Trial

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**BACKGROUND:** Negative symptoms in schizophrenia remain a challenge with limited therapeutic strategies. The novel compound RG7203 promotes reward learning via dopamine D1-dependent signaling and therefore holds promise to improve especially the apathy dimension of negative symptoms. When tested as add-on to antipsychotic medication apathy did not change significantly with RG7203 versus placebo. However, the response varied across patients, and a subset showed clinically relevant improvement of apathy. It remains unclear if these interindividual differences are related to neurobiological correlates.
**METHODS:** Due to the predominant binding of RG7203 in the striatum, we investigated how apathy changes with RG7203 are related to changes in cortico-striatal connectivity by computing rank correlations. We focused on cortico-striatal circuits that have been associated with apathy and previously showed connectivity alterations in schizophrenia. In a double-blind, 3-way randomized crossover study, resting state functional magnetic resonance imaging was acquired in 24 individuals with schizophrenia following a 3-week administration of placebo, 5mg or 15mg of RG7203 as add-on to antipsychotics.
**RESULTS:** We found that 5mg or 15mg of RG7203 did not lead to significant changes in striatal connectivity. However, changes in the apathy response across individuals were reflected by striatal connectivity changes. Apathy improvement with 5mg RG7203 vs. placebo was associated with increased connectivity between ventral caudate and paracingulate gyrus as well as anterior cingulate cortex. The same trend was observed for 15mg RG7203 vs. placebo, and such associations were not observed for the negative symptom dimension of expressive deficits. We additionally observed that lower connectivity of ventral caudate with paracingulate gyrus and anterior cingulate cortex during placebo was associated with greater apathy improvement during RG7203 treatment at both doses.
**DISCUSSION:** These findings suggest that striatal connectivity with paracingulate gyrus and anterior cingulate cortex was associated with apathy modulation under RG7203 treatment. Replication and further elaboration of these findings in larger clinical studies could help to advance biologically informed and personalized treatment options for negative symptoms.

## T94. Trauma Exposure and Hostile Attributional Biases in Young People With and Without Clinical High Risk for Psychosis

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**BACKGROUND:** Trauma exposure has been related to many adverse psychological outcomes, including interfering with one's ability to adaptively assess and interpret ambiguous situations. Some work has related trauma to hostile attributional biases, or the tendency to perceive other's actions as malevolent or hostile. Research suggests that psychosis spectrum disorders may be characterized by elevated hostile attributional biases; however, little is understood regarding the mechanisms that may lead to these biases. There is evidence that supports a relationship between trauma exposure and hostile attributional biases in other populations, in that history of trauma may be related to one's propensity to perceive others as hostile, but research is limited regarding this relationship in individuals with psychosis spectrum disorders. Though prior research has repeatedly found that trauma exposure is elevated in individuals at clinical high risk for

psychosis (CHR-p), there is mixed evidence about whether attributional biases are also elevated, as well as whether trauma exposure is related to attributional biases in this population. The present study sought to assess the relationship between trauma exposure and hostile attributional biases among individuals with CHR-p and healthy controls. It was hypothesized that 1) compared to healthy controls, young people at CHR-p would report more trauma exposure and higher hostile attributional biases, and 2) trauma exposure will be more strongly related to hostile attribution bias in youth at CHR-p compared to healthy controls.
**METHODS:** A sample of adolescents (n = 44; 27 CHR; 17 Control) aged 13-20 years (M = 16.98, SD = 2.14) completed self-report measures, the Childhood Trauma Questionnaire (CTQ) and the Ambiguous Intentions Hostility Questionnaire (AIHQ), which provided summary scores for trauma exposure and hostile attributional biases. Independent sample t-tests assessed group differences in trauma exposure and hostile attributional biases. Linear regressions assessed for the association between trauma exposure and hostile attributional biases across the full sample. Moderation by group was also examined.
**RESULTS:** Relative to healthy controls, young people with CHR-p reported more trauma exposure ($t(38)= -5.37$ $p < .001$; Cohen's $d=1.42$), but not hostile attributional biases ($p=.813$; Cohen's $d=.07$). Trauma exposure was not found to predict hostile attributional biases in the full sample ($p > .05$, $\beta=.23$). Follow up analyses examining moderation by group also found no moderation effect ($p > .05$, $\beta=.035$).
**DISCUSSION:** Results indicate that individuals with CHR-p have more trauma exposure, consistent with prior research, but not elevated hostile attributional biases. Other work has explored a relationship between persecutory thinking and attributional biases, which may be unaccounted for in this group-based analysis, and an important are for future research. Interestingly, a relationship was not found between trauma exposure and hostile attributional biases, but it should be noted that results may be underpowered to detect effects. Future work should explore factors that may contribute to variability in hostile attributional biases along the psychosis spectrum. The present study is in ongoing data collection and therefore may be able to continue addressing these questions, provide further evidence of factors that may contribute to development of hostile attributional biases, and inform future work examining potential protective factors that may buffer the development of hostile attributional biases. Findings also emphasize the need for ongoing research in trauma-informed care for individuals with CHR-p.

## T95. **Item-Level Analysis of Psychotic Experiences and Associated Risk Factors in Migrants and Natives: Insights From the European Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EU-GEI) Consortium**

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BACKGROUND: Psychotic-like experiences (PLEs) occur along a continuum and are associated with increased risk of psychosis and other mental health conditions (Van Os, 2009;

Linscott & Van Os, 2013). Migrants are at higher risk for psychosis, potentially due to psychological and psychosocial stressors (e.g., trauma, discrimination, and social exclusion; Bourque et al., 2011; Cantor-Graae & Selten, 2005). This study examines the factors associated with PLE in migrants and potential measurement bias using Item Response Theory (IRT) methods.

METHODS: Preliminary analyses compared total and subscale scores of the Community Assessment of Psychic Experiences (CAPE) between 230 migrants and 1,106 natives sampled across Italy, France, Spain, Holland, and the UK. Ongoing analyses employ Differential Item Functioning (DIF) and Differential Test Functioning (DTF) to examine item-level performance. Psychological- and- sociocultural factors (e.g., trauma and discrimination) will be incorporated to assess their influence.

RESULTS: Preliminary findings reveal no significant differences in total CAPE scores ($p = 0.340$) by migrant status. However, migrants exhibit significantly higher scores in the positive symptom domain ($p = 0.012$). Ongoing IRT analyses aim to identify specific items contributing to these observed subscale-level group differences and associated factors.

DISCUSSION: This research is expected to inform culturally sensitive psychosis assessments, helping to mitigate potential measurement bias among migrant populations as well as elucidate the associated factors with PLEs by migrant status.

## T96. Neurochemical Signatures in Brain Structure: Discriminating Schizophrenia Patients From Healthy Controls Through Neurotransmitter Mapping

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**BACKGROUND:** Schizophrenia (SCZ) is associated with significant structural brain alterations, including volume reductions in frontal, temporal, and parietal lobes. Recently, several studies have explored whether structural alterations co-localize with the distribution of specific neurotransmitter systems in health – an indication of neurotransmitter vulnerability – to gain insight into the underlying disease mechanism. By utilizing this co-localization approach in a machine learning framework, we aim to assess whether this approach can serve as a diagnostic tool for SCZ and provide insight into the underlying disease mechanism.
**METHODS:** Grey matter volume (GMV) maps were derived from T1-weighted structural magnetic resonance imaging scans of 445 SCZ patients (mean age = 34.0 ± 11.3, 103 females) and 414 healthy controls (HC; mean age = 34.4 ± 12.1, 185 females) across several cohorts: MIMICSS (part of the PsyCourse study), COBRE (COIN study), MCIC (COIN study), the

UCLA Consortium for Neuropsychiatric Phenomics LA5c Study, and the Munich cohort. Site-related variance was corrected using offset correction, and age- and sex-related variation were corrected using a dynamic standardization procedure. Two linear classifiers were applied using a leave-site-out nested cross-validation (CV) design (inner CV: 1x10, outer CV: 10x8). Computed within the inner CV, one classifier was trained on correlations between GMV and 25 neurotransmitter maps derived from a healthy volunteer population for cortical and subcortical regions separately using the JuSpace toolbox, while a control classifier was trained on 50 eigenvariates derived from principal component analysis. Both classifiers were then applied to remaining HC and patient groups in the cohorts to examine the classifiers' specificity for SCZ, including major depression (MDD), clinical high risk for psychosis (CHR), bipolar disorder (BD), attention deficit hyperactivity disorder (ADHD), and borderline personality disorder (BPD).
**RESULTS:** The neurotransmitter-based classifier achieved a balanced accuracy of 63.8 % and an area under the curve (AUC) of 0.70 (sensitivity: 58.2 %, specificity: 69.3 %). The PCA-based control classifier yielded a balanced accuracy of 70.4 % and an AUC of 0.80 (sensitivity: 57.8 %, specificity: 83.1 %). Significant predictors based on sign-based consistency included correlations with cortical serotonin, subcortical dopamine and GABA for the neurotransmitter model, while the control model relied on a frontotemporal cluster. The neurotransmitter classifier was also moderately sensitive for MDD (45.2 %), BPD (45.8 %), BD (40.6 %), ADHD (39.0 %), and CHR (38.5 %). Similarly, the control classifier was moderately sensitive for MDD (48.1 %) and BD (47.5 %) and less sensitive for ADHD (36.6 %), BPD (28.8 %), and CHR (17.3 %).
**DISCUSSION:** The findings indicate that co-localizing brain structural alterations with neurotransmitter maps provided moderate accuracy in distinguishing schizophrenia patients from controls, while the control model achieved accuracies comparable to existing literature. However, the significant contributions from serotonin, dopamine, and GABA systems highlight the value of gaining neurochemical insights. The sensitivity of both models to other disorders like MDD, BPD, and BD supports the notion of shared neurochemical vulnerabilities across diagnoses, though further refinement is needed to improve diagnostic specificity. This approach offers a promising avenue for understanding underlying mechanisms in psychotic and affective disorders.

## T97. Investigating the Effects of Antipsychotics on Brain Insulin Action: A Resting-State Functional Connectivity Study in Healthy Controls

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**BACKGROUND:** Antipsychotics (APs) are associated with serious metabolic adverse effects including weight gain and type 2 diabetes. Brain insulin resistance has emerged as a possible explanatory mechanism underlying these effects. Preclinical studies have shown that an acute dose of olanzapine (OLA) has a direct anti-insulin effect in the brain that is independent of

weight gain. While currently there are no methods to investigate brain insulin resistance directly, the neurophysiological response to intranasal insulin (INI) can be used as a reliable albeit surrogate marker. In this proof-of-concept study, we leveraged neural signatures of brain insulin action with INI to examine if an acute dose of OLA can disrupt brain insulin action in healthy humans.

**METHODS:** This was a single blind, crossover study in which 24 healthy volunteers (N=14 females; age = 21.8 years; BMI = 21.9 kg/m2) received 4 different treatment combinations, 2-4 weeks apart, in a random sequence. Participants received 5 and 10 mg of OLA (or PL) over two days, which was followed by functional MRI (fMRI) testing on a third day. A 10-minute resting state fMRI scan was acquired 15 minutes after administering 160 IU of INI or INP. A repeated measures ANOVA was conducted to determine any changes in resting-state functional connectivity (rsFC) with INI/PL relative to INP/PL (a whole-brain false discovery rate (FDR) corrected threshold of $p < 0.05$ was used). The subsequent effect of OLA was investigated by restricting the second-level analysis to the seeds that were noted to have significant rsFC changes with INI/PL.

**RESULTS:** Significantly higher rsFC was found in the INI/PL condition compared to INP/PL between the anterior cingulate cortex (ACC) of the salience network (SN) and the right lateral parietal cortex (LPC) of the default mode network (DMN) (T= 3.64, whole brain p-FDR=0.029). These findings were significant while controlling for age, sex, and BMI. rsFC between SN-ACC and DMN-LPC in the INI/PL condition was significantly higher than that in the INP/OLA (T=2.30, p- FDR=0.032) and INI/OLA (T=3.08, p-FDR=0.006) conditions. There was no difference in rsFC between the INI/OLA and INP/OLA or INP/PL conditions. Interestingly, these findings were only observed among male participants alone.

**DISCUSSION:** In this pilot investigation, increased rsFC was observed between regions of the salience and default mode networks with INI/PL compared to INP/P; this was subsequently diminished with the introduction of OLA. Interestingly, this finding was only observed among the male participants, suggesting that there may be an intrinsic sex difference between males and females in terms of brain insulin sensitivity. Further research is needed to unequivocally delineate how APs may induce deficits in brain insulin action in relation to neurocognitive processes.

## T98. Disparities in Accelerated Brain Aging in Recent-Onset and Chronic Schizophrenia

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**BACKGROUND:** Patients with schizophrenia experience accelerated aging, accompanied by abnormalities in biomarkers such as telomere length. Brain age prediction based on neuroimaging data has gained significant attention in schizophrenia research, with increased brain-predicted age difference (brain-PAD) consistently reported. However, the clinical implications of brain-PAD and its relationship with illness duration remain unclear.

**METHODS:** We developed brain age prediction models using structural MRI data from 10,938 healthy individuals obtained from 20 public databases. The models were validated on an independent test dataset comprising healthy controls (n=79), patients with recent-onset schizophrenia (n=57), and patients with chronic schizophrenia (n=71). Group comparisons and the clinical implications of brain-PAD were analyzed using multiple linear regression. Feature importance was assessed using SHapley Additive exPlanations (SHAP) values. Group differences in SHAP values and group-by-SHAP value interactions were also investigated
**RESULTS:** Patients with recent-onset schizophrenia and chronic schizophrenia exhibited increased brain-PAD values of 1.2 and 0.9 years, respectively, compared to healthy controls. Significant group differences in SHAP values were identified in the right lateral prefrontal area (FDR p=0.022), with group-by-SHAP value interactions observed in the left prefrontal area (FDR p=0.049). A negative association between brain-PAD and FSIQ in chronic schizophrenia was noted but did not remain significant after correction for multiple comparisons.
**DISCUSSION:** Brain-PAD increases were more pronounced in the early phase of schizophrenia. Regional brain abnormalities contributing to brain-PAD may vary with illness duration. Future longitudinal studies are required to address limitations related to sample size, heterogeneity, and the cross-sectional design of this study.

## T99. The Localization for Aberrant Salience and Functional Connectivity of the Midbrain-Striatum Circuit in Schizophrenia: An Exploratory Resting-State FMRI Study

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**BACKGROUND:** Schizophrenia spectrum disorders are predominantly characterized by positive symptoms, including hallucinations and delusions. Recently, the distinct roles of the striatal subregions have been considered as the limbic ventral striatum in emotional, cognitive, and reward processing, the executive dorsal striatum in executive functions, and the sensorimotor caudal striatum in sensory and motor processing. Research in rodent models of schizophrenia has suggested that abnormalities in the ventral stream of the midbrain-striatum circuit (MSC) may contribute to aberrant salience, whereas human PET and primate studies have shown that psychiatric symptom severity and salience encoding are associated with the dorsal stream of the MSC. The precise relationship between these neural pathways and the development of delusions or hallucinations remains unclear, as no study has identified salience localization in the human MSC.
**METHODS:** To address this, a seed-based functional connectivity (FC) analysis was performed in 116 patients with schizophrenia spectrum disorders and 224 healthy controls (matched with sex and age), with six striatal subregions (limbic [defined as ventral], executive and sensorimotor [defined as dorsal and caudal] in left and right) as seed ROIs and one midbrain (VTA+SN) as target mask. The Aberrant Salience Inventory (ASI) was used, a questionnaire that captures the subjective experience of aberrant salience in three subscales(① the enhanced interpretation and

emotionality, ② unveiling experiences, ③ the sharpening of senses). We tested 1) the existence of a specific localization (ventral stream or dorsal stream) in human MSC, 2) the interaction between the diagnosis and the ASI subscale scores on the FC of the MSC, as well as the main effect of diagnosis/ASI. Potential correlations with PANSS, DOI and antipsychotic use were also analyzed.
**RESULTS:** Our results showed that the limbic striatal FC to a broad region of the midbrain (VTA+SN) was stronger than the executive/sensorimotor striatal FC to the midbrain (VTA+SN) in the whole group ($p < 0.0001$, TFCE-wise, family-wise error [FWE] corrected for contrasts and subregions). An interaction between Factor 3 (The sharpening of senses) of the ASI and diagnosis was found in the FC between the left sensorimotor striatum and the midbrain (less in the VTA but greater in the ventral SN) ($p < 0.5$, TFCE-wise, FWE corrected for factors, groups, contrasts and subregions). In addition, Factor 3 scores were positively correlated with the PANSS positive, cognitive and depressive symptom scores in the SCZ ($p < 0.05$, $r=0.26$, 0.37 and 0.47 respectively, Bonferroni corrected for factors). On the other hand, we found the main effect of diagnosis (reduced connectivity in SCZ than in HC) between the left limbic striatum and the VTA+ventral SN ($p < 0.05$, TFCE-wise, FWE corrected for factors, groups, contrasts and subregions), which was negatively correlated with PANSS depressive symptom scores ($p < 0.05$, $r=-0.17$, Bonferroni corrected for factors). We also found that Factor 1 (The enhanced interpretation and emotionality) showed a negative effect on the FC between the left limbic striatum and the VTA+SN during the main effect of ASI, but it did not remain significant after multiple comparison correction ($p > 0.05$, TFCE-wise, FEW corrected for subregions). No significant effect was observed in the correlation analysis of antipsychotic use or duration of illness.
**DISCUSSION:** Our study revealed a distinct stronger limbic striatal-midbrain (VTA+SN) connectivity in all participants, emphasizing the limbic dominance of the human midbrain-striatum circuit in the neural processing. Notably, the interaction between Factor 3 (the sharpening of senses) of the ASI and altered sensorimotor striatal connectivity to the ventral SN and VTA, showing an inverse correlation in the SCZ and HC, is consistent with the previous animal studies proposed functional feedback that limbic ventral striatal efferent influence dopaminergic neurons in the VTA and ventral SN, which in turn project to more sensorimotor striatal areas. This finding also pointed to disrupted sensory and motor integration may be involved in aberrant salience processing of schizophrenia. Reduced limbic striatal connectivity to VTA+ventral SN was correlated with more severe depressive symptoms in SCZ, which is in line with previous studies, suggesting that the abnormality in the limbic striatum is associated with the dysregulation of mood and emotion. These findings highlight the distinct involvement of the midbrain (the VTA + ventral SN)-sensorimotor (caudal) striatum circuit in aberrant salience.

## T100. Altered Hypothalamic Subunit Volumes in Schizophrenia and At-Risk Mental State

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**BACKGROUND:** Hypothalamus is involved in several pathways which are impaired in schizophrenia (SZ) patients such as hypothalamic-pituitary-adrenal (HPA) axis activity, circadian rhythm regulation, and regulation of appetite and satiety. Recent studies suggest that such disruptions are also seen in individuals with at-risk mental state (ARMS).
**METHODS:** Eighty-one SZ patients, 56 individuals with ARMS, and 90 healthy controls were recruited at the Toyama University hospital. Subjects underwent a 3-D T1-weighted magnetic resonance imaging (MRI) scanning using a 3-T scanner. Five hypothalamic subunits were automatically extracted by FreeSurfer (version 7.2). The volumes of subunits were compared by the repeated measures multivariate analysis of covariance. Correlations between clinical/neurocognitive measures and subunit volumes were examined by calculating Pearson's partial correlation coefficients.
**RESULTS:** The volume of the left tubular-inferior hypothalamic subunit was significantly larger in the SZ and ARMS groups compared with the healthy controls. On the other hand, both SZ and ARMS subjects exhibited significantly smaller volume for the right tubular-superior hypothalamic subunit relative to the heathy subjects. There were no significant correlations between hypothalamic subunit volumes and clinical/cognitive measures.
**DISCUSSION:** The regional volume anomalies in hypothalamus may underlie the disrupted hormonal and autonomous nervous system such as HPA-axis dysregulation and circadian rhythm disruption in SZ and ARMS.

## T101. Real World Expression of Positive, Negative, and Disorganized Schizotypy: Converging Evidence Across Nine Experience Sampling Methodology Studies

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**BACKGROUND:** Schizotypy provides a useful and unifying construct for understanding subclinical and clinical expressions of schizophrenia-spectrum psychopathology. Schizotypy (and by extension schizophrenia) has a multidimensional structure with positive, negative, and disorganized dimensions. We used experience sampling methodology (ESM) to demonstrate the real-world expressions of positive, negative, and disorganized schizotypy in nine independent studies.
**METHODS:** ESM data were collected from 2,663 nonclinically ascertained participants. The nine studies were conducted across 20 years in two different countries. Participants completed either the Wisconsin Schizotypy Scales (studies 1-5) or the Multidimensional Schizotypy Scale (studies 6-9). Participants were signaled 8 times daily for one week to complete ESM surveys assessing a wide array of affect, activities, social functioning, and schizotypic experiences in daily life.
**RESULTS:** The results were strikingly consistent across the nine studies (n=2,663). Positive schizotypy was robustly associated with psychotic-like experiences in daily life. Negative schizotypy was associated with reduced positive affect, diminished social contact and closeness, diminished thoughts, and flattened affect. Disorganized schizotypy was robustly associated with disorganized thoughts and behavior, dysregulated emotions, elevated negative affect, reduced

positive affect, and feeling rejected by others. Subsequent analyses indicate distinct temporal patterns of affect and schizotypic experiences for the three dimensions.
**DISCUSSION:** The findings demonstrate: 1) support for the multidimensional model of schizotypy as a comprehensive framework for understanding schizophrenia-spectrum psychopathology, 2) robust and reliable results that the three schizotypy dimensions are associated with distinct, hypothesized patterns of symptoms, impairment, and experiences in daily life, and 3) ambulatory assessment provides powerful approaches for assessing the phenomenology, context, and dynamics of psychopathology in real world settings. The consistency of the findings across time and samples is especially notable given the prominent and often unaddressed replication crisis in psychology and psychiatry.

## T102. Neurometabolites in Antipsychotic-Responsive Versus Non-Responsive Psychosis: A Mega-Analysis

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**BACKGROUND:** Understanding the mechanisms that contribute to antipsychotic response/non-response in psychosis may be helpful to predicting outcome or refining targets for new interventions. Some 1H-MRS studies suggest that regional neurometabolite levels may vary with

antipsychotic treatment response, with poor treatment response being associated with elevated glutamate levels in the Medial Frontal Cortex (MFC). However, not all studies have reported this finding. This study presents collaborative research, combining individual datasets relating to neurometabolites and antipsychotic treatment response in a mega-analytic approach, to increase power to detect smaller effects and allow investigation of contributing variables.
**METHODS:** A systematic literature search was conducted using The Web of Science database to identify 1H-MRS studies reporting metabolite levels (Glu, Glx, Gln, NAA, Cho, mI, GABA, GSH) in patient groups classified by antipsychotic treatment response (responders and non-responders) and healthy controls. The authors of the identified studies were invited to provide individual participant neurometabolite data. Where studies included more than one timepoint, the baseline data was used for analyses. Neurometabolite levels were compared between groups using linear mixed models with study as a random factor. Regions of interest included the MFC (including the anterior (ACC) and midcingulate cortex (MCC)), Dorsolateral Prefrontal Cortex (DLPFC), thalamus, and basal ganglia. Subgroup analyses investigated the impact of differences in patient subgroups (defined as 'treatment resistant' or 'non-responsive' but below the threshold for treatment resistant), study design (cross-sectional or prospective), MFC voxel placement (ACC or MCC) and metabolite correction method (CSF or creatine scaled).
**RESULTS:** Data were available from 19 studies and a total of 1277 participants, comprising data from 505 treatment non-responders (NR), 458 treatment responders (R), and 314 healthy controls (HC). In the MFC, Glx (Estimate (E) = 0.5259, P= 0.0037), NAA (E = 0.2532, P= 0.011), mI (E = 0.283, P = 0.004), choline (E = 0.0626, P= 0.0419) and creatine (E = 0.263, P= 0.0182) were elevated in treatment non-responders compared to treatment responders; whereas in the DLPFC glutamate (E = 0.628, P= 0.0028) was lower in treatment non-responders compared to responders. In subsequent subgroup analyses, in the MFC glutamatergic metabolites were elevated in treatment non-responders compared responders in studies reporting CSF corrected values (E = 0.635, P= 0.003), with voxels in the anterior cingulate (E = 0.278, P= 0.038) and in studies employing prospective designs (E=0.822, P= 0.003); MFC mI was elevated in non-responders compared to responders and controls for studies with voxels in the mid-cingulate (R vs NR: E=0.436, P= 0.0181, NR vs HC: E=0.727, P= 0.0001) and CSF corrected metabolites (R vs NR: E = 0.399, P = 0.0097, R vs HC: E = 0.428, P= 0.0145, NR vs HC: E = 0.827, P < .0001); and MFC choline was elevated compared to controls in studies with treatment-resistant samples (E = 0.1928, P= 0.0001) and reporting CSF corrected values (E = 0.1711, P= 0.0003).
**DISCUSSION:** This mega-analysis further adds to evidence showing increases MFC glutamate metabolites may be related to, and predictive of, a poor antipsychotic response in psychosis. Additionally, our findings extend glutamatergic theories of antipsychotic response to implicate wider neurometabolites, related to neuronal energy metabolism (NAA and creatine), glial activation (mI) and membrane turnover (choline). These associations may be more apparent when applying voxel CSF correction and show regional specificity within the MFC.

## T103. Aberrant Preparation of Hand Movement in Schizophrenia Spectrum Disorder: An FMRI Study

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**BACKGROUND:** Schizophrenia spectrum disorder (SSD) is linked to impaired self-other distinction and action feedback monitoring, largely stemming from sensory-motor predictive mechanisms. However, the neural correlates of these predictive processes during movement preparation are unknown. Here, we investigated whether patients with SSD exhibit aberrant sensory-motor predictive processes reflected in neural activation patterns prior to hand movement onset
**METHODS:** Functional MRI data from patients with SSD (n = 20) and healthy controls (n = 20) were acquired during actively performed or passively induced hand movements. The task required participants to detect temporal delays between their movements and video feedback, which either displayed their own (self) or someone else's (other) hand moving in accordance with their own hand movements.
**RESULTS:** Patients compared to healthy controls showed reduced preparatory blood-oxygen-level-dependent activation (active > passive) in clusters comprising the left putamen, left insula, left thalamus, and lobule VIII of the right cerebellum. Reduced activation in the left insula and putamen was specific to own-hand feedback. Additionally, patients with SSD revealed reduced suppression (passive > active) in bilateral and medial parietal (including the right angular gyrus) and occipital areas, the right postcentral gyrus, cerebellum crus I, as well as the left medial superior frontal gyrus. Ego-disturbances were negatively correlated with left insula and putamen activation during active conditions, and with right angular gyrus activation patterns during passive conditions when own-hand feedback was presented.
**DISCUSSION:** These findings suggest that group differences are primarily evident during preparatory processes. Our results show that this preparatory neural activation is further linked to symptom severity, supporting the idea that the preparation of upcoming events as internal predictive mechanisms may underlie severe symptoms in patients with SSD. These findings could improve our understanding of other deficits in action planning, self-monitoring, and motor dysfunction in various psychiatric, neurological, and neurodegenerative disorders.

## T104. Disruptions in Intersubject Variability of Functional Connectomes Across Schizophrenia, Major Depressive Disorder, and Bipolar Disorder

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**BACKGROUND:** Empirical evidence suggests that psychiatric disorders such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are associated with alterations in brain function and connectivity. However, very limited research has explored transdiagnostic disruptions in functional connectome variability across these psychiatric disorders. The mechanisms underlying intersubject variability in functional brain architecture across these disorders remain unclear. This study aimed to examine the patterns of intersubject variability in functional connectomes (IVFC) in SCZ, BD, and MDD using a transdiagnostic approach to identify shared and disorder-specific neural correlates.
**METHODS:** We recruited 78 patients with SCZ, 43 with MDD, 44 with BD, and 85 healthy controls (HCs) to undertake structural MRI and resting-state fMRI scanning. All participants received rating on the Clinical Assessment Interview for Negative Symptoms (CAINS), while only patients received the rating on the Positive and Negative Syndrome Scale (PANSS). We examined the IVFC across these participants and performed group comparisons to identify transdiagnostic and disorder-specific patterns of IVFC. Additionally, we also examined correlations between IVFC and clinical variables in patients.
**RESULTS:** Our findings showed that SCZ patients exhibited significantly higher global mean variability ($p < .001$) and lower standard deviation of variability ($p < .001$) than HCs, while BD patients exhibited higher global mean variability ($p < .001$) but no difference in standard deviation ($p = 1.000$). MDD patients exhibited no significant difference in global mean variability ($p = .053$) but higher standard deviation ($p = .016$, Bonferroni-corrected). Network-level analyses showed significantly higher IVFC in the Limbic, Salience, Somatomotor, and Subcortical Networks across all three patient groups. Both SCZ and BD patients also exhibited significantly higher IVFC in the Frontoparietal Control and Default Mode Networks comparing to HCs ($p < .05$, Bonferroni-corrected). Further analysis based on ROI-level showed significant IVFC alterations in multiple regions across patient groups. SCZ patients exhibited 29 regions with significant higher IVFC within the Default Mode, Salience, and Limbic Networks. BD patients exhibited 6 regions with significantly increased IVFC within the Default Mode and Salience Networks, while MDD patients exhibited 2 regions with significantly higher IVFC within the Limbic Network ($p < .05$, FDR-corrected). Notably, regions with IVFC alterations observed in the BD and MDD groups were also present in SCZ patients.
**DISCUSSION:** The findings demonstrated a gradient of connectomes disruption across SCZ, MDD and BD patients. SCZ patients displayed the most widespread alterations, with significantly higher IVFC compared to HCs, followed by BD patients and MDD patients.

## T105. Are There Shared Genetic Effects Between Schizophrenia and Voxel-Wise Neural Activation Across Multiple Cognitive Tasks? A Multiplex Extended Pedigree Study

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**BACKGROUND:** Schizophrenia is a highly heritable disorder; however, understanding how schizophrenia genetic risk affects brain pathology is not well understood. Performance on cognitive tasks have shown poorer performance in both patients and their family members and performance is both heritable and genetically correlated with schizophrenia. Examination of brain activation during cognitive tasks should provide an important window on the brain effects of genetic risk for schizophrenia. The present study therefore sought to examine the degree to which voxel-wise brain activation across six different cognitive tasks may reflect effects of schizophrenia genetic risk using an extended pedigree design.
**METHODS:** The total sample for the study includes 1306 participants, of which 538 provided quality fMRI data (36 schizophrenia probands from families with two or more first degree relatives with schizophrenia, 209 of their relatives (1st to 4th degree), and 293 unrelated controls). Six cognitive task-based fMRI measures were included: abstraction and mental flexibility, sustained attention, verbal memory, visuo-spatial memory, emotion identification, and facial memory. Voxel-wise brain activation for 139,034 voxels comparing task activation to a fixation baseline were extracted for each of the tasks. Heritability of all voxels for each task were computed and those that were significantly heritable were then assessed for their genetic correlation with schizophrenia using SOLAR-Eclipse. Heritability and genetic correlations were corrected for multiple comparisons using FDR correction.
**RESULTS:** Performance averaged across all 6 tasks was significantly heritable ($h^2=0.55$, $p < 0.001$) and genetically correlated with schizophrenia ($Rg=-0.48$, $p < .001$), with lower performance correlated with a diagnosis of schizophrenia ($Rp=-0.55$, $p < .001$). A total of 16,392 voxels (11.79% of all voxels assessed) were significantly heritable, for activation averaged across all tasks. Of the significantly heritable voxels for each task, and aggregated across all tasks, 3,295 (2.37%) brain-wide voxels were significantly genetically correlated with schizophrenia. This included 907 frontal voxels (2.10%), 465 temporal voxels (1.87%), 545 parietal voxels (2.19%), 760 occipital voxels (2.79%), 441 paralimbic voxels (3.99%), and 177 subcortical voxels (2.20%).
**DISCUSSION:** Numerous measures of voxel-wise brain activation (3,295 voxels) were found to be heritable and genetically correlated with schizophrenia. Aggregated across tasks, approximately two percent of voxels spread widely across the brain were significantly genetically correlated with schizophrenia, indicating significant effects of genetic risk for schizophrenia on brain activation during cognitive tasks. These results suggest advantages of assessing a wide range of cognitive functions to better capture the impact of genetic risk for schizophrenia on neural functioning.

## T106. White Matter Integrity and Verbal Memory Following a First Episode of Psychosis: A Longitudinal Study

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**BACKGROUND:** Studies of white matter differences in psychotic disorders have reported lower fractional anisotropy (FA), an MRI based measure, in individuals with schizophrenia relative to controls, but the evidence in First Episode Psychosis (FEP) samples remains equivocal. Many cross-sectional FEP studies failed to reveal group differences in FA, whereas the few available longitudinal studies observed a reduction in FA in certain regions relative to controls. Importantly, these studies were limited by short follow-up periods (6 and 12 weeks, respectively), and did not investigate the relationship between changes in FA and verbal memory, the cognitive domain most impaired in FEP. However, some cross-sectional examinations found positive correlations between verbal memory and FA in the anterior limb of the internal capsule and the cingulum. In the present study, we aimed to examine, over 18 months, longitudinal changes in FA and their association with changes in verbal memory in a large sample of individuals with a FEP.
**METHODS:** Eighty Individuals with a FEP aged 18-35 were recruited from the 2-year Prevention and Early Intervention for Psychosis Program (PEPP) located in the catchment area of Southwest Montreal. Following clinical stabilization, they were scanned and assessed within the first 3 months of admission to PEPP and at months 6, 12, and 18. Fifty-five healthy controls were similarly scanned four times over 18 months. Verbal memory was assessed using the logical memory subtest of the Wechsler Memory Scale shortly prior to the scan at every timepoint. Two successive whole-brain diffusion-weighted images were acquired using a single-shot EPI sequence parallel to the anterior-posterior commissural plane. Preprocessing of diffusion images was performed using the FMRIB software library tools. Subsequent diffusion image processing was performed using MRtrix 3.0. Tract-based spatial statistics were generated using the procedure outlined by the ENIGMA consortium-DTI group where each subject's FA map was skeletonized and used to extract the average FA per white matter region using the JHU-White matter parcellation. Group differences in FA and verbal memory over time were examined using linear mixed-effects models with age, sex, and years of education as covariates. Tests were corrected for multiple comparisons and considered significant at a 5% false discovery rate.
**RESULTS:** At baseline, the FEP group was 62.5% male and 37.5% female, and the healthy control group was 65.4% male and 34.6% female. Individuals with a FEP had fewer years of education ($t(133)=3.90$, $p < .001$), and lower IQ relative to controls ($t(133)= 3.66$, $p < .001$).

We observed no significant effect of group in FA over time after adjusting for multiple comparisons (all corrected p's > .92). Similarly, there was no significant effect of time in any ROIs (all corrected p's=.97). There was also no significant interaction of group and time on FA (all corrected p's=.99). Furthermore, the independent linear mixed-effects models relating verbal memory to FA per group revealed no significant differences in any ROI for both FEP (all corrected p's > .16) and controls (all corrected p's > .20). Finally, we found no significant interactions between verbal memory and group across all ROIs (all corrected p's > .78) and no significant interactions between verbal memory, group, and time across all ROIs (all corrected p's=.99).

**DISCUSSION:** In this 18-month longitudinal study, we observed no change in FA over time. Furthermore, FEP and controls did not significantly differ in FA, and there was no relationship between change in FA and change in verbal memory over time. Our results are consistent with previous work that found no differences in FA between FEP and controls early in the course of illness but inconsistent with some longitudinal studies with much shorter timeframes of 6 and 12 weeks. It is possible that group differences are small in the early stages of psychosis but progressively evolve over longer time periods. Relative to other imaging markers such as grey matter or volume, white matter appears stable early on. Indeed, studies in later stages of the illness do find changes in FA, suggesting FEP as a critical window of intervention. Future studies should follow individuals with a FEP for longer timeframes and integrate different measures of diffusion (e.g., mean diffusivity) to capture a more comprehensive picture of white matter changes over time.

## T107. Hippocampal Subfield Trajectories in Negative Symptom Subgroups Following a First Episode of Psychosis

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**BACKGROUND:** Persistent negative symptoms (e.g., avolition, anhedonia, alogia) impact up to 30% of individuals diagnosed with a first episode of psychosis and greatly impact functional outcomes. Within those with persistent negative symptoms (NS) there are different NS profiles which are thought to indicate distinct pathophysiologies. These NS profiles include those with primary PNS and secondary PNS (concomitant with positive, depressive, or extrapyramidal symptoms).
The hippocampus has been proposed as central to the development of schizophrenia. Additionally, it has been associated with NS, showcasing different trajectories particularly in the left hippocampus across various NS profiles. However, the specific influence of hippocampal subfields on NS remains unexplored, even though these subregions play distinct roles and are differently affected by the progression of illness.

**METHODS:** Longitudinal volumetric trajectories within nine bilateral subregions of the hippocampus were investigated in 59 patients with first-episode psychosis and 59 healthy controls over 1.5 years. Generalized estimating equations were created to investigate main effects of time and group (control, non-PNS, primary PNS, secondary PNS), and their interaction. Model was controlled for relevant factors and multiple testing corrections were applied using the false discovery rate.
**RESULTS:** Left mamillary body showed a significant Group*Time interaction ($\chi2$=23.951 , df= 9, p uncorrected =0.004). Left CA2/CA3 showed a significant Group*Time interaction ($\chi2$=25.117, df= 9, p uncorrected =0.003). Both were significant after correcting for multiple testing.
**DISCUSSION:** This study emphasizes unique trajectories within hippocampal subfields, underscoring the significance of examining individual subfields alongside the entire

hippocampus. Our findings suggest that diverse NS profiles correspond to differing trajectories within specific subfields, implications on research and on our understanding of the disorder will be discussed

## T108. A Systematic Review of Structural And Functional Magnetic Resonance Imaging Studies on the Neurobiology of Depressive Symptoms in Schizophrenia Spectrum Disorders

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**BACKGROUND:** Depressive symptoms in Schizophrenia Spectrum Disorders (SSDs) negatively impact suicidality, prognosis, and quality of life. Despite this, efficacious treatments are limited, largely because the neural mechanisms underlying depressive symptoms in SSDs remain poorly understood. We conducted a systematic review to provide an overview of studies that investigated the neural correlates of depressive symptoms in SSDs using neuroimaging techniques.
**METHODS:** We searched MEDLINE, PsycINFO, EMBASE, Web of Science, and Cochrane Library databases from inception through June 19, 2023. Specifically, we focused on structural and functional magnetic resonance imaging (MRI), encompassing: (1) T1-weighted imaging measuring brain morphology; (2) diffusion-weighted imaging assessing white matter integrity; or (3) T2*-weighted imaging measures of brain function.
**RESULTS:** Our search yielded 33 articles; 14 structural MRI studies, 18 functional (f)MRI studies, and 1 multimodal fMRI/MRI study. Reviewed studies indicate potential commonalities in the neurobiology of depressive symptoms between SSDs and major depressive disorders, particularly in subcortical and frontal brain regions, though confidence in this interpretation is limited.
**DISCUSSION:** The review underscores a notable knowledge gap in our understanding of the neurobiology of depression in SSDs, marked by inconsistent approaches and few studies examining imaging metrics of depressive symptoms. Inconsistencies across studies' findings emphasize the necessity for more direct and comprehensive research focusing on the neurobiology of depression in SSDs. Future studies should go beyond "total score" depression metrics and adopt more nuanced assessment approaches considering distinct subdomains. This could reveal unique neurobiological profiles and inform investigations of targeted treatments for depression in SSDs.

## T109. Diazepam Modulates Hippocampal CA1 Functional Connectivity in People at Clinical High-Risk for Psychosis

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**BACKGROUND:** Identifying novel pharmacological interventions for people at clinical high-risk for psychosis (CHR-P) is a significant unmet clinical need. Preclinical evidence suggests that pharmacological enhancement of hippocampal γ-aminobutyric acid (GABA) signalling through diazepam administration normalises downstream brain function in this circuit and prevents the emergence of psychosis-like phenotypes. Hippocampal network dysfunction, including a cortico-limbic-striatal circuit with relevance to psychosis, originating from the anterior CA1 subfield has been observed in people at CHR-P, and therefore represents a potential pharmacological target for psychosis prevention. However, mechanistic evidence of these effects in humans is lacking. The aim of this study was to determine whether a single dose of diazepam would normalise CA1 and anterior hippocampal functional connectivity (FC) alterations with this cortico-limbic-striatal circuit.

**METHODS:** In this randomised, double-blind, placebo-controlled, crossover study, 18 CHR-P individuals were studied twice using magnetic resonance imaging (MRI) three weeks apart: once following a single dose of diazepam (5 mg) and once following placebo (50 mg ascorbic acid). FC was measured using a multi-echo resting-state functional MRI (rs-fMRI) sequence and data from 20 healthy controls were used for comparison. rs-fMRI data was preprocessed using fMRIPrep, SPM, FSL, and CONN, including robust TE-dependent denoising using TEDANA. Study-specific CA1 subfield and anterior hippocampus masks were used as seeds to calculate FC with the ventromedial prefrontal cortex (vmPFC), amygdala, and nucleus accumbens (NAc). Mixed-effects models (FLAME-1 in FSL) investigated the effect of group (CHR-P placebo/diazepam vs. HC, controlling for age and sex) and condition (CHR-P diazepam vs. placebo, controlling for fatigue) on seed FC to each region per hemisphere. Small volume correction and voxel-level thresholding were used, with significance set at $P < 0.05$ (FWE-corrected). Multiple comparison corrections for the number of models was done using FDR correction.

**RESULTS:** In the placebo condition, CHR-P individuals showed significantly lower CA1 FC to the vmPFC ($Z=3.17$, $PFWE=0.002$) and NAc ($Z=2.94$, $PFWE=0.005$) compared to HC. In CHR-P individuals in the diazepam compared to the placebo condition, CA1-vmPFC FC was significantly increased ($Z=4.13$, $PFWE=0.008$), and in CHR-P individuals in the diazepam condition, both CA1-vmPFC and CA1-NAc FC were normalised to HC levels. In contrast, compared to HC, CA1-amygdala FC was significantly lower contralaterally and higher ipsilaterally in CHR-P individuals under both the placebo and diazepam conditions (lower contralaterally: placebo $Z=3.46$, $PFWE=0.002$; diazepam $Z=3.33$, $PFWE=0.003$; higher ipsilaterally: placebo $Z=4.48$, $PFWE < 0.001$; diazepam $Z=4.22$, $PFWE < 0.001$). No significant

differences in anterior hippocampus FC were found between groups or conditions for any cortico-limbic-striatal regions.
**DISCUSSION:** This study demonstrates that a GABA-enhancing compound can partially restore alterations in hippocampal CA1 FC in CHR-P individuals, suggesting they might be useful in the treatment of this clinical group. Future studies using longer treatments should aim to map these neurobiological changes onto symptoms and clinical outcomes such as psychosis prevention.

## T110. Muscarinic M1 Receptor Availability in Schizophrenia: An In Vivo Pet Imaging Study

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**BACKGROUND:** Muscarinic M1 receptors are G-protein coupled receptors that are present throughout the cortex and subcortical regions. Converging lines of evidence from postmortem studies provide strong evidence that brain muscarinic M1 receptor deficit is present in a subset of schizophrenia (SZ) patients. M1 receptors are an important target for the treatment of SZ and recently, the FDA approved COBENFY which contains the muscarinic M1/M4 agonist xanomeline, as the first non-dopaminergic medication for the treatment of schizophrenia. The development of a novel positron emission tomography (PET) ligand, [11C] LSN3172176 ([11C]EMO), at Yale PET Center has made it possible to examine in vivo brain muscarinic M1 receptor availability in schizophrenia (SZ) and concurrently, elucidate the relationship of M1 receptors to symptom severity.
**METHODS:** We compared M1 receptor availability in SZ patients who were not on anticholinergics (n=11) and age-, gender-matched healthy controls (n=10) using [11C]EMO and the High Resolution Research Tomograph (HRRT), a PET scanner with high sensitivity and resolution available for human brain imaging. The one-tissue compartment model (1TC) was applied to regional time-activity curves (TACs) and the distribution volume (VT) values were computed.
**RESULTS:** Compared to healthy controls, patients with schizophrenia showed significant reductions in M1 receptor availability (VT) across several cortical and subcortical regions of interest (ROI), including frontal ( -17%, $p < 0.05$), temporal (-19%, $p < 0.05$), parietal (-19%, $p < 0.05$), occipital (-21%, $p < 0.05$), hippocampus (-18%, $p < 0.05$), caudate (-19%, $p < 0.05$), amygdala (-22%, $p < 0.05$), and ventral striatum (-23%, $p < 0.05$). There were no significant correlations between M1 receptor availability and symptom severity as measured by the PANSS (Total score, subscale scores and Marder Factors). M1 receptor availability was also not correlated with antipsychotic dose (CPZ equivalents).
**DISCUSSION:** This is the first in vivo PET imaging study of muscarinic M1 receptor availability in schizophrenia using [11C]EMO. We show that muscarinic M1 receptor availability is lower across several cortical and subcortical regions, including hippocampus and ventral striatum and supports the potential for M1 as a target for developing treatments for SZ.

## T111. Formal Thought Disorder Across Psychiatric Disorders: Prevalence, Brain Structural And Functional Correlates

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**BACKGROUND:** Formal thought disorder (FTD) involves impairments in language production and thought processes. While commonly studied in schizophrenia-spectrum disorders (SSD), FTD is also significantly prevalent in Major Depressive Disorder (MDD), with rates up to 53%. Despite this, comprehensive studies characterizing FTD in acute MDD using both operationalized rating scales and neurobiological measures are surprisingly scarce.
**METHODS:** This study assessed the prevalence and severity of FTD in n=758 acute MDD patients compared to age, sex, and education-matched healthy controls (HC) and n=160 SSD patients. Whole-brain MRI analyses were employed to explore associations between FTD and MRI derived gray (GMV) and white matter brain structure, as well as functional resting-state connectivity in acute MDD using SPM, FSL, and CONN toolboxes. We hypothesized that FTD would be prevalent in acute MDD, though at lower rates than in SSD. Associations with brain structure and functional connectivity were anticipated in regions previously identified in SSD studies.
**RESULTS:** 37.5% of acute MDD patients presented with any FTD symptom compared to 69.4% of SSD patients and 11.1% of HC. Negative FTD were present in 29% of MDD patients, while positive FTD were present in 14.5%. 6.1% of MDD patients presented with both negative and positive FTD at the same time. Increased latency of response was the most frequently observed FTD symptom. FTD prevalence was not related to biological sex or comorbidity. The total amount of FTD was negatively correlated with the GMV of the right posterior cingulate gyrus and with white matter fractional anisotropy of the right corticospinal tract. Functional resting state seed-to-voxel analyses showed total, positive, and negative FTD to be positively correlated with functional connectivity between the amygdala-hippocampus complex and the right pre- and postcentral gyri. Positive FTD was negatively associated with the functional connectivity of the orbito-frontal cortex and left lateral occipital gyrus as well as the superior temporal gyri and the subgenual cingulate cortex. All identified brain structural and functional correlates of FTD were not correlated with age of onset, current depression severity, lifetime number and duration of depressive episodes and hospitalizations, the duration of the current episode, and current medication.

**DISCUSSION:** This study highlights the prevalence and importance of FTD in acute MDD, replicating (in part) findings from SSD research. Results underscore the need for comprehensive FTD assessments in MDD and further exploration of its neurobiological underpinnings and predictive value.

## T112. Negative Emotional Context Modulates Auditory P300 Responses to Target Stimuli in People With Schizophrenia and Major Depressive Disorder

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**BACKGROUND:** The capacity to seek and experience pleasure may relate to basic cognitive processes that help us flexibly navigate emotionally distracting environments to attain goals. The P300 event-related potential reflects attention allocation to salient events. Attenuated P300 amplitudes have been associated with trait anhedonia, or deficits in the ability to experience pleasure. Anhedonia is a symptom of both schizophrenia and depression. In the current study we examined whether emotional context influenced P300 amplitudes among people with schizophrenia, depression, and unaffected comparison participants. We expected greater blunting of the P300 in people with greater anhedonia when viewing negative distractor images.
**METHODS:** Participants with major depressive disorder (MDD, n=32), schizophrenia spectrum disorder (SCZ, n=35) and unaffected comparison participants (UCP, n=31) performed an emotional oddball task in which P300s to target and novel sounds were recorded during passive viewing of distractor positive, negative, and neutral International Affective Picture System (IAPS) images. We examined the effects of diagnostic group and emotion condition on P300s via t-tests (correcting for multiple comparisons with the false discovery rate). We then correlated P300 responses during different emotion conditions with a composite anhedonia metric derived from clinical symptom (Scale for the Assessment of Negative Symptoms, Clinical Assessment Interview for Negative Symptoms) and trait-level inventories (Dimensional Anhedonia Rating Scale).
**RESULTS:** Compared to UCP, MDD and SCZ showed attenuated P300s to targets during negative imagery ($t[94] = -2.95$, $padj = .004$). Compared to MDD, SCZ also showed attenuated P300s to targets during neutral and positive imagery (both $padj = .04$), consistent with a general blunting of P300 in SCZ. MDD and SCZ also showed attenuated P300 amplitudes to novels during the neutral imagery ($t[94] = -2.74$, $padj = .04$). Among MDD, reduced P300s to target stimuli during the negative emotion condition (versus neutral) corresponded with greater anhedonia ($r=-.54$, $p < .001$), indicating a diversion of resources away from the target sound when simultaneously processing negative images in depression. Amplitudes based on other emotion/task conditions were unrelated to anhedonia. These models also controlled for depression symptom levels.
**DISCUSSION:** Emotional distractors impacted attention and salience processes among individuals with MDD during specific negative or neutral emotional contexts. Conversely, SCZ showed more extensive P3 blunting, regardless of emotional context. Thus, the pattern of P300 blunting differed across diagnostic group, and correlated with anhedonia among MDD only.

## T113. Real-World Antipsychotic Prescription Patterns Among Patients With Schizophrenia in Australia: Results From the ARIEL Study

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**BACKGROUND:** Treatment nonadherence is one of the most challenging aspects of managing schizophrenia (SCZ). It can lead to relapse of symptoms, which negatively impacts patients' functioning and quality of life (QoL) and increases hospitalization rates and healthcare resource utilization (HCRU). While oral antipsychotics (OAs) are typically prescribed in the first-line setting, long-acting injectable antipsychotics (LAIs) may improve adherence in the short and longer term. This study investigated trends in antipsychotic (AP) usage in Australia, focusing on LAIs as first-line SCZ treatment.

**METHODS:** The Antipsychotics pRescrIption pattErns in AustraLia (ARIEL) study evaluated AP prescription patterns using a 10% random sample dataset of the Pharmaceutical Benefits Scheme (PBS), an Australian database. Monthly data were collected for patients with SCZ aged 16–40 years who initiated a PBS-reimbursed AP between Jan 2014 and Dec 2023. APs were categorized into 5 classes: first-generation (FG) OAs, second-generation (SG) OAs, FG LAIs, SG LAIs, and clozapine. Patients were grouped based on AP initiation from Jan 2014–Dec 2018 (period 1, before COVID-19) and Jan 2019–Dec 2023 (period 2), and changes in prescription patterns and switching between AP classes over time were analyzed. Treatment persistence and switching between AP formulations were also examined.

**RESULTS:** In total, 14,547 patients met the inclusion criteria; 55% were male and 43% were aged 16–24 years upon starting an AP. Over the study period, an average of 121 patients initiated an AP per month, of which 94% initiated SG OAs, 3% SG LAIs, 3% FG OAs, and < 1% FG LAIs. Among all APs, the average number of patients monthly receiving SG OAs increased from 265 to 1820 in period 1 and from 2038 to 2721 in period 2; corresponding values for SG LAIs were 16 to 270 and 358 to 664. Median time on treatment was 88 days with an SG OA and 278 days with an SG LAI during the study overall and 86 days and 314 days, respectively, among those who initiated the AP during period 2. In the final month of the study, Dec 2023, the most commonly initiated SG OAs were olanzapine (34.1%), quetiapine (25.5%), aripiprazole (21.5%), and risperidone (8.1%). Of those who initiated an SG OA in period 1 (n=7178), 75% discontinued and an additional 15% switched to an LAI (median time on OA before switching to FG LAI vs SG LAI: 721 and 590 days, respectively); corresponding values for those who initiated an SG OA in period 2 (n=6491) were 74% and 10% (median time on OA: 295 and 181 days, respectively). Among patients who initiated an SG LAI during the study period, paliperidone and aripiprazole were the most common (56% and 30%, respectively, in Dec 2023). Paliperidone once-monthly LAI was the most commonly initiated formulation of paliperidone (58%); 54% of those who started it discontinued without trying another formulation. 93% of patients who initiated aripiprazole received the OA formulation; of those, 73% discontinued without trying another formulation. Of those who initiated oral paliperidone or aripiprazole, 39% and 19% switched to the respective LAI formulation. Of those who initiated oral olanzapine or risperidone, only 2% and 5% switched to the respective LAI formulation.

**DISCUSSION:** Among patients with SCZ in Australia, treatment initiation with an SG LAI vs an SG OA was associated with increased time on therapy and reduced discontinuation rates. Oral olanzapine and risperidone were among the most commonly used first-line treatments, but low

switching rates from the OA to LAI formulations were observed. This represents an opportunity to improve treatment adherence, which can benefit patients and the health system by reducing relapses, improving patients' functioning and QoL, and reducing rehospitalizations and HCRU costs.

## T114. Antipsychotics and Risk of Mortality in 41,695 Patients With Schizophrenia: An 11-Year Population-Based Cohort Study

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**BACKGROUND:** Patients with schizophrenia experience significantly reduced life expectancy, with a gap of 10-15 years compared to the general population. While antipsychotics (APs) are essential for treatment, they are associated with cardiometabolic, anticholinergic, sedative, and neuromotor side effects that may impact mortality. Previous studies indicate that AP use generally lowers mortality compared to non-use, but the differential impacts of specific AP regimens, formulations, and doses on mortality risk remain unclear among treated patients.
**METHODS:** This population-based cohort study analyzed the territory-wide medical record database of public healthcare services in Hong Kong from 2006 to 2016. Cox regression analysis with time-varying covariates was used to examine associations between different AP exposures and mortality risks. Three main comparisons were conducted: 1) individual AP monotherapy versus oral perphenazine, 2) AP regimens versus first-generation AP (FGA) oral monotherapy, and 3) AP low- ( > 0.5–1 DDD/day), moderate- ( > 1–1.5 DDD/day), and high-dose (≥ 1.5 DDD/day) exposure versus minimal-dose exposure use ( > 0–0.5 DDD/day). Outcomes included all-cause, natural-cause, and unnatural-cause mortality risk estimates.
**RESULTS:** The study included 41,695 patients with schizophrenia (mean age = 46.0±14.9 years; males=49.1%), of which 13,283 were incident cases (median age =38.0 [IQR: 28.0, 50.0]; males=45.6%). Over a median follow-up time of 11.0 (IQR: 6.5, 11.0) years, 6,234 (15.0%) of patients died. Clozapine had the lowest risk of mortality relative to perphenazine across all mortality categories (all-cause adjusted hazard ratio [aHR], 0.41; 95% CI, 0.33-0.52; natural-cause aHR, 0.52; 95% CI, 0.40-0.69; unnatural-cause aHR, 0.16; 95% CI, 0.09-0.27). Paliperidone long-acting injectable (LAI) showed better outcomes than oral perphenazine for all-cause (aHR, 0.51; 95% CI, 0.36-0.72) and natural-cause mortality (aHR, 0.55; 95% CI, 0.37-0.83). Other second-generation antipsychotics (SGAs) also showed a lower mortality risk. Five AP regimens showed lower all-cause and natural-cause mortality compared to FGA oral monotherapy: SGA-clozapine oral monotherapy, SGA-non-clozapine oral monotherapy, SGA-

LAI monotherapy, SGA-LAI-non-clozapine polypharmacy, and FGA-LAI-non-clozapine polypharmacy. High-dose AP exposure was linked to reduced unnatural-cause mortality in the prevalent cohort (aHR, 0.76; 95% CI, 0.60-0.95). Most results with incident cohort were consistent with the primary analyses; however, low-dose exposure showed better outcomes for all-cause and natural-cause mortality in incident cohort.
**DISCUSSION:** This study constitutes one of the most comprehensive investigations on mortality associated with APs in schizophrenia. Our findings indicate that clozapine is linked to the lowest mortality risk, underscoring its critical role in schizophrenia treatment. Furthermore, LAI APs showed a protective effect against mortality, suggesting their utility in improving treatment adherence and outcomes. AP combinations involving clozapine or LAIs may mitigate mortality risks when administered appropriately. The differential effects of different dose exposures emphasize the need for individualized dosing strategies. These advocate for identifying barriers and strategies to facilitate early clozapine and LAI use, optimizing clinical outcomes for patients with schizophrenia. Future research is warranted to investigate the mechanisms underlying these mortality differences and examine potential confounding factors not captured in electronic health records.

## T115. Retrospective Chart Review to Identify Deficiencies in Clinical Documentation for Patients Treated With Clozapine in an Outpatient Teaching Clinic With Focus on FDA Black Box Warning Conditions

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**BACKGROUND:** Clozapine is an atypical antipsychotic that is effective in treatment resistant schizophrenia but is underutilized. Common barriers to prescribing Clozapine are concerns regarding the side effects and monitoring requirements. The goal of this study is to standardize the screening parameters and documentation guidelines for patients who are treated in our outpatient teaching clinics during the induction and maintenance phases of Clozapine management. The protocol was designed after compiling practice guidelines from the American Psychiatric Association, American Association of Psychiatry Pharmacists, Food and Drug Administration medication package insert, Up to Date, and Clozapine Risk Evaluation and Mitigation Strategies.
**METHODS:** Chart review was conducted for 34 patients who were started on Clozapine prior to implementation of the protocol to assess thoroughness of documentation regarding screening appropriate candidates for treatment, medication risk monitoring, and management during initiation and maintenance of Clozapine treatment. Charts during initiation phase of Clozapine treatment were also reviewed for documentation of potential factors which could complicate Clozapine treatment including potential barriers to care, screening for pre-existing medical conditions, factors which could impact Clozapine metabolism, discussion of consent, and history of prior Clozapine treatment. Charts documented during Clozapine maintenance phase of treatment were reviewed for thoroughness of review of systems, documentation of vital signs, and regularity of diagnostic testing and lab monitoring.

**RESULTS:** Absolute neutrophil count (ANC) was documented in 96% of charts during Clozapine initiation in 69% of charts during follow up visits. Only 12% of charts documented screening for concomitant use of bone marrow suppressants, and no charts documented screening for preexisting bone marrow disorders or conditions that could contribute to neutropenia.

CRP, Troponin I and EKG were documented 31%, 58% and 50%, respectively. Only 12% of the charts documented screening for pre-existing cardiac history, and no charts documented obtaining an echocardiogram.

Chart review revealed no documentation of prescreening for the history of syncope or orthostatic hypotension during Clozapine initiation or documentation of baseline orthostatic vital signs. During follow up visits, 17% of charts had documented orthostatic vital signs compared to 70% charts documenting routine HR and BP monitoring.

In 26% of charts screening for seizure history was documented and 23% of charts documented screening for pre-existing conditions that can increase seizure risk. During follow up visits, 35% of charts documented screening for any neurological side effects that included seizures.

**DISCUSSION:** The study identifies significant deficiencies in documentation of screening for Clozapine related FDA black box conditions during Clozapine initiation and follow-up visits. This study is limited by the fact that these recognized deficiencies are for documentation only and exclude the fact that clinicians might have considered these issues without documenting them and also excludes the barriers associated with screening for such conditions in patients with severe psychiatric illnesses. As part of the quality improvement initiative, we recognize these deficiencies and plan to implement a standardized protocol designed for use at our outpatient teaching clinic for monitoring and documenting the care for Clozapine patients both in the induction and maintenance phases of treatment.

## T116. Adolescent Cannabis Vapour Exposure and Neurodevelopmental Risk for Schizophrenia: Testing the Two-Hit Hypothesis With Translationally Relevant Exposure Methods

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**BACKGROUND:** Adolescent cannabis use is associated with an increased risk of developing schizophrenia. The "two-hit" hypothesis suggests that early-life neurodevelopmental insults, combined with adolescent cannabis exposure, can trigger the onset of symptoms. Delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is believed to play a crucial role in these effects. Despite the prevalence of adolescent cannabis use, particularly high-THC cannabis flower, and its perceived low risk, preclinical studies have

demonstrated that adolescent THC exposure can induce schizophrenia-like behaviors in rats. However, these studies often rely on parenteral THC administration, which may not fully replicate the effects of real-world cannabis consumption. Furthermore, less is known about how adolescent cannabis exposure affects rats with an early-life neurodevelopmental insult. This study aimed to investigate the impact of adolescent cannabis flower vapor exposure on schizophrenia-relevant behaviors in rats with and without a neurodevelopmental risk factor.
**METHODS:** Male Sprague Dawley rats (N = 25) were subjected to either neonatal ventral hippocampal lesion (NVHL) surgery to induce a schizophrenia-like phenotype or sham surgery as a control. During adolescence (postnatal day 28 – 42), rats were exposed daily to either high-THC cannabis flower vapor ( > 25% THC) or air vapor control. Two weeks post-exposure, rats were assessed for various schizophrenia-relevant behavioral measures, including deficits in acoustic sensorimotor gating (pre-pulse inhibition of the acoustic startle response), locomotor activity, conspecific social interactions, associative learning via trace fear conditioning and conditioned avoidance, and spontaneous object memory.
**RESULTS:** Compared to sham controls, NVHL rats had sensorimotor processing impairments, motor hyperactivity, and deficits in associative fear learning, contextual fear recall, and spontaneous object memory (all $p < 0.05$). Exposure to high THC cannabis vapor during adolescence produced differential outcomes on sensory, social and cognitive measures: compared to air vapor controls, sensorimotor processing was improved in NVHL rats and worsened in sham controls in the cannabis exposed groups, social behaviors were increased in both NVHL rats and sham controls exposed to cannabis, associative fear learning was improved in NVHL rats and impaired in sham controls exposed to cannabis, and contextual fear recall was improved in NVHL rats to control levels (all $p < 0.05$) in the cannabis exposed group. Spontaneous object memory was also worsened in sham controls to NVHL levels ($p < 0.05$) after cannabis exposure.
**DISCUSSION:** Adolescent cannabis flower vapor exposure can have divergent effects on schizophrenia-related behaviors depending on the presence of a neurodevelopmental risk factor. These findings highlight the importance of considering individual vulnerability when evaluating the impact of cannabis use, particularly during adolescence. Furthermore, preclinical research that incorporates more ecologically valid models, such as vapor exposure, may provide valuable insights into the mechanisms underlying cannabis-related neuropsychiatric outcomes.

## T117. Prescription of Anticholinergic Drugs in Patients With Schizophrenia: Analysis of Antipsychotic Prescription Patterns and Hospital Characteristics

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**BACKGROUND:** In several clinical guidelines for schizophrenia, long-term use of anticholinergic drugs is not recommended. We investigated the characteristics of the use of

anticholinergics in patients with schizophrenia by considering psychotropic prescription patterns and differences among hospitals.
**METHODS:** A cross-sectional, retrospective prescription survey at the time of discharge was conducted on 2027 patients with schizophrenia from 69 Japanese hospitals. We examined the relations among psychotropic drug prescriptions regarding anticholinergic prescription. We divided the hospitals into three groups-low rate group (LG), medium rate group (MG), and high rate group (HG)-according to their anticholinergic prescription rates, and analyzed the relationship between anticholinergic prescription rates and antipsychotic prescription.
**RESULTS:** Anticholinergic drugs were prescribed to 618 patients (30.5%), and the prescription rates were significantly higher for high antipsychotic doses, antipsychotic polypharmacy, and first-generation antipsychotics (FGAs) use. The anticholinergic prescription rate varied considerably among hospitals, ranging from 0 to 66.7%, and it was significantly higher in patients with antipsychotic monotherapy, antipsychotic polypharmacy, and normal and high doses of antipsychotics in HG than in those LG and MG. The anticholinergics prescription rate in patients with second-generation antipsychotic monotherapy in HG was also significantly higher than in those LG and MG; however, the difference was no longer significant in patients with FGA monotherapy.
**DISCUSSION:** Conclusively, institutional and biological (pharmacological) factors contribute to the prescription of anticholinergics. Institutional factors influence anticholinergic prescription in antipsychotic monotherapy, high dose of antipsychotics, and SGA monotherapy, whereas biological factors influence anticholinergics prescription in FGA monotherapy.

## T118. Opioid Detoxification Among People With Schizophrenia: Preliminary Findings of a Matched Case Control Study

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**BACKGROUND:** Substance use disorders (SUDs) affect nearly 50% of people with schizophrenia and exacerbate the challenges faced by these individuals, including worsened psychotic symptoms, poor treatment adherence, increased risk of hospitalization and aggression, and heightened mortality from suicide or other causes. Opioid use disorder (OUD) is particularly concerning, as it elevates the overall risk of death by 15 times. Despite these harms this population is under researched.
**METHODS:** Aims
To identify and compare the characteristics of patients with schizophrenia to those without schizophrenia receiving the same treatment for opioid detoxification and evaluate and contrast the outcomes and predictors of outcomes in these two groups.

Methodology

Ethically approved research study (IRAS 342549 and REC x760) employing a retrospective, matched case-control study design utilising data extracted from the healthcare records of patients who underwent inpatient opioid detoxification at the Chapman Barker Unit, a specialist regional facility in Manchester. Cases will include adults aged 18–65 with co-occurring schizophrenia (ICD-10-CM diagnosis codes F20–29) and opioid use disorder (ICD-10-CM diagnosis code F11), while controls will include age- and gender-matched individuals with OUD but without schizophrenia.

Descriptive and inferential statistical analyses will be conducted to explore differences between cases and controls, using chi-squared tests for proportions and regression analysis for predictors of treatment outcomes. The study will provide valuable insights into factors influencing detoxification success and guide evidence-based management of patients with co-occurring schizophrenia and OUD.

**RESULTS:** We conducted a retrospective, age- and gender-matched case-control study (2:1 ratio) with 36 cases and 72 controls.

There were no significant demographic differences between the schizophrenia and control groups. Methadone detoxification was the most common intervention in both cohorts. However, detoxification completion rates were lower among individuals with schizophrenia, with 47.2% failing to complete detoxification compared to 27.8% of controls. Moreover, patients with schizophrenia had over twice the odds of failing to complete detox (OR 2.24, 95% CI 1.01–5.35), highlighting the need for targeted interventions to improve treatment outcomes in this population.A forthcoming comparative analysis will examine outcomes and predictors of detoxification success between patients with schizophrenia and those without.

**DISCUSSION:**

Our findings highlight the challenges faced by individuals with schizophrenia during opioid detox, underscoring the need for tailored interventions. Our next steps involve exploring predictors of detox success to enhance treatment pathways.

## T119. Nonprescriber Participation and Outcomes in a Randomized Controlled Trial of an Extension for Community Healthcare Outcomes (ECHO) Tele-Mentoring Program to Increase Clozapine Utilization

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**BACKGROUND:** Schizophrenia (SCZ) is a leading cause of disability worldwide. Collaboration between providers promotes optimal recovery. While services provided differ between nonprescribers (nPs) and prescribers (Ps), the two groups share the same goal: improved outcomes. Research has shown that Clozapine (CLZ) is the most effective antipsychotic medication for treatment-resistant (TX-RES) SCZ and is the only medication approved by the FDA to treat suicidality, yet CLZ is prescribed in < 5% of individuals with SCZ nationally. Many nPs have general knowledge about medications used to treat SCZ but the degree of familiarity with CLZ rests upon their access to specialty training. The aim of the CHAMPION ECHO study was to increase knowledge and competence in using CLZ in effort to increase actual prescribing rates of CLZ. Though nPs may not affect prescribing rates directly, they do collaborate with Ps about treatment. With specialty training, nPs could be valuable advocates for increased utilization of CLZ.
**METHODS:** In a randomized controlled design, we tested the effectiveness of an ECHO-based intervention over 12-months for improving the use of CLZ in people with TX-RES SCZ. The intervention, Clozapine CHAMPION-ECHO (Center for Help and Assistance for Maryland Prescribers-Improving Outcomes Network) using ECHO, or "CHAMPION," consisted of 26 biweekly tele-mentoring sessions that included 1) active dissemination of knowledge and information by the expert "hub" followed by 2) CLZ case presentations and vignettes submitted by the "spokes." This was compared to an enhanced treatment as usual (eTAU) group. nPs completed baseline and endpoint assessments for knowledge and self-reported competence. Assessment of CLZ knowledge was calculated as the proportion of 52 multiple-choice questions answered correctly. Self-reported competence was calculated as the mean rating of a nPs perceived competence in using CLZ rated on a scale of 0-100.
**RESULTS:** There were 82 nPs enrolled in CHAMPION ECHO of which 41 were randomized to ECHO and 41 to eTAU. Thirty-one (37.8%) were nurses, 27 (32.9%) were social workers, and 24 (29.3%) were psychologists or therapists. 81.7% were female and 63.4% were White (26.8% AA). 100% of those who were randomized to ECHO attended at least 1 session with a mean attendance of 10.2 ± 8.4 sessions. Baseline and endpoint knowledge scores were 48% and 52% in the ECHO group attending 1-13 sessions and 57% and 77% in the group attending 14-26 sessions. Baseline and followup scores in the eTAU group were 48% and 54%, respectively. Significant improvement was noted in knowledge between those who attended 14-26 ECHO sessions compared to the eTAU group [t-5.38, beta (SE)=0,28 (0,05), $p < 0.0001$]. While nPs overall knowledge was < Ps at baseline and followup ($p < 0.001$), the percent increase in knowledge did not differ between nPs and Ps for those participating in the ECHO sessions ($t=0.83$, $df=212$, $p=0.8$). Moreover, 12/18 (67%) nPs stated they benefitted from the attending the program.
**DISCUSSION:** Results from this study show that nPs are motivated to learn about CLZ. While they may not be the ones prescribing, they are talking with patients about symptoms, functional impairments, suicidality, and medication adherence. Additionally, they are collaborating about patient care with Ps. Participation in the CHAMPION ECHO study led to improved knowledge of CLZ among nPs, particularly those who attended 14-26 ECHO sessions. The majority of attendees identified participation as beneficial. Despite its effectiveness, CLZ remains grossly underutilized. Inclusion of nPs in specialty education on CLZ is perhaps a viable strategy to help increase CLZ utilization and promote improved clinical outcomes in people with SCZ.

**T121. Efficacy of Oral and Lai Aripiprazole vs Paliperidone in Patients With Early-Phase Schizophrenia: Secondary Analysis From a Large-Scale, Open-Label, Randomized Trial (EULAST)**

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**BACKGROUND:** Aripiprazole is the oldest member of a new generation of antipsychotics. Some, but not all, studies have found that partial dopamine agonists may be less efficacious than the classic, second-generation D2 dopamine antagonists. We analyzed data from a recently published open-label, pragmatic RCT in patients with early phase schizophrenia and compared time to all-cause discontinuation, time to hospitalization, and symptom reduction between aripiprazole and paliperidone.

**METHODS:** This is a secondary analysis from the EULAST trial, a multicenter, RCT conducted across 15 European countries and Israel, on patients with up to 7 years of illness duration and randomized 1:1:1:1 to LAI paliperidone, LAI aripiprazole, or their corresponding oral formulations. The primary results of the EULAST study indicated no difference in time to all-cause-discontinuation (ACD) between long-acting and oral antipsychotics. This current study compares the oral and long-acting formulation of aripiprazole with paliperidone, alongside separate analyses for the four groups of LAI paliperidone, oral paliperidone, LAI aripiprazole, and oral aripiprazole.

**RESULTS:** In total, 523 patients were randomly allocated, 255 to aripiprazole group (131 LAI and 124 oral) and 268 to the paliperidone group (141 LAI and 127 oral). Overall, both time to ACD (HR = ?, p =??) and time to hospitalization (HR = ?, p =??) did not significantly differ between the combined aripiprazole and paliperidone groups. However, comparisons of the four groups found that patients who took oral paliperidone had shorter times to ACD (Paliperidone oral vs. LAI (HR = 1.49, p = 0.05), aripiprazole oral (HR = 1.43, p = 0.09), and aripiprazole LAI (HR = 1.52, p = 0.05)) and trends to shorter times to hospitalization compared to the other groups (Paliperidone oral vs. paliperidone LAI (HR = 1.79, p = 0.08), aripiprazole oral (HR = 1.69, p = 0.12), and aripiprazole LAI (HR = 1.23, p = 0.49)). Similarly, there was no significant difference in changes in total PANSS scores between aripiprazole and paliperidone, however, patients treated with oral paliperidone showed less improvement in PANSS positive score compared to the other three groups (Paliperidone oral vs. paliperidone LAI (coef = -0.11, p = 0.02), aripiprazole oral (coef = -0.07, p = 0.13), and aripiprazole LAI (coef = -0.10, p = 0.03)). The trajectory of negative, general, and total scores did not show significant differences by group over time. When analyzing results for only participants who completed the entire study, similar results were found. There were no differences in time to hospitalisation or PANSS scores between the two combined groups or time to hospitalisation for the four groups; oral Paliperidone showed less improvement in PANSS positive scores (Paliperidone oral vs

paliperidone LAI (coef = -0.12, p = 0.01), aripiprazole oral (coef = -0.07, p = 0.15), and aripiprazole LAI (coef = -0.09, p = 0.06)).
**DISCUSSION:** This is the first head-to-head RCT directly comparing oral and long-acting injectable aripiprazole and paliperidone. Overall, the real-world effectiveness of the combined aripiprazole and paliperidone groups was comparable in this study although, of the four groups, patients on oral paliperidone were more likely to stop the medication early and require hospitalization.

## T122. Psychosis and Disorganized Symptoms Measured With Ecological Momentary Assessment (EMA): Changes Over a 12-Month Treatment Trial Of Xanomeline and Trospium Chloride in Schizophrenia

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**BACKGROUND:** Xanomeline/trospium chloride (X/T) has recently been approved for the treatment of schizophrenia based on the results of three double-blind acute 5-week treatment studies. Analyses of the data from those studies also suggested improvements in negative symptoms and cognition. This 12-month open-label switch study explored the monthly progression of psychotic and disorganized symptoms in clinically stable participants (Total PANSS score capped at 80) with schizophrenia (SCZ) who transitioned from their current treatment to open-label X/T. Ecological momentary assessment (EMA) was used to track symptoms and experiences 3 times per day, 7 days per week, one week per month.
**METHODS:** 350 participants with SCZ completed EMA surveys that queried about their location, social context, moods, and activities. The surveys also assessed the presence of psychotic symptoms during the last hour (hallucinations, paranoia and other delusions) and disorganization (feeling disorganized, communicating poorly) using a yes/no questions followed by a 1-7 severity rating for affirmative responses. The proportion of surveys answered affirmatively, and average severity ratings, were analyzed monthly. Duration of treatment was the repeated measure and momentary mood states (positive and negative affect [PA, NA]) were examined as covariates.
**RESULTS:** Participants completed a total of 43,542 EMA surveys with a study-long adherence rate of 67%. At baseline (month 1), 175 participants reported hearing voices in the last hour at least once (24% of all surveys), 105 participants reported at least one delusional experience (10% of all surveys) and 98 reported at least episode of disorganization (9% of all surveys). The frequency of occurrence of all of these symptoms declined significantly over time (all $X2 > 38.98$, all $p < .001$). All reductions were significant by the second monthly EMA burst assessment ($p < .001$). Interestingly, the frequency of these symptoms changed considerably more than their severity. For instance, hallucinations decreased in prevalence from 24% at baseline to 8% at month 2 and 4% at month 6, while the average severity when voices were heard changed minimally from an average of 3.02/7 at baseline to 2.76/7 at month 6 (p=.025). Similar trends were found for delusions (p=.24), communication disturbance (p=.045) and disorganization (p=.037). Momentary intensity ratings of NA were a significant dynamic

covariate that predicted the severity of symptoms when they occurred (all $X2 > 74.15$, all $p < .001$).
**DISCUSSION:** We found a treatment-related shift toward reductions of hallucinations, delusions, and disorganized behavior in an ambulatory population of participants with SCZ treated with X/T, which is consistent with the antipsychotic efficacy shown in the pivotal trials and the results of smaller qualitative studies. This reduction was more pronounced for frequency of these symptoms than their intensity/severity when they occurred. NA was dynamically associated with symptom severity, but further analysis will be required to determine whether the increased NA is an antecedent or consequence of psychotic or disorganized experiences.

## T123. Nothing About Caregivers Without Caregivers!: Implementation of a Stepped Family Psychoeducation Program in Routine Care in France

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**BACKGROUND:** in France , psychoeducation for caregivers of individuals with schizophrenia has been integrated into the broader mental health system as part of a person-centered approach to care. National guidelines such as those from Haute Autorité de Santé HAS and psychosocial rehabilitation structuration with DGOS Ministry of Health emphasize the importance of involving families in the treatment process. late data show the positive impact as well on caregivers' health, and patients with less suicidal behaviors, symptoms reduction. nevertheless access to care services is delayed in care pathways on average ten years.
**METHODS:** we propose an implementation method to systematically provide access to a graduated offer of family psychoeducation in routine care for individuals with schizophrenia
**RESULTS:** we propose the following methodology: 1. systematic training of professionals through an innovative training program designed to support families. this programdrawson motivational thermiques and cognitive behavioral therapies, delivered over two days, followed by a supervision day after implementation. 2. subsequent training in BREF-AIDANTS program and the PROFAMILLE program. 3. support from psychosocial rehabilitation center ti structure and guide the implementation of the caregiver pathway within routine care services.
**DISCUSSION:** we discuss the evaluation of the impact on care transformation, the improvement of caregivers' set determination, and on the consequences on the patient's care pathway. this incudes supporting destigmatization efforts, assessing the medico-economic impact

and the attractiveness of practices. we also aim to develop professional family peer support, strengthen partnerships with associations of concerned caregivers - such as La Maison Perchée, Pouvoir d'Agir 60, Promess, ...- and to contribute to healthcare transformation policies. Further perspectives include the possibility of integrating additional trans diagnostic psychoeducational programs addressing UHR, first psychotic episodes, borderline disorders.

## T124. Unveiling the Sense of Presence: Key Predictors in Cinematic Virtual Reality Interventions for Schizophrenia

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**BACKGROUND:** Virtual reality (VR) is a technology that enables the digital simulation of real-world scenarios in environments resembling the real world, allowing users to interact with these settings and experience realistic social engagement. Presence, along with immersion, is a key component of virtual reality. In this study, we investigated the predictors of presence in a 12-session cinematic VR intervention program (cVR-PTP) designed to enhance social functioning in patients with schizophrenia.
**METHODS:** cVR-PTP was developed to enhance psychosocial functioning in patients with schizophrenia. Fourteen patients with schizophrenia (13 male, 1 female) were included in the study. Baseline and post-treatment evaluations were conducted across clinical (Positive and Negative Syndrome Scale), psychosocial (Personal and Social Performance Scale and Social Functioning Scale), neurocognitive (Screen for Cognitive Impairment in Psychiatry), and social cognitive (Dokuz Eylül Theory of Mind Index and Reading the Mind in the Eyes) domains. Each session was conducted weekly. After each session, participants completed the Presence Questionnaire (PQ). The PQ, in its Turkish version, consists of 29 items and provides a total score along with 5 subscale scores: involvement, interface quality, sensory fidelity, adaptation/immersion, and interaction.
**RESULTS:** The mean age of the participants was 38.3 ± 10.5 years, with a mean education level of 12.35 ± 4.2 years. The mean age of illness onset was 21 ± 5.5 years, and the mean duration of untreated psychosis was 4.5 ± 12.6 months. Baseline scores were as follows: Personal and Social Performance Scale (PSP), 51.6 ± 5.8; Positive and Negative Syndrome Scale (PANSS) positive subscale, 14 ± 4.1; PANSS negative subscale, 17 ± 3.5; PANSS general psychopathology subscale, 26.1 ± 5.2; and PANSS total score, 57.1 ± 7.8. The mean total score on the PQ was 114.0 (SD = 17.8) out of a possible maximum of 145. Subscale means and standard deviations were as follows: interface quality, 10.6 (SD = 3.2) out of 15; involvement, 37.1 (SD = 5.5) out of 45; sensory fidelity, 21.1 (SD = 3.0) out of 25; interaction, 18.0 (SD = 4.7) out of 25; and adaptation/immersion, 27.4 (SD = 5.9) out of 35. In order understand the predictors of PQ score, we performed a linear regression analysis between baseline PSP scores and PANSS scores with total PQ score and PQ subscales. Baseline PSP scores [β = 1.52, 95% CI (0.22, 2.82), p = .025]

and negative symptom severity [β = -2.69, 95% CI (-4.84, -1.09), p = .005] were significant predictors of the sense of presence and its subscales, explaining 30% and 45% of the variance, respectively. For the subscales, PANSS negative symptoms and PSP scores also significantly predicted sensory fidelity [β = -0.45, 95% CI (-0.76, -0.15), p = .007; β = 0.23, 95% CI (0.023, 0.44), p = .032], adaptation/immersion [β = -1.03, 95% CI (-1.68, -0.37), p = .005; β = 0.60, 95% CI (0.19, 1.01), p = .008], involvement [β = -0.79, 95% CI (-1.34, -0.25), p = .008; β = 0.41, 95% CI (0.045, 0.78), p = .031] and interaction [β = -0.94, 95% CI (-1.33, -0.55), p < .001; β = 0.39, 95% CI (0.032, 0.75), p = .035], explaining variances ranging from 25% to 67%.
**DISCUSSION:** The patients demonstrated a relatively high level of sense of presence, indicating that the VR program effectively induced a strong sense of presence. The findings emphasize that baseline negative symptoms of schizophrenia and psychosocial functioning level are significant predictors of presence and its subcomponents. These results suggest that tailoring VR interventions to address specific clinical profiles may enhance immersive experience and therapeutic outcomes for patients with schizophrenia. Future studies with larger sample sizes are needed to further validate these findings and explore their implications for improving psychosocial functioning through VR-based interventions.

## T125. A Study on the Effectiveness of Cognitive Behavior Program on Chronic Schizophrenia Patients in the Community

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**BACKGROUND:** This study was designed to understand the effects of cognitive behavioral programs on positive emotions, mental health recovery, quality of life, and interpersonal changes in people with chronic schizophrenia using community mental health welfare centers(CMHWC) in Korea.
**METHODS:** The subjects of this study were a total of 28 people who met the selection criteria for schizophrenia registered at a CMHWC in one small city. The cognitive behavioral program was conducted once a week as a group program for a total of 8 weeks, 60 minutes, using the program room in CMHWC. The contents of the program include expressing daily experiences and emotions, understanding the process of emotions, understanding cognitive processes, cognitive reconstruction, planning social activities, identifying social roles and relationships, confirming changes, and making positive self-statements, etc.
The subjects maintained the existing treatment while receiving regular outpatient treatment during the study period. The effects on positive emotions, mental health recovery, quality of life, and interpersonal change were measured before and after the program, and the collected data were analyzed using the SPSS WIN 20.0 program

**RESULTS:** After applying the cognitive behavioral program, the positive emotional score increased significantly (t=6.026, p < .000), and the mental health recovery score also increased significantly (t=4.041, p < .000). The quality of life score (t=5.837, p < .000) and interpersonal change score (t=2.910, p=.004) also increased significantly.

**DISCUSSION:** This study confirmed that there were significant effects on positive emotions, mental health recovery, quality of life, and interpersonal relationships. It is expected to be a useful program that can be used in the community in the future.

## T126. Accelerated Intermittent Theta Burst Stimulation: Advancing Treatment for Persistent Negative Symptoms of Schizophrenia

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**BACKGROUND:** Transcranial Magnetic Stimulation (TMS) is an effective treatment for depressive symptoms. However, its efficacy in alleviating negative symptoms of Schizophrenia remains uncertain. Persistent negative symptoms of Schizophrenia are denoted by at least two clinically significant negative symptoms present for a minimum of 12 months. A retrospective study showed that negative symptoms were observed in 95% of individuals with Schizophrenia. While treatment for positive symptoms of Schizophrenia is well established, treatment protocols for the negative symptoms remain underexplored. This remains a key unmet clinical need with little to no pharmacological or psychotherapeutic treatment approaches with significant effect size. Therefore, novel treatments for negative symptoms are sorely needed. We aim to examine the efficacy of a novel accelerated intermittent Theta Burst Stimulation (iTBS) protocol for patients with persistent negative symptoms of Schizophrenia.
**METHODS:** Nineteen patients were recruited and received accelerated iTBS therapy at 100% resting motor threshold five sessions daily for five continuous days. The target location will be randomized at either the left dorsolateral prefrontal cortex (DLPFC) or frontal medial (FM) region. Patients were assessed at pretreatment, immediately post treatment, and a month post treatment. Data analysis was conducted using one-way ANOVA with the Bonferroni correction.
**RESULTS:** Presently, we have achieved a response rate of 47% immediately post treatment and 50% a month post treatment. Approximately 60% of the responders at both timepoints received therapy at the DLPFC region, while the remaining 40% were attributed to the treatment at the FM region. The response rate is categorised by a reduction of more than or equal to 20% in the PANSS Negative subscale. Patients showed improvements immediately post treatment as assessed by the Positive and Negative Syndrome Scale (PANSS) negative subscale 21.950±0.664 vs 17.370±0.952, p=0.010. The therapeutic effects persisted a month post treatment as well, 21.950±0.664 vs 17.810±1.754, p=0.030.

The overall Brief Negative Symptom Scale displayed a significant decrease (BNSS) (Baseline vs post treatment, mean±SE) 31.840±2.549 vs 21.370±2.419, p=0.009 . Multiple subdomains in BNSS also showed improvements, namely the Asociality domain, 5.846±0.359 vs 3.684±0.501,

p=0.005, the Avolition domain, 6.158±0.427 vs 3.3±0.49, p=0.0003, and the Blunted Affect category, 8.421±0.876 vs 5.474±0.731, p=0.019.

A sustained treatment effect was observed a month post treatment across the BNSS scale with an overall decrease, (Baseline vs a month treatment, mean±SE) 31.840±2.549 vs 22.190±2.792, p=0.0241. These strides were consistent with improvements in most subdomains, such as the Asociality domain from BNSS, 5.684±0.359 vs 4.063±0.528, p=0.037 , the Avolition domain from BNSS, 6.158±0.427 vs 3.813±0.578, p=0.003, and the Blunted Affect category from BNSS, 8.421±0.876 vs 5.438±0.752, p=0.024.

**DISCUSSION:** Accelerated iTBS produced rapid and sustained efficacy in alleviating negative symptoms in schizophrenia. These findings suggest potential for integration into clinical practice pending larger, blinded controlled trials.

## T127. Examining the Effectiveness of Virtual Reality in Treating Auditory Hallucination in Schizophrenia Spectrum Disorders: A Systematic Review and Meta-Analysis

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**BACKGROUND:** The use of virtual reality (VR) has grown in recent years, particularly for productivity and entertainment purposes. VR has also been recently explored as a therapeutic intervention for psychiatric disorders, including auditory hallucinations (AH) in schizophrenia spectrum disorders (SSD). Specifically, VR has been used to simulate direct conversations between SSD patients with AH and their voices in a controlled environment. Clinical work has demonstrated that conversing more directly with these distressing voices is beneficial in reducing feelings of helplessness and increasing control over voices. The aim of this meta-analysis was to assess the effectiveness of VR in treating AH in SSD.

**METHODS:** A comprehensive literature search was conducted on Embase, APA PsychInfo, and MEDLINE via the Ovid Database to identify human studies that use VR as an intervention for AH. Full-text articles are screened as per PRISMA and Cochrane guidelines. Studies with a randomized-controlled trial or cross-over trial design that had a treatment and control/treatment-as-usual group (TAU) were included. The primary outcome measure is the symptom severity of AH. A random-effect meta-analysis of pre-post AH symptom severity score differences between VR and control/TAU groups will be conducted. Exploratory moderator analysis will examine the effects of demographic and clinical variables on the effectiveness of VR in reducing AH in SSD.

**RESULTS:** We identified 109 papers from the initial search. Seven full-text studies (n=900) met the inclusion criteria. The mean age of participants in the studies were 37.8 (SD=16.7), with 43% females. Three studies were randomized partial cross-over trials and 4 studies were randomized controlled trials. All studies employed Avatar Therapy, a VR-based intervention where individuals with SSD interact with a therapist-animated avatar that reflects their description of

the person behind their voice. All studies measured AH severity using the Psychotic Symptom Rating Scales (PSYRATS), AH subscale. Participants received between 6 to 12 weekly treatment sessions. All 7 studies found improvement in AH symptom severity with the use of VR, with 5 studies finding VR therapy more effective than the control/TAU condition. The remaining 2 studies found both VR and TAU to have similar beneficial effects in reducing AH. No studies reported any significant adverse effects arising from the VR therapy.
**DISCUSSION:** As the first systematic review and meta-analysis on the effect of VR in treating AH in SSD, positive findings would advance our understanding of the beneficial effects of VR as a novel and safe treatment for AH. VR may represent an innovative intervention to improve clinical outcomes and the overall well-being of individuals with SSD who experience AH and their loved ones.

## T128. Randomized Controlled Trial of Understanding Social Situations Versus Problem Solving Training in Improving Social Function in People With Schizophrenia Spectrum Disorders

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**BACKGROUND:** Schizophrenia and other schizophrenia spectrum disorders (SSD) are characterized by severe, persistent impairments in functioning. Social function impairments play a large role in a person's level of disability, community integration, and likelihood of relapse. Poor social function has been linked to social cognitive skill, which in turn has been identified as a promising treatment target for interventions aimed at improving social function. Using methods largely adapted from successful lab-based experimental trials, we developed a novel social cognitive intervention that minimizes cognitive load by leveraging delivery methods common to cognitive rehabilitation (e.g. massed drill and practice, performance-based increases in difficulty, scaffolding, verbal mediation, etc.). The training is called Understanding Social Situations (USS), and focuses on helping people make good judgments about what others may be feeling and thinking in social interactions. In the current RCT, we evaluated the efficacy of USS versus active control.
**METHODS:** One hundred three Veterans with SSD were randomized to 2 months (16-20 sessions) of remotely-delivered USS training or active control condition (problem solving training) matched for duration, therapist contact, presentation type, and delivery mode. Comprehensive assessments were conducted at baseline, post-training, and 2-month follow-up. Measures included symptoms, neurocognition, and social functioning, as well as a measure of target engagement. Smartphone-delivered ecological momentary assessments (EMA) captured additional information about extent and quality of social interactions, appraisals of these social interactions, and expectations about future interactions.
**RESULTS:** USS condition was associated with significantly greater improvement on a measure of target engagement (post-baseline, $p = .012$), with trend-level evidence of durability (follow up

– baseline, p = .06). For USS condition, there were significant within but not between group improvements on an interviewer-administered measure of social function, but not a role-play measure of social skills. Analyses of EMA are underway and will be presented as part of the symposium. Potential impact of race, gender, and age on these outcomes will also be examined.
**DISCUSSION:** While we did find evidence of target engagement, we failed to find significantly greater improvements on interviewer-administered and role-play measures of social function in the USS condition. Results of EMA analyses will provide valuable information about congruence of assessment methods. Implications for how to best define and capture outcomes of interest will be discussed.

## T129. Efficacy of Non-Invasive Brain Stimulation on Positive Symptoms and Auditory Hallucinations for Treatment-Resistant Schizophrenia: A Systematic Review and Network Meta-Analysis

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**BACKGROUND:** About one-third of patients with schizophrenia are classified as treatment-resistant schizophrenia (TRS) experiencing persistent symptoms despite adequate antipsychotic trials. While clozapine remains the only effective pharmacological treatment for TRS, its utility is limited by severe side effects and mandatory blood monitoring. Non-invasive brain stimulation (NIBS) emerged as a promising alternative therapeutic approach. Although previous meta-analyses showed significant improvements on treatment-resistant auditory hallucinations with repetitive transcranial magnetic stimulation (rTMS), the comparative efficacy of specific NIBS protocols remains largely unexplored. Hence, this study aimed to investigate the comparative efficacy of different NIBS modalities for positive symptoms and auditory hallucinations in TRS patients.
**METHODS:** This systematic review and network meta-analysis (NMA) followed the PRISMA guideline and was registered with PROSPERO (CRD42023442563). Six electronic databases, China National Knowledge Infrastructure, EMBASE, MEDLINE, PsycINFO, PubMed, and Web of Science, were searched from inception to November 10, 2024 for randomized trials comparing NIBS interventions with sham or other active interventions in TRS patients. Peer-reviewed articles published in Chinese or English were included. Primary outcomes were changes in positive symptoms and auditory hallucinations measured using standardized instruments. Effect sizes were calculated as standardized mean differences (SMD) with 95% confidence intervals (CIs) using Hedge's correction for small sample sizes in pretest-posttest-control group designs. A frequentist random-effects model was employed for the NMA, and evidence quality was evaluated using Confidence in Network Meta-Analysis (CINeMA). Sensitivity analyses were conducted to assess result robustness by excluding studies with single/no blinding, crossover design, high risk of bias, or minimum TRS definition. Publication bias was evaluated using comparison-adjusted funnel plots and Egger's test.

**RESULTS:** Of 1586 studies identified from databases, 53 studies encompassing 1,962 TRS patients (mean age = 36.8; mean female proportion = 40.7%) were included in the NMA. Regarding TRS definition, eight studies provided a minimum definition, 21 had an adequate definition, and 24 had a good definition. Six trials employed a crossover study design, while the remainder used parallel designs. Most studies (47 out of 53) were double-blinded, four were single-blinded, and two did not report blinding procedures. Risk of bias assessment revealed 29 studies with low risk, 13 studies with some concerns, and 11 studies with high risk.
For positive symptoms, 38 studies evaluating 24 NIBS modalities with 50 comparisons across 1,450 TRS patients were analyzed. The NMA revealed significant improvements compared to sham conditions with low-frequency rTMS over the LTPJ (LF-rTMS-LTPJ) ($k = 10$; SMD = -0.430, 95% CI = -0.770 to -0.090, $p = 0.013$) and neuronavigated continuous theta burst stimulation targeting the left temporoparietal cortex (cTBS-LTPC) ($k = 2$; SMD = -0.767, 95% CI = -1.519 to -0.016, $p = 0.045$). LF-rTMS-LTPJ remained significant across sensitivity analyses except for double-blind studies, while neuronavigated cTBS-LTPC maintained significance only in the double-blind sensitivity analysis.

For auditory hallucinations specifically, 36 studies evaluating 22 NIBS modalities with 60 comparisons across 1,313 TRS patients were analyzed. Similarly, significant improvements versus sham were observed with LF-rTMS-LTPJ ($k = 13$; SMD = -0.784, 95% CI = -1.202 to -0.366, $p < 0.001$) and neuronavigated cTBS-LTPC ($k = 3$; SMD = -1.118, 95% CI = -1.947 to -0.261, $p = 0.011$). Both interventions maintained significance across all sensitivity analyses.

Based on CINeMA evaluation, the overall confidence in the evidence ranged from moderate to low. No evidence of publication bias was detected for positive symptoms ($p = 0.718$) and auditory hallucinations ($p = 0.864$).

**DISCUSSION:** This NMA demonstrated that LF-rTMS-LTPJ and neuronavigated cTBS-LTPC are efficacious for positive symptoms and auditory hallucinations in TRS patients, with particularly robust evidence for LF-rTMS-LTPJ in treating auditory hallucinations. While further validation is needed, these findings support NIBS as a promising alternative treatment for TRS. Future large-scale, multi-arm trials incorporating personalized approaches, such as closed-loop stimulation protocols, are warranted to establish optimal therapeutic strategies.

## T130. Impact of Mindfulness-Based Intervention on Relapse Prevention in Remitted Psychosis Patients: A Randomized Controlled Trial

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**BACKGROUND:** Relapse rates are high in patients with psychosis. Although maintenance medications are effective, antipsychotics cause side effects. Non-pharmacological interventions such as cognitive-behavioral therapy are resource-intensive. Stress significantly affects psychosis relapse, as evidenced by prospective and retrospective studies linking life events, such as environmental changes and unemployment, to relapse prediction in schizophrenia. Mindfulness, with its stress resilience and well-being benefits, has shown promise in preventing relapse in depressive disorders. However, its role in psychosis relapse prevention remains untested. This study examined the effects of mindfulness-based intervention (MBI) in preventing relapse among patients with remitted psychosis in Hong Kong.

**METHODS:** Mindfulness-based intervention for psychosis (MBI-p) is a simplified manual mindfulness protocol developed by a pilot study that uses accepting and embracing attitudes toward fear and sadness. The manual was developed from multiple sources such as Mindfulness Based Stress Reduction, the works of Thich Nhat Hanhv, and Rezekw, where key components and concepts of mindfulness such as present moment experience, focused attention and acceptance, through low-intensity practices were selected and simplified. The aim was to facilitate patients' handling of everyday stress and conflicts, as well as to promote self-appreciation among participants and help them let go of painful experiences brought by the mental illness.

This multisite, single-blind, 1-year randomized controlled trial (RCT) tested MBI-p's effects on psychosis relapse prevention (Trial registration: NCT04060498). In total, 152 fully remitted patients diagnosed with schizophrenia or non-affective psychosis were recruited. Patients were randomized to receive either a 7-week MBI-p or a 7-week psychoeducation program.

The primary outcome was relapse, which was assessed before and after the intervention, and then monthly for one year. The rate and severity of relapse at one year were analyzed using intention-to-treat and per-protocol principles. Secondary outcomes included short-term (baseline versus post-intervention) and long-term (baseline versus one year) impacts on psychopathology, functioning, mindfulness, and psychosocial factors such as stress and expressed emotions.

**RESULTS:** Of 152 participants, 77 were in the MBI-p and 75 in the psychoeducation group. At the one-year follow-up, 10 (13.0%) participants in the MBI-p group and 10 (13.3%) in the psychoeducation group relapse, and rate and severity of relapse between the two groups were not significantly different in either intention-to-treat or per-protocol analyses. While MBI-p improved observation and non-reactivity to the inner experience of mindfulness, psychoeducation was found to benefit functioning and psychosocial functioning more than MBI-p.

**DISCUSSION:** This is the first RCT to test MBI-p's effectiveness in preventing relapse among patients with remitted psychosis in Hong Kong. Observed relapse rates are lower than expected, which can be explained by the relatively stable sample of our study. We also postulate several factors contribute to the insignificant results. There might be a heightened effectiveness of psychoeducation in coping with stress during the COVID-19 pandemic. Preventing relapse requires comprehensive care and MBI-p only contribute to certain aspect such as stress management. Our secondary outcome shows effectiveness of MBI-p in enhancing mindfulness facets. Due to the various beneficial impacts that each intervention brings, this suggests the possibility of combining these two interventions to improve their efficacy.

## T131. Success and Challenges in Establishing A Schizophrenia Day Care Centre in Lebanon

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**BACKGROUND:** There is a lack of daycare centers developed to provide psychosocial support for schizophrenic patients in Lebanon. This study describes the successes and challenges involved in developing a daycare program for people suffering from psychosis
**METHODS:** The pilot program implemented a structured multimodal group therapy approach. We combined a variety of evidence-based group therapies along three major axes: therapies focused on improving cognitive function, psychosocial therapies, and kinesthetic and art-based therapies. Each therapy was chosen with the intent of tackling specific deficits that characterize schizophrenic patients
**RESULTS:** The major success of the program is the positive feedback received from participants relating to the development of their social skills and re-integration back into society. The major challenges faced by the program include the disruption caused by the Lebanese revolution and the lack of pre-post testing which would have allowed for more quantitative rather than qualitative analysis of the results
**DISCUSSION:** In Lebanon, psychotic disorder treatment involves outpatient follow-ups, inpatient care, and long-term facilities for treatment-resistant cases, but there is a need for more integrative mental health services. In contrast, the center's full-day care program offers a highly specialized, evidence-based approach. It incorporates both well-established interventions and emerging therapies like cinema and culinary therapy. A key framework guiding the program is the recovery model, which challenges the Kraepelinian assumption that schizophrenia is strictly a biological disease with an invariably downward trajectory and little hope for improvement. Instead, the recovery model emphasizes a person-oriented approach, focusing on self-determination, resilience, and the attainment of a meaningful life despite mental illness. While such recovery-focused programs are rare in Lebanon, this initiative seeks to fill the gap by emphasizing recovery from a consumer-based perspective.

## T132. Evaluating a Smartphone-Based Symptom Self-Monitoring App for Psychosis in China (YOUXIN): A Non-Randomised Validity And Feasibility Study With A Mixed-Methods Design

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**BACKGROUND:** Psychosis causes a significant burden globally, including in China, where limited mental health resources hinder access to care. Smartphone-based remote monitoring offers a promising solution. This study aimed to assess the validity, feasi- bility, acceptability, and safety of a symptom self-monitoring smartphone app, YouXin, for people with psychosis in China.
**METHODS:** A pre-registered non-randomised validity and feasibility study with a mixed-methods design. Participants with psychosis were recruited from a major tertiary psychiatric hospital in Beijing, China. Participants utilised the YouXin app to self-monitor psychosis and mood symptoms for four weeks. Feasibility outcomes were recruitment, retention and outcome measures completeness. Active symptom monitoring (ASM) validity was tested against corresponding clinical assessments (PANSS and CDS) using Spearman correlation. Ten participants completed qualitative interviews at study end to explore acceptability of the app and trial procedures.
**RESULTS:** Feasibility parameters were met. The target recruitment sample of 40 participants was met, with 82.5% completing outcome measures, 60% achieving acceptable ASM engagement (completing > 33% of all prompts), and 33% recording sufficient passive monitoring data to extract mobility indicators. Five ASM domains (hallucinations, suspiciousness, guilt feel- ings, delusions, grandiosity) achieved moderate correlation with clinical assessment. Both quantitative and qualitative evaluation showed high acceptability of YouXin. Clinical measurements indicated no symptom and functional deterioration. No adverse events were reported, suggesting YouXin is safe to use in this clinical population.
**DISCUSSION:** The trial feasibility, acceptability and safety parameters were met and a powered efficacy study is indicated. However, refinements are needed to improve ASM validity and increase passive monitoring data completeness.

## T133. Exploring Consistencies in Schizophrenia Symptoms Captured During Routine Clinical Assessment and Measured Using Clinical Rating Scales: An Analysis of Electronic Health Records

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**BACKGROUND:** Clinical rating scales are the gold standard for measuring schizophrenia symptoms in clinical research but are rarely used in routine care.1 Conversely, mental state examinations (MSEs) are extensively conducted and documented in electronic health records (EHRs). Although descriptors of clinical presentation in the MSE may be used to characterize real-world patient cohorts2, it is unclear whether the nature and extent of schizophrenia symptoms compares well to validated instruments. We explored relationships between positive and negative symptoms recorded in the MSE and those measured on a clinical rating scale.
**METHODS:** This is a retrospective analysis of de-identified EHRs. Data were collected during provision of routine mental healthcare across institutions in the United States (US) throughout years 1999–2024 (NeuroBlu v24r5). Adults (≥18 years) with an ICD diagnosis of schizophrenia and subsequent MSE record were included. Patients with either a Positive Symptom Rating Scale (PSRS) or Brief Negative Symptom Assessment (BNSA) record on the same day as the MSE

were identified (PSRS or BNSA cohorts, respectively). MSE descriptors of positive and negative symptoms were identified and reviewed by three psychiatrists.
Negative symptoms in the BNSA cohort were identified using MSE descriptors and total BNSA scores (≥9), while positive symptoms in the PSRS cohort were identified using MSE descriptors and total PSRS scores (≥5). The proportion of records with evidence of positive or negative symptoms via MSE and clinical rating scales was estimated. Additionally, mean BNSA and PSRS scores were compared between patients with and without corresponding MSE descriptors. Finally, the frequency of records with MSE descriptors of positive and negative symptoms relative to total scale scores was described.

**RESULTS:** A total of 65,561 adult patients with schizophrenia and MSE data were identified. Of those, 4,605 (7.0%) formed the BNSA cohort and 4,610 (7.0%) formed the PSRS cohort. Patients in the BNSA cohort contributed a total of 9,494 events of concurrent MSE and BNSA assessments. Negative symptoms were identified in 4,064 (42.6%) BNSA records and in 3,381 (35.6%) MSE records. The median (IQR) total BNSA score was higher in records where MSE also indicated negative symptoms (10.0 [7.0, 13.0]), compared to MSE record without indication of negative symptoms (7.0 [4.0, 10.0]). Where BNSA score was 19-24, 80.6% of negative symptoms phenotype were also captured in the MSE. Where BNSA score was 4-9, MSE has identified 22.0% events of negative symptoms.

Patients in the PSRS cohort contributed a total of 9,497 distinct records with concurrent MSE and PSRS assessments. Positive symptoms were identified in 3,871 (40.8%) of records via the PSRS and in 2,351 (24.8%) via the MSE. The median (IQR) total PSRS score was higher in records with MSE positive symptoms compared to those without (with: 11.0 [7.0–15.0], without: 6.0 [4.0–10.0]). The median (IQR) PSRS score increased as the number of MSE-positive symptoms increased (one MSE symptom: 9 [6–12], > 5 MSE symptoms: 18.9 [16–23]).

**DISCUSSION:** We provide preliminary evidence of a relationship between the presence of schizophrenia symptoms ascertained via routine clinical examination and those measured using a clinical rating. Using routine MSE could allow assessment of large cohorts with defined symptomatology of interested, otherwise not commonly.

## T134. A Systematic Review of Contingency Management in Psychosis

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**BACKGROUND:** Contingency management (CM) is evidence-based psychosocial intervention where patients receive tangible rewards to reinforce positive behaviours. CM is commonly used in the treatment of substance-use disorders (SUDs; Prendergast et al., 2006) and has been most commonly studied in relation to stimulants, opioids, tobacco, and alcohol. While CM has been

previously applied to patients with a primary diagnosis of SUD, research has begun investigating CM in the context of comorbid SUDs and psychiatric conditions.

SUDs are estimated at 7.9% in the general population (Von Gunten and Wu, 2021), whereas SUDs in schizophrenia is markedly higher (37%; Toftdahl et al., 2016). Indeed, comorbid SUD and schizophrenia has been found to increase hospitalization and mortality rates by 50-100% in comparison to those without SUD (Lähteenvuo et al., 2021). These findings demonstrate the importance of investigating CM strategies within this population to determine if CM is a feasible intervention. Therefore, we conducted a systematic review to examine the efficacy of CM interventions in concurrent SUDs and mental health disorders, specifically focusing on psychosis.

**METHODS:** An electronic database search was performed in EMBASE using the following keywords: ("Contingency*" OR "behavioral contingency" OR "token economy" OR "token reinforcement" OR "incentive-based" OR "positive reinforcement" OR "reward system") AND ("Mental Disorder" OR "Psychiatric Disorder" OR "Schiz*" OR "Bipolar*" OR "Depress*" OR "MDD" OR "Anxiety*" OR "SAD" OR "GAD" OR "Neurodevelopmental*" OR "ADHD" OR "Trauma*"). Filters applied to the search specified that the research was peer reviewed and written in English and included all articles up to October 22, 2024. Inclusion criteria were a diagnosis of mental health disorder by a clinician, including a contingency management intervention, sample size $\geq 5$. Articles were excluded if the sample did not have a formal diagnosis or was subclinical, used secondary sources, sample size was $< 5$, or based on animal models.

Articles were then imported into Covidence for screening. Articles were screened by 3 independent reviewers (TD, JC, BC) at the title and abstract level. Articles were then subsequently screened through full text review prior to inclusion/extraction.

**RESULTS:** The electronic database search in EMBASE resulted in 3374 articles being imported for screening. 46 duplicates were identified and excluded. 3328 studies were screened at the title and abstract level and 3279 studies were excluded. 41 full-text studies were assessed for eligibility. 19 studies were excluded (4 not a journal article, 4 subclinical samples, 4 wrong outcomes, 2 insufficient sample size, 2 wrong intervention, 2 wrong study design, 1 wrong patient population). Therefore, 22 studies were included in the extraction. Of these 22 studies, 9 included patients with a schizophrenia spectrum disorder diagnosis (schizophrenia, schizoaffective, psychosis NOS). Substances targeted with CM were nicotine (4), cannabis (2), alcohol (1), stimulants (1), and polysubstance (1).

Significant reductions in substance use were noted with the following substances: cannabis (2/2), Nicotine (3/4), stimulants (1/1). No significant reductions were seen in polysubstance, alcohol, and 1 of the nicotine studies.

**DISCUSSION:** Of the 9 studies examining CM in schizophrenia spectrum disorders, 6 demonstrated a reduction in substance use. Notably, cannabis, nicotine, and stimulants appeared to benefit most from CM, which is consistent with previous studies examining CM in primary

SUDs. However, alcohol and polysubstance use did not appear to benefit from CM based on the current, albeit limited, studies.

Several limitations were observed in the current literature. First, most studies had small sample sizes, and significant attrition rates. Second, although the current literature demonstrates decreased rates of substance use during the study, there is no data suggesting translation to long-term abstinence, bringing to question treatment generalizability of CM. This suggests future work should employ a longitudinal methodology to further assess abstinence following CM.

Overall, the current studies indicate that CM is an effective treatment method for cannabis, nicotine, and stimulants abstinence. However, the current research is limited in terms of sample size and length of abstinence, future work should address these gaps.

## T135. Measurement of Schizophrenia Symptoms Through Speech Phenotyping From Panss Recordings: A Cross-Study Validation

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**BACKGROUND:** Speech is a clinically meaningful indicator of schizophrenia symptom severity and speech phenotyping often requires dedicated task paradigms on proprietary platforms using closed-source code to phenotype speech. Here, we use audio recordings of Positive and Negative Syndrome Scale (PANSS) interviews and open source code to calculate speech measures and evaluate them as meaningful indicators of schizophrenia symptom severity.

We previously demonstrated that such clinical interactions are a reliable source of audio for speech phenotyping (under review at Schizophrenia Bulletin). Here, we report results from an expansion of this project using ~2,000 hours of PANSS interview recordings from three separate clinical trials, leading to what we believe is the largest study on speech-based digital phenotyping in psychiatry to date.

**METHODS:** Audio recordings of PANSS interviews from three schizophrenia clinical trials (NCT03697252, NCT04659161, NCT04738123) were analyzed. Speech features, including amount of speech, rate of speech, pause characteristics, emotional sentiment, and lexical richness, were extracted using the OpenWillis open-source Python library (github/bklynhlth/openwillis). Mixed effects models were used to examine the association between speech measures and PANSS scores, controlling for age, sex, and race.
**RESULTS:** Approximately 1,984 hours of audio data were analyzed from a total of 3,482 PANSS interviews.

PANSS positive symptom subscale scores were associated with a greater amount of speech (adjusted speech length in minutes β=3.355; p-value < 0.01; adjusted speech length in words β=0.027; p-value < 0.01), an increased rate of speech (words per minute β=0.015; p-value < 0.01; syllables per minute β=0.009; p-value < 0.01), a change in pause characteristics (pause length mean β=-3.819; p-value < 0.01), and reduced lexical richness (moving-average token-type ratio (MATTR) β=-13.008; p-value < 0.01).

By contrast, the score on the PANSS negative subscale was associated with a reduced amount of speech (adjusted speech length in minutes β=-2.905; p-value < 0.01; adjusted speech length in words β=-0.025; p-value < 0.01), a decreased rate of speech (words per minute β=-0.017; p-value < 0.01; syllables per minute β=-0.010; p-value < 0.01), a change in pause characteristics (pause length mean β=4.969; p-value < 0.01; increased pause between the clinician's question and the patient's response β=0.784; p-value < 0.01), and increased lexical richness (MATTR β=5.302; p-value < 0.01).

**DISCUSSION:** This study demonstrates the feasibility and value of using clinical interview recordings for large-scale speech analysis in schizophrenia, confirming and expanding on previous findings linking specific speech patterns to symptom severity. This approach allows for efficient and scalable analysis of readily available data, potentially enhancing clinical assessment and treatment development.
Future research will explore higher-order linguistic features to capture more complex aspects of schizophrenia, such as disorganized thought. Speech measures may also be used to develop predictive models of disease severity and stratify patients for personalized interventions. This methodology can be extended to other psychiatric and neurological conditions where speech may be affected.

## T136. Development of LTX-001, A Novel Oral Small Molecule for the Treatment of Schizophrenia

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**BACKGROUND:** Schizophrenia is a devastating disease affecting 0.3-1% of the adult population. Psychopathology in schizophrenia includes positive (hallucinations, delusions, disorganized or intrusive thoughts), negative (anhedonia, social withdrawal), and cognitive (processing speed, attention, memory) symptoms. Current treatments for schizophrenia that modulate the dopaminergic system are effective in some patients for treating positive symptoms of schizophrenia, but do not fully address negative or cognitive symptoms. Furthermore, these treatments are not effective in all patients and can have significant side effects. Excessive and

aberrant glutamate signaling has been hypothesized to play a central role in the pathophysiology of schizophrenia. Glutamate is the major excitatory neurotransmitter in the CNS and directly mediates trans-synaptic signaling at most CNS synapses and plays a central role in mechanisms of plasticity in CNS circuitry. Excessive glutamate levels can lead to inappropriate glutamatergic synaptic signaling and plasticity, as well as excessive dopamine release, excitotoxicity, oxidative stress, and inflammation. All of these pathological mechanisms may play roles in the onset and progression of schizophrenia. In addition to treating positive symptoms of schizophrenia, modulation of the glutamatergic pathway has the potential to ameliorate negative and cognitive symptoms, while mitigating dopamine-related adverse effects. We have developed LTX-001, an investigational oral small molecule targeting glutaminase (GLS1), the rate-limiting enzyme for glutamate biosynthesis in the central nervous system (CNS), for the treatment of schizophrenia.
**METHODS:** LTX-001 was assessed preclinically in multiple species, including rodents and large animals, for its safety, distribution, target engagement, and efficacy. The PK/PD profile was assessed in rodents and large animals, and the well-validated amphetamine-induced hyperactivity mouse model of schizophrenia was used to assess efficacy.
**RESULTS:** Oral administration of LTX-001 resulted in broad CNS distribution in multiple species. Furthermore, LTX-001 treatment resulted in significantly reduced CNS glutamate/glutamine, and a corresponding significant improvement in ameliorating the amphetamine-induced hyperactivity response, in a dose-dependent manner.
**DISCUSSION:** These results demonstrate that LTX-001, a novel oral small molecule, was able to successfully achieve brain penetration in animal models and support its potential as a therapeutic option to treat schizophrenia by targeting the glutamatergic pathway and impacting both positive and negative symptoms of schizophrenia.

## T137 .An Exploratory Study on Inflammatory Biomarkers and Antipsychotic Side Effects in Patients With Schizophrenia

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**BACKGROUND:** Extrapyramidal symptoms (EPS) are common side effects of antipsychotic medications and can contribute to medication non-adherence and subsequent relapse in schizophrenia. Recent research suggests that inflammatory markers, such as the neutrophillymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR),
and systemic immune-inflammation index (SII), may serve as biomarkers for treatment response in schizophrenia. This study explores the relationship between these inflammatory markers and EPS in patients with schizophrenia.

**METHODS:** 50 outpatients with a confirmed diagnosis of schizophrenia or schizoaffective disorder were recruited. EPS was assessed using the Extrapyramidal Symptom Rating Scale (ESRS), and overall side effects were evaluated using the Glasgow Antipsychotic Side Effect

Scale (GASS). 28 patients completed bloodwork and CBC data were analyzed to calculate NLR, PLR, MLR, and SII.

**RESULTS:** The median age was 44 years (IQR, 20.5), and the sample was predominantly male (76%), single (78%), and financially supported by provincial social assistance programs. Analysis revealed no significant association between total GASS scores and inflammatory markers. However, a negative correlation was found between monocyte count and ESRS akathisia subscale ($r_s(26) = -0.386$, $p = 0.043$). Higher SII scores ( > 625.7) were significantly associated with higher self-reported parkinsonism ($t(26)=2.198$, $p=.019$, cohen's $d=.831$) and hyperkinesia ($t(26)=2.249$, $p=.033$, cohen's $d=.850$). Patients on clozapine had significantly higher PLR ($t(8)=3.866$, $p=0005$, Cohen's $d = 3.072$) and MLR ($t(8)=3.617$, $p=0.007$, Cohen's $d= 2.860$) compared to those on any other antipsychotics. Lastly, a significant negative correlation between SII and length of time on antipsychotics ($r_s=-0.452$, $p=0.016$) was observed.

**DISCUSSION:** This study is one of the first to explore the relationship between CBC-derived inflammatory markers and EPS in schizophrenia patients. The significant negative relationship between monocyte count and akathisia suggest that high monocyte counts may be indicative of lower akathisia symptoms. The linear relationship between SII and EPS, particularly with parkinsonism and hyperkinesia, suggests that elevated inflammation may correlate with more EPS in patients on antipsychotics. The inverse relationship between SII and duration of antipsychotic use, suggest that SII may reflect adherence and inflammation improvement over time. Limitations of this study include small sample size and lack of control for confounding variables affecting inflammatory status. Further research should consider a longitudinal approach with larger samples to confirm these findings and evaluate the potential applications of inflammatory markers in guiding antipsychotic treatment strategies.

## T138. Comorbid Medical Conditions, Service Utilization, and Costs Among Individuals With Serious Mental Illness (SMI) and Treated With Antipsychotic Drugs

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**BACKGROUND:** Antipsychotics are effective in managing serious mental illness (SMI); however, they are associated with significant side effects, such as metabolic syndrome, which can lead to adverse cardiovascular outcomes. Research has consistently shown an increased risk of mortality among individuals with SMI. Nevertheless, the common comorbid conditions in this population and their impact on healthcare cost and service utilization remain unclear. The

purpose of this study is to examine the prevalence of selected medical conditions, healthcare utilization, and associated costs among individuals treated with APDs compared to those who have not received APDs.
**METHODS:** This study is a retrospective observational cohort analysis utilizing national-level data from the VA's electronic health records and VA Corporate Data Warehouse. Eligible subjects included adults who initiated APD treatment for schizophrenia or bipolar disorder between January 1, 2004, and Dec 31, 2007, as well as adults in a control group who did not take any APD during the same timeframe and had data available 10 years later. The International Classification of Diseases (ICD) codes were used to identify cardiovascular diseases (e.g., hypertension, ischemic heart disease, other forms of heart disease, cerebrovascular disease), metabolic disease (e.g., diabetes), and other contributing conditions (e.g., hyperlipidemia, obesity). Nosos risk scores derived from the Greek word for "chronic condition "were analyzed to predict healthcare costs, along with the number of clinical visits associated with each ICD code. Descriptive statistics at the patient level were conducted using STATA.
**RESULTS:** A total of 14,998 adults had been treated with APD while 1,550,991 had not. The prevalence rates of selected medical conditions are significantly different between the two groups: obesity (23% vs. 16%; $z=23.24$, $p < .001$), diabetes (22% vs. 18%; $z=13.62$, $p < .001$), and cerebrovascular disease (8% vs. 6%; $z=9.12$, $p < .001$). However, there were no significant differences in the prevalence of hypertension (76% vs. 79%; $z = -8.21$), ischemic heart disease (20% vs. 25%; $z = -11.85$), other forms of heart disease (30% vs. 31%; $z = -1.41$), hyperlipidemia (78% vs. 78%; $z = 1.84$), and disease of arteries (15% vs. 15%; $z = -0.61$) (ps > .05). Nosos scores for each diagnosis in the APD group were significantly higher, ranging from approximately 2-fold to more than 3-fold > those in the control group (ps < .001). The APD group also had significantly more outpatient clinic visits for conditions including hypertension, hyperlipidemia, obesity, diabetes, and cerebrovascular disease (ps < .05). In contrast, the control group had more outpatient clinic visits for ischemic heart disease, other forms of heart disease, and disease of arteries compared to the APD group (ps < .02).
**DISCUSSION:** The study highlights the complex comorbidity health profiles, healthcare utilization, and costs among individuals using APD. Healthcare providers should implement regular screening, ongoing monitoring, and proactive management plans. Further research should develop and validate clinical prediction models that include the complex comorbidity characteristics of individuals with SMI being treated with APDs to identify patients at higher risk of morbidity and mortality, enabling targeted intervention to improve health outcomes.

## T139. Effects of Semaglutide on Body Weight in Clozapine-Treated Individuals With Schizophrenia and Obesity: A Randomized Controlled Trial

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**BACKGROUND:** People with schizophrenia experience significantly higher rates of obesity and related cardiometabolic disorders, largely due to antipsychotic medications, especially clozapine. This metabolic burden contributes to decreased life expectancy and increased health complications. Current pharmacological interventions, such as metformin, show limited efficacy in addressing antipsychotic-induced weight gain. Semaglutide, a glucagon-like peptide-1 receptor agonist, has demonstrated promise in reducing body weight and improving metabolic health. This study investigates the efficacy of semaglutide in managing clozapine-associated obesity.
**METHODS:** The Clozapine associated Obesity and Semaglutide Treatment (COaST) trial is a 36-week, double-blinded, placebo-controlled randomized study. It will include 32 adults diagnosed with schizophrenia or schizoaffective disorder, currently treated with clozapine, and presenting with obesity (BMI $\geq$ 26 kg/m$^2$). Participants are randomly assigned to receive either 2.0 mg of semaglutide subcutaneously or a placebo once weekly (titrated over 16 weeks). The primary outcome measure is the percentage change in body weight from baseline to 36 weeks. Secondary outcomes include changes in metabolic syndrome components, insulin resistance, and cognitive function.
**RESULTS:** This will be world's first reporting of an RCT of semaglutide for clozapine associated obesity. The trial will assess whether semaglutide produces significant weight reduction and metabolic improvements in clozapine-treated individuals compared to placebo. Secondary analyses will explore the impact on metabolic syndrome, insulin resistance, and cognitive outcomes.
**DISCUSSION:** The COaST trial is expected to provide critical data on the efficacy of semaglutide as a weight loss intervention for individuals with schizophrenia experiencing clozapine-induced obesity. If successful, this could lead to new therapeutic strategies for reducing cardiometabolic risk in this population. Results will inform future clinical guidelines and public health interventions.The COaST trial is expected to provide critical data on the efficacy of semaglutide as a weight loss intervention for individuals with schizophrenia experiencing clozapine-induced obesity. If successful, this could lead to new therapeutic strategies for reducing cardiometabolic risk in this population. Results will inform future clinical guidelines and public health interventions.

## T140. Hyperlipidemia Correlated With Better Neurocognition in Patients With Schizophrenia

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**BACKGROUND:** Cognitive dysfunction is a core feature of schizophrenia and is associated with functional dysfunction. It is generally believed that metabolic abnormalities may impair neurocognition in schizophrenia. This study analyzed prospective data from the NIMH-funded schizophrenia CATIE study to examine the effects of hyperlipidemia on neurocognitive measures.
**METHODS:** Screening data was collected on 1460 patients, including demographics, psychiatric history, and metabolic variables. Serum cholesterol and triglycerides were measured

in a subsample (N=741, mean age 40.4 years, 75% male, 61% white) who were in a fasting (≥ eight hours) state. Neurocognition was assessed at baseline using the Neurocognitive Composite (NC) Score, an average of five composite subscale z-scores: 1) Processing Speed 2) Verbal Memory 3) Vigilance Summary Score 4) Reasoning Summary Score and 5) Working Memory Summary Score. Regression and analysis of variance models were used to examine the relationships between metabolic variables and neurocognition.
**RESULTS:** Patients with low HDL cholesterol levels had significantly lower NC Scores than patients with high HDL levels ($p = 0.04$). Conversely, patients with high total cholesterol had significantly higher NC scores than patients with low total cholesterol ($p = 0.002$). Participants with high triglycerides had significantly higher NC scores when compared to participants with low triglycerides ($p = 0.02$).
**DISCUSSION:** Our study found that hyperlipidemia correlated with better neurocognition in patients with schizophrenia. The clinical and research implications of these unexpected findings will be discussed.

## T141 A Cognitive-Behavioral Suicide Prevention Treatment Among Adults With Psychosis In Community Mental Health

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**BACKGROUND:** Suicide is among a leading cause of death for individuals with schizophrenia spectrum disorders (SSDs). Cognitive Behavioral Suicide Prevention for psychosis (CBSPp) is one of few suicide-focused interventions tailored for psychosis symptoms and was developed in the UK. This abstract presents on Aim 1 of a NIMH-funded pilot effectiveness clinical trial (R34) study of treatment modifications with use of stakeholder input and an open pilot trial for preliminary testing prior to a clinical trial.
**METHODS:** Stakeholders (n=25) participated in modification efforts, including clients with SSDs and recent suicide ideation or attempt, peer advocates, and mental health providers in a community mental health (CMH) setting. All stakeholders attended a qualitative in-depth interview with research staff to inform treatment modifications. Clients (n=5) received 10 individual therapy sessions across 10 weeks by trained CBSPp providers (n=5) and completed clinical assessments at 4 timepoints.
**RESULTS:** Final modifications include tailoring CBSPp content and protocol for psychosis clients in CMH, increasing the feasibility of provider training, and enhancing client engagement to boost content and provide added support to clients. Clients made improvements in suicide ideation, depression, hopelessness, general symptoms of psychosis, entrapment, defeat, coping, psychological stress, and impulsivity from baseline to post-treatment in the open pilot study.
**DISCUSSION:** Consistent with prior literature, buy-in and stakeholder support in the implementation of a treatment innovation emerged as important factors. Stakeholder involvement was essential in the modification process and open pilot findings reinforced the potential of CBSPp as a suicide prevention approach in CMH.

## T142. OPEN BOARDS

## T143. The Role of Personal Recovery in Predicting Mental Health-Related Quality of Life in Individuals With Persisting Psychotic Disorders

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**BACKGROUND:** Consumer-defined concepts of recovery, often referred to as personal recovery, have been contrasted with symptom remission as a target for mental health delivery to persons with severe mental illness. However it remains unclear the extent to which health-related quality of life if impacted by individual differences in personal recovery above the impact of symptom burden.
**METHODS:** A sample of 178 participants with psychotic disorders and in receipt of Australian community-based specialist mental health services completed assessments during the baseline phase of a treatment study. Main measures included the AQoL-8D assessment of health-related quality of life, together with the Process of Recovery Questionnaire and the Positive and Negative Syndrome Scales. Regression analysis was used to determine the incremental variance explained by personal recovery above symptoms and other clinical variables.
**RESULTS:** Personal recovery accounted for a substantial proportion of mental health related quality of life above the impact of clinical symptoms, diagnosis, and demographic variables alone.
**DISCUSSION:** Personal recovery has a significant relationship with health-related quality of life. Interventions and service delivery models that can successfully target personal recovery may be important in reducing the overall burden of illness in community mental health care.

## T144. Improvement in Personal/Social Functioning and Quality of Life in Adults With Schizophrenia Following 8 Weeks of Once-Monthly Olanzapine Extended-Release Injectable Suspension for Subcutaneous Use (TV-44749; Phase 3 Solaris)

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**BACKGROUND:** Long-acting injectable (LAI) antipsychotics are associated with improved clinical and functional outcomes in schizophrenia. TV-44749 is a once-monthly subcutaneous extended-release injectable olanzapine with innovative copolymer-based technology, designed to provide sustained efficacy without risk of post-injection delirium/sedation syndrome (PDSS) observed with intramuscular LAI olanzapine. Efficacy and safety of once-monthly TV-44749 administered at select doses to adults with schizophrenia are being evaluated in the ongoing phase 3 Subcutaneous OLAnzapine extended-Release Injection Study (SOLARIS; NCT05693935).
**METHODS:** The SOLARIS study includes an 8-week randomized, double-blind, placebo-controlled acute treatment phase (period 1) and an open-label, long-term safety phase (up to 48 weeks; period 2). Key eligibility criteria included patients aged 18–64 years diagnosed with schizophrenia for ≥1 year and acute exacerbation ≤8 weeks before screening, who would benefit from hospitalization. In period 1, patients were randomized 1:1:1:1 to once-monthly TV-44749 (318 mg, 425 mg, or 531 mg) or placebo. These selected TV-44749 doses correspond with 10, 15, and 20 mg/day oral olanzapine, respectively. The primary endpoint was change in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to week 8. Other endpoints included: change in Clinical Global Impression-Severity (CGI-S) scale from baseline to week 8 and change in Personal and Social Performance (PSP) scale from baseline to week 8 (alpha-controlled key secondary endpoints); change in Schizophrenia Quality of Life Scale (SQLS) from baseline to week 4 and week 8 (secondary endpoint); and change in EuroQoL-5 Dimensions-3 Levels (EQ-5D-3L) scale (exploratory endpoint).
**RESULTS:** Overall, 675 patients were randomized (169 to each TV-44749 arm; 168 to placebo). Mean (SD) age was 44.6 (11.7) years; 75% (n=381) were male and 67% (n=341) were Black or African American. The SOLARIS study met its primary endpoint and key secondary endpoints. PSP. The mean difference in change in PSP total score from baseline to week 8 was statistically significant for all TV-44749 doses (318 mg [4.63], 425 mg [3.15], and 531 mg [4.93]) versus placebo (all $P < 0.05$). The mean difference in change from baseline to week 4 was statistically significant for TV-44749 318 mg ($P < 0.05$). SQLS. There was a significantly greater mean difference in change in SQLS total score from baseline to week 8 with TV-44749 318 mg (-3.99), 425 mg (-5.39), and 531 mg (-5.65) versus placebo (all $P < 0.05$). For the SQLS psychosocial feelings domain, there was statistically significant improvement from baseline to week 8 for all TV-44749 doses (318 mg [-4.83], 425 mg [-6.54], and 531 mg [-6.50]; all $P < 0.05$). For the SQLS cognition and vitality domain, there was a significantly greater mean difference in change from baseline to week 8 for TV-44749 531 mg (-4.55) versus placebo ($P < 0.05$). EQ-5D-3L. There was statistically significant improvement in change in the Visual Analog Scale score from baseline to week 8 for TV-44749 425 mg versus placebo ($P < 0.005$). From baseline to week 4, TV-44749 treatment resulted in an improvement in the proportion of study participants reporting ‘some problems’ (level 2 or 3) to ‘no problems’ (level 1) in all health domains: self-care (-38%), usual activities (-36%), pain/discomfort (-22%), anxiety/depression (-18%), mobility (-2%). By week 8, further improvements in the proportion of participants shifting from ‘some problems’ to ‘no problems’ were seen in all health domains. No events of PDSS have been reported with 3485 injections.
**DISCUSSION:** In this population of patients with acute exacerbation of schizophrenia treated with TV-44749 and hospitalized for ≥28 days, overall significant improvements in patient functioning and quality of life (QoL) were observed at weeks 4 and 8 of treatment, reinforcing the potential value of TV-44749 for schizophrenia treatment and improving patient-centered

outcomes. Potential additional benefits of TV-44749 on patient functioning and QoL will be explored further in the ongoing SOLARIS open-label long-term safety period, which is being conducted in an outpatient setting (period 2).

## T145. Risk vs Intent: Examining Convergent Validity Between Perceived Barriers to Taking Medication and Intent to Stop Medication Among Early Psychosis Program Service Users

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**BACKGROUND:** Prescription of antipsychotics is a component of fidelity to coordinated specialty care(CSC), an evidence-based treatment for first episode psychosis (FEP)). However, studies that measure an individual's adherence to oral antipsychotic medications frequently observe adherence rates below 50%. An individual's choice to follow a prescribed medication plan is extremely personal and influenced by their own risk-benefit analysis. The Adherence Estimator is a "brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease" which measures beliefs which may influence an individual's medication-taking behavior. It has been chosen as part of the Core Assessment Battery for NIH'S EPINET project which has created a network of EP program hubs across the country, including California's EPI-CAL project. Using data from the EPI-CAL project, we will examine the convergent validity between an individual's expressed intent to stop taking medication and their perception of barriers to taking medication.
**METHODS:** CSC service users completed surveys at EPI-CAL enrollment and every 6 months throughout treatment. Surveys include demographics, intent to stop taking medication, and beliefs related to medication taking behaviors. Intent to stop taking medication is measured by a single item, "do you plan to stop taking your medication?", developed in response to qualitative work with EPI-CAL programs. Beliefs related to medication taking behaviors are measured by the Adherence Estimator, responses from which produce a score associated with low-, medium-, or high-risk of non-adherence to medication. Descriptive analyses summarized demographics and self-report outcomes. Medication self-report outcomes were coded into ordered data. A Spearman's rank ordered correlation analysis was used to examine the relationship between overall risk of non-adherence to medication and intent to stop taking medication.
**RESULTS:** At baseline, 210 service users (Ages 10-35, M=17, SD=4.44) who were taking prescription medication completed medications measures. Of these individuals, 10% (n=22)

indicated that they intended to stop taking medication. On the adherence estimator, 33% (n=70) scored as high-risk and 38% (n=79) scored as medium-risk. There was a statistically significant, positive correlation between intent to stop taking medication and the overall adherence risk score, $rs = .336$, $p < 0.001$.
**DISCUSSION:** While the domains of risk of non-adherence and intent to stop taking medication are related, the lack of a strong association suggests that these domains may be capturing separate but related information or that one may be more predictive of actual discontinuation of medication than the other. Longitudinal analyses of adherence estimators will be examined.

## T146. Validation of the Patient Global Impression of Severity (PGI-S) for Schizophrenia

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**BACKGROUND:** The Patient Global Impression of Severity (PGI-S) is a self-report scale adapted from the Clinical Global Impression Scale of Severity (CGI-S). There has been no large-scale validation studies on the use of the PGI-S in assessing patients with schizophrenia.
**METHODS:** 149 patients with schizophrenia from a tertiary psychiatric institution in Singapore were recruited and completed the PGI-S and the World Health Organisation Disability Assessment Schedule (WHODAS). Trained clinicians assessed the patients on the Clinical Global Impression-Schizophrenia scale (CGI-SCH) and Social and Occupational Functioning Assessment Scale (SOFAS). We compared the PGI-S against the CGI-SCH ratings for the overall and four symptom domains, i.e. positive, negative, cognitive and depression using Spearman correlations. We further examined the impact of insight, determined on the Positive and Negative Syndrome Scale (PANSS) item G12, on the relationship between patient and clinician rated ratings.
**RESULTS:** We found that PGI-S scores and CGI-SCH scores were significantly correlated in overall score ($r= 0.343$, $p < 0.001$) and in all symptom domains. PGI-S was also significantly correlated with WHODAS and SOFAS. Overall, patients' ratings on the PGI-S tended to be lower than clinicians' ratings on the CGI-SCH. When stratified by insight, patients with good insight (PANSS G12 $\leq 3$) had no significant difference in PGI-S and CGI-SCH overall score ($Z= -1.619$, $p= 0.105$); but the group with impaired insight (PANSS G12 $> 3$) showed significantly lower patient ratings ($Z= -2.916$, $p= 0.004$).
**DISCUSSION:** Our study demonstrated moderate agreement between patient and clinician ratings on overall illness. Patients often rated their symptom severity lower compared to clinician. Our study suggests that insight plays a significant role in patient reported clinical outcomes, with impaired insight associated with lowered severity scores.

## T147. Perspectives on Medication Adherence of Long-Term Clozapine Patients: A Qualitative Study

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**BACKGROUND:** Clozapine is the gold-standard for treatment resistant schizophrenia, yet remains widely underused. There are few studies exploring patient perspectives on clozapine. Our objective was to qualitatively investigate patient viewpoints on clozapine adherence in order to identify unmet concerns and novel perspectives.

**METHODS:** We used a semi-structured topic guide to interview patients (n = 11) in the Johns Hopkins Bayview Clozapine Clinic. Participants had been taking clozapine for at least 1 year (mean = 5.4 years, range = 1.4 - 9.2 years) and represented a cross section of clinic gender (female = 4, male = 7), race (white = 6, black = 3, biracial = 2), age (mean = 37.2 years, range = 26 - 68 years), and symptom severity (mean PANSS = 62, range = 37 - 92). Participants were interviewed either in-person or remotely via Zoom. Interviews were conducted until thematic saturation was reached, calculated using the methods developed by Guest et al., 2020. Two investigators independently coded transcripts using Atlas.ti. The codebook was tested and edited until coders achieved 80% intercoder agreement. Thematic content analysis was carried out in discussion with psychiatrists both involved with and independent from the clinic.

**RESULTS:** Key themes included rationale for clozapine adherence, facilitators of adherence, barriers to adherence, and patients' advice to others taking clozapine. Patients emphasized the utility of the Clozapine Clinic model, including the availability of therapy, management of side effects, career guidance, availability of group sessions, and personalization of clozapine dose. Participants described a months-long process of working with clinic staff to identify a dosing regimen that minimized side effects while maximizing symptom reduction. For instance, one patient discontinued clozapine due to side effects but was able to re-establish adherence after taking smaller doses twice a day. In a novel finding, many participants reported that they adhered to clozapine to avoid what they perceived as withdrawal-like experiences that could result from even a single missed dose. Multiple participants described distressing experiences with insomnia (eg. "I felt like I was gonna die from not sleeping") following missed doses of clozapine. Most patients also reported substantial improvement in symptoms and quality of life due to adherence to clozapine (eg. "The world isn't ending anymore"). Consistent with past studies, participants generally did not consider mandatory blood work a major obstacle to clozapine adherence; only a few participants described negative experiences receiving blood work. Almost all participants described substantial family emotional and practical support in helping them to maintain adherence to clozapine.

**DISCUSSION:** The study is consistent with the notion that long-term adherence to clozapine requires attention to patient experiences. Participants cited the importance of tailored dosing regimens and side effect management in maintaining long-term clozapine use. Furthermore, the nearly unanimous descriptions of strong family support suggest that investment by family members and other caregivers could be imperative for long-term adherence to clozapine. This study was limited to individuals who had successfully maintained long-term clozapine use. Alternative themes about barriers to clozapine adherence would likely emerge from studies of

individuals for whom clozapine was recommended but who never began clozapine, did not tolerate initiation of clozapine, or discontinued clozapine after treatment initiation.

### T148. The Effect of Group-Based Metacognitive Reflection and Insight Therapy (MERITG) on Recovery-Oriented Beliefs in Comorbid Serious Mental Illness and Substance Use Disorder

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**BACKGROUND:** Metacognitive Reflection and Insight Therapy (MERIT) and its group format, MERITg, are recovery-oriented, evidence-based interventions created to help improve insight and metacognition in individuals with serious mental illness (SMI). Individuals with SMI are at increased risk for substance use disorders (SUD) and comorbid SUD is associated with a host of acute and long-term negative clinical and functional outcomes. The recovery movement highlights the importance of individualized, strengths-based approaches to help individuals find meaning and purpose in their lives and is deeply integrated into both SMI and SUD treatment programs. Group interventions in particular are a mainstay of both SMI and SUD programs and may provide unique opportunities to pursue recovery-oriented goals. The aim of the present study was to evaluate the effect of SUD status on recovery-oriented beliefs following engagement in MERITg.
**METHODS:** Twenty-one (21) individuals enrolled in an outpatient SMI treatment program participated in a weekly adjunctive group therapy intervention (MERITg). Participants completed a short-form of the Maryland Assessment of Recovery in Serious Mental Illness (MARS-12), which is a self-reported measure of six core themes related to or describing recovery: self-direction or empowerment, holistic, non-linear, strengths-based, responsibility, and hope. Participants completed the MARS-12 at baseline and following each group participation. Demographic and diagnostic information was obtained by chart review.
**RESULTS:** RESULTS: On average, participants were middle-aged (M=48.85 years old, SD=13.52), high-school educated (M=12.95 years of education, SD=1.61), male (70%), White (60%), and did not identify as Latinx (80%). MERITg was offered in an outpatient setting for 13 weeks and participants attended 3 groups on average. Individuals who did not have a comorbid SUD (N=12) reported significantly improved recovery-oriented beliefs from baseline (M=46.50, SD=6.35) to the end of participation in MERITg (M=49.73, SD=5.66; $t(10) = 2.27$, $p=0.047$) with a moderate effect size (Cohen's $d=0.68$). Individuals who did have a comorbid SUD (N=9) did not show significant improvement from baseline (M=46.44, SD=10.41) to end of participation (M=47.44, SD=9.66; $t(8)=0.59$, $p=0.57$), with modest effect size (Cohen's $d=0.20$). In addition, there was no significant difference in the total number of groups attended between the SUD (M=3.11, SD=2.20) and non-SUD (M=2.18, SD=1.47) groups ($F(1,18)=1.127$, $p=0.27$).
**DISCUSSION:** The current study suggests that a novel group-based metacognitive intervention (MERITg) is associated with significant improvements in recovery-oriented beliefs in individuals with SMI, but that individuals with SMI and comorbid SUD may need additional

interventions around recovery-oriented beliefs. In general, attendance and engagement tend to be lower for individuals with comorbid SMI and SUD; however, there was no significant difference in the number of MERITg sessions attended between the SUD and non-SUD groups, suggesting that the group difference is unlikely to be due to a dose effect of the intervention. Given the complexity of experience and presentation for individuals with comorbid SMI and SUD, additional research is necessary to help clarify what additional supports might be necessary to best support improvements in recovery-oriented beliefs in this population, such as an extended MERITg course.

## T149. Autonomy Support From Healthcare Professionals to Functional Gains in First Episode Psychosis: Mediation by Psychological Growth

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**BACKGROUND:** Schizophrenia and related disorders are among the most disabling psychiatric disorders, with widely prevalent long-term impairments in social and occupational functioning. While symptomatology and cognitive abilities are significant predictors of prognosis, improvements in these areas do not consistently lead to enhanced functioning. Scales have been developed that capture patient-described experiences of psychological growth processes (e.g., empowerment, regained control, hope) integral to their functional recovery. Self-Determination Theory (SDT) posits that environments supportive of autonomy can facilitate such recovery processes, thereby enhancing treatment outcomes. Despite this theoretical alignment, few studies have assessed patients' perceived autonomy support from healthcare providers; thus, its effect on important psychological growth processes and functioning in this population is largely unknown. To bridge this gap, we used data from the 2-year Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) to evaluate whether perceived autonomy support from healthcare providers in treatment predicts functional outcomes through psychological growth as a mediator.

**METHODS:** Longitudinal data of 403 RAISE-ETP participants were analyzed using SEM. Mediation models tested the direct and indirect effects of perceived autonomy support following treatment initiation (HCCQ; 3 and 12 months) on functional outcomes (QoL; 12 and 24 months), mediated by patient-described psychological growth processes (MHRM; 6 and 18 months). Separate mediation models were conducted given that the NAVIGATE program (n=223) was guided by SDT principles and yielded better functional outcomes than treatment as usual (TAU; n=180) reported in previous studies. Covariates included symptom severity (PANSS), student status, and sex. SDT and temporal precedence guided model specification. Model fit was assessed using standard indices (RMSEA, CFI, SRMR, TLI), with missing data managed via FIML estimation. Direct effects were significant at $p < .05$; bootstrap resampling (k=1,000) determined significance of indirect effects (95% CI excluding zero).

**RESULTS:** Model fit indices were adequate: RMSEA≤.05, CFI > .95, SRMR < .08 TLI > .95. In the NAVIGATE group, autonomy support at 3 months predicted functioning at 12 months through psychological growth processes at 6 months ($ab_I$=1.86, SE=.86, 95% CI [.57,3.86]); this effect remained significant when extrapolated to year two. Direct effect of autonomy support on

functioning was not significant (p=.69), indicating full mediation. No indirect or direct effects were detected for the TAU group across both years
**DISCUSSION:** Treatment programs that emphasize autonomy-supportive principles, such as NAVIGATE, lead to improved functional outcomes by fostering psychological growth processes, including enhanced empowerment, resilience, and hope. These findings highlight the relevance of SDT in clinical practice, providing a framework to optimize treatment outcomes by cultivating autonomy-supportive environments.

## T150. Perceived Stigma by Peer Workers: A Mixed Method Study

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**BACKGROUND:** Peer support is increasingly recognized as a valuable tool for implementing person-centered, rights-based and recovery approaches (WHO, 2021). Notably, the benefits of peer-support, with a small but significant effect size (Smit et al., 2022: Yim et al., 2023) are primarily related to personal recovery variables such as hope, empowerment and self-efficacy (Thomas et al., 2018; Burke et al. 2019; White et al. 2020; Jambawo et al., 2024). However, qualitative data (Adams, 2020; Lynn Ng and Barlas, 2023; Wall et al., 2022) and literature addressing the facilitators and the barriers to peer support (Ibrahim et al., 2020; Mutschler et al., 2022) indicate that peer-workers (PWs) may experience painful and stigmatizing experiences in the workplace during their integration to the organization. However, the literature is scarce regarding the specific situations of stigmatization as well as their experienced effects on PWs. This study aims to i) identify stigmatizing situations experienced by PWs in their workplace ii) characterize these situations in terms of frequency, perceived stigmatization, and associated distress, iii) identify factors associated with these situations.
**METHODS:** A multi-phase mixed-methods approach was adopted to address these objectives. Initially, a focus group-like method was used, including PWs (N=9) to identify and collaboratively select the 15 most relevant situations of stigmatization that PWs may experience. Subsequently, an online survey was disseminated among PWs and other mental health professionals to characterize the frequency, perceived stigmatization and distress associated to these situations. The mental health professionals sample was used as a comparison basis to determine whether the stigmatization situations mentioned were specific to peer-support workers. Moreover factors associated with perceived stigmatization were explored (i.e. perceived consequences such as professional activity on physical and mental health; perceived determinants such as recovery oriented practice of the team; sociodemographic characteristics such as gender or professional framework).
**RESULTS:** The pre-survey allowed the identification of 15 situations experienced as stigmatizing by PWs in the mental health workplace. A total of 152 participants were then included in the online survey: 71 PWs and 81 other mental health professionals. The situations associated with the highest stigma scores were i) being denied the right to access a mental health professional union and ii)being victim of mistreatment in my job, to which no follow-up was

given, or which were concealed of suppressed iii)being considered too fragile and sometimes left out for this. Furthermore, among the 15 identities studied, only two were more frequently experienced by peer-support workers. Indeed, They report more frequently that the conditions of their employment are more precarious than those of their colleagues. They also reported more frequently that they had to justify/defend their compensation based on their work/interventions (e.g., work recognition, professional certification registry, etc.). However, having to justify oneself/being denied access to training for professional practice was more frequently reported by other mental health professionals. Multiple linear regression revealed the sense of usefulness at work ($p < 0.05$), perceived consequences of professional activity on health ($p < 0.05$) and the subjective experience of personal support ($p < 0.05$) were positively associated with perceived stigmatization. Further results are currently under analysis and will be available for the 2025 SIRS

**DISCUSSION:** Using a mixed-methods approach (qualitative with the focus group like methodology and quantitative with the online survey questionnaire) and a participatory design, this study identified 15 potentially stigmatizing situations and highlighted associated factors. Although it appears that, on average, these situations were not experienced significantly more frequently by peer-support workers, their experience of these situations were different. They perceived stigmatization through these situations. Peer-support workers' experiences of stigmatization as service users in psychiatry may increase their sensitivity to such experiences once they are practicing. These findings suggest potential strategies for better integrating PWs into mental health services, highlighting ways to create a more cohesive, supportive environment.

## T151. The Anticholinergic Effect was not Associated With Recovery and Remission in Patients With Schizophrenia: A-Cross Sectional Study

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**BACKGROUND:** Recovery is an important goal for patients with schizophrenia; however, the rate of recovery in these patients is 13.5 %, which is lower than that in remission (Jaaskelainen et al., 2013) (Lally et al., 2017). This indicates that achieving recovery is difficult for patients with schizophrenia.

Cognitive impairment is a core symptom (Jauhar et al., 2022) and cholinergic signals may be related to the pathophysiological mechanisms of cognitive impairment in patients with schizophrenia (McCutcheon et al., 2023). The Anticholinergic Cognitive Burden (ACB) scale evaluates the anticholinergic effect of each medication (Salahudeen et al., 2015) and several studies have reported that a higher ACB score is associated with poor cognitive function in patients with schizophrenia (Ang et al., 2017) (Joshi et al., 2021). However, it is unclear how the anticholinergic effects influence recovery in patients with schizophrenia and how these effects differ between recovery, remission, and non-remission. This study aimed to compare different states (recovery, remission, and non-remission) with the ACB score and assess whether lower anticholinergic effects can contribute to recovery.

**METHODS:** This cross-sectional study included 68 Japanese patients with schizophrenia. The inclusion criteria for patients were a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013), age ranging 20–65 years, no change in antipsychotics for ≥3 months, and not using anticholinergics. Recovery was defined based on Liberman's criteria (Liberman et al., 2002) and remission was defined based on Andreassen's criteria (Andreasen et al., 2005). Non-remission was defined as failure to meet the recovery, remission, or treatment-resistant criteria for schizophrenia. The prescription for each patient was calculated and summed using the ACB scale, which was rated 0–3 for each medication. The Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) was used to evaluate the cognitive function. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to evaluate the psychiatric symptoms of patients. This study was approved by the Fukuoka University Medical Ethics Committee (U-21-11-018), and verbal and written informed consent was obtained from all participants. All statistical analyses were performed using the SPSS software (v. 27) with the $\chi$-square test, Kruskal–Wallis analysis, and Spearman's correlation. Statistical significance was set at $p < 0.05$.
**RESULTS:** There were no significant differences in the demographic and clinical characteristics of each group, except for the number of admissions, duration of employment, duration of illness, chlorpromazine equivalent, and BPRS. The ACB scores differed significantly among the groups. The ACB score of the remission group was significantly lower than that of the non-remission groups; however, no significant difference was observed between that of the recovery and non-remission, and the recovery and remission groups. Furthermore, no significant difference in the ABC score of antipsychotics was observed among the three groups; however, when excluding antipsychotics, the score of the non-remission group was tended to be higher than that of the recovery and remission groups. Notably, no correlation was observed between the ACB scores and any of the BACS-J scores in either group.
**DISCUSSION:** To the best of our knowledge, this is the first report on pharmacotherapy for recovery from schizophrenia. The findings suggest that a lower anticholinergic effect prescription did not contribute to recovery. In addition, further research on the anticholinergic effects of medications other than antipsychotics is required.

## T152. Sexual and Romantic Relationships in Schizophrenia – Update on 15 Years of Research

Tania Lecomte*[1], Justin Lamontagne[1], Briana Cloutier[1], Meryl Caiada[2], Amal Abdel-Baki[3], Marie Villeneuve[4], Martin Lepage[5]

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**BACKGROUND:** Romantic relationships are one of the principal recovery goals of people with schizophrenia (80%) with < 25% of adults being in a romantic relationship (compared to 66% in the general population). People with schizophrenia are at high risk of experiencing loneliness.

Healthy romantic relationships can act as protective factors and facilitate recovery. Oddly, it is one of the recovery domains least supported by actual services.
**METHODS:** This presentation reviews 15 years of studies on the sexuality, intimacy and romantic relationships in people with schizophrenia. Literature reviews on sexuality, well-being and romantic relationships, and intimacy treatments, as well as comparisons between single adults with and without schizophrenia, qualitative studies on romantic relationship experiences, and on mental health professionals' attitudes on the topic, and finally treatment studies on a novel group intervention for developing healthy romantic relationships from our team are presented.
**RESULTS:** Several obstacles are similar across single adults, with specificities linked to stigma, attachment, social competence, and medically-related sexual difficulties in schizophrenia. Taboos and perceptions of relational incompetence, as well as training needs to discuss intimacy issues were documented by mental health. Trauma and difficult relationships can also exacerbate symptoms. Sexuality is mostly studied in terms of problems. The Power of two intervention is one of the only existing treatments, with promising results, based on three studies, on romantic functioning (E.S.=1.22), ToM (E.S.=0.86), dating (E.S.=0.51), and overall symptoms (E.S= 1.08). More recent results from an ongoing study on its impact on loneliness and social integration will be presented.
**DISCUSSION:** Few research teams are currently studying this domain. There is a pressing need to increase our knowledge and offer interventions regarding sexuality, intimacy and romantic relationships in schizophrenia and other psychotic disorders. Future directions are discussed.

## T153. Internalized Stigma in Schizophrenia: The Impact of Symptomatic Remission

Alex Hofer*[1], Falko Biedermann[1], Monika Edlinger[1], Beatrice Frajo-Apor[1], Timo Schurr[1]

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**BACKGROUND:** Previous studies have shown that internalized stigma, i.e. the inner subjective experience of stigma resulting from applying negative stereotypes and stigmatizing attitudes to oneself, may impact negatively on schizophrenia patients' quality of life, hope, and self-esteem and hinder the recovery process. The aim of the current study was to investigate to what extent patients' internalized stigma correlates with symptomatic remission.
**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. Psychopathological symptoms were rated by means of the Positive and Negative Syndrome Scale (PANSS) with symptom remission being assessed by applying the severity component of the remission criteria. Stigma resistance and self-stigma were quantified by the Internalized Stigma of Mental Illness (ISMI) Scale.
**RESULTS:** So far, 80 patients (47 males, 33 females) with a mean age of 43.0 ± 10.9 years, 19 of whom were symptomatically remitted, took part in this study. The mean PANSS total score was 41.3 ± 5.9 in remitted, and 80.4 ± 21.7 in non-remitted patients. Compared to non-remitted study participants, those in remission presented with a significantly lower self-stigma mean score (2.19 ± 0.57 vs. 1.69 ± 0.42, range: 1 - 4) and a significantly higher stigma resistance mean score (2.75 ± 0.52 vs. 3.08 ± 0.33, range: 1 - 4).

**DISCUSSION:** These preliminary data highlight once again that in the treatment of people with schizophrenia, special emphasis should be placed on improving symptoms in order to promote patients' stigma resistance.

## T154. Faris and Dunham Remembered, Revoked and Reimagined: Chicago's Pioneering Place in Understanding the Social Determinants of Schizophrenia and Other Psychoses

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**BACKGROUND:** One hundred years ago, the sociologists Robert E. L. Faris and H. Warren Dunham embarked on a groundbreaking study of mental disorders in urban areas, focusing on Chicago during the period of the Great Depression, Prohibition and Organized Crime. Their work, published in 1939, laid the foundation for understanding the relationship between urban environments and mental health, most notably schizophrenia. This abstract commemorates the centennial of their pioneering research and explores its lasting impact on our understanding of the social determinants of psychosis.
**METHODS:** Faris and Dunham analyzed the geographic distribution of mental disorders in Chicago using data on first admissions to public and private mental hospitals between 1922 and 1934. They mapped the incidence of various mental disorders across different socio-economic areas of the city, including the central business district, transition zones, working-class neighborhoods, and affluent residential areas.
**RESULTS:** The study revealed a striking pattern: schizophrenia rates were highest in areas of high social disintegration near the city center, decreasingly progressively towards more suburban and affluent residential districts on the periphery. This pattern was similar for substance use disorders. In contrast, bipolar disorders showed a more even distribution throughout the city, with a slight tendency for higher rates in upper-class residential areas. Their research suggested a relationship between the distribution of mental disorders and unfavorable social conditions, particularly for schizophrenia, which inspired numerous studies in various cities across the United States and Europe until the 1960s that largely replicated their findings.
**DISCUSSION:** In this talk, I will critique the lasting relevance of Faris and Dunham's pioneering work a century later. I will reveal how their work initially sparked a new era in psychiatric epidemiology and the pursuit to understand the social etiology of mental disorders until the 1960s. I will show how early concerns over the ecological nature of their studies and causal inference, combined with accelerated interest in biological psychiatry and psychiatric genetics, cast a long shadow over efforts to understand the role of social determinants of schizophrenia and mental health disorders for almost half a century. I will discuss how these challenges have been supplemented by contemporary concerns over the generalizability of these findings to other contexts, most notably in the Global South.

Despite these critiques, I will argue that the relevance of Faris and Dunham's work has experienced a renaissance in recent years. Their pioneering approach has never been more salient, influencing a new generation of researchers seeking to delineate the causal role of social

determinants in psychosis. I will illustrate this with rigorous examples from the past 30 years that have used increasingly sophisticated traditional and modern causal inference METHODS: in epidemiology, incorporating a broader range of social and environmental factors, to better understand the social determinants of schizophrenia and other psychoses.

I will show how Chicago's place in the history of psychiatric epidemiology remains central to psychiatry, epidemiology and public mental health, with contemporary researchers continuing to explore the complex interplay between urban environments and severe mental illness. I will conclude by outlining the outstanding challenges and priorities that remain in translating our understanding of the social determinants of psychotic disorders into actionable insights for primary and secondary prevention in public mental health in both urban and rural populations in both the Global North and Global South.

## T155. Open Board

## T156. AI-Based Multimodal Treatment Response Prediction and Subtyping in Schizophrenia: Combining Inflammation and Imaging

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**BACKGROUND:** Immune dysfunction is implicated in the aetiology of schizophrenia with cytokines such as IL-6 and CRP detected at elevated levels. Identifying clusters of patients with differential immune dysfunction and brain alterations might provide clinically relevant novel treatment targets. Here we performed a semi-supervised machine learning analysis to identify such clusters. Furthermore, evidence suggests that patients with schizophrenia who do not respond to antipsychotics exhibit similar antipsychotic dopamine receptor binding as responsive patients. One suggested theory is that non-responsive patients have more prominent immune system dysregulation than antipsychotic responders. Here we also developed AI-based prediction models of treatment response based on inflammatory markers and imaging data.
**METHODS:** We used HYDRA (HeterogeneitY through DiscRiminant Analysis) which utilizes a convex polytope formed by combination of multiple linear max-margin classifiers to assess disease-related heterogeneity in the ASRB dataset. An SVM model that classified treatment response vs non treatment response was developed using the “Schizophrenia: Treatment Resistance and Therapeutic Advances” (STRATA) dataset. The model was trained in a repeated nested pooled cross-validation framework with 5 outer CV2 permutations, 5 outer CV2 folds, 5 inner CV1 permutations, and 5 inner CV1 folds. The model was then applied to the BeneMin dataset.

**RESULTS:** The optimal clustering solution was two transdiagnostic clusters in the PRONIA dataset (Cluster 1, n=153, 67 ROP, 86 ROD and Cluster 2, n=149, 88 ROP, 61 ROD, ARI: .618) and eight clusters in the ASRB dataset (Cluster 1, n=121, Cluster 2, n=142, Cluster 3, n=80, Cluster 4, n=82, Cluster 5, n=5, Cluster 6, n=2, Cluster 7, n=32, and Cluster 8, n=3, ARI: 0.573. Combining inflammatory and imaging data the SVM model classifying treatment response vs non treatment response achieved a balanced accuracy of 70.8 and an area under the curve of 0.71.
**DISCUSSION:** This is the first study to date to show that inflammation in schizophrenia is not merely a case of low vs high, but rather there are pluripotent, heterogeneous mechanisms at play. Leveraging Support Vector Machine (SVM) learning models to investigate the classification of treatment response in patients with schizophrenia based on inflammatory markers and structural neuroimaging we showcase the predictive utility of such models in distinguishing treatment responders from non-responders.

## T157. Maternal Childhood Trauma and Adolescent Psychopathology: The Role of Adolescent Inflammatory Markers as Putative Mediators

Nare Amasi-Hartoonian*[1], Xuemei Ma[1], Andrew J. Lawrence[1], Rebecca Pollard[1], Pei-Jung Cheng[2], Maryam Matter[1], Svenja Kretzer[1], Corentin Vallee[1], Olivia Johnson-Trewick[1], Craig Morgan[1], Seeromanie Harding[3], Gunter Schumann[1], Naghmeh Nikkheslat[4], Carmine Pariante[1], Mitul Mehta[5], Giovanni Montana[6], Ana Rodriguez-Mateos[7], Chiara Nosarti[1], Paola Dazzan[8]

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**BACKGROUND:** There is evidence that maternal childhood maltreatment is related to the offspring's emotional and behavioural outcomes, including during adolescence. However, the biological mechanisms of this relationship are not well understood. Given the role of immune activation in the pathophysiology of major psychiatric conditions, it is important to examine whether inflammatory markers in early adolescents serve as a mediating factor between the experience of maternal childhood trauma and the development of psychopathology in adolescents.
**METHODS:** A total of 230 school adolescents aged 11-14 (mean age = 12.9 years (SD 0.94); 44.8% male) were recruited in the eBRAIN study. These participants (n=185) were followed up one year later (mean age = 14.0 years (SD 0.93); 47.0 % male) and completed questionnaires about psychopathology (anxiety, depression, internalising and externalising symptoms and psychotic-like experiences). Maternal childhood trauma was assessed using the Childhood

Trauma Questionnaire (CTQ) from mothers, and a total CTQ score was obtained by summing the scores of the five subscales. In their offspring, we evaluated CRP and cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13) from plasma samples collected at baseline and values were log-transformed. We conducted a factor analysis for dimension reduction of the psychopathology measures and the inflammatory marker variables, and chose factors based on Kaiser's criterion. We then used mediation analysis to investigate whether baseline inflammatory markers mediated the relationship between maternal childhood trauma and adolescent psychopathology at the one-year follow-up.
**RESULTS:** The factor analysis conducted for five psychopathology variables (n=166) resulted in the extraction of a single factor that included all five variables. For the ten inflammatory marker variables, the factor analysis (n=157) resulted in the extraction of two factors: the first factor included cytokines IL-2, IL-4, IL-8, IL-10, IL-12 and IL-13; the second factor included cytokines IFN-γ, IL-6, TNF-α, and CRP. The mediation analysis (n=80) revealed that the inflammatory marker factors did not significantly mediate the relationship between maternal childhood trauma and the adolescent psychopathology factor, with standardised indirect effects of -0.0454 (95% CI = [-0.1613, 0.0510]) and 0.0114 (95% CI = [-0.0473, 0.1034]) for the first inflammatory factor and second inflammatory factor, respectively. Linear regression revealed that maternal childhood trauma was not significantly associated with the adolescent psychopathology factor (beta= 0.001, p=0.849).
**DISCUSSION:** Adolescent inflammation at baseline was found to not be a significant mediator between maternal childhood trauma and adolescent psychopathology at one-year follow-up. This finding suggests that the mechanism of intergenerational transmission of maternal childhood trauma may involve additional factors, including prenatal maternal measures, maternal postnatal depression and the postnatal environment, as these have all been implicated in the pathway from maternal childhood trauma to altered offspring development and mental health. It is also possible that the role of inflammation in this relationship may emerge later in life. Future research will explore associations between maternal childhood trauma and maternal depression as well as offspring childhood trauma, and investigate if these intermediary factors are linked to inflammation and psychopathology in offspring at later time points.

## T158. Sleep and Cognitive Performance in Individuals With Chronic Schizophrenia

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**BACKGROUND:** Individuals with schizophrenia present with substantial neurocognitive deficits that have been associated with poor functional outcomes. Although prior studies have identified a number of predictors of neurocognitive deficits in schizophrenia, there is limited research on the effect of sleep and sleep disturbances on neurocognition in individuals with schizophrenia. This study explored the mediating effect of sleep disturbances (i.e., number of hours of sleep, sleep interruption, prn medications for sleep) on the relationship between sleep and cognitive impairment in individuals with schizophrenia participating in computerized cognitive remediation.

**METHODS:** We included 51 participants diagnosed with DSM-V schizophrenia who participated in a study of cognitive remediation and collected data on three sleep-related measures and MCCB domain scores obtained at baseline (?). To explore the association between sleep and cognition, linear regression was performed separately for each of the seven MCCB domains as dependent variables and the sleep-related measures as independent variables. Data on sleep (number of hours of sleep prior to cognitive testing, sleep interruptions, whether prn medications were given for sleep) were collected from medical charts. All participants were inpatients enrolled in a computerized Cognitive Remediation program.
**RESULTS:** Participants' mean age was 38 years and the majority were male (84%), AA(49%), and had received a high school education or less (75%). Moreover, 61% reported having at least 8 hours of sleep, 67% reported having uninterrupted sleep, and 63% requested PRN medication for sleep. Using linear regression to explore the association between the MCCB domains and sleep, reporting ≥ 8 hours of sleep was significantly associated with higher MCCB domain scores, except for Social Cognition. In contrast, sleeping < 8 hours was associated with lower MCCB Composite score (Ƀ=-12.88; 95% confidence interval [CI]: -20.04, -5.71; p =0.0007). Interrupted sleep was significantly negatively associated with all the MCCB domains, except for Attention and Social Cognition. In addition, the number of PRN medications for sleep was significantly associated with lower MCCB scores, except for Social Cognition. Participants who requested PRNs for sleep had significantly lower MCCB Composite score than those who did not request PRNs (Ƀ =-18.64; 95% CI: -24.70, -12.58; p < 0.0001).
**DISCUSSION:** Poor sleep quality was associated with cognitive performance among the participants. Results of this study indicate that cognitive function should be monitored in individuals with sleep interruption and lower sleep duration. Future studies will examine the effect of poor sleep parameters on the level of improvement in the cognitive remediation intervention. It may be important to optimize sleep quality in patients undergoing clinical trials for cognitive treatments.

## T160. Speech-Based Screening of Different Psychiatric Conditions

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**BACKGROUND:** Speech pattern analysis has emerged as a promising diagnostic tool in mental health research. While machine learning approaches show potential, most studies have been limited by unmatched demographics and single-condition focus. This study aims to develop and validate speech-based diagnostic models across nine psychiatric conditions using demographically matched populations between positive and negative cases.
**METHODS:** 5-minutes of self-recorded, prompt-based speech were collected from participants with self-reported diagnoses of mental disorders and healthy control via online research settings (N = 900). We developed machine learning models to detect Major Depressive Disorder (MDD), Bipolar Disorder (BPD), Schizophrenia Spectrum Disorders (SSD), Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Clinical High Risk for psychosis (CHR), Generalized Anxiety Disorder (GAD), and Obsessive-Compulsive

Disorder (OCD), using same features of acoustic and linguistic speech characteristics and building ensemble learning algorithms on these features. Training utilized the five-minute speech samples from 80% of participants with English as first and second language (1:2 ratio). Each model employed condition-specific demographic matching, with age restrictions (18-35 years) and ethnicity matching. Feature selection utilized statistical significance thresholds ($p < 0.05$ or $p < 0.001$) and removed low-variance features. Participants were divided into a condition and non-condition group, therefore one person with comorbidities could 'collect; multiple diagnostic labels. Also, this design aimed to facilitate the model to capture disorder-specific speech characteristics, instead of discriminating healthy-non-healthy individuals. The models have been also implemented at 5 Behavioral Health Centers to monitor real-life, clinical performance.
**RESULTS:** All models demonstrated strong performance across multiple metrics in the research data-set. Outstanding results include ADHD (accuracy=83%, AUC=0.90, sensitivity=95.6%), ASD (accuracy=90.4%, AUC=0.924, specificity=94%), and GAD (accuracy=87.1%, AUC=0.91, sensitivity=95%). The OCD model achieved high specificity (90%) with 88.2% accuracy, while CHR showed robust performance (accuracy=83.6%, specificity=88%). Core psychiatric condition models maintained acceptable performance: MDD (accuracy=77.6%, specificity=86%), BPD (accuracy=76.3%, specificity=85%), and SSD (accuracy=88.1%, specificity=95%). All models demonstrated clinically viable inference latency (0.088-0.201 seconds). Notably, balanced accuracy exceeded 72% across all conditions, with several models achieving over 85%. Data on real-life clinical accuracy are not sufficient by the time of abstract submission but preliminary results (N = 100-200 patients) will be presented at the conference.
**DISCUSSION:** These results demonstrate the feasibility of automated speech-based screening across a comprehensive range of psychiatric conditions while controlling for demographic confounds. The consistent high performance across diverse conditions, particularly the exceptional sensitivity in ADHD and GAD models ( > 95%) and high specificity in ASD and SSD models ( > 94%), suggests potential clinical utility. The successful implementation of condition-specific demographic matching and feature selection strategies indicates a reliable, generalizable approach to automated psychiatric assessment. This comprehensive system offers a scalable, accessible method for mental health evaluation, triage or screening that could significantly impact clinical practice.

## T161. A Pilot 18(F)-Flutemetamol Pet and Neurocognitive Assessment Study in Severe Cognitive Impaired Schizophrenia Patients

Andrea de Bartolomeis*[1], Mariateresa Ciccarelli[1], Benedetta Mazza[1], Annarita Barone[1], Felice Iasevoli[1], Licia Vellucci[1], Giuseppe De Simone[1], Federica Iannotta[1], Claudio Ricci[1], Alberto Cuocolo[1], Valeria Gaudieri[1], Sabina Pappatà[2]

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**BACKGROUND:** Multiple lines of evidence suggest that schizophrenia has neurodevelopmental origins. However, this theory alone cannot explain the progressive neurodegenerative processes described in SZ that partially justify its heterogeneity, including the severe difficult-to-treat condition known as treatment-resistant schizophrenia (TRS). According

to the view of a neurodevelopmental neurodegenerative disorder, multiple pieces of evidence showed a prominent cognitive impairment in TRS patients compared to those who respond to treatment with antipsychotics. This project aims to investigate the cerebral β-amyloid (Aβ) accumulation as a putative measure of neurodegeneration in patients affected by TRS with cognitive impairment, using Aβ Positron Emission Tomography (PET).
**METHODS:** TRS patients (n=12) underwent Aβ PET acquisition with 18(F)-Flutemetamol. Early images were acquired immediately after the injection (early-phase), and late images approximately 90 minutes post-injection (late-phase). The clinical features were evaluated using the Positive and Negative Syndrome Scale (PANSS), and the 5-factor model. The cognitive symptoms were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS), and Brief Intelligence Test (TIB). Statistical procedures for clinical data were performed with the SPSS using a t-test ($p \leq 0.01$). TRS patients were classified according to the severity of cognitive deficits into Mild Cognitive Impairment (MCI) (n=5) and Severe Cognitive Impairment (SCI) (n=7) patients. PET images were reconstructed using OSEM and corrected with CT for attenuation. The standardized uptake value region (SUVr) was calculated. The visual analysis between the TRS patients with MCI and SCI in the early- and late-phase scanning was performed with SPM12, and the images were spatially normalized in the anatomical brain space MNI. Pearson's correlation analysis between SUVr and the clinical scores was performed ($p \leq 0.01$) with Bonferroni's post hoc correction ($p \leq 0.003$).
**RESULTS:** 1)TRS patients (males/female 8/4; age 36.25±8.82; duration 17.33±7.81; chlorpromazine equivalents 552.67±238.81; education 13.25±1.36; onset 18.83±4) did not differ in the clinical characteristics. Cognitive domains such as verbal fluency, processing speed, problem solving, the BACS composite t-score, and TIB scores were significantly lower in SCI patients compared to MCI patients ($p \leq 0.01$).
2) Visual analysis of the Aβ PET distribution in TRS patients reveals a pattern of reduced uptake in the frontal cortex during the early-phase acquisition. The SCI group showed a moderate reduction in radiotracer uptake in the posterior cortical regions (i.e., the parietal and temporal cortices). The late-phase images do not show increased uptake in the cerebral cortex.

3) The correlation analysis between Aβ SUVr and clinical scores in TRS patients revealed significant negative correlations between the Left Parietal Cortex and PANSS POS scores ($p < 0.003$, $r=0.597$) and 5-factor DIS scores ($p < 0.002$, $r=0.645$). Additionally, Aβ SUVr in the Right Sensorimotor Cortex was negatively correlated with PANSS POS scores ($p < 0.003$, $r=0.602$) and 5-factor EXC scores ($p < 0.002$, $r=0.619$).

**DISCUSSION:** This pilot study underscores the complex interplay between neurodevelopmental and neurodegenerative processes in TRS. While Aβ PET imaging did not reveal significant differences in global amyloid deposition among patients, the negative correlations between Aβ levels and clinical scores suggest a potential link between prodromal neurodegenerative pathology and psychotic symptoms in TRS.
Disclosure: The authors declare no conflicts of interest in relation to this study.

**T162. Reproductive Factors Correlate With Psychosis Prodrome Risk in Perimenopausal Women**

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**BACKGROUND:** Psychosis is a serious mental disorder characterized by a disconnect from reality, with a prodromal period of attenuated symptoms occurring prior to psychosis conversion. Understanding this prodromal phase is essential for identifying individuals with high risk for converting to psychosis. One period of heightened risk is perimenopause, a time of atypical menstruation leading to the cessation of menstrual periods and the end of reproductive years. This transition is marked by the gradual decline of ovarian function and a decrease in estrogen levels. It has been proposed that the sudden decline in reproductive hormones during this developmental timepoint could trigger psychotic symptom emergence. We thus hypothesized that the length of the reproductive lifecycle, when reproductive hormones are intact, may differ in those who are and are not at risk for psychosis. Here, we investigate how reproductive history relates to menopause associated psychosis risk variance.
**METHODS:** Female participants aged 40-60 were pre-screened for the presence of attenuated psychotic symptoms and presence of perimenopause. They completed a modified version of the reproductive history questionnaire (NIH Document Name Form 31 - Reproductive History Questionnaire) and the Prodromal Questionnaire (PQ-B), a self-report tool to quantify psychosis prodromal features. Three regression analyses were conducted to assess the relationship between reproductive lifecycle factors and prodromal risk. Age at menarche (n=131) and age at perimenopause onset (n=71), corresponding with two reproductive developmental time points, were used as regressors predicting PQB score. Additionally, number of reproductively normal years was calculated as the difference between age of menarche and age of perimenopause onset (n=71).
**RESULTS:** Age at menarche was positively correlated with PQ-B score, suggesting that earlier menarche corresponds to a lower burden of attenuated psychotic symptoms (R=0.613, p=0.034). Age of perimenopause onset was negatively correlated with PQ-B score, indicating that earlier onset of perimenopause correlates with greater psychosis risk (R=-0.382; p=0.038). Total reproductively normal years negatively correlated with PQ-B score, implying that women with more reproductively normal years are at lower psychosis risk (R=-0.375; p=0.036).
**DISCUSSION:** These findings suggest that reproductive history is relevant for menopausal psychosis risk, supporting the hypotheses that sex hormones like estrogen are relevant to psychosis emergence and indicating that reproductive factors should be considered when assessing psychosis risk, particularly for those in perimenopause.

## T163. Altered Cerebellar-Cerebrum Dynamics in Social Gaze Processing: Implications for Schizophrenia and Social Cognitive Deficits

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**BACKGROUND:** People with schizophrenia (SZ) exhibit deficits in social cognition—including abnormal eye gaze processing (GP). Previous results show decreased perceptual

precision and increased self-referential bias for gaze in SZ. This was associated with top-down inhibition from cortical social-cognition regions to visual cortex during explicit GP. While these cerebral regions have been implicated in GP, recent research has also linked cerebellar-cerebral connections to cognitive functioning. However, how these cerebellar-cerebral dynamics are altered in SZ is unknown. Here, we utilized dynamic causal modeling (DCM) to investigate how posterior cerebellar activity influences social processing nodes during GP. We hypothesized that there would be bidirectional cerebellar-cerebral connections during general GP with cerebellar outputs to cerebral nodes being more upregulated in SZ during explicit GP. We also hypothesized that cerebellar connectivity parameters would better explain the GP data.
**METHODS:** Two datasets were used to see if bi-directional cerebellar-cerebral dynamics were present and altered in SZ. The primary dataset contained 39 participants with schizophrenia or schizoaffective disorder (SZ) (51.3% F; age=33.2 ± 10.3) and 33 healthy controls (HC) (48.5% F; age=33.5 ± 9.3). The secondary dataset contained 27 SZ participants (55.6% F; age=33.6 ± 10.7) and 22 HC participants (50% F; age=32.1 ± 13.3). All participants underwent a GP task during BOLD fMRI with explicit and implicit blocks. A GLM contrast of explicit-implicit GP was used to identify four social processing nodes for DCM analysis: Crus II (cerebellum), inferior parietal lobule (IPL), insula, and fusiform. Connectivity of these nodes during general (explicit and implicit) gaze processing and modulation of each connection during explicit gaze discrimination was used to identify the cerebellar parameters that contributed most to explaining gaze processing activity. Three models were also created for structural model comparison: one model with bidirectional connections among all nodes, self-connections, and modulation of parameters during explicit GP (full model), one that did not include modulation of cerebellar connections during explicit gaze (no modulation), and one that did not include any cerebellar connections to cerebral regions (no connection). Relative free energy of the models was used to determine the more accurate model (adjusted for complexity).
**RESULTS:** Both datasets showed excitatory cerebellar inputs from the insula (95% posterior probability/Pp) and inhibitory cerebellar outputs (95% Pp) to the fusiform in both HC and SZ groups. Cerebellar outputs to the insula and fusiform were consistently upregulated during explicit gaze processing (95% Pp). Inputs from the fusiform were also upregulated during explicit gaze processing (95% Pp). Cerebellar output to IPL was lower in SZ compared to HC in both the primary dataset (95% Pp) and secondary dataset (75% Pp). Furthermore, outputs to IPL and fusiform were less upregulated in SZ in the primary dataset (75% Pp) and more downregulated in the secondary dataset (75% Pp) during explicit GP. In both datasets, the full model received very strong evidence ( > 99.99% Pp) compared to the no modulation and no connection models in HC. In SZ, the primary dataset's full model also had strong evidence (97% Pp) and the secondary dataset had positive evidence (74% Pp) relative to the no modulation model.
**DISCUSSION:** Our model comparison results provide strong evidence that cerebellar connections to cerebral social processing nodes explain GP brain activity well. This is more prevalent in HC compared to SZ showing that cerebellar connectivity alterations may be related to social cognition deficits. Furthermore, the parameter estimates also show that cerebellar connectivity to social processing regions is reduced in SZ and not upregulated to the same extent as HC during explicit gaze. Due to the cerebellum's physical isolation from other brain structures and its accessibility for noninvasive interventions such as transcranial magnetic stimulation, this may provide a potential therapeutic target for social functioning deficits. Future directions will

focus on neuromodulation of the cerebellum to determine causally if limiting cerebellar activity influences social functioning.

### T164. Microstructural Changes in the Orbitofrontal Cortex Following Clozapine Treatment in Patients With Treatment-Resistant Schizophrenia: A Diffusion Kurtosis Imaging Study

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**BACKGROUND:** While clozapine has remained an essential therapeutic option for patients with treatment-resistant schizophrenia (TRS) for many decades, the neurobiological underpinnings of clozapine treatment are still poorly understood. Using diffusion kurtosis imaging (DKI), we investigated the gray matter microstructural changes that may be associated with clozapine treatment in patients with TRS.
**METHODS:** Twenty-six patients with TRS and 21 with schizophrenia in a stable course of illness participated in this study. Mean kurtosis values were acquired from DKI scans at baseline and after 18 weeks of follow-up in five regions of interest: the lateral prefrontal, lateral temporal, medial prefrontal, medial temporal, and orbitofrontal cortex. During the study period of 18 weeks, clozapine was initiated and titrated in the TRS group, whereas the control group received standard treatment. Linear mixed models were used to evaluate group, time, and interaction effects, while controlling for possible confounders.
**RESULTS:** The two groups did not differ significantly in terms of age, sex, or duration of illness. There was a significant group-by-time interaction effect ($t = -2.750$, $p = 0.00843$) in the orbitofrontal mean kurtosis. While the baseline values did not differ between the groups, the TRS group showed a significant decrease in orbitofrontal mean kurtosis at the 18-week follow-up compared to the controls. Exploratory correlation analysis indicated that in the TRS group, a higher baseline orbitofrontal mean kurtosis was moderately associated with a greater degree of improvement in positive symptoms ($r = 0.460$, $p = 0.018$).
**DISCUSSION:** These findings suggest that clozapine treatment may be associated with microstructural changes in the orbitofrontal cortex in patients with TRS. A decrease in gray matter mean kurtosis may reflect alterations in cellular complexity or density. Further research is needed to investigate the utility of DKI in quantifying possible microstructural changes following clozapine treatment and their relationship with clinical outcomes in TRS.

### T165. Safety, Tolerability, and Durability of Treatment Effect of Olanzapine and Samidorphan: A Patient Subgroup Analysis of a 4-Year Open-Label Study

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**BACKGROUND:** Results from a 4-year, open-label study showed that the combination of olanzapine and samidorphan (OLZ/SAM) provides sustained symptom control and weight gain mitigation in patients with schizophrenia, schizophreniform disorder, or bipolar I disorder. The objective of this analysis was to evaluate the safety, tolerability, and durability of treatment effect of OLZ/SAM across different demographic subgroups in the 4-year open-label study.
**METHODS:** Patients completing studies in the ENLIGHTEN clinical trial program were eligible to receive ≥2–4 years of additional treatment in a phase 3, open-label study assessing OLZ/SAM's safety, tolerability, and durability of treatment effect. Prespecified subgroup analyses were conducted by age (18–29 or ≥30 years), sex (male or female), race (Black/African American or non-Black/African American), baseline body mass index (BMI; < 25 or ≥25 kg/m2), and geographic region (US or non-US). Safety assessments included changes from baseline in body weight and waist circumference and adverse event (AE) incidences. Durability of treatment effect was assessed using the Clinical Global Impressions–Severity (CGI-S) scale.
**RESULTS:** Overall, 523 patients were included; 53.7% (242/451) and 32.5% (109/335) received 2 and 4 years of treatment, respectively. At 2 years, OLZ/SAM treatment was associated with small mean changes from baseline in body weight (range: 0–2.15 kg) and minimal mean changes from baseline in waist circumference (range: −1.13–0.15 cm) across subgroups. Mean changes in body weight (range: 1.51–5.49 kg) and waist circumference (range: 0.67–3.85 cm) were generally similar across subgroups at 4 years. No clinically meaningful subgroup differences in AEs were observed. Mean CGI-S scale scores were stable across subgroups at 2 and 4 years.
**DISCUSSION:** Outcomes following up to 4 years of OLZ/SAM treatment were generally similar across age, sex, race, BMI, and geographic subgroups.

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## T167. Automated Analysis of Head Movements in Youth at Clinical High-Risk for Psychosis During Clinical Interviews

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**BACKGROUND:** Impaired social function is commonly observed in individuals at Clinical High Risk (CHR) for psychosis. Previous research has focused on perception and interpretation of social stimuli, and assessments of performative elements such as nonverbal behavior have been limited or are typically run through time-consuming, manual, and unreliable methods. The current study aimed to characterize patterns of head movements, a critical feature of nonverbal social interactions, to determine whether there were abnormalities among CHR individuals, using novel automated tools.
**METHODS:** A total of 90 CHR and 87 healthy control participants completed recorded clinical interviews. Segments when they were responding to questions where then processed using an open-access machine learning-based head tracking program. This program extracted target variables such as total head movement, amplitude, and speed in each direction (x, y, and z). Relationships between head movement patterns and symptoms were then examined.
**RESULTS:** Findings indicated that the CHR group exhibited the same amount of head movements as the control group, establishing that results were not the reflection of a more global deficit. Notably, the CHR group executed spontaneous head turns in side-to-side movements (such as the "no" gesture) at a significantly slower speed when compared to controls ($U = 2860$, $p = .0019$, $d = -0.41$). Slower side-to-side head movement was also associated with elevated clinician-rated scores of "disorganized communication" ($r = -0.23$), but not with other symptoms in the positive domain nor negative or depressive phenomenology.
**DISCUSSION:** These findings provide new insights into components contributing to social impairment and highlight the promise of using automated tools to capture spontaneous head movements, thereby expanding the assessment of social communication and behavioral implementations of social cognitive processes.

## T168. Optically Pumped Magnetometers as a Novel Tool for Investigating Circuit Dysfunctions in Schizophrenia

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**BACKGROUND:** Optically pumped magnetometers (OPMs) utilize atoms in the gas phase that serve as sensitive magnetic field probes for the electric activity of the brain and have rapidly developed in the past decade and now reach sensitivities similar to conventional SQUID-MEG-systems. Accordingly, OPMs could constitute a breakthrough technology for brain imaging and have the potential to provide novel insights into psychiatric syndromes, such as schizophrenia. In this study, we utilized for the first time OPMs to investigate circuit dysfunctions in schizophrenia patients using auditory and visual steady steady-state responses (A/VSSRs). In addition, our study aimed to compare the signal-to-noise (SNR) ratio of OPM-data to conventional EEG and SQUID-MEG measurements.
**METHODS:** SQUID-MEG measurement were acquired with a 102-channel (gradiometers) Yokogawa system. Parallel EEG-OPM measurements were obtained with a modified ANT-Neuro EEG cap with 56 electrodes arranged in the 10-10 system and 20 OPM-sensors (Gen2 QuSpin). To compare SNR-level between OPM vs. EEG and SQUID-MEG measurements, we obtained 40 Hz ASSRs from n= 23 controls. ASSRs consisted of 1-second 40-Hz amplitude

modulated tones while participants were engaged in a visual attention task. In a second condition, participants passively listened to 40 Hz ASSRs.
In addition, we compared n = 20 schizophrenia patients and n = 26 controls on a A/VSSRs. VSSRs were elicited by reversing checkerboard patterns either at 7.5 Hz or at a 10 Hz frequency (total = 100 trials per condition). To control for attention, participants were asked to respond to rare stimuli with a button press.

EEG, OPM- and SQUID-MEG-data were analyzed using time- as well as frequency decomposition and inter-trial phase coherence (ITPC) measures. Significance was tested using a cluster-based permutation approach. SNR of the power spectrum over averaged trials and of the ITPC were calculated by calculating ratio between signal (power or ITPC in the stimulated frequency) and noise (the same time-window as signal but for surrounding frequency bins) with the following formular (signal-noise)/(signal+noise).

**RESULTS:** OPM-data in controls showed similar V/ASSRs over occipital and temporal sensors in time course and amplitude than EEG- and SQUID-MEG measurements. Statistical analyses showed that OPM-recorded 40 HZ ASSRs were characterized by higher SNRs compared to both EEG and SQUID-MEG data. This was particularly the case for smaller numbers of trials. Analyses of OPM-data in schizophrenia data vs. controls revealed reduced ITPC and amplitude of 40 Hz ASSRs. For VSSRs, patients with schizophrenia showed increased responses to 7.5 Hz stimulation compared to controls. Moreover, 3-7 Hz activity was observable in schizophrenia patients when stimulating at 10 Hz, which was absent in the HC group. Finally, VSSR responses in schizophrenia patients were very focal, predominantly measured by a singular lateral occipital sensor, contrasting with the broader distribution of SSR responses across parietal sensors observed in the healthy controls (HCs).

**DISCUSSION:** Our data show that OPMs represent a novel and promising neurophysiological approach for the investigation of circuit dysfunctions in schizophrenia. OPMs have improved SNRs compared to both EEG and SQUID-MEG for the measurement of 40 Hz ASSRs in controls. Moreover, our findings show that the pattern of both ASSR/VSSRs deficits in schizophrenia patients is in agreement with previous EEG/MEG-studies.

## T169. Mapping Lipid Dysregulation in Schizophrenia Using Imaging Mass Spectrometry

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**BACKGROUND:** Schizophrenia (SCZ) is a complex psychiatric disorder with an unclear etiology, exerting a significant impact on healthcare and society. The dorsolateral prefrontal cortex (DLPFC) has emerged as a key brain region involved in SCZ pathophysiology, particularly in cognitive impairments. Lipids play crucial roles in brain function, including membrane formation, neuronal signalling, and energy storage. Dysregulated lipid profiles have been observed in various brain disorders, including Alzheimer's disease and SCZ, both peripherally and within the central nervous system. However, precise lipid mapping of the human brain remains challenging. Matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) is a label-free technique that enables the visualization and localization of metabolites within tissue sections. This powerful tool can identify new potential biomarkers relevant to brain function and disease pathogenesis.
**METHODS:** Our study employed MALDI-IMS to analyze the lipidome profile of post-mortem human DLPFC samples obtained from the Human Brain Collection Core (NIMH-IRP), encompassing healthy and SCZ subjects. Brain tissue blocks were sectioned into 10 µm slices and coated with 9-AA matrix before data acquisition. The analyzed m/z range was set between 200 and 1800 Da, to encompass a broad spectrum of lipid species. Adjacent tissue sections were subjected to histological and immunofluorescence staining for subsequent overlay with MS images. Spectral data were normalized and analyzed using SCiLS Lab software to visualize and characterize lipid distributions.
**RESULTS:** Preliminary results from healthy subjects demonstrate that MALDI-IMS is a suitable approach to determine the anatomical distribution of lipid species in DLPFC slices at a resolution of a few µm (between 50 and 100 µm). The lipid profiles revealed unique features for the gray (GM) and white matter (WM) areas, that were similar across all analyzed samples. Additionally, we observed a strong correlation between the lipid profile and specific histological and structural characteristics. Ongoing analyses comparing SCZ and healthy samples are providing valuable insights into the role of lipids in disease etiology.
**DISCUSSION:** MALDI-IMS is an advanced, untargeted imaging technique that provides detailed spatial lipidomic information within tissue sections. Our findings in healthy subjects underscore the potential of this approach to elucidate the role of lipids in brain function and the etiology of psychiatric disorders like SCZ. This research has a significant translational impact, as it may lead to the identification of novel diagnostic and prognostic biomarkers with clinical relevance, emphasizing the critical importance of lipidomics in psychiatric research.

## T170. **The Relationship Between Glutamate, N-Acetylaspartate and Translocator Protein Binding in Schizophrenia: A Cross-Sectional PET/MRS Study**

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**BACKGROUND:** Glutamatergic dysregulation in the anterior cingulate cortex (ACC) and aberrant microglial activation have been implicated in the neurobiology of schizophrenia. It has been hypothesised that glutamate may trigger microglial activation, suggesting that glutamatergic dysregulation may underlie increased microglial activation in people with schizophrenia, which may in turn result in impaired neuronal viability.

**METHODS:** We investigated the relationship between microglial activation and ACC glutamate and neuronal viability in a cross-sectional case-control study of people with early course schizophrenia (within 5 years of symptom onset) using simultaneous positron emission tomography-magnetic resonance (PET-MR) imaging. 71 individuals with schizophrenia and 41 healthy volunteers consented to participating in the study. Subjects received a PET scan using [18F]DPA-714, which binds to the translocator protein (TSPO) which is expressed by activated microglia. ACC glutamate, glutamate/glutamine (glx) and NAA, the latter a marker of neuronal viability, were estimated using proton magnetic resonance spectroscopy (MRS). Student's t-tests and Mann-Whitney U-tests were used to test for group differences between cases and controls in ACC metabolite concentrations. Linear regression was used to test for associations between ACC metabolite concentrations and TSPO binding in total, frontal, parietal, and ACC grey matter in both cases and controls after controlling for age, sex and TSPO binding status.

**RESULTS:** A total of 68 cases and 40 controls were included in the analysis. We found no significant differences between cases and controls for ACC glutamate ($t = -1.45$, $p = 0.151$), glx ($t = -2.08$, $p = 0.115$), or NAA ($W = 1446$, $p = 0.587$). We identified a significant negative association between ACC NAA and ACC TSPO binding in controls ($\beta = -0.027$, $SE=0.009$, $p=0.003$) but not in individuals with schizophrenia ($\beta=-0.007$, $SE=0.009$, $p=0.414$). There were otherwise no significant associations between TSPO binding in total, frontal, parietal or ACC grey matter and ACC metabolite levels. There were no significant associations between ACC metabolite levels and symptom severity among patients.

**DISCUSSIONS:** This is the largest study to date assessing the relationship between glutamate and TSPO levels in schizophrenia, using a combined PET/MRS approach. We did not find a significant association between measures of ACC glutamatergic dysregulation and microglial activation in healthy controls or individuals with schizophrenia, suggesting that glutamate levels do not underlie microglial activation in schizophrenia. Contrary to the literature, we did not observe significant differences in ACC glutamate concentrations between cases and controls. There were, however, differences in the relationship between markers of microglial activation in the ACC and neuronal viability in cases and controls.

## T171. Cortical Gyrification in Treatment-Resistant Schizophrenia: A Longitudinal Study on Clozapine Effects

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**BACKGROUND:** Treatment-resistant schizophrenia (TRS) represents a significant clinical challenge, as many patients with schizophrenia fail to respond adequately to antipsychotic medications. Early identification of neurobiological markers for TRS is crucial for timely intervention and improving clinical outcomes. This study aimed to investigate cortical gyrification deficits as markers of neurodevelopmental vulnerabilities contributing to treatment resistance and to explore whether these deficits are affected by clozapine treatment.
**METHODS:** In this study, 33 patients with TRS and 31 with first-line responder schizophrenia (FLR) were classified based on well-established TRS criteria. The local gyrification index (lGI) was measured using vertex-wise analysis in FreeSurfer and compared between the two groups at baseline and after a 4-month follow-up of clozapine treatment. For the lGI clusters showing significant group differences, we further explored their association with reasoning and problem-solving deficits, which are considered trait-related neurocognitive impairments in schizophrenia, to better define cortical gyrification abnormalities as potential neurodevelopmental markers.
**RESULTS:** TRS patients exhibited significantly decreased cortical gyrification in the medial parieto-occipital regions compared to FLR at baseline. These deficits persisted consistently after a 4-month follow-up of clozapine treatment. Reasoning and problem-solving abilities were impaired in TRS patients at baseline and remained impaired at follow-up. Furthermore, impaired reasoning and problem-solving abilities were consistently correlated with clusters of hypogyrification in TRS patients at both baseline and follow-up.
**DISCUSSION:** Our findings highlight significant neurobiological distinctions between TRS and FLR patients, with reduced cortical gyrification in TRS emphasizing the role of neurodevelopmental vulnerabilities in treatment resistance. Persistent deficits in the medial parieto-occipital regions, linked to impaired reasoning and problem-solving abilities even after clozapine treatment, further support hypogyrification as a potential neurodevelopmental marker for identifying treatment-resistant schizophrenia.

## T172. Cluster Profiles of Distressing Psychotic-Like Experiences Among Children and Associations With Genetic Risk, Prenatal Cannabis Exposure, and Social-Environmental Characteristics: A Set of Exploratory Analyses

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**BACKGROUND:** Distressing psychotic-like experiences (PLEs) in children are associated with an increased risk for psychiatric disorders. Recent studies suggest that different domains of

psychotic symptoms could be associated with distinct risk factors, but less is known about PLEs. This study clustered PLEs into subgroups and explored the genetic and environmental characteristics associated with these profiles.
**METHODS:** Data from children (N=11,854) recruited as part of the Adolescent Brain and Cognitive Development Study v5.1 assessed PLEs using 21-items from the Prodromal-Questionnaire-Brief Child Version. K-medoid clustering of PLEs was conducted among children with at least one distressing PLE item at baseline (n=3,155). Associations of polygenic risk scores for schizophrenia (PRS-SCZ) and social-environmental characteristics with PLE subgroups were estimated using generalized multinomial mixed models, adjusting for age, sex, race/ethnicity, parental education, income-to-needs, and family psychosis history.
**RESULTS:** We identified three distressing PLE subgroups: hallucinatory-like (n=1,110), paranoid-like (n=1,229), and multiple PLE domains (n=816). Compared to those without any distressing PLEs (n=8,699), those with hallucinatory-like PLE were more likely to have had prenatal cannabis exposure (Odds Ratio(OR)=1.578, 95% CI: 1.230–2.023); paranoid-like individuals had higher PRS-SCZ (OR=1.080, 95% CI: 1.001–1.165); those with multiple PLE domains participated in less physical activities (OR=0.879, 95% CI: 0.803–0.964). All groups experienced greater childhood adversity and worse school environments.
**DISCUSSION:** We found that those with different aspects of distressing PLEs had distinct and similar genetic and environmental characteristics. These results suggest that it may be important to consider the heterogeneity of PLE in conceptualizing the development of psychosis.

## T174. The Effect of Gender on Frontostriatal Brain Wiring Organization in Early Psychosis Affective Subjects and Healthy Controls: A Diffusion Imaging Tractography Study

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**BACKGROUND:** Disrupted brain connectivity is thought to underlie neuropsychiatric disorders such as affective and non-affective psychoses. We assessed frontostriatal brain wiring organization using diffusion MRI tractography from the Human Connectome Project in 56 healthy controls, and 46 Early Psychosis Affective patients; Mean age: 23.9 years; sex: 44 females; 58 males; 25 EP-AFF females and 21 EP-AFF males; 19 HC females and 37 HC males. We used our method of fiber cluster analysis of whole brain diffusion Magnetic Resonance Imaging (dMRI) tractography in a novel way to assess brain wiring. This method allows us to quantify the degree of deviation from a topographic, parallel, arrangement in brain wiring connectivity between the frontal cortex (FCtx) and the caudate (Cd), a component of the associative striatum.

**METHODS:** The data used in this study come from the shared data set from the Human Connectome Project for Early Psychosis (HCP-EP) study (MPI: Shenton, Breier). Diffusion MRI Data from 3 HCP sites (University of Indiana, Massachusetts General Hospital and McLean Hospital) were harmonized (Cetin-Karayumak S et al, 2019). From this harmonized data set we generated whole brain tractography using our unscented Kalman filter (UKF) 2-tensor tractography methodology (Malcolm JG et al, 2010). We used a data-driven fiber clustering atlas that allows for a whole brain tractography parcellation into 2000 white matter fiber clusters according to white matter (WM) fiber geometric trajectory (Zhang et al., 2018). Then, fiber clusters of interest (i.e., from FCtx to Cd) based on FreeSurfer parcellation from the whole brain WM were identified for each subject. We identified 17 WM fiber clusters connecting FCtx and Cd in both each hemisphere in each subject group. To determine the pattern of frontostriatal connectivity in both groups in both genders, first, we generated scatter plots for each hemisphere (not shown) based on the 17 fiber clusters (with 136 pairs of fiber clusters, yielding 136 data points), showing the relationship between the cortical distances and the corresponding caudate distances of fiber cluster pairs connecting the FCtx and the caudate. In addition, we assessed the between-group difference for each cluster pair in each cluster in the degree of convergence, reflected by a convergence quotient (CQ). Our CQ was calculated as: (Cortex Distance - Caudate Distance)/ (Cortex Distance + Caudate Distance). For each cluster, we used a mixed model regression analysis of CQ in each hemisphere, separately. For each of 17 clusters in each hemisphere, we assessed the between-group difference in CQ for the 16 pairings with all other clusters in the same hemisphere. We fit a mixed-model regression for each of 17 clusters in a hemisphere, with CQ as response, and subject as a random effect. Fixed effects in these models were all 16 cluster pairings, group (EP-AFF vs HC), and the interaction of pairing with group. Where appropriate, we covaried for gender as the groups significantly differed in gender proportion ($p=0.038$).

**RESULTS:** First, for within-group analyses, we found in HCs and EP-AFFs in the left hemisphere (LH) and right hemisphere (RH), in both genders, a non-linear relationship, that is, a non-topographic relationship between inter-cluster FCtx distances and Cd distances driven by the results from10 cluster pairs. Of note, fiber cluster 6, coming from IFG, pars. triangularis, was significantly over-represented in these 10 cluster pairs. Of further note, the correlation curve in the LH in female EP-AFFs showed a flattened concave curve compared both to the LH curve in HCs and to the LH and RH curves in EP-AFFs, visually, and qualitatively, suggesting its wiring pattern differed from the usual pattern. Figures not shown. Second, for between-group analyses, a) in a RH frontal pole cluster, across genders, we found a significant diagnosis by cluster pair interaction ($p=0.013$); and b), in a LH inferior frontal gyrus (IFG), pars triangularis cluster, we found a gender x diagnosis x cluster pair interaction ($p < 0.0085$), with the diagnosis x cluster pair interaction much greater in females ($p < 0.0001$) than in males ($p=0.98$).

**DISCUSSION:** There are 3 principal findings in this abstract. First, we found that the wiring pattern of connectivity between FCtx and Cd, bilaterally, was non-linear, i.e., not strictly topographic, for both groups, in both sexes, driven by the same 10 cluster pairs. However, in female EP-AFFs, the concave curve in the LH was more flattened. Second, in a RH frontal pole cluster, we found a significant diagnosis by cluster pair interaction across both genders. Lastly, third, in a LH inferior frontal gyrus (IFG), pars triangularis cluster, we found a significant gender x diagnosis x cluster pair interaction, with the diagnosis x cluster pair interaction much greater in females than in males.

**T175. Using Randomized Trials as a Benchmark for Observational Analyses in First Episode Psychosis**

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**BACKGROUND:** Randomized trials are the gold standard approach to choose the best course of action for patients with First Episode Psychosis. However, many treatment decisions have to be made in the absence of randomized evidence because conducting a trial is either unfeasible, untimely, or unethical. In those instances, using observational (i.e., real-world data) may be a good substitute to guide clinical decision-making. Here, we propose a method to strengthen observational research to guide clinical decisions in First Episode Psychosis.
**METHODS:** We will describe a method that combines the strengths of observational and randomized studies: benchmarking analyses. In benchmarking analyses, the investigator first aims to replicate findings from a previously published randomized trial before extending the observational analysis to answer a broader question. If findings from the randomized trial can be accurately replicated in the observational data, confidence is gained that the data sources and analyses were adequate to adjust for confounding. Here, we will showcase benchmarking analyses using two case studies.

First, we will use the data from the FEP-CAUSAL Collaboration (an international consortium of observational databases in North America and Europe) to emulate a target trial with a similar protocol than The European First Episode Schizophrenia Trial (EUFEST) (i.e., comparing haloperidol to olanzapine and quetiapine in the 12-month risk of all-cause treatment discontinuation and other outcomes). If the benchmarking is deemed successful, that is, if our observational estimates match those from the trial, we will then extend our analyses to include newer antipsychotic agents in the comparison: aripiprazole, paliperidone, and risperidone.

In the second case study, we will use the data from the FEP-CAUSAL Collaboration to emulate a target trial identical to the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST), that is, comparing oral continuation of aripiprazole and paliperidone with switching to long-acting formulation of these agents in the 18-month risk of all-cause discontinuation and other outcomes. If the benchmarking is deemed successful, that is, if our observational estimates match those from the trial, we will then extend the analyses to study a longer time horizon of 3 years, replacing the outcome to psychotic relapses, and studying the effect of LAI on clinically relevant subgroups.

**RESULTS:** In the first case study, we included 1097 patients with a psychotic disorder diagnosis and < 2 years since psychosis onset. Inverse probability weighting was used to control for confounding. The 12-month hazard ratios of discontinuation as compared to haloperidol were 0.32 (0.24, 0.43) for olanzapine and 0.41 (0.28, 0.59) for quetiapine, similar to 0.28 (0.18, 0.43) and 0.52 (0.35, 0.76), respectively, in EUFEST. Since the benchmarking was deemed successful,

in extending our findings to newer agents, we found that compared with aripiprazole, the 12-month risk differences of discontinuation (95% CI) were -15.3 (-30.0, 0.0) for olanzapine, and -12.8 (-25.7, -1.0) for risperidone. The 12-month risks of hospitalization were similar between agents.

In the second case study, of 2,228 individuals with FEP, 1,067 were eligible for the benchmarking analyses. The estimated 18-month hospitalization risks for LAI therapy initiation and oral therapy continuation were 18.5% (95% CI: 12.2, 23.2) and 19.3% (95% CI: 16.3, 22.6), respectively. The corresponding estimates in EULAST were 22.0% (15.2, 29.4) and 19.2% (11.6, 25.6). Since the benchmarking was deemed successful, in the extended analysis (1,193 eligible individuals), the 3-year risk difference risk difference of psychotic relapse comparing LAI therapy initiation with oral continuation was -7.0% (95% CI:-12.1, -0.7). The risk difference was substantially lower in subgroups with a prior relapse (-15.5%, 95%CI: -24.1, -5.5) or prior non-adherence (-21.9, 95%CI: -41.9, -2.0).

**DISCUSSION:** This approach to observational analysis (target trial emulation with benchmarking analysis) using high-quality data can be used to complement and extend results from randomized evidence. In particular, we found that our estimates support use of aripiprazole and paliperidone as first-line therapies for FEP due to their lower all-cause discontinuation by 1 year. In the second case study, we estimated that, compared with oral therapy continuation, LAI therapy initiation reduced psychotic relapses over 3 years. LAI therapy initiation may be particularly beneficial in more vulnerable subgroups, such as those with prior relapses or documented non-adherence.

## T176. Patterns of Diagnosis in Patients With Early Psychosis in Coordinated Specialty Care

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**BACKGROUND:** Connection Learning Healthcare System (CLHS) is a consortium of 23 early psychosis programs in Pennsylvania and Maryland providing Coordinated Specialty Care (CSC) treatment. This study examines the range of diagnoses across CLHS, determines factors associated with diagnoses, and if diagnoses change over time.
**METHODS:** Demographics and clinical data were examined for a cohort of patients (n = 915) in CLHS. Associations were explored between admission diagnosis, demographics, and clinical measures, as well as changes in diagnosis from admission to 12 months post-admission for the subset (n = 381) with a diagnosis recorded at both time points.
**RESULTS:** The full cohort (n = 915): mean age=20.7 yrs; Black=45.2%, White=42.6%, Other=12.1%; Hispanic=9.6%; female=34.9%. Admission diagnosis: other specified/unspecified

psychosis=48.2%, schizophrenia=16.0%, mood disorder with psychosis=13.4%, schizoaffective=8.7%, schizophreniform=5.2% , other psychosis-related diagnosis=5.9%, brief psychotic disorder=2.5%. There was a significant association between race and diagnosis at admission ($\chi 2 = 37.97$, df = 12, $p < 0.0001$); patients diagnosed with other specified/unspecified psychosis were more likely to be Black than White ($p < 0.001$) and with a mood disorder were more likely to be White than Black ($p = 0.017$). No significant differences in racial distribution were found for diagnoses of schizophrenia or schizoaffective disorder. Frequency of diagnoses varied widely across clinic site. Patients with a mood disorder had significantly higher COMPASS-10 General (depressed mood, anxiety, suicidal ideation, hostility) scores (M = 2.15, SD =0.99), than those with schizophrenia (M = 1.50, SD = 1.15) or schizophreniform disorder (M = 1.29, SD = 0.83). There were no significant associations between diagnosis and age, ethnicity, sex, or COMPASS-10 Negative, Positive, or Global Functioning Role/Social scores. A majority of the subset with a 12-month diagnosis (n = 381) had no change in diagnosis at 12 months (schizophrenia=66.67%, schizoaffective=87.5%, schizophreniform=64.71%, mood=63.64%, and, of particular interest, other specified/unspecified psychosis=64.25%). A multinomial logistic regression model assessing if admission diagnosis predicted 12-month diagnosis revealed that patients admitted with schizophrenia ($p = 0.001$), mood disorder ($p = 0.001$), and other specified/unspecified psychosis ($p < 0.001$) had a strong likelihood of retaining the diagnosis, and admission with brief psychotic disorder predicted transition to other specified/unspecified psychosis ($p = 0.043$). Rates of change in diagnosis over time also varied widely across clinic site. A schizoaffective disorder diagnosis was less likely to change in those reporting marijuana use in the month prior to 12 month assessment ($t(17) = 2.2$, $p = 0.042$), and a mood disorder diagnosis was less likely to change in individuals with a high COMPASS-10 General Score ($t(32) = 2.3$, $p = 0.027$).

**DISCUSSION:** Results demonstrate that 86.6% of patients admitted to CLHS programs have a schizophrenia-spectrum disorder. The diagnosis of other specified/unspecified psychosis is higher in Black patients, while mood disorder with psychosis diagnoses are higher in White patients, consistent with findings in other clinical populations. Future work will investigate potential reasons for the high frequency of other specified/unspecified diagnosis and lack of diagnostic change over time, such as an inherent lack of diagnostic clarity in the very earliest stages of psychosis, general deprioritization of diagnosis at some sites or other local diagnostic practices, and/or reluctance to make the potentially stigmatizing diagnosis of schizophrenia. Whether a greater focus on diagnostic specificity would alter racial disparities in care, improve pharmacotherapy, better guide psychotherapy and psychoeducation, and enhance (or detract) from patient and family engagement remains to be determined.

## T177. Linking Speech Patterns to Brain Structure in Affective and Psychotic Disorders: An Integrative Natural Language Processing Approach

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**BACKGROUND:** Language disturbances are prominent features of affective and psychotic disorders, significantly impacting communication abilities and quality of life. Traditional assessment methods often lack objectivity and sensitivity to subtle language abnormalities. Recent advancements in natural language processing (NLP) offer a novel, objective approach to analyzing language impairments, providing deeper insights into the cognitive and neural mechanisms underlying psychiatric conditions.

**METHODS:** This study integrated NLP-derived linguistic metrics with neuroimaging data to investigate the neural correlates of language disturbances across affective and psychotic disorders. Speech samples were collected from 372 participants, including 194 patients (Major Depressive Disorder, Bipolar Disorder, Schizoaffective Disorder, and Schizophrenia) and 178 healthy controls, using narratives elicited from the Thematic Apperception Test (TAT). NLP techniques were applied to the transcribed speech to extract 18 linguistic features across multiple domains, including syntactic features (e.g., subordination ratio), semantic features (e.g., semantic coherence), pragmatic features (e.g., use of connectives), lexical features (e.g., type-token ratio), and disfluency measures (e.g., filled pauses ratio). Exploratory factor analysis identified three linguistic factors. Linear regression models were used to examine associations between these factors and brain structures, controlling for age, sex, total intracranial volume (TIV), and diagnostic group.

**RESULTS:** The exploratory factor analysis revealed three linguistic factors: (1) Syntactic Complexity, reflecting complex grammatical constructions; (2) Lexical Diversity and Fluency, indicating vocabulary richness and speech fluency; and (3) Narrow Thematic Focus, characterized by frequent pronoun usage and maintained semantic coherence through simpler expressions. Significant negative correlations were found between the Syntactic Complexity factor and Formal Thought Disorder (FTD) symptoms of Disorganization, Emptiness, and Incoherence. The Lexical Diversity and Fluency factor negatively correlated with negative symptoms of FTD. Neuroimaging analyses revealed that Narrow Thematic Focus was negatively associated with gray matter volume in the right posterior insula and with fractional anisotropy (FA) in the left corticospinal tract. Lexical Diversity and Fluency showed negative associations with FA in multiple white matter tracts, including the bilateral anterior thalamic radiation, bilateral uncinate fasciculus, right inferior longitudinal fasciculus, and right superior longitudinal fasciculus. Syntactic Complexity was negatively associated with FA in the left anterior thalamic radiation and the left uncinate fasciculus. Medication did not significantly influence these associations.

**DISCUSSION:** This study identified latent linguistic features associated with structural brain abnormalities across psychiatric conditions and healthy controls. These findings contribute to a deeper understanding of the neural mechanisms underlying language function in mental disorders.